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Effects of Ethinylestradiol/Cyproterone Acetate and Ethinylestradiol/Desogestrel Alone and in Combination with Low-Dose Metformin on Glucose and Lipid Homeostasis and Androgenic Hormone Profile in Hirsute Women with Polycystic Ovary Syndrome: A Randomized, Double-Blind, Triple-Dummy Study

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Abstract

Background: The effects of combined oral contraceptive pills and metformin on glucose and lipid metabolism and androgenic hormone profile of hirsute women with polycystic ovary syndrome (PCOS) are not clearly known. **Aims**: To determine the effect of ethinylestradiol (35 microg)/cyproterone acetate (2 mg) (EE/CPA) and ethinylestradiol (20 microg)/desogestrel 0.15 mg (EE/DES) alone and in combination with metformin on glucose and lipid metabolism and androgenic hormone profile in hirsute women with PCOS. **Settings and Design:** This randomised, double-blind, triple dummy study was conducted at the Department of Pharmacology, Faulty of Science, University of Peradeniya, Sri Lanka. **Methods and Material:** A total of 107 patients with PCOS (Rotterdam Consensus Conference Criteria 2003) having hirsutism of 8 or more in the modified Ferriman-Gallwey Score (mFGS), were randomised to receive four drug therapies (arm A: EE/CPA, arm B: EE/DES, arm C: EE/CPA plus metformin, arm D: EE/DES plus metformin). Body mass index, fasting plasma glucose, area under the curve of the oral glucose tolerance test, fasting serum insulin, serum leptin, fasting lipids, serum total testosterone, serum sex hormone-binding globulin were determined at initiation and 12 months. Homeostasis model assessment of beta cell function (HOMA-β),

homeostasis model assessment-estimated insulin resistance (HOMA-IR) and free androgen index were calculated. Statistical analysis was done with two ways ANOVA. **Results:** There was no significant difference in outcome measures at 12 months between the treatment arms. Within the treatment arms, there was reduction of HOMA-β in arm B, serum leptin in arm C, CHO/HDL ratio in arm D and an increase in total cholesterol and LDL-cholesterol in arms B and C. **Conclusions:** EE/DES and EE/CPA with and without low-dose metformin did not have a significant overall effect on glucose and lipid metabolism and androgenic hormonal profile in hirsute women with PCOS. However, desogestrel has reduced the beta-cell function and both desogestrel and cyproterone have adversely affected the lipids.

Keywords

Polycystic Ovary Syndrome, Ethinylestradiol, Cyproterone Acetate, Desogestrel, Metformin

1. Introduction

This Polycystic ovary syndrome (PCOS) is a common disorder affecting women with diverse hormonal and metabolic abnormalities. It is characterized by irregular menstruation, hyperandrogenism and polycystic ovaries. Impaired glucose tolerance and unfavourable lipid profile with increased risk of atherosclerosis are well-known to be associated with PCOS [1].

Insulin resistance and impaired pancreatic beta-cell function have been reported in women with PCOS [2]. Homeostasis model assessment (HOMA) is an index related to glucose homeostasis calculated using fasting insulin and glucose. It is an estimate of patient's hepatic glucose output and pancreatic β-cell function. The homeostasis model assessment-estimated insulin resistance (HOMA-IR) index is a measure of insulin resistance whereas the HOMA of β-cell function (HOMA-β) index is a measure of β-cell function [3]. High HOMA-IR and low HOMA-β are associated with impaired glucose tolerance.

Women with PCOS often have higher serum leptin levels than expected for their body mass index (BMI) [4]. Insulin resistance is associated with elevated plasma insulin and leptin levels.

Elevated plasma free testosterone level is also a characteristic feature of PCOS [5]. As direct assays of free testosterone are not reliable, free androgen index is calculated from total testosterone and sex hormone-binding globulin (SHBG) concentrations [6].

PCOS has usually managed with lifestyle modification and drug therapy with different combinations of hormonal preparations and insulin sensitising agents. Antiandrogens such as cyproterone acetate and drospirenone combined with oestrogen (to regularise the menstrual cycle) are the preferred hormonal treatments. Combined oral contraceptive pills containing progestins with less andro-

genic properties are an alternative option. Previous studies on the effects of currently available treatments for PCOS on glucose and lipid homeostasis and androgenic hormone profile have shown conflicting results [7] [8].

The objective of this study was to determine the effectiveness of ethinylestradiol/cyproterone (EE/CPA) and ethinylestradiol/desogestrel (EE/DES) alone and in combination with low-dose metformin on glucose and lipid homeostasis and androgenic hormone profile in hirsute women with PCOS.

2. Methods

2.1. Study Population

A total of 157 patients attending medical and gynaecology clinics at Teaching Hospitals Kandy and Peradeniya, Sri Lanka were assessed for eligibility and 107 were recruited. The inclusion criteria were subjects aged 18 to 40 years with PCOS diagnosed according to Rotterdam Consensus Conference Criteria 2003 with a modified Ferriman-Gallway hirsutism score of 8 or more. Patients with secondary causes of hyperandrogenism, with contraindications to the use of trial drugs, taking any form of hormonal contraceptives during the last 3 months and seeking fertility were excluded. Ethical approval was obtained from the Institutional Ethics Review Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka (protocol 2013/EC/52). The trial was registered at the Sri Lanka Clinical Trials Registry (https://slctr.lk/trials/slctr-2015-007) and the registration number was SLCTR/2015/007.

Written informed consent was obtained from all subjects and the study was conducted in accordance with the Declaration of Helsinki. Patient recruitment commenced in April 1, 2015 and each patient was followed up for a period of 12 months.

2.2. Sample Size

Based on previous studies, the sample size was calculated using the formula:

$$N = \frac{2\sigma^2}{\left(\mu_1 - \mu_2\right)^2} f\left(\alpha, \beta\right)$$

where σ is the standard deviation and μ is the sample mean. The value of α was taken at 95% confidence level and β at 80% confidence level.

According to the calculation, a sample size of 100 patients in each arm was planned. During the trial, an interim analysis was done by an independent statistician to ascertain the adequacy of the sample because of logistic reasons using the same formula as above. Accordingly, a sample size of 25 patients in each arm was considered adequate and patient recruitment was stopped when that target was reached.

2.3. Randomization and Masking

Simple randomization to four study arms was done by a computer-generated

random number table. Treatment was started according to the assigned arm (A, B, C or D). All logistics were overseen by an administrator who was not involved in the rest of the study.

Subjects of all four arms were given three kinds of tablets using appropriate placebos. All the investigators, statistician and patients were blinded to the treatment except the pharmacist who dispensed the drugs.

2.4. Treatment Allocation

Treatment allocation for the four arms is shown in Table 1. Treatments used in the study were EE/CPA (Diane-35, Schering AG, Berlin, Germany), EE/DES (Fermion, Infar (India) Ltd., India), metformin (State Pharmaceuticals Manufacturing Corporation, Sri Lanka) and three placebo pills (State Pharmaceuticals Manufacturing Corporation, Sri Lanka) equal to the above three drugs.

Metformin or placebo was commenced on the day of recruitment and continued daily. The other two tablets or placebos were started on the first day of the menstruation and continued for 21 days and resumed after a 7-day interval. Likewise, treatment was continued for 12 months and subjects were assessed according to the protocol detailed below.

2.5. Outcome Measures

Body mass index (BMI), fasting plasma glucose (FPG), area under the curve (AUC) of the oral glucose tolerance test (OGTT), fasting serum insulin, HOMA-β and HOMA-IR, serum leptin, fasting lipid levels, sex hormone-binding globulin (SHBG), serum total testosterone level and free androgen index (FAI) were determined at the beginning and end of 12 months.

2.5.1. Body Mass Index

BMI was calculated using the weight (in kilograms) measured by a digital

Table 1. Medications used in each treatment arm.

Arm	Drugs
A	1) Cyproterone acetate (2 mg) and of Ethinylestradiol (35 microg) daily 2) Placebo pill equal to metformin daily 3) Placebo pill equal to desogestrel 0.15 mg/Ethinylestradiol (20 microg) daily
B	1) Desogestrel 0.15 mg/Ethinylestradiol (20 microg) daily 2) Placebo pill equal to metformin daily 3) Placebo pill equal to Cyproterone acetate (2 mg) and of Ethinylestradiol (35 microg) daily
C	1) Metformin 500 mg daily 2) Cyproterone acetate (2 mg) and of Ethinylestradiol (35 microg) daily 3) placebo pill equal to desogestrel 0.15 mg/Ethinylestradiol (20 microg) daily
D	1) Metformin 500 mg daily 2) Desogestrel 0.15 mg/Ethinylestradiol (20 microg) daily 3) Placebo pill equal to Cyproterone acetate (2 mg) and of Ethinylestradiol (35 microg) pill daily

weighing scale and height (in meters) measured by a standard height measuring scale.

2.5.2. Collection and Analysis of Blood Samples

The tests were carried out in the laboratories of the Department of Biochemistry, Department of Medicine, Department of Pharmacology, and Nuclear Medicine Unit, Faculty of Medicine, University of Peradeniya.

The tests were performed on venous blood samples drawn after 12 hours of fasting followed by OGTT.

2.5.3. Oral Glucose Tolerance Test

Oral glucose tolerance test was done according to WHO guidelines [9]. Samples were collected and centrifuged in a bench top centrifuge (Humax 4k Germany) at 3000 rpm for 10 min to obtain plasma. Plasma was analysed with DR-7000D Semi-Automatic Chemistry Analyser (DIRUI, Changchun, China) using glucose oxidase method to measure plasma glucose level. Plasma glucose levels at fasting state, at one hour and two hours after glucose load, were measured. The AUC of the OGTT was calculated by the trapezoidal method

2.5.4. Serum Insulin, Leptin and SHBG Measurements

Fasting serum insulin, leptin and SHBG were measured using commercially available ELISA kits (Calbiotech Inc. Canada).

2.5.5. Homeostasis Model Assessment (HOMA)

The HOMA calculators that were used to estimate these values are as follows:

$$\text{HOMA} - \text{IR} = \left(\text{FPI} \times \text{FPG}\right)/22.5$$

$$\text{HOMA} - \beta = \left(20 \times \text{FPI}\right)/\left(\text{FPG} - 3.5\right)$$

(FPI is fasting plasma insulin and FPG is fasting plasma glucose).

2.5.6. Measurement of Fasting Lipids

Plasma triglyceride concentration (TAG) was determined using an enzymatic colorimetric test (Triglycerides liquicolor mono, Human Diagnostics, Wiesbaden, Germany). Serum total cholesterol concentrations (TC) were determined by using an enzymatic colorimetric test (Triglycerides liquicolor, Human Diagnostics, Wiesbaden, Germany). HDL cholesterol (HDL-C) was also measured by an enzymatic method after heparin and calcium precipitation (HDL liquicolor, Human Diagnostics, Wiesbaden, Germany). LDL cholesterol (LDL-C) in mg/dl was calculated with the Friedewald equation (LDL cholesterol) = (total cholesterol) − (HDL cholesterol) − (triglycerides)/5).

2.5.7. Testosterone Measurement

Testosterone levels were determined using the testosterone radioimmunoassay kit (TESTO-CT2 assay; Cisbio Bioassays, Codolet, France).

2.5.8. Free Androgen Index

Free androgen index was calculated by the following formula.

$$\text{Free androgen index} = \frac{\text{Total testosterone}}{\text{SHBG}} \times 100$$

2.6. Statistical Analysis

Statistical analysis was done with SPSS software version 22. Per-protocol analysis was done to find out the baseline group differences between completed subjects, within-group differences and group differences from baseline to 12 months.

Two-way mixed ANOVA model for repeated measures was used during the analysis. Additionally, one way ANOVA and categorical data analytical methods were used wherever appropriate.

Before applying two way mixed ANOVA model, the significant outliers in each variable were excluded. Leven's and Mauchly's tests were used to ensure the homogeneity and spherecity of the outcome variables respectively. Where spherecity is not assured, Greenhouse Geisser or Huynh-Feldt test was used to calculate the P values. Statistical significance was defined as $P < 0.05$.

3. Results

Figure 1 shows the summary of the patient recruitment and follow-up. In group

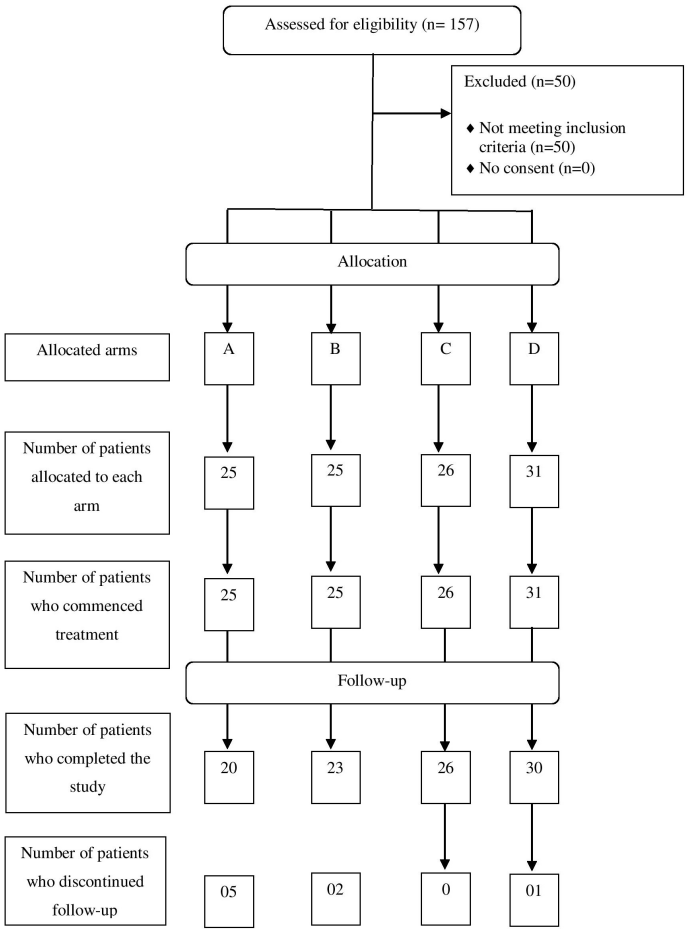

Figure 1. Summary of the patient recruitment and follow-up.

A, there were 5 dropouts. All five patients had treatment-related adverse effects which include migraine-type headache, joint stiffness, severe breast tenderness, vomiting, and faintness. In group B, there were two dropouts. One patient was diagnosed of papillary carcinoma of the thyroid and other wanted to conceive. In group C, there were no dropouts. In group D, there was one dropout due to recurrent faintness.

Table 2 shows the baseline variables of the four treatment arms. None of the baseline variables other than the age in arm D showed a statistically significant difference.

None of the outcome measures showed a significant difference between the treatment arms at the end of 12 months. However, there were statistically significant changes seen within the treatment arms in certain outcome measures.

Table 3 summaries the glucose and androgenic hormone profile changes of each treatment arm, while Table 4 shows lipid profile changes. There was a statistically significant reduction in BMI within treatment arm A, HOMA-β within arm B, leptin level within arm C and TC/HDL ratio in arm D at the end of 12 months. A statistically significant rise in total cholesterol and LDL-C were seen in arms B and C.

Three patients had FPG values in the diabetic range at the end of 12 months. However, the number of patients with normal fasting glucose at recruitment later developing impaired fasting glucose or diabetes did not show a statistically significant difference ($X^2 = 0.8449$; df = 3; P = 0.8387). Statistically significant changes in outcomes observed at 12 months are summarized in Table 5 and Table 6.

4. Discussion

The main findings in our study were reduction of HOMA-β in EE/DES arm, reduction of serum leptin in EE/CPA plus metformin arm, reduction of CHO/HDL ratio in EE/DES plus metformin arm and an increase in TC and LDL-C in both EE/DES arm and EE/CPA plus metformin arm.

The reduction of BMI within the EE/CPA group is unlikely to be due to the drug because the EE/CPA plus metformin group did not show the similar change. Impaired beta-cell function with desogrestrel indicated by the reduced HOMA-β is a notable finding in our study. Previous studies on oral contraceptives containing cyproterone, desogestrel and drospirenone have failed to demonstrate changes in biochemical parameters of insulin resistance [10] [11] [12]. This is in keeping with our findings as well.

The effects of COCPs on lipid and carbohydrate metabolism depend on the dose of the estrogen and the dose, type and androgenicity of the progestin [13]. Studies on the effects of DES on glucose homeostasis have shown decreased insulin sensitivity in some studies and no effect on fasting insulin and fasting glucose, reduced postprandial glucose and increased insulin sensitivity in others [12] [14] [15].

Table 2. Baseline values of variables of patients who completed the follow-up.

	A		B		C		D		
	Baseline		Baseline		Baseline		Baseline		
Variables	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**N**	**Mean ± SD**	**P value**
Age	20	23.35 ± 5.10	23	22.39 ± 6.45	26	24.81 ± 6.24	30	27.90 ± 6.89	P = 0.013
Marital status									
Married		5		5		8		8	
Unmarried		15		18		18		22	
BMI (kg/m^2)	20	28.27 ± 6.94	23	26.74 ± 4.88	26	27.93 ± 4.89	29	27.20 ± 4.28	P > 0.05
Waist /Hip ratio	20	0.84 ± 0.09	23	0.83 ± 0.09	26	0.84 ± 0.06	29	0.83 ± 0.12	P > 0.05
Ferriman-Gallwey Score	20	20.95 ± 5.50	23	20.00 ± 6.67	26	21.08 ± 5.24	29	18.38 ± 5.53	P > 0.05
Systolic blood pressure (mm Hg)	20	118.80 ± 17.03	23	117.87 ± 12.16	25	116.64 ± 11.38	29	120.66 ± 13.44	P > 0.05
Diastolic blood pressure (mm Hg)	20	78.75 ± 13.60	23	76.43 ± 8.86	25	77.44 ± 10.72	29	80.10 ± 9.07	P > 0.05
Hormones									
Testosterone (ng/dL)	20	2.51 ± 2.71	23	19.60 ± 83.82	25	2.79 ± 1.82	30	2.84 ± 2.50	P > 0.05
SHBG (nmol/L)	20	103.24 ± 72.79	22	82.07 ± 69.78	26	87.06 ± 84.11	30	88.87 ± 70.87	P > 0.05
FAI	20	4.99 ± 8.86	22	4.31 ± 4.82	25	6.29 ± 7.23	28	4.08 ± 3.41	P > 0.05
HOMA-IR	20	14.02 ± 22.06	23	10.11 ± 27.57	26	17.41 ± 40.32	29	5.39 ± 11.39	P > 0.05
HOMA-B	20	86.33 ± 234.26	22	257.63 ± 569.49	26	52.99 ± 132.01	29	79.46 ± 238.73	P > 0.05
Leptin	20	23.79 ± 25.62	22	21.32 ± 16.32	26	23.58 ± 17.34	28	27.70 ± 26.38	P > 0.05
Lipid parameters									
Cholesterol (mg/dL)	20	200.45 ± 37.60	23	178.72 ± 40.04	26	198.58 ± 39.80	30	189.91 ± 34.99	P > 0.05
HDL (mg/dL)	20	47.20 ± 11.15	23	42.43 ± 8.86	26	42.92 ± 7.32	30	44.31 ± 24.58	P > 0.05
LDL (mg/dL)	20	130.85 ± 31.92	23	116.34 ± 29.03	26	129.80 ± 35.04	30	119.17 ± 33.22	P > 0.05
Triglycerides (mg/dL)	20	111.20 ± 40.19	23	119.57 ± 71.73	26	129.27 ± 66.01	30	137.87 ± 78.63	P > 0.05
Cholesterol/HDL Ratio	20	4.37 ±0.95	23	4.56 ± 1.15	26	4.72 ± 1.10	29	4.84 ± 1.24	P > 0.05
Glycemic parameters from OGTT									
Fasting glucose (mg/dL)	20	83.80 ± 17.61	23	82.00 ± 15.42	26	87.23 ± 14.33	30	86.37 ± 18.19	P > 0.05
Fasting insulin (μU/mL)	20	5.77 ± 5.77	23	9.33 ± 15.22	26	8.84 ± 14.76	30	6.81 ± 13.93	P > 0.05

Note: SHBG, Sex hormone binding globulin. FAI, Free androgen index. BMI, Body mass index. HOMA-IR, homeostasis model assessment-estimated insulin resistance. HOMA-β, homeostasis model assessment of β-cell function. HDL, High density lipoprotein. LDL, Low density lipoprotein.

The results of studies on the effect of cyproterone acetate on carbohydrate metabolism are also conflicting. Insulin sensitivity was increased or unchanged in non-obese women with PCOS and worsened in obese patients [16]. Worsening

Table 3. Glucose and androgenic hormone profile.

		BMI Mean ± SD	Fasting glucose (mg/dl)	Fasting Insulin (IU/)	HOMA β	HOMA IR	AUC	Leptin	SHBG	Testosterone	FAI
Arm A	0 month	28.3 ±6.9	83.8 ± 17.6	5.8 ± 5.8	86.3 ± 234.3	14.0 ± 22.1	209.8 ± 34.8	23.79 ± 25.62	107.41 ± 72.29	2.51 ± 2.71	4.99 ± 8.86
	12 months	26.9 ±6.7	95.1 ± 32.0	4.3 ± 6.5	44.3 ± 101.1	3.8 ± 4.2	230.4 ± 29.9	24.86 ± 22.63	148.18 ± 95.14	2.85 ± 2.92	2.39 ± 2.54
	P value	0.009	0.9	0.659	0.565	0.196	1	0.789	0.066	0.97	0.104
Arm B	0 month	26.7 ±4.9	82 ± 15.4	9.3 ± 15.2	257.6 ± 559.4	10.1 ± 27.6	216.7 ± 39.5	21.32 ± 16.32	82.80 ± 71.42	19.60 ± 83.82	4.31 ± 4.82
	12 months	26.1 ±4.4	95.1 ± 23.7	8.3 ± 15.0	91.4 ± 160.7	4.3 ± 4.8	232.2 ± 28.8	20.89 ± 19.38	110.49 ± 76.76	3.68 ± 2.84	6.20 ± 10.49
	P value	0.775	0.9	0.732	0.019	0.427	1	0.91	0.246	0.063	0.213
Arm C	0 month	27.9 ±4.9	87.2 ± 22.5	8.8 ± 14.8	53.0 ± 132.6	17.4 ± 40.3	230.7 ± 80.3	23.58 ± 17.34	88.80 ± 85.36	2.79 ± 1.82	6.29 ± 7.23
	12 months	27.1 ±4.6	92.7 ± 22.8	5.5 ± 11.8	35.8 ± 52.4	11.9 ± 39.7	224.7 ± 25.1	16.44 ± 9.74	93.57 ± 82.57	2.49 ± 1.64	4.98 ±5.79
	P value	0.224	0.407	0.264	0.788	0.428	0.737	0.044	0.921	0.971	0.357
Arm D	0 month	27.2 ±4.3	86.4 ± 28.5	6.8 ± 13.9	79.5 ± 239.0	5.4 ± 11.4	213.4 ± 35.0	27.70 ± 26.38	86.06 ± 70.40	2.84 ± 2.50	4.08 ± 3.41
	12 months	26.8 ±3.6	98.4 ± 30.9	7.6 ± 16.4	128.8 ± 116.5	7.3 ± 23.9	223.6 ± 37.3	21.58 ± 21.57	101.78 ± 85.09	3.03 ± 2.60	4.09 ± 3.93
	P value	1.000	0.019	0.777	0.416	0.768	0.737	0.073	0.511	0.98	0.996

Note: BMI, Body mass index. HOMA-β, homeostasis model assessment of β-cell function. HOMA-IR, homeostasis model assessment-estimated insulin resistance. AUC, Area under the curve of oral glucose tolerance test. SHBG, Sex hormone binding globulin.

Table 4. Lipid profiles.

		Total Cholesterol	Triglyceride	HDL	LDL	Ratio
Arm A	0 month	200.4 ± 37.6	111.2 ± 40.1	47.2 ± 11.1	130.8 ± 31.9	4.3 ± 0.9
	12 months	215.7 ± 46.4	121.2 ± 82.5	50.2 ± 1.6	50.2 ± 5.8	4.3 ± 0.8
	Mean changes from baseline (%)	−7.63	−8.95	−6.36	−5.67	1.08
	P value	0.062	0.368	0.487	0.193	0.827
Arm B	0 month	178.7 ± 40.0	119.6 ± 71.7	42.4 ± 8.9	116.3 ± 29.0	4.6 ± 1.2
	12 months	205.0 ± 36.5	116.3 ± 45.0	49.9 ± 10.4	127.4 ± 36.0	4.2 ± 0.9
	Mean changes from baseline (%)	−14.68	2.73	−17.52	−9.46	7.22
	P value	0.001	0.751	0.067	0.040	0.104
Arm C	0 month	198.6 ± 39.8	129.3 ± 66.0	42.9 ± 7.3	129.8 ± 35.0	4.7 ± 1.1
	12 months	217.3 ± 41.6	141.0 ± 61.6	49.1 ± 9.9	139.6 ± 35.1	4.5 ± 0.9
	Mean changes from baseline (%)	−9.45	−9.1	−14.43	−7.56	4.93
	P value	0.010	0.226	0.104	0.051	0.219
Arm D	0 month	189.9 ± 35.0	137.9 ± 78.6	44.3 ± 24.6	119.2 ± 33.2	4.8 ± 1.2
	12 months	198.5 ± 41.8	143.2 ± 66.2	44.7 ± 11.2	121.0 ± 36.5	4.4 ± 0.8
	Mean changes from baseline (%)	−4.5	−3.84	−0.87	−1.57	8.32
	P value	0.200	0.557	0.913	0.686	0.026

Table 5. Variables which have statistically significantly decreased at the end of 12 months.

Arm	Variable
A	BMI
B	HOMA-β index
C	Serum leptin,
D	Total cholesterol/HDL-C ratio

Note: BMI, Body mass index. HOMA-β, Homeostasis model assessment of β-cell function.

Table 6. Variables which have statistically significantly increased at the end of 12 months.

Arm	Variable
B	Total cholesterol, LDL-cholesterol
C	Total cholesterol, LDL cholesterol

Note: LDL, Low density lipoprotein.

of glucose homeostasis has been noted in obese women with PCOS with higher doses of cyproterone acetate (12.5 mg/day) in another study [17]. In the present study, we employed a dose of 2 mg of cyproterone acetate with oestrogen and there was no significant change in insulin sensitivity. We did not analyse results according to body weight and it is a shortcoming in our study.

The effects of metformin therapy on insulin sensitivity in PCOS patients also have conflicting evidence. Some investigators assessing insulin sensitivity have shown a significant improvement during metformin treatment [18] [19] [20] whereas others have failed to confirm it [21] [22]. Adding metformin to either of hormonal therapies in this study has not changed the outcome probably due to the low dose of metformin.

EE/DES, EE/CPA and metformin have been shown to reduce serum testosterone and increase SHBG in women with PCOS [23] [24]. Adding metformin (500 mg three times per day) to CPA improves serum androgenic hormone profile in non-obese women with PCOS [25]. Metformin (500 mg three times per day) has been shown to reduce the testosterone level after 6 months of therapy [26]. It is hypothesised that reduction of weight with metformin may increase the circulating level of SHBG [21]. However, the failure of metformin to influence circulating SHBG concentration has also been reported previously [27]. In our study, we did not find a significant change of serum testosterone, SHBG and FAI in the four study arms.

Serum leptin was significantly reduced only in treatment arm C (EE/CPA plus metformin). Serum leptin levels highly correlate with the body fat content and fall in response to weight loss [28].

In arm C, there was no significant change of BMI although the leptin level came down. In arm A, there was a significant reduction of BMI but leptin level remained unchanged. The change of leptin did not clearly correlate with BMI in this study, perhaps because of the small sample size.

There are conflicting findings about serum leptin levels in PCOS. One study

found no difference in serum leptin level between normal and PCOS subjects [29]. Another study showed that PCOS patients have leptin levels higher than the expected for their BMI, free testosterone and insulin sensitivity [4]. Metformin has been shown to decrease serum leptin level in PCOS [30].

Oestrogen favourably changes the lipid metabolism by increasing HDL-C and decreasing LDL-C [31]. Desogestrel elevates serum HDL-C more than second generation COCPs [14]. LDLC has been shown to remain unchanged with desogestrel [12] but it increases TC and TAG [12]. However, a study conducted on obese women with PCOS showed that desogestrel-containing OCP increases the LDL-C as well [15]. On the other hand, some studies have not observed changes in LDL-C or HDL-C levels [32].

Cyproterone acetate-containing COCPs reduce serum HDL-C and increase TC, LDL-C and TAG concentrations in both non-obese and obese subjects [33]. But some studies show a rise in HDL-C [7] [34]. Some do not show any change in LDL-C or HDL-C. Therefore, the effects of EE/DES and EE/CPA on lipids in PCOS women are not yet well established.

In diabetic patients, metformin has a beneficial effect on lipid levels due to reduced concentrations of plasma TAG and TC and LDL-C, and increased HDL-C and HDL: LDL cholesterol ratio [35]. In PCOS, metformin mainly increases serum HDL-C concentrations [20]. But some studies have shown negligible or no effect of metformin on lipids in PCOS [36]. These effects may change according to the BMI, duration of the study and dose of metformin.

5. Conclusion

This study has shown that treatment of hirsute women with PCOS with desogestrel is associated with reduced beta-cell function. Both desogrestrel and cyprpterone have favorable as well as unfavorable effects on serum lipids. Both hormones did not have a significant effect on serum androgen hormone profile. These outcomes may have been different with a longer duration of the treatment and a higher dose of metformin.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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