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ORIGINAL RESEARCH

Effect of combined oral contraceptives and cyperoterone acetate-ethinyl estradiol combination on metabolic syndrome in polycystic ovarian syndrome (PCOS)

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ABSTRACT

Introduction: Polycystic ovarian syndrome (PCOS) is an endocrine disorder with multiple etiology and affecting women in reproductive age group. It has become a major problem in modern era and requires a multimodality of treatment.

Material and methods: The study was conducted on 100 PCOS patients attending PGIMS, Rohtak outpatient department to compare the efficacy of combined oral contraceptives (COCs) and cyperoterone acetate-ethinyl estradiol (CPA-EE) combination on metabolic parameters. This was a prospective interventional study conducted for one and half year. Patients were followed at one, three and six months of treatment and comparison was made from baseline to six months of treatment.

Results: Both the drugs did not change the waist circumference and blood pressures of the patients, while improved fasting blood sugars from third month of treatment. COCs were found to deteriorate the sugar levels more significantly when compared to CPA-EE. Both the drugs significantly derange the triglyceride and high density lipoprotein levels, CPA-EE being more than COCs.

Conclusion: Any of the drug can be used in the treatment of PCOS patients but with caution in diabetic and hyperlipidemic patients.

Keywords: Polycystic ovarian syndrome (PCOS), combined oral contraceptives (COCs), cyperoterone acetate-ethinyl estradiol (CPA-EE), metabolic syndrome, diabetes, hyperlipidemia.

Synopsis: Both the drugs are equally effective in improving the metabolic parameters but derange the blood sugars and lipid profile.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a complex, multifaceted and heterogenous endocrine disorder in women of reproductive age group across the globe with prevalence ranging from 5% to 10% in different populations[1]. PCOS affects not only clinical parameters but also metabolic parameters like insulin resistance with compensatory hyperinsulinemia leading to diabetes mellitus type 2, cardiovascular diseases, hypertension, hyperlipidemia, obesity. Metabolic syndrome has been defined according to the new international diabetes federation (NCEP ATP III 2001) as: central obesity as waist circumference >88 cm or 35 inches plus any two of the following: i) triglycerides >150 mg/dl (ii) high density lipoprotein (HDL) <50

mg/dl (iii) blood pressure systolic BP >130 or diastolic BP >85 mmHg iv) fasting plasma glucose >100 mg/dl[2].

There are various treatment modalities for PCOS, but unless metabolic and underlying endocrinal disturbances are corrected, medical management is of little importance. Many drugs are being marketed now but Combined Oral Contraceptives (COCs) and Cyperoterone acetate- ethinyl estradiol combination (CPA-EE) still remains the first choice by most practitioners. The key mechanism of COCs action is the inhibition of folliculogenesis. CPA-EE, an oral contraceptive with anti androgen properties, blocks the androgen receptors thereby treating hyperandrogenism.

However as there are few studies comparing the efficacy of two drugs simultaneously on metabolic syndrome, the present study was conducted.

AIMS AND OBJECTIVES

To compare the efficacy of Combined Oral Contraceptives with Cyproterone acetate and ethinyl estradiol combination on metabolic syndrome in PCOS.

MATERIAL AND METHODS

STUDY DESIGN

This was a prospective interventional study conducted in outpatient department of Obstetrics and Gynaecology at Pt. B.D. Sharma PGIMS, Rohtak in females diagnosed with PCOS.

STUDY DURATION

1st December 2018 to 31st May 2020

STUDY SUBJECTS

100 patients were enrolled in the study in two groups which were randomised alternately. Group A with 50 patients received COCs and group B with 50 patients received CPA-EE

INCLUSION CRITERIA

Patient with PCOS diagnosed according to Rotterdam's criteria. According to Rotterdam criteria, the diagnosis of PCOS may be made if any two out of the following three abnormalities are present: 1) chronic anovulation (oligomenorrhea or amenorrhea); 2) clinical (hirsutism, acne) and/or biochemical hyperandrogenism (raised testosterone levels) and 3) polycystic ovaries on pelvic ultrasound which includes: a) one or both ovaries demonstrating 12 or more follicles measuring 2-9 mm in diameter or b) the ovarian volume exceeds 10 cubic cm[3, 4].

EXCLUSION CRITERIA

Hyperprolactinemia, hyper or hypothyroidism, infertility, females on oral contraceptive pills, pregnancy, lactation, any active liver or renal disease, overt diabetes, hypertension, familial hyperlipidaemia.

Patients were enrolled and informed and written consent was taken. Evaluation was made for any improvement in the waist circumference, triglyceride, HDL, blood pressure, fasting blood sugar at one, three and six month followup and efficacy of the drugs in either group was compared.

STATISTICAL ANALYSIS

It was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean±SD or median (IQR) for non-normally distributed data. The comparisons of normally distributed continuous variables were

performed using Student's t test and non-normal distribution continuous variables were compared using Mann Whitney U test. Categorical variables were expressed as frequencies and percentages and were compared using Chi-squared test or Fisher's exact test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

Detailed results are shown in table 1-5

Table 1: Comparison of waist circumference (WC) at enrolment, one, three and six months of treatment in two groups

WC (cm)	Group A (COC)			Group B (CPA-EE)			Inter group p value
	mean±SD	% changes	p value	mean±SD	% changes	p value	
Baseline	31.10±4.93			33.88±5.51			0.45
1 month	31.12±4.87	0.3	0.45	33.9±5.63	0.05	0.89	0.46
3 month	31.18±4.74	0.06	0.9	34.12±5.709	0.7	0.38	0.51
6 month	31.20±4.73	0.1	0.83	34.28±5.606	1.1	0.14	0.49

Table 1 shows comparison of waist circumference (WC) at enrolment, one, three and six months of treatment in two groups. No significant difference was seen among two groups at baseline 1 month, 3 month and 6 month (p >0.05 NS).

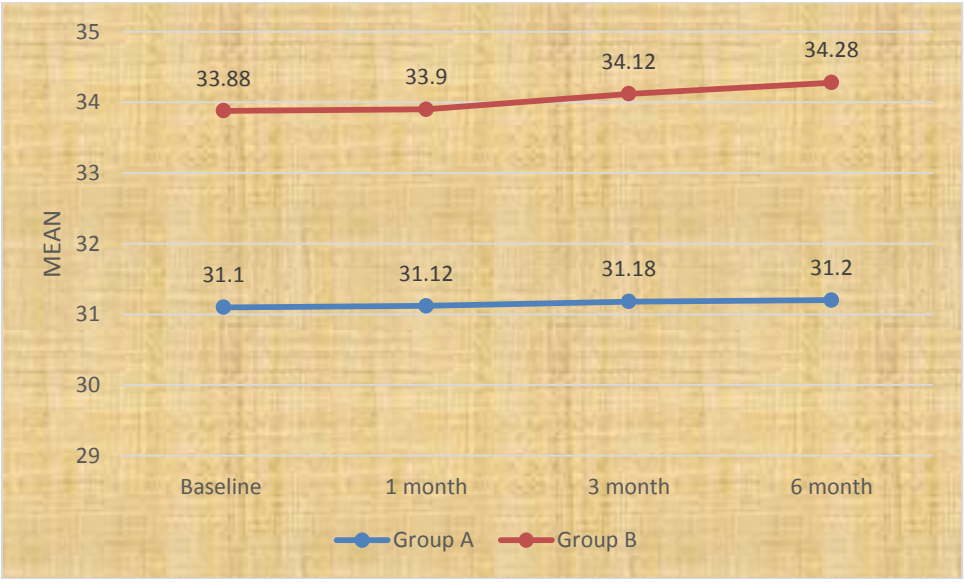


Table 2: Effect on Fasting Blood Sugar (FBS) at enrolment, one, three and six months of treatment in two groups

Fasting Blood Sugar (mg/dl)	Group A (COC)			Group B (CPA-EE)			Inter group p value
	mean±SD	% changes	p value	mean±SD	% changes	p value	
Baseline	81.20±13.14			86.92±13.76			0.21
1 month	83.04±12.69	2.26	0.14	88.18±13.3	1.44	0.22	0.05
3 month	86.12±13.71	6.05	**0.01 (S)**	91.70±12.11	5.49	**0.005 (S)**	**0.03 (S)**
6 month	88.74±12.49	9.28	**0.001 (S)**	94.00±12.82	8.01	**0.001 (S)**	**0.04 (S)**

Table 2 shows effect on Fasting Blood Sugar (FBS) at enrolment, one, three and six months of treatment in two groups. In the present study, significant changes were observed at 3 month and 6 month among both the groups in inter group as well as intragroup comparison.

Table 3: Effect on Triglyceride and High Density Lipoprotein (HDL) at enrollment to one, three and six months of treatment in both the groups

	Group A (COC)			Group B (CPA-EE)			Inter group p value
	mean±SD	% changes	p value	mean±SD	% changes	p value	
Triglyceride (mg/dl)							
Baseline	117.02±59.42			125.54±65.01			0.68
1 month	127.22±59.61	8.7	0.39	139.86±66.08	11.4	**0.001 (S)**	0.31
3 month	143.48±65.69	22.6	**0.03 (S)**	159.48±75.1	27.03	**0.001 (S)**	0.26
6 month	160.88±73.4	37.48	**0.001 (S)**	186.62±82.03	48.6	**0.001 (S)**	**0.01 (S)**
HDL (mg/dl)							
Baseline	52.92±12.27			52.80±12.52			0.96
1 month	59.86±13.93	13.11	**0.001 (S)**	61.14±12.87	15.79	**0.001 (S)**	0.63
3 month	71.34±13.24	34.8	**0.001 (S)**	76.08±15.72	44.1	**0.001 (S)**	0.1
6 month	85.12±11.49	60.8	**0.001 (S)**	90.28±21.04	70.9	**0.001 (S)**	0.13

Table 3 shows effect on Triglyceride and High Density Lipoprotein (HDL) at enrollment to one, three and six months of treatment in both the groups. Triglyceride was found to be significant at 3 month and 6 month in both the groups i. In group B, triglyceride was also found to be significant at 1 month. Intergroup analysis shows significant improvement at 6 month.

Table 4: Effect on blood pressure at enrollment to one, three and six months of treatment in both the groups

Blood pressure (mmHg)		Group A (COC)			Group B (CPA-EE)			Inter group p value
		mean±SD	% changes	p value	mean±SD	% changes	p value	
SBP	**Baseline**	114.48±8.9			116.24±9.7			0.34
	1 month	113.72±7.28	0.66	0.39	116.40±8.9	0.13	0.84	0.1
	3 month	113.48±6.12	0.87	0.34	116.88±6.96	0.55	0.35	0.11
	6 month	115.56±7.1	0.94	0.28	115.28±7.65	0.82	0.38	0.85
DBP	**Baseline**	75.6±7.48			76.84±8.43			0.42
	1 month	75.76±7.24	0.21	0.89	76.96±9.46	0.15	0.92	0.48
	3 month	75.80±6.66	0.31	0.86	77.12±7.78	0.26	0.88	0.30
	6 month	75.75±6.89	0.20	0.87	76.44±8.18	0.48	0.83	0.34

Table 4 shows effect on blood pressure at enrollment to one, three and six months of treatment in both the groups and found to be statistically insignificant among both the groups – intergroup as well as intragroup (p >0.05 NS).

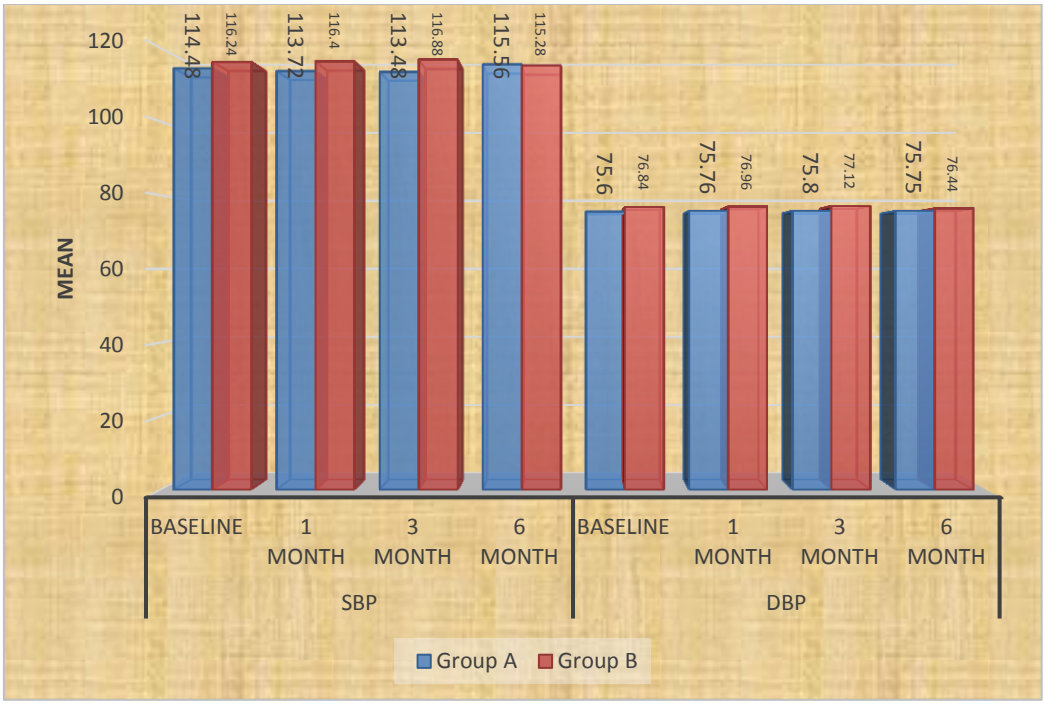
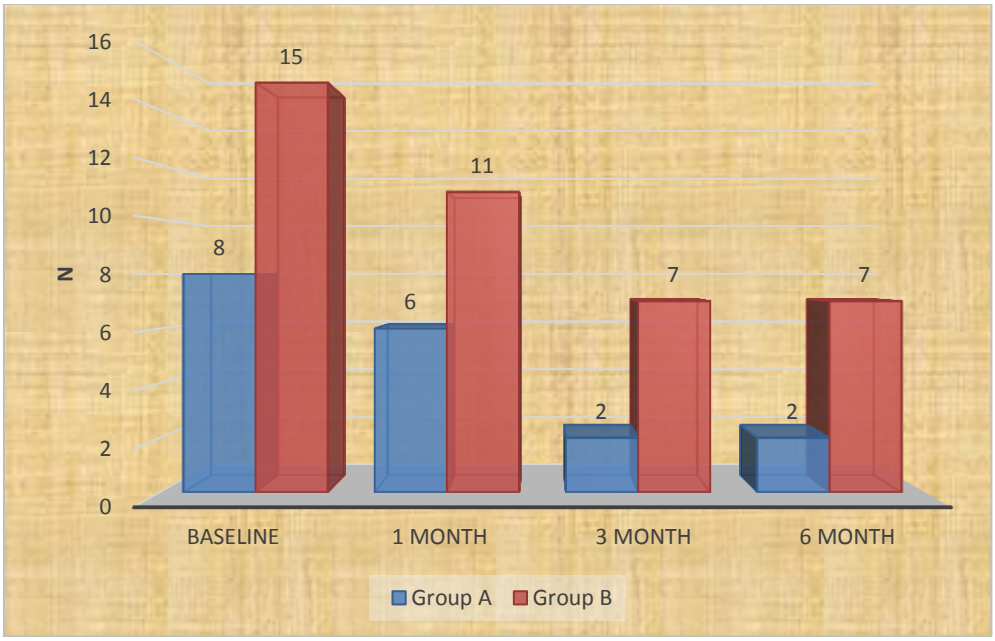


Table 5: Effect on Metabolic Syndrome after one, three and six months of treatment in both the groups

Metabolic Syndrome	Group A (COC)			Group B (CPA-EE)			Inter group p value
	N (%)	% changes	p value	N (%)	% changes	p value	
Baseline	15 (30)			8 (16)			0.09
1 month	11	26.66%	0.36	6	25%	0.54	0.18
3 month	7	53.33%	0.05	2	75%	**0.04 (S)**	0.08
6 month	7	53.33%	0.05	2	75%	**0.04 (S)**	0.08

Table 5 shows effect on Metabolic Syndrome after one, three and six months of treatment in both the groups. Statistical significant difference was seen in group B at 3 month and 6 month.



DISCUSSION

In the present study, effect of COCs and CPA-EE was studied on waist circumference as well as blood pressure and it was observed to have no effect even after six month (Table 1, 4). Other authors like Bhattacharya et al[5]and Podfigurna et al[6] also did not observed any effect by any of the drug groups. Similarly no significant effect was seen by Feng et al[7] and Dahlgren et al[8]for CPA-EE on Blood pressure. Min Min et al[9] on the contrary showed a significant decrease in waist circumference in their study.

In this study a significant increase was seen on fasting blood sugar levels after three and six months of treatment with COCs as well as with CPA-EE (Table 2). On comparing the two drug groups, the blood sugar levels deteriorated significantly more by COCS (p value 0.03 and 0.04). Dahlgren et al[8] and Morin-Papunen et al[10] observed increase in blood sugar with CPA-EE. While Bhattacharya et al[11]and Prelevic et al[12] didn't find any significant alteration in serum glucose levels. There is no study comparing the effects of both the drugs.

In the study, triglycerides level increased significantly in both the drug groups. In CPA-EE the effect was seen after one month while it deteriorated after three months of COCs use. However CPA-EE deteriorated triglycerides levels more than COC after six months of use (p value 0.01). Similar results were observed by Prelevic et al[12] and Falsetti and Pasinetti[13] with CPA-EE while with COC was observed by Halperin et al[14] and Kriplani et al[15]. Significantly beneficial effect was seen on HDL levels by the two drug groups which started as early as first month of treatment and continued till six months. although there was no statistically significant difference seen between the two groups, similar to the studies by Halperin et al[14] and Kriplani et al[15] on COC and Falsetti and Pasinetti[13] on CPA-EE whereas Prelevic et al[12] showed no significant changes in HDL with CPA-EE.

In the present study metabolic syndrome was found in 30% and 16% in the group A and B respectively (Table 5). Quite similar prevalence of metabolic syndrome in PCOS was observed by Spandana et al (21.3%) [16], Rossi et al (26%) [17] and Zahiri et al (28.8%) [18.] There was decrease in the number of metabolic syndrome patients with treatment in both the drug groups; from 16% to 4% in CPA-EE group and from 30% to 14% in COC group. Though the number of patients decreased in both the treatment groups, the decrease was significant in CPA-EE group as compared to COCs group. Maghraby et al[19] found similar results of deterioration of metabolic syndrome by COCs.

CONCLUSION

Both the drugs (Cyproterone acetate-Ethinyl estradiol combination and combined oral contraceptives) are equally effective in improvement of metabolic syndrome; therefore any of the drug can be used in the treatment.

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AUTHOR CONTRIBUTIONS

1. Shivangi: did the entire study, followed up the patients
2. Savita Rani Singhal: Support and guidance throughout the study
3. Latika: Support and guidance throughout the study

CONFLICT OF INTEREST

None

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