ORIGINAL RESEARCH VOLUME 3; ISSUE 2 (2025)

Effect of Cyproterone Acetate and Ethinyl Estradiol in Infertile Polycystic Ovarian Syndrome in Females with Increased Ovarian Volume

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Abstract

Background: The infertility in women can be attributed to endocrine, metabolic and gynecological disorders in polycystic ovarian syndrome (PCOS) which impacts the function and quality of ovary. PCOS can be measured by clinical and biochemical markers and radiologically by polycystic ovarian morphology (PCOM). Ultrasonography (USG) in PCOS shows increase in ovarian stroma, ovarian volume and the number of follicles which are placed peripherally along the ovary.

Objectives: To estimate the effect of standard available combination of ethinyl estradiol and cyproterone acetate (CPA+EE) on increased ovarian volume in infertile PCOS patients of reproductive age.

Methods: A prospective interventional cohort study was done in infertile patients having PCOS with increased ovarian volume as diagnosed by Rotterdam's criteria. The patients included in the study were divided into 3 groups according to their ovarian volume. These patients were given combination of CPA + EE for a period of 3 months and at the end of which change in the ovarian volumes was noted. The non responders were either subjected to laparoscopic ovarian drilling (LOD) or 3 more months of CPA+EE. Change in ovarian volume was statistically analyzed thereafter.

Results: In Group 1, out of 25 patients 17 showed reduction in ovarian volume on USG after 3 months of the therapy & 8 were non-responders. In Group 2, of 15 patients 7 showed a reduction in the ovarian volume & 8 were non-responders. In Group 3, of 10 patients 4 showed a significant reduction in ovarian volume & 6 were non-responders. The non responders of all the groups either opted for LOD or continued CPA+EE. The ovarian volume was assessed after 3 more months. A statistically significant decrease ($p < 0.05$) in ovarian volume was observed in 32 patients enrolled in the study after treatment with CPA+EE with 28 responding after 3 months of CPA + EE & 4 after 6. When these patients were subjected to ovulation induction a positive pregnancy test was obtained in 20 patients.

Conclusions: Thus it can be concluded that CPA+EE can be used effectively in infertile PCOS patients with raised ovarian volume for treatment as well as for pre-induction.

Keywords: Cyproterone acetate, Ethinyl estradiol, Polycystic ovarian morphology, Polycystic ovarian syndrome, Ovarian volume

Journal of Research in Medical and Interpathy Sciences. 3(2);2025; doi: 10.61081/jremedis/3v2i103

Introduction

The most common endocrinopathy in women of reproductive age group is a multifocal disorder known as PCOS (polycystic ovarian syndrome).[1] This heterogeneous condition affects around 5-10% of the women.[2,3] PCOS is said to be a complex interaction of environmental and genetic traits.[4] PCOS is associated primarily with hyperandrogenism and oligo-anovulation in the reproductive age group and is more oftenly associated with clinical and metabolic disorders and sub fertility or infertility.[5] There has been a 10-foldrise in infertility in patients having PCOS with the prevalence varying from 40% to as high as 80%.[5,6]

The infertility observed in women can be attributed to endocrine, metabolic and gynecological disorders in PCOS which have an impact on the function and quality of ovary. Normal follicular growth is hampered leading to follicular growth arrest with no dominant follicle development, and hence no ovulation. Hormonal imbalance is also seen as increased insulin resistance and reversal of follicule stimulating hormone (FSH) to luteinizing hormone (LH) ratio and decreased sex hormone binding globulin (SHBG), thus causing hyperandrogenism. Thus, giving poor pregnancy outcomes in these women.[6-9]

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Conflict of Interest: None

Source of Funding: None

How to cite: Naik S, Naik A. Effect of Cyproterone Acetate and Ethinyl Estradiol in Infertile Polycystic Ovarian Syndrome in Females with Increased Ovarian Volume. Journal of Research in Medical and Interpathy Sciences. 2025;3(2):44–48

PCOS can be measured by markers (clinical and biochemical) and radiological assessment which shows polycystic ovarian morphology (PCOM). Ultrasonography (USG) of the ovaries in PCOM reveals increase in ovarian stroma and ovarian volume and also increase in the number of follicles which are placed peripherally along the ovary.[9,10] PCOS is commonly diagnosed using the Rotterdam's criteria. Defining PCOS by Rotterdam criteria needs any 2 of the following clinical and/or biochemical hyperandrogenism, oligo or anovulation, polycysticovaries. The diagnosis of PCOS on USG was made if there was presence of 12 or more peripheral follicles each 2-9 mm in diameter in 1 or both ovaries. Increase in volume (10 cc) is seen in one or both ovaries.[11]

All these 3 parameters hamper the fertility of a woman. To improve fertility, these abnormal parameters need to be normalized. The choice of treatment for normalizing the irregular cycles is oral combination pills and is proved by various studies as revealed by literature review.[9,12-14] Combined estrogen and progesterone pills (COCs) are recommended as primary treatment of chronic anovilation and hyperandrogenism.[4,15,16] Among COCs, Cyproterone acetate (CPA) plus ethinyl estradiol (EE) have been commonly used to treat androgen dependent conditions like PCOS and is also known to normalize menstrual function and treat hirsutism and acne.[17] Also, a study conducted in women revealed that is effective in reducing the raised ovarian volume.[14] Panidis *et al.* showed that it significantly causes suppression of serum LH.[18]

Also, when used before starting Clomiphene citrate, 2 months of CPA/EE produced effective ovulation and pregnancy rates.[4] CPA + EE are also found to improve ovulation and pregnancy rates by using 42 days pretreatment with CPA/EE before ovulation induction.[19] All the studies conducted have studied individual outcomes of CPA+EE. Hence the aim of this study was to study all these individual outcomes in a single study and further confirm the positive effect of CPA+EE in PCOS women with infertility in the form of positive pregnancy test.

Aim & Objectives

- To estimate the effect of standard available combination of ethinyl estradiol and cyproterone acetate on increased ovarian volume in infertility patients of PCOS of reproductive age.
- To estimate number of women ovulating after induction and confirming same with positive pregnancy test.

Materials And Methods

Study Design: A prospective interventional cohort study was conducted in the department of gynecology of a rural tertiary referral teaching hospital in the hilly area after obtaining ethical approval.

Study Population: Women of reproductive age attending the gynecology and infertility outpatient department (OPD) from Jan 2022 to Dec 2022, i.e., over a year were screened. Women with infertility having PCOS as defined by Rotterdam's criteria with increased ovarian volume on USG (i.e., >10cc) and/or abnormal hormonal levels were included in the study after obtaining their consent. Infertile women with PCOS & normal ovarian volume, male factor infertility only and not willing to participate in the study were excluded from the study.

Study treatment: These patients were subjected to the oral combination of CPA and EE cyclically for a period of 3 months initially and if needed for 3 more months cyclically.

Study end points: The primary outcome was to study the reduction in the ovarian volume after giving the standard combination. The secondary outcome was assessed in the form of a positive pregnancy test.

Study assessment: Women of reproductive age attending the gynecology and infertility OPD in the year 2022 were subjected to detailed history taking, general and gynecological examination. Patients with history of infertility and clinical evidence of PCOS as defined by Rotterdam's criteria were subjected to a baseline transvaginal ultrasonography and investigations as per institutional protocol. The ovarian volume of each ovary was calculated using the ovarian diameters in the three perpendicular directions and those with ovarian volume of more than 10 cc were included in the study. Investigations done were serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and other hormonal assays as per the clinical examination.

The patients included in the study were divided into 3 groups according to their ovarian volume, Group I were patients with 10 to 15cc ovarian volume, Group II with 16 to 20 cc and Group III with volume > 21 cc. All the groups were given the standard combination of CPA+EE cyclically for a period of 3 months. At the end of 3 months a repeat USG was done to assess if any change in ovarian volume and those with abnormal biomarkers were asked to repeat the same to assess improvement in them if any. The cases in which the ovarian volume reduced or was normal after 3 months were subjected to ovulation induction and were further followed up with follicular monitoring to assess evidence of ovulation.

12 of the non-responders were given another 3 months of the standard combination. While 10 opted for laparoscopic ovarian drilling. After another 3 months of the standard combination, again USG was done to assess the improvement in ovarian volume and those with the same were given ovulation induction and followed up with follicular monitoring. Final outcome in all the responders as well those subjected to laparoscopic ovarian drilling was assessed in the form of positive pregnancy test.

Data was collected in a preformed case record format and entered in the Excel sheet. Tabulation of the observations done and data analysis done using appropriate statistical tests.

Statistical analysis: Data are expressed as mean +/- standard deviation and analysis done using the paired t test to compare parameters related to ovarian volume i.e. total ovarian volume, right ovarian volume and left ovarian volume (TOV, ROV, and LOV); done at baseline and after 3 months of treatment. Statistical significance was set at $p < 0.05$.

Sample size: Sample (Size and technique) reference from Chan Hong Park *et al*.[14]
d: average reduction in size of ovarian mass in ml /cc =3cm^2
z/t: significance level
z1-α/2: alpha significance level
z1-β: beta significance level
6(sigma): standard deviation
n=[z1-α/2+z1-β]2 62 /d2=45.94

Considering loss to follow up or attrition a sample size of 50 is taken

Observation

After applying the paired t test using the information obtained from the above table it was found the decrease in ovarian volume after use of the standard combination was statistically significant giving a *p-value* < 0.05 in all groups.

Table 1: Reduction in ovarian volume at 3 months with patients on CPA+EE.

Groups	Cases	Responders	Non-responders	Reduction in ovarian volume in %)
I	25	17	8	68%
II	15	7	8	46%
III	10	4	6	40%
Total	**50**	**28**	**22**	

28 out of 50 patients (56%) responded to the combination in the first three months

Table 2: Treatment for non-responders after 3 months.

Groups	Non-Responders After 3 Cycles	Opted for Laparoscopic Drilling after 3 Months of Regime	Continued with CPA+EE for Next 3 Months
I	8	4	4
II	8	2	6
III	6	4	2
Total	**22**	**10**	**12**

Results

Total fifty patients with infertility having PCOS attending OPD at the rural tertiary teaching hospital, fulfilling the inclusion criteria were selected for the study and given CPA+EE from day 2 of menses for 3 cycles.

In Group 1 (Table 1) overall 68% patients showed reduction in ovarian volume on trans vaginal sonography after 3 months of CPA+EE, while 8 patients did not respond. Among the non-responders 4 opted for laparoscopic drilling (Table 2) after 3 months of treatment while the remaining 4 opted for more 3 months of therapy (Table 3). At the end of the cyclical therapy only 1 showed reduction in ovarian volume while 3 were non responders and opted for laparoscopic drilling. Thus, in this group, 18 patients responded to the combination while 7 underwent laparoscopic drilling. A total 11 patients had a positive pregnancy test (Table 4) with 10

Table 3: Months combinations repeated in 12 patients.

Groups	Refractory cases after 3 Months	Opted for Laparoscopic Drilling at 6 Months	Responder
I	4	3	1
II	6	3	3
III	2	2	0
Total	**12**	**8**	**4**

4 out of the 22 non-responders showed decrease in ovarian volume after 6 months of the combination

Table 4: Pregnancy rate after ovulation induction.

Group	Cases	CPA + EE cases	Lap Drilling cases	Pregnant Cases
I	25	10	1	11
II	15	3	2	5
III	10	3	1	4
Total	**50**	**16**	**4**	**20**

Table 5: Pre- and post-treatment mean & SD values of change in ovarian volume

Cases	Pre value (Mean +/- SD)	Pre value (Mean +/- SD)	Post value (Mean +/- SD)	Post value (Mean +/- SD)
	Right ovarian volume	Left ovarian volume	Right ovarian volume	Left ovarian volume
Total	18.30+/-	17.06+/-	12.32+/-	10.91+/-
	7.66	6.57	6.93	5.58
Group I	13.09+/-	12.44+/-	8.77+/-	8.08+/-
	1.44	1.55	3.07	2.83
Group II	17.73+/-	17.46+/-	11.10+/-	10.51+/-
	1.53	1.84	4.05	3.92
Group III	32.21+/-	28.03+/-	23.02+/-	18.6+/-
	4.45	5.51	6.79	6.02

after the combination therapy and 1 after laparoscopy. Seven patients with abnormal biochemical markers showed normal values after treatment.

In the second group (Table 1) out of 15 patients 7 patients showed a reduction in the ovarian volume after 3 months while 8 were non responders. 2 opted for laparoscopic drilling after 3 months (Table 2) while 6 patients opted for the combination for 3 more months. Out of the 6 3 responded while 3 were non responders and were subjected to laparoscopic drilling. Post ovulation induction 3 of the combination therapy while 2 of the laparoscopic group had a positive pregnancy test (Table 4). 3 out of 6 patients with abnormal FSH to LH ratio revealed a normal ratio after treatment

In the third group with ovarian volume more than 21 cc, 40% patients showed a significant reduction in ovarian volume (Table 1) after 3 months while 6 were non responders. 4 out of six refractory cases (Table 3) opted for ovarian drilling after 3 months while the remaining 2 cases opted for 3 more months of the combination. These 2 cases were non-responders and were subjected to ovarian drilling. 6 cases were put on ovulation induction protocol a positive pregnancy test achieved in four cases (Table 4). Four out of five patients with abnormal biochemical markers reveal normal values post therapy.

Out of total 50 patients enrolled, 42 patients that is 84% showed a reduction in ovarian volume (Table 1) in 6 months of therapy while eight patients were refractory (Table 3). 18 patients over all that is 36% required ovarian drilling (Table 2). 20 patients conceived building a positive pregnancy rate of 40% (Table 4). 14 patients out of 21 patients with abnormal biochemical markers showed normal parameters or values after treatment. 28 patients responded with therapy for 3 months while 4 responded after another three cycles.

Discussion

Raised ovarian volume is one the key features to state that PCOM exists in a patient of PCOS. Combined estrogen progesterone pills (COCs) are recommended as primary treatment for chronic anovulation and hyperandrogenism in PCOS.[20] We found a significant decrease in baseline total ovarian values in right and left ovaries after 3 months of treatment in infertile patients with PCOS. Our finding is in line with another study by Mes-Krowinkel which reported a similar reduction in mean total ovarian volume of both ovaries, mean ovarian follicle count, and AMH level in patients using COCs.[21] In yet another study by Park *et al.*,[14] it was observed that COC treatment can improve PCOM (ovarian volume and follicle counts) and AMH levels, although the mean values in the participants still satisfied the diagnostic criteria of PCOS after 1-year of treatment. This finding was consistent with Mes-Krowinkel *et al*.

In another study by Teede *et al*. cyproterone acetate (CPA) 2 mg/EE 35µg were used in PCOS women and they reported that the ovarian volumes of right and left ovary as well as the total ovarian volume were significantly decreased after 3 months of COC treatment.[20] A significant decrease in ovarian volume was observed after treatment with COCs for 3 cycles in a study by Plouvier *et al*.[22] Another study by Fabrigues *et al*. reported that treatment with desogestrel 2 mg/EE 20 there were significant reductions in ovarian volume & follicle counts after 6 months of COC use. [23]

In a study by Dursun *et al*., COCs caused significant decrease in right ovarian volume (ROV),and left ovarian volume (LOV) in PCOS showing correlation between LOV and Anti-Mullerian hormone (AMH) (rho = 0.336 and 0310; $P = 0.018$ and 0.034, respectively).[24,] Panidis *et al*.[18] reported changes in AMH levels in 2 other COC treatment groups (CPA 2 mg/EE 35 µg and drospirenone 3 mg/EE 2 µg) at 3 time points (baseline, 3 months, and 6 months). A study by Ghosh *et al*. showed a change not only in the ovarian volume but also in biochemical markers and improved ovulation rates.[25]

Branigan and Estes (2003) found that 2 months of CPA/EE use before repeating CC treatment in CC resistant women produced effective ovulation and pregnancy rates.[26] Salama and Hamza (2019) also found improved ovulation and pregnancy rates by using 42 days pretreatment with CPA/EE before ovulation induction with letrozole in CC resistant patient.[19] The studies conducted by Banu *et al*., Chowdhary *et al*. & Ruan *et al*. also concluded the use of combination as pre induction protocol to improve ovulation & pregnancy rates. These findings are consistent with our study where we subjected our patients to ovulation induction post treatment with CPA+EE and obtained effective ovulation and pregnancy rate.

To summarize the combination of CPA+EE showed a reduction in the ovarian volume in infertile PCOS women with raised ovarian volume and was proven to be statistically significant.

There were some limitations in this study. Firstly, this study was conducted over a short period of time. Second limitation was the relatively small sample size. Lastly, the patients were recruited from a single hospital location, so our findings may not be generalized and might not represent the community; we recommend further multicentric studies to consolidate the evidence provided in this study.

Conclusion

It can be concluded that the standard combination of EE+CA for 3-6 months reduces increased ovarian volume in PCOS and can serve as pre induction protocol in low resource setting.

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