THE EFFECTS OF TREATMENT WITH ORAL CONTRACEPTIVE PILL CONTAINING ETHINYL ESTRADIOL-CYPROTERONE ACETATE ALONE OR IN COMBINATION WITH METFORMIN ON CLINICAL, HORMONAL, METABOLIC AND ULTRASONOGRAPHIC CHARACTERISTICS IN POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

BACKGROUND
Poly Cystic Ovary Syndrome (PCOS) is a heterogeneous disorder, characterized by chronic anovulation and hyperandrogenism, which affects between 5 to 10% of women in reproductive age, and it is considered one of the most common endocrine disorders in premenopausal women

The objective of this study was to evaluate the effects of 6 months of administration of Oral Contraceptive Pill (OCP) alone or in combination with metformin on clinical, hormonal, metabolic and ultrasonographic characteristics in polycystic ovarian syndrome (PCOS).

MATERIALS AND METHODS
One hundred and thirty PCOS patients were enrolled in this prospective single blind randomized control trial. PCOS was defined according to the Rotterdam criteria. Patients were randomized to either oral treatment with OCP containing ethinyl estradiol-cyproterone acetate alone (n = 66) or OCP in combination with metformin (n = 64). Body Mass Index (BMI), waist circumference (WC), Ferriman–Gallwey (FG) score, luteinizing hormone (LH), total testosterone (TT), lipid levels, fasting insulin, fasting glucose and ultrasonographic parameters such as ovarian volume (OV), follicle number (FN) and ovarian stromal pulsatility index (PI) and resistive index (RI) were measured at baseline and at the end of treatment.

RESULTS
There was significant reduction in BMI and WC only in the OCP + Metformin group, however the menstrual cycle, serum LH, testosterone and HDL-Cholesterol levels normalized in both groups. Fasting insulin levels reduced significantly only in the OCP + Metformin group. OV and FN were significantly reduced in both the groups and similarly PI & RI values increased in both the groups

CONCLUSION
We conclude that OCP and metformin should be considered for the treatment of PCOS patients, yet the choice for each drug requires careful consideration of the patient's clinical characteristics and preference.

KEYWORDS
Polycystic ovarian syndrome, Metformin, Oral contraceptives, Colour doppler ultrasonography.

BACKGROUND
Polycystic ovary syndrome (PCOS) is a heterogeneous disorder, characterized by chronic anovulation and hyperandrogenism. It affects between 5 to 10% of women in reproductive age, and it is considered one of the most common endocrine disorders in premenopausal women.[1] PCOS is characterized by clinical and/or biochemical hyperandrogenism, menstrual irregularities, ovarian growth and cysts formation polycystic ovary (PCO) and it is probably the most frequent cause of hirsutism, obesity and infertility.[2] Insulin resistance is a common feature in obese (75%) and to a less extent in lean PCOS (50%) Upto 35% of women with PCOS exhibit impaired glucose tolerance and 7-10% meet criteria for type 2 diabetes.

Available first line treatment options for PCOS include oral contraceptive pills (OCP) containing cyproterone acetate and ethinyl estradiol and metformin. OCP are considered the first-line therapy against menstrual disturbances and hyperandrogenism in PCOS women who do not require fertility. They typically suppress ovarian function and adrenal

androgen production and improve clinical hirsutism scores in PCOS women.[3] However, there are some controversial issues concerning OCs, in that they may elevate insulin levels and fail to diminish insulin resistance.[4,5] Therfore to counteract this effect insulin lowering drugs are used in PCOS patients.[6,7,8] Metformin, a biguanide normally used to treat non-insulin-dependent diabetes, is the most thoroughly investigated insulin-lowering agent used to treat PCOS patients with insulin resistance.[9,10]

Aims and Objectives

We designed a prospective study to investigate the clinical, endocrine, metabolic and ultrasonographic effects of two treatment modalities: (1) Metformin and OCP containing ethinyl estradiol (EE)–cyproterone acetate (CPA); (2) OCP alone; in obese and non-obese PCOS patients, which could provide a more appropriate treatment of patients with PCOS. The objectives of this study can be broadly divided into two 1) To compare the combined effect of metformin and OCPs on the clinical, hormonal, metabolic and ovarian ultrasonographic characteristics in patients with PCOS. 2) To evaluate whether this combination of drugs is more advantageous than OCPs alone in improving the metabolic profile.

MATERIALS AND METHODS

The present study is a randomized clinical trial which was approved from the Institutional Ethics Committee of SCB Medical College, Cuttack. The target population of this study was one hundred and thirty premenopausal females aged 18 - 40 years that were diagnosed as polycystic ovary syndrome (PCOS), who were attending outpatient department of Department of Obstetrics & Gynaecology at SCB Medical College, between January 2016 and June 2017. Women were excluded from study who were diagnosed or treated for thyroid dysfunction, hyper-prolactinaemia, non-classical congenital adrenal hyperplasia (NCCAH), Cushing s syndrome, ovary neoplasm, acromegaly, type 1 Diabetes Mellitus, use of medication known to affect sex steroid metabolism, such as oral contraceptives or insulin sensitizing drugs and other hormonal agents known to affect menstrual cyclicity for at least 3 months before collection of the samples.

The body weight of each individual dressed in light clothing without shoes was measured using a carefully calibrated electrical balance then the height of each individual was measured using vertical measuring rod. BMI was calculated as weight (kg) divided by squared height (m^2). Waist circumference was measured for all individual in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest in cm.

For all women, fasting overnight venous blood (10 mL) was collected by well-trained technician from each woman in the day 3 to 5 of their menstrual cycle into two plain vacutainer tubes without anticoagulant, under quality control and safety procedure. For all women serum glucose, total cholesterol, triglyceride, HDL-C, LDL-C were analysed by chemistry autoanalyzer (Hitachi 902 device from Roche Diagnostics) according to manufacturer instructions. Luteinizing hormone (LH), free testosterone and Insulin hormone quantitative determination were done by using enzyme linked immunosorbent assay (ELISA) kits, on ELISA reader (Stat fax-2100 technology instrument). Results were compared by the reference range that was set by the laboratories.

For every patient, ultrasound (USG) examination was performed with a Philips HD-7 machine (Philips Co. Ltd. Bothell, WA, USA) with a 5–9 MHz transducer. USG measurements were taken in real-time, according to as standardized protocol. After determination of the longest medial axis of the ovary, the length and thickness were measured and the ovarian volume (OV) was calculated. For each ovary, the total number of all visible follicles smaller than 10 mm in diameter was counted by slow and continuous scanning of the entire ovary, from one margin to the other in longitudinal cross section. By means of colour and power Doppler flow imaging, colour signals were searched in the ovarian stroma away from the ovarian surface and not adjacent to the wall of a follicle. Areas of maximum colour intensity, representing the greatest Doppler frequency shifts, were chosen for pulsed Doppler examination. The pulsatility index (PI) and resistance index (RI) were electronically calculated for each selected Doppler wave.

After providing informed consent, patients were allocated randomly to receive either an anti-androgenic low-dose OCP in cycles of 28 d (21 pills containing 35 μg of ethinyl estradiol plus 2 mg of cyproterone acetate followed by 7 placebo pills with, or 500 mg of metformin twice daily with OCP as stated previously for 6 months. At the end of the study, all of the clinical, anthropometric, biochemical, hormonal and Doppler parameters were measured again using the same methods and compared with the pre-treatment values.

Data were analysed using SPSS version 19 for Windows. All data were represented as mean ±standard deviation (SD). A Kolmogorov-Smirnov test was applied to test for normality of the data. The differences between groups were tested with the either an unpaired t-test and differences between pre- and post-treatment values were compared using a paired t-test. Statistical significance was set at $p < 0.05$.

RESULTS

Of the 66 patients in the OCP group, 60 patients completed the study, whereas 57 of the 64 patients assigned to OCP + Metformin group completed the study. In both the treatment arms 5 patients each were lost to followup whereas others discontinued their treatment due to development of side effects. The dropouts were excluded from the analysis.

There were no differences with respect to baseline in BMI and waist circumference in the OCP treatment group whereas there was significant reduction in these two parameters in the OCP + Metformin group (Table 1). However, the menstrual cycle got regularized in both the treatment groups. There was significant reduction in both

serum LH levels and serum testosterone levels in both treatment groups. Similarly, SHBG levels also significantly increased in both the treatment groups (Table 2). There was significant improvement in the levels of HDL-C in both OCP & OCP+Metformin treatment groups. However other lipid profile parameters such as total cholesterol, LDL-Cholesterol and total triglycerides didn't alter significantly. There was

significant reduction in fasting insulin levels in the OCP + Metformin group (Table 3). Ovarian volume and follicle number was significantly reduced in both the groups and similarly PI & RI values increased in both the groups (Table 4).

Parameters	OCP + Metformin Group			OCP Group		
	Pre-treatment (n = 42)	Post-treatment (n = 42)	p^a	Pre-treatment (n = 44)	Post-treatment (n = 44)	p^a
Clinical Parameters						
BMI (kg/m2)	25.7 ± 2.7	24.6 ± 1.6	< 0.001	25.6 ± 2.8	25.8 ± 2.8	0.085
WC (cm)	87.4 ± 6.9	84.4 ± 4.2	< 0.001	87.7 ± 7.4	87.9 ± 7.4	0.067
Cycle duration	84.4 ± 14.7	39.9 ± 10.2	< 0.001	84.4 ± 13.3	33.8 ± 6.9	< 0.001
Hirsutism	8 ± 2	7 ± 2	< 0.001	8 ± 3	5 ± 2	< 0.001

Table 1. Effects of Treatments on Clinical Characteristics of Patients

Parameters	OCP + Metformin Group			OCP Group		
	Pre-treatment (n = 42)	Post-treatment (n = 42)	p^a	Pre-treatment (n = 44)	Post-treatment (n = 44)	p^a
Hormonal Parameters						
LH (mIU/ml)	11.2 ± 3.1	9.40 ± 2.4	< 0.001	11.5 ± 2.8	8.4 ± 1.4	< 0.001
TT (ng/dL)	2.3 ± 0.5	1.8 ± 0.4	< 0.001	2.4 ± 0.5	1.6 ± 0.3	< 0.001
SHBG (nmol/L)	45.3 ± 7.2	79.6 ± 14.8	< 0.001	44.5 ± 7.4	94.5 ± 19.3	< 0.001

Table 2. Effects of Treatments on Hormonal Profile of Patients

Parameters	OCP + Metformin Group			OCP Group		
	Pre-treatment (n = 42)	Post-treatment (n = 42)	p^a	Pre-treatment (n = 44)	Post-treatment (n = 44)	p^a
Metabolic Parameters						
TC (mg/dL)	169.7 ± 19.2	169.0 ± 18.2	0.803	171.1 ± 18.4	174.1 ± 19.3	0.070
HDL-C (mg/dL)	49.9 ± 5.9	53.6 ± 4.1	< 0.001	49.3 ± 6.4	53.2 ± 4.1	< 0.001
LDL-C (mg/dL)	89.3 ± 7.6	89.4 ± 7.6	0.114	88.9 ± 8.5	89.3 ± 8.4	0.147
TG (mg/dL)	116.6 ± 13.3	117.5 ± 13.9	0.064	117.3 ± 15.4	118.5 ± 15.4	0.005
FG (mg/dL)	86.9 ± 6.0	85.5 ± 5.5	0.002	86.5 ± 7.2	87.6 ± 6.0	0.165
FIN (IU/dL)	17.2 ± 5.3	11.8 ± 3.9	< 0.001	17.3 ± 4.5	17.0 ± 3.9	0.904

Table 3. Effects of Treatments on Metabolic Profile of Patients

Parameters	OCP + Metformin group			OCP group		
	Pre-treatment (n = 42)	Post-treatment (n = 42)	p^a	Pre-treatment (n = 44)	Post-treatment (n = 44)	p^a
Ovarian Doppler Parameters						
Ovarian Volume	11.5 ± 2.1	8.5 ± 1.9	0.05	10.9 ± 2.7	9.1 ± 3.2	0.05
Follicle Number	12 ± 2	8 ± 3	0.05	11 ± 3	8 ± 2	0.05
PI	1.21 ± 0.31	1.88 ± 0.38	< 0.001	1.24 ± 0.35	2.09 ± 0.51	< 0.001
RI	0.54 ± 0.11	0.72 ± 0.13	< 0.001	0.53 ± 0.11	0.77 ± 0.11	< 0.001

Table 4. Effects of Treatments on Ultrasound and Doppler Profile of Patients

DISCUSSION

Our present results confirm that both OCP alone or in combination with metformin are safe and effective in the treatment of PCOS patients, both drugs showing overall beneficial effects on most of the clinical complaints characteristic of this common disorder. However, data

suggest that OCP is a more efficient way of treating hyperandrogenism and menstrual dysfunction, considering that the improvement in hirsutism, the amelioration of hyperandrogenemia, and the restoration of regular menstrual cycles occur earlier and more frequently with OCP than with metformin.

Our data shows that OCP is a safe drug when considering cardio-metabolic risk factors, and may have positive effects on the lipid profile in PCOS women. Improvement in insulin resistance with metformin didn't result in any alteration in lipid profile of PCOS women. OCP induced an increase in HDL-cholesterol levels, explaining the increase in plasma HDL-cholesterol concentrations observed in the whole group of PCOS patients. This finding is especially important considering that decreased HDL-cholesterol levels are among the commonest lipid abnormalities associated with PCOS[11,12] and are a recognized cardiovascular risk factor.[13,14,15]

Considering our present finding with those reported by others, it appears that OCP has an effect on the regulation of HDL-cholesterol metabolism. This possibly involves the activity of plasma hepatic lipase activity, an enzyme that is remarkably sex steroid sensitive: oestrogens decrease its activity, whereas androgens and androgenic progestins increase it.[16]

In conceptual agreement, and although certain oral contraceptives may worsen the lipid profile in the general population,[17,18] the amelioration of hyperandrogenism in PCOS women, combined with the antiandrogenic properties of cyproterone acetate and the oestrogen component of OCP might overcome this undesirable effect, explaining its beneficial effect in PCOS patients.[19] Moreover, OCP had a minor impact on glucose tolerance because only a minimal increase in fasting glucose.

Therefore, our present results are in agreement with previous reports showing minor effects, if any, of OCP on glucose tolerance in PCOS patients.[20,21] Of note, the amelioration of insulin resistance observed during the 6 months of our study in the patients treated with metformin was not accompanied by an actual reduction in the frequencies of abnormalities in glucose tolerance in these women.[22]

However, our study is not free from limitations, especially the relatively short duration of treatment considering that PCOS is a chronic condition that requires long-term interventions. Yet also, it must be noted that our present results were obtained in a relatively small sample of PCOS patients in whom overweight and obesity were frequent findings and who presented with the classic hyperandrogenic and oligo-ovulatory PCOS phenotype. Therefore any extrapolation of these results to PCOS patients of different race, ethnicity, and grade of obesity or presenting with different PCOS phenotypes should be made with prudence.

CONCLUSION

OCP and OCP+metformin are safe and effective single drugs for the treatment of PCOS. However, in unselected patients presenting with this disorder, OCP appears to be superior in terms of control of clinical and biochemical hyperandrogenism and restoration of menstrual regularity. Furthermore, this superior efficacy is not obtained at the expense of any clinically significant worsening in the metabolic parameters and cardiovascular risk profile of these women. On the contrary, use of OCP might even result in an increase in plasma HDL-Cholesterol levels that is not observed with metformin. Though only metformin improved insulin resistance, in population with disorders of glucose tolerance, it's routine use in PCOS needs to be individualized. We conclude that OCP (ethinyl estradiol + cyproterone acetate) and metformin should be considered for the treatment of PCOS patients, yet the choice of each drug requires careful consideration of the patient's clinical characteristics and preference. Furthermore, our present results stress that a putative deterioration of the metabolic and cardiovascular risk profile of PCOS patients during administration of OCP is not supported by current scientific evidence and therefore should not be weighed against the use of this drug in any treatment and decision making.

Abbreviations

Polycystic Ovary Syndrome (PCOS), Oral Contraceptive Pill (OCP/OC).

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