Original Research Article

COMPARISON OF COMBINED ORAL CONTRACEPTIVES AND CYPEROTERONE ACETATE-ETHINYL ESTRADIOL COMBINATION ON CLINICAL AND HAEMATOLOGICAL PARAMETERS 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 clinical and hematological 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 showed improvement in acne and hirsutism while no effect was seen on acanthosis nigricans, and anthropological parameters (basal metabolic rate, waist circumference, and waist hip ratio). Serum testosterone levels and sonographical parameters (ovarian volume, necklace appearance) also improved. On the contrary both the drugs deteriorated blood sugar levels and lipid profile of the patients on successive follow ups. However on comparison COCs deteriorated blood sugar levels more as compared to CPA-EE and CPA-EE deteriorated lipid profile (triglyceride and cholesterol levels) more than COCs. CPA-EE also improved the serum testosterone levels more when compared to COCs. **Conclusion:** Any of the drugs 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) combination, comparison, efficacy.

Introduction

Polycystic ovarian syndrome (PCOS) is a very common endocrine disorder that is encountered these days, having a wide range of clinical manifestations with the prevalence ranging from 2.2% to 26% globally[1] and affecting specially the reproductive age group. It was first described by Stein and Leventhal in a case series of seven women in 1935.[2] Women with PCOS present with clinical features which include acne, hirsutism, increased weight gain, menstrual irregularities; reproductive problems like infertility, pregnancy complications; metabolic abnormalities, cardiovascular diseases; psychological problems like reduced quality of life, poor self-esteem, depression and anxiety.[3] There are various treatment modalities for PCOS, most important being lifestyle modification followed by medications, of which oral contraceptives alone or in combination are the most commonly used ones. Mechanism of action of combined oral contraceptives (COCs) is by suppressing the release of gonadotropin thus reducing androgen formation from ovary and restoring normal menstrual cycle. Anti androgen drugs inhibit androgen synthesis by blocking androgen receptors, (blocks 5-alpha-reductase). Cyproterone Acetate (CPA) is a progestogenic compound having additional anti androgenic properties. There are very few studies regarding the comparison of efficacy of these most commonly used drugs in PCOS, worldwide, hence the present study was planned to throw some light on the efficacy of these drugs.

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Aims and objectives

To compare the efficacy of Combined Oral Contraceptives (COCs) with Cyproterone acetate and ethinyl estradiol (CPA-EE) combination on clinical, hematological and sonographical parameters in PCOS.

Material and Methods

Study design: This was a prospective interventional study conducted in the outpatient department of Obstetrics and Gynecology at Pt. B.D. Sharma PGIMS, Rohtak in females diagnosed with PCOS.
Study duration: 1st December 2018 to 31st May 2020

Study subjects: A total of 100 patients were randomized alternately into two groups with 50 patients in each group; Group A receiving COCs and Group B receiving CPA-EE.

Inclusion criteria
Patient with Polycystic Ovarian Syndrome diagnosed according to Rotterdam's criteria were included in this study. 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 $cm^{1,}$[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.

Research method: All the women were examined with special reference to acne, acanthosis nigricans (AN), hirsutism, waist to hip ratio, basal metabolic rate, and waist circumference. All the following investigations were carried out; fasting blood sugar, lipid profile, serum testosterone and ultrasound (on day two to day three of menstrual cycle) for arrangement of follicles and bilateral ovarian volume. Effects of respective drugs were studied on clinical, hematological and sonographical parameters in PCOS patients at their first visit, after one, three and six months but comparison for efficacy of the drugs was done after 6 months of treatment.

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.

Ethical approval: The study is ethically approved by the institutional ethical committee, PGIMS/UHS, Rohtak on 22 February, 2019 with reference number IEC/Th/18/Obs & Gynae12. Informed and written consent was taken from each participant before conducting any tests and measurements.

Observations and Results

The mean age in the present study was 21.84±4.27 and 22.92±4.35 in the groups A and B respectively with minimum age being 13 years and maximum age being 37 years. Mean age at menarche was 13.06±1.36 and 13±1.44 in the groups A and B respectively, most of the patients in either group had menarche during 11-13 years of age. There was significant effect of COC and CPA-EE on acne after six month; however on comparison both the drugs were equally effective. Both the drugs, (COC or CPA-EE) were highly and equally effective in improving hirsutism from first month of use (p value 0.001).Of the two, COC was observed to deteriorate the blood sugar levels significantly more as compared to CPA-EE. A statistically significant decrease in the levels of serum testosterone was noted in both the groups at each follow up month. Levels of total cholesterol, HDL, LDL, and VLDL level all showed an increasing trend on successive follow up although there was no statistically significant difference seen between the two groups except for total cholesterol levels which showed significant increase of 50.3% after use of CPA-EE as compared to 40.3% after use of COC; p value being 0.02 after six months. CPA-EE deteriorated triglycerides levels more than COC after six months of use. Both the drugs (COC and CPA-EE) were associated with significant reduction in ovarian volume and significant improvement in necklace appearance six month of treatment. Detailed results are shown in Tables 1 to 4.

Table 1: Comparison of clinical symptoms in two groups at one and six months

Clinical findings		Group A (COC)			Group B (CPA-EE)			Inter group p value
		N	% changes	p value	N	% changes	p value	
Acne (N)	**Baseline**	20			23			0.54
	6 month	1	95	**0.001 (S)**	5	78.26	**0.001 (S)**	0.16
Acanthosis nigricans (N)	**Baseline**	14			11			0.48
	6 month	9	35.71	0.34	8	27.27	0.44	0.45
Hirsutism (mean±SD)	**Baseline**	6.72±6.99			7.96±7.95			0.7
	6 month	1.18±2.08	82.4	**0.001 (S)**	1.08±1.51	86.4	**0.001 (S)**	0.78

Comparison among values of group A and B at the end of six month were insignificant (p value > 0.05) for all the three parameters i.e., acne, acanthosis nigricans, hirsutism.

Table 2: Comparison of drugs on anthropological parameters in two groups at one and six months

		Group A (COC)			Group B (CPA-EE)			Inter group p value
		mean±SD	% changes	p value	mean±SD	% changes	p value	
BMI (Basal Metabolic Rate)	**Baseline**	23.39±3.91			23.73±4.81			0.35
	6 month	23.47±3.61	0.1	0.75	23.95±4.9	0.9	0.33	0.48
WC (Waist Circumference)	**Baseline**	31.10±4.93			33.88±5.51			0.45
	6 month	31.20±4.73	0.1	0.83	34.28±5.606	1.1	0.14	0.49
WHR (Waist Hip Ratio)	**Baseline**	0.82±0.06			0.85±0.14			0.57
	6 month	0.83±0.06	0.4	0.2	0.86±0.14	1.05	0.6	0.14

All the values at the end of six months when compared in both the groups were insignificant (p value >0.05).

Table 3: Comparison of drugs on haematological parameters in two groups at one and six months

		Group A (COC)			Group B (CPA-EE)			Inter group p value
		mean±SD	% changes	p value	mean±SD	% changes	p value	
FBS (fasting blood sugar)	**Baseline**	81.20±13.14			86.92±13.76			0.21
	6 month	88.74±12.49	**9.28**	**0.001 (S)**	94.00±12.82	8.01	**0.001 (S)**	**0.04 (S)**
Testosterone	**Baseline**	76.48±40.75			94.17±44.66			0.82
	6 month	27.9±17.75	63.5	**0.001 (S)**	39.07±19.41	**68.5**	**0.001 (S)**	**0.003 (S)**
TG (triglyceride)	**Baseline**	117.02±59.42			125.54±65.01			0.68
	6 month	160.88±73.4	37.48	**0.001 (S)**	186.62±82.03	**48.6**	**0.001 (S)**	**0.01 (S)**
Cholesterol	**Baseline**	163.4±33.7			165.66±36.99			0.74
	6 month	229.28±41.05	40.3	**0.001 (S)**	249.08±46.96	**50.3**	**0.001 (S)**	**0.02 (S)**
HDL (high density lipoprotein)	**Baseline**	52.92±12.27			52.80±12.52			0.96
	6 month	85.12±11.49	60.8	**0.001 (S)**	90.28±21.04	70.9	**0.001 (S)**	0.13
LDL (low density lipoprotein)	**Baseline**	91.14±26.52			98±36.15			0.28
	6 month	123.58±33.59	35.5	**0.001 (S)**	136.16±48.81	38.9	**0.001 (S)**	0.13
VLDL (very low density lipoprotein)	**Baseline**	23±17.05			22.74±15.28			0.93
	6 month	45.26±2.02	96.7	**0.001 (S)**	43.16±14.71	89.7	**0.001 (S)**	0.43

Fasting blood sugar levels increased significantly after six months in group A as compared to group B (p value 0.04). All the values at the end of six months of serum testosterone when compared in both the groups were insignificant (p value >0.05). Triglyceride and Cholesterol levels increased significantly in group B as compared to group A after six months of use (p value < 0.05). HDL, LDL and VLDL levels had no significant change when compared in both groups after six months.

Table 4: Comparison of drugs on sonographical parameters in two groups at one and six months

		Group A (COC)			Group B (CPA-EE)			Inter group p value
		mean±SD	% changes	p value	mean±SD	% changes	p value	
Right Ovary Volume	**Baseline**	13.73±4.95			13.14±4.58			0.68
	6 month	6.3±1.68	54.1	**0.001 (S)**	6.68±1.98	49.1	**0.001 (S)**	0.3
Left Ovary Volume	**Baseline**	12.29±4.75			12.89±4.11			0.15
	6 month	5.64±1.57	54.1	**0.001 (S)**	6.22±1.6	51.7	**0.001 (S)**	0.07
Necklace appearance	**Baseline**	37			41			0.33
	6 month	2	94.59	**0.001 (S)**	3	92.68	**0.001 (S)**	0.64

Comparing values of ovarian volume in right and left ovary at the end of six months no significant difference in seen (p value > 0.05). On comparing both the groups no significant change in necklace pattern was observed (p value >0.05).

Discussion

In the study, both the drugs were highly and equally effective in treating acne and hirsutism (Table1; p value >0.05). It is in accordance with a study by Golland et al[5] after 12 cycles of CPA-EE, Bhattacharya et al[6] and Kriplani et al[7] after six cycles of COCs, for acne. For hirsutism too, similar results were seen by Bhattacharya et al[6] and Cinar et al[8] on COCs; Golland et al[5] and Dahlgren et al[9] with CPA-EE. Podfigurna et al[10] in their study stated that both COCs and CPA-EE significantly decrease the hirsutism score after six months of treatment but equally effective. In the present study there was no significant effect of either of the drug group i.e., COC or CPA-EE on BMI , WC and WHR at the end of six months (Table 2) as can also be seen in study of Bhattacharya et al[6], and Cinar et al[8] for COCs while Feng et al[11] and Dahlgren et al[9] for CPA-EE. No significant effect of treatment on AN was seen either with COCs or CPA-EE which correlates with the study of Bhattacharya et al.[6]

FBS deteriorated significantly at the end of six month (Table 3) but deterioration was significantly higher with COCs as compared to CPA-EE (p value 0.04 after 6 month). It correlates well with the study of Dahlgren et al[9] and Morin-Papunen et al[12] while Bhattacharya et al[6] and Prelevic et al[13] didn't find any significant alteration in serum glucose levels even after 12 months of treatment with COCs and CPA-EE respectively. Contrary to the present study Kriplani et al[7] found a significant decline in fasting blood glucose after six month of treatment with COCs (p value <0.01) which might be due to the fact that they used a different progesterone in their study i.e., drospirenone. No other study compared COCs and CPA-EE for the effect of FBS. At the end of six months of treatment, testosterone levels were decreased in the groups A and B respectively (Table 3). Comparing the two groups, CPA-EE is more effective in decreasing the testosterone levels. Results of the study by Feng et al[11], Morin-Papunen et al[12], Dahlgren et al[9], Falsetti and Pasinetti[14] and Prelevic et al[13] also showed similar results with CPA-EE. Similarly Bhattacharya et al[6], Kriplani et al[7] and Cinar et al[8] observed similar results with COCs.

In the present study while on treatment in both the groups (COCs and CPA-EE) the mean value of TG increased (Table 3). On comparing the two groups deterioration, it was significantly more in CPA-EE group as compared to COCs group at the end of six months similar to the study of Prelevic et al[13] and Falsetti and Pasinetti[14] with CPA-EE while with COCs was observed by Halperin et al[15] and Kriplani et al.[7] Both the drug groups increased the HDL levels i.e., improvement which were highly significant (p value 0.001), similar to the studies by Halperin et al[15] and Kriplani et al[7] on COCs and Falsetti and Pasinetti[14] on CPA-EE whereas Prelevic et al[13] showed no significant changes in HDL with CPA-EE. Cholesterol as well as LDL levels started to deteriorate significantly in the two drug groups at the end of six months. On comparing the two drugs, CPA-EE caused more deterioration in cholesterol level after six months of use than COCs i.e., by 50.3% in CPA-EE group and by 40.3% in COCs group. Prelevic et al[13] showed significant increase in total cholesterol and LDL levels with CPA-EE. Kriplani et al[7] found a significant rise in total cholesterol and significant decrease in LDL levels with COCs use, which could be explained as she used drospirenone in the study group subject. Halperin et al[15] found no change of LDL or cholesterol levels with COCs when given for three months for treatment, as the study characteristics such as BMI, mean age, duration of study were different. The baseline mean values of baseline VLDL in the present study were 23±17.05 and 22.74±15.28 respectively in the groups A and B which increased i.e., deteriorated significantly, as was observed by Halperin et al[15] and Kriplani et

al.[7] Mean value of ovarian volume decreased after follow up in both right and left ovaries in either of the groups which was highly significant (Table 4; p value 0.001). Likewise can be seen in studies by Kriplani et al[7], Prelevic et al[16], and Elter et al.[17] However the study sample size was only 100 and conducted for 6 months period on each participant, hence the results cannot be generalized.

Conclusion

Both the drugs, CPA-EE and COCs are equally and highly effective in improvement of clinical parameters (acne, hirsutism) in PCOS. The deterioration of triglyceride and cholesterol is significantly more with CPA-EE as compared to COCs, so it should be used with caution. Blood sugar levels deteriorate more by COCs as compared to CPA-EE. Testosterone levels improved by both the drugs after one and six months and improvement was significantly better by CPA-EE than COCs. Hence, it is concluded that, either of the drugs can be used in the treatment of PCOS.

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List of Abbreviations: PCOS = Polycystic ovarian syndrome, COC=Combined oral contraceptive pills, CPA-EE=Cyproterone acetate and ethinyl estradiol combination, VLDL=Very low-density lipoprotein , HDL=High-density lipoprotein, LDL=Low-density lipoprotein, TG=Triglycerides, FBS =Fasting blood sugar

Key Message: Either of the most commonly used drugs i.e., COCs and CPA-EE were compared only in few studies earlier, hence the study. Both the drugs showed significant improvement in clinical and hematological parameters but on comparison were equally effective.

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