GENERAL GYNECOLOGY

Alteration of cardiovascular risk parameters in women with polycystic ovary syndrome who were prescribed to ethinyl estradiol–cyproterone acetate

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Abstract

Purpose We aimed to evaluate the alteration of cardiovascular and metabolic risk parameters of polycystic ovary syndrome (PCOS) patients after a 6-month treatment with an oral contraceptive (OC) containing cyproterone acetate (CPA).

Methods Forty women with PCOS were evaluated at baseline and after treatment with an OC. Carotid intima-media thickness (CIMT), brachial artery flow-mediated dilatation (FMD), nitrate-mediated dilatation (NMD), high sensitive (hs)-CRP, lipid levels, index of glucose sensitivity, and homeostasis model assessment of insulin resistance index (HOMA) were assessed.

Results Mean CIMT was significantly elevated (0.03 ± 0.01 mm) ($p < 0.05$). There was a tendency of reduction in FMD, which was significant among overweight patients ($p < 0.05$). Total cholesterol, low-density lipid (LDL), and triglyceride levels were significantly elevated ($p < 0.05$).

Conclusion CIMT as an indicator of early atherosclerosis and FMD as a finding of endothelial dysfunction seem to be deteriorated especially in overweight PCOS patients who were prescribed to OC containing cyproterone acetate for 6 months.

Keywords Polycystic ovary syndrome · Cardiovascular risk · Oral contraceptives · Metabolic risk

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive age women with a prevalence of 6–8% [1]. It is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries [2]. Obesity, hypertension, dyslipidemia, metabolic syndrome, and impaired glucose tolerance may accompany this syndrome which could lead to cardiovascular disease. However, the exact cardiovascular risk has not been clearly identified due to lack of long-term studies [3].

To date combined oral contraceptive pills (OCPs) have been the first-line treatment for PCOS [4]. They induce predictable cyclic menses, reduce luteinizing hormone secretion, lower ovarian androgen production, increase sex hormone binding globulin (SHBG), thus reduce free androgens [5]. Estrogen component is almost always ethinyl estradiol (EE) in doses ranging from 15 to 50 µg The progestin component is of variable potency and androgenicity. Among the OCPs containing antiandrogenic progestins, EE and cyproterone acetate (CPA) combination has been widely used and cyproterone acetate is the most potent antiandrogenic progesterone [4, 6]. The OCPs are known to have effects on lipid and carbohydrate metabolism [4]. Increased risk of stroke and myocardial infarction among healthy OCP users was reported in a previous meta-analysis [7]. Potential adverse cardiometabolic effects of these drugs may be exaggerated with extra risk factors such

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as obesity, metabolic syndrome, and polycystic ovary syndrome.

Various markers have been currently used for detection of subclinical atherosclerosis in clinical studies such as carotid intima-media thickness (CIMT), brachial artery flow mediated dilatation (FMD) and high sensitive C-reactive protein (hs-CRP) [8–10]. Women with PCOS have been found to exhibit increased CIMT, impaired FMD and elevated hs-CRP in some previous studies [10–14]. However, there is little evidence about the alteration rate of these risk parameters during follow up which may help the management of these patients.

Hence the aim of our study was to evaluate the cardiovascular and metabolic risk parameters in PCOS patients who were prescribed to an OCP (35 μg ethinyl estradiol plus 2 mg cyproterone acetate) for 6 months.

Materials and methods

The study protocol was approved by local ethics committee of Dokuz Eylul University and Turkish Ministry of Health. All subjects gave written informed consent before the study commencement. Study was conducted in Reproductive Endocrinology Department of Dokuz Eylul University Hospital (Turkey) between January 2009 and November 2009.

Patients

Inclusion criteria

All PCOS patients who presented to the reproductive endocrinology outpatient clinic of Dokuz Eylul University Hospital were informed about the study. For inclusion into the study patients who accepted and were eligible for the terms of the study, were screened and questioned. Forty-four patients were eligible for the study and 40 of them concluded the study. Diagnosis of PCOS was made in the presence of at least two of the following criteria in accordance with Rotterdam Concensus [15]: menstrual irregularity (oligomenorrhea or amenorrhea), clinical or biochemical hyperandrogenism and polycystic ovaries in ultrasonographic evaluation. Hirsutism was defined as a Ferriman–Gallwey score > 8.

Exclusion criteria

Congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia and thyroid disease were excluded by biochemical testing. Also patients with a history of known hypertension, hyperlipidemia or diabetes were not included in the study. Smokers, regular intense exercise performers, and patients who had received hormone therapy in last 6 months were excluded from the study.

Study design

All subjects were assessed at baseline during the early follicular phase (cycle days 3–5) with a detailed history, gynecologic examination and pelvic ultrasound, anthropometric measurements and blood pressure levels. A fasting blood sample was drawn for hormone, lipid, glucose and hs-CRP levels. In addition, doppler measurement of CIMT, FMD, and nitrate-mediated dilatation (NMD) were performed. All of these parameters were evaluated at the beginning and the end of the 6 months follow up.

All patients were prescribed a monophasic OCP containing 35 μg EE plus 2 mg CPA (Diane 35; Schering AG, Berlin, Germany) for 6 months. No changes in lifestyle were implemented throughout the study.

Instrumentation

Systolic and diastolic blood pressure measurements were performed by the same trained physician using a standard mercury sphygmomanometer with an appropriate cuff size in each patient. Anthropometric measurements which included body weight, height, body mass index (BMI), waist circumference, hip circumference and waist to hip ratio (WHR) were assessed.

Measurement of endothelial function and carotid intima media thickness

Sonographic examinations were performed in a semi-darkened, isolated and temperature controlled room (20–25°C). Images were obtained by high-resolution Doppler sonography machine (HDI-5000; ATL, Bothell, WA, USA) with a 5–12 MHz broadband linear-array transducer. All of the sonographic examinations were performed by the same examiner.

Intima-media thickness of carotid arteries

Longitudinal plane sonographic images of the both common carotid arteries (CCA) of each patient at approximately 1 cm proximal to the carotid bulb were obtained and archived in the PACS system. Care was taken to keep the frequency level and other imaging parameters (general 2D optimization, persistence, etc.) the same in each patient. Archived images were retrospectively analyzed in a

blinded fashion using computer software program (Q-LAB, ATL-Philips, Bothell, WA, USA) in which IMT measurements were semi-automatically made.

Flow-mediated dilatation of brachial artery

Each subject was studied for FMD in the morning hours (8:00 a.m. to 09:00 a.m.) after being abstained from alcohol, caffeine, tobacco, vasoactive agents, and food for 12 h before the examination. Subjects were in the supine position with the arm outstretched. The brachial artery was imaged over a longitudinal section approximately 5 cm proximal to the brachial artery curve in the antecubital fossa. After baseline measurements, a blood pressure cuff was placed around the arm above the scanned part of the artery and was inflated to 200 mmHg for 5 min. The blood pressure cuff was then deflated, resulting in a reactive hyperemia to cause an increase in shear stress and dilatation of the brachial artery. After cuff deflation brachial artery diameters at 30, 60, and 90 s were measured and sonographic images were recorded. After 10 min of rest, a single dose of sublingual isordile dinitrate of 5 mg was administered and brachial artery diameter was measured after 3 min in order to evaluate endothelium-independent dilatation. Among 30, 60, and 90 s measurements, the largest value of the brachial artery diameter was accepted as the reference value for dilatation and FMD was expressed as the percentage of change in brachial artery diameter from baseline value. Likewise, nitrate-mediated endothelium-independent dilatation was expressed as the percentage change in brachial artery diameter 3 min after sublingual nitrate administration, relative to baseline values.

Assays

Total testosterone (TTE), dehydroepiandrostenedione-sulfate (DHEAS), insulin and SHBG were measured with automated chemiluminescent immunoassays on the Immulite 2500 (Siemens). The intra-assay coefficient of variations (CVs) were: TTE 3.39–3.43%, DHEAS 1.96–2.32%, insulin 3.35–3.32%, SHBG 1.0–1.4%. The interassay CVs were: TTE 6.82–7.16%, DHEAS 3.32–5.85%, insulin 5.6–4.5%, SHBG 3.2–2.8%. 17 OH-progesterone (17-OHP) and free testosterone (FTE) concentrations were determined by RIA [Diagnostic system Laboratories (DSL), Texas, USA]. The intra-assay CVs were: 17-OHP 6.3–7.8%, FTE 3.7–5.2%. The interassay CVs were: 17-OHP 8.1–7.9%, FTE 7.3–7.9%. Total cholesterol (TC), HDL, LDL, triglyceride (TG), glucose, and hsCRP were determined with immunoassay kits (Abbott Architect c16000).

Free androgen index (FAI) was calculated according to the formula: TTE × 100/SHBG. The presence of insulin resistance was investigated using basal insulin levels, glucose/insulin (G/I) ratio and homeostasis model assessment (HOMA) score. The estimate of insulin resistance by HOMA score was calculated with the formula: [fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5].

Statistical analysis

Data are shown as means ± SD and raw numbers (percentages) unless otherwise stated. SPSS 17.0 software; SPSS Inc, Chicago, IL was used for statistical analysis. A p value < 0.05 was considered as statistically significant. Paired sample t test and Wilcoxon test were used before and after treatment analysis. Pearson bivariate test was used for correlation analysis.

Results

Forty women completed the study. Mean age of the patients was 20.8 ± 4.0 years.

Baseline characteristics of patients and alteration of metabolic parameters

Mean and p values of metabolic, clinical, and anthropometric parameters of 40 patients before and after 6 months are shown in Table 1. The difference of BMI or anthropometric measures were not statistically significant ($p > 0.05$). Serum fasting glucose and insulin levels, glucose/insulin ratio and HOMA were remained unchanged ($p > 0.05$). Mean TC levels were 169.20 ± 35.60 and 189.80 ± 36.10 mg/dL, LDL levels were 98.0 ± 27.80 and 109.30 ± 29.60 mg/dL, and mean TG levels were 94.90 ± 65.20 and 117.80 ± 51.30 mg/dL before and after 6 months, respectively ($p < 0.05$). Whereas HDL remained unchanged ($p > 0.05$).

A significant improvement in testosterone and free testosterone levels was observed ($p < 0.05$). FAI and Ferriman–Gallway score were also decreased significantly ($p < 0.05$). SHBG was increased ($p < 0.05$) whereas, DHEAS level remained unchanged ($p > 0.05$). The correlation of change in the androgenic parameters with the cardiovascular ones was statistically insignificant ($p > 0.05$).

Alteration of cardiovascular parameters

Mean and p values of cardiovascular parameters in 40 patients before and after 6 months are shown in Table 2. Difference in the systolic or diastolic blood pressure levels

Table 1 Comparison of metabolic, clinical, and anthropometric parameters of all patients before and after the treatment

Parameter	Baseline	After treatment	p
BMI (kg/m^2)	24.06 ± 6.40	24.08 ± 6.40	>0.05
Waist circumference (cm)	77.0 ± 2.30	77.30 ± 2.70	>0.05
Hip circumference (cm)	100.80 ± 10.70	101.70 ± 11.70	>0.05
WHR	0.76 ± 0.070	0.75 ± 0.07	>0.05
Glucose/insulin ratio	18.58 ± 12.60	18.36 ± 13.60	>0.05
HOMA	2.08 ± 2.80	1.75 ± 1.40	>0.05
Total cholesterol (mg/dL)	169.20 ± 35.60	189.80 ± 36.10	**<0.05**
HDL (mg/dL)	52.50 ± 13.60	55.0 ± 17.30	>0.05
LDL (mg/dL)	98.0 ± 27.80	109.30 ± 29.60	**<0.05**
Triglyceride (mg/dL)	94.90 ± 65.20	117.80 ± 51.30	**<0.05**
Ferriman–Gallwey score	12.10 ± 2.50	10.50 ± 2.70	**<0.05**
Testosterone (ng/dL)	51.90 ± 29.0	36.0 ± 22.20	**<0.05**
F.testosterone (pg/mL)	3.30 ± 1.10	1.8 ± 0.80	**<0.05**
SHBG (nmol/L)	33.40 ± 15.70	148.50 ± 72.0	**<0.05**
FAI	9.83 ± 17.50	2.41 ± 5.90	**<0.05**
DHEAS (µg/dL)	232.30 ± 84.80	207.80 ± 100.0	>0.05

Data are presented as mean ± SD

BMI body mass index, *WHR* waist to hip ratio, *HOMA* homeostasis model assessment, *HDL* high density lipid, *LDL* low density lipid

Table 2 Comparison of cardiovascular risk parameters of all patients before and after the treatment

Parameter	Baseline	After treatment	p
Central SBP (mmHg)	107.50 ± 10.50	106.20 ± 10.0	>0.05
hsCRP (mg/L)	3.31 ± 3.20	3.87 ± 2.90	>0.05
FMD (%)	18.50 ± 8.90	16.60 ± 7.70	>0.05
NMD (%)	29.90 ± 10.70	30.30 ± 10.90	>0.05
CIMT (mm) (right)	0.44 ± 0.03	0.46 ± 0.04	**<0.05**
CIMT (mm) (left)	0.44 ± 0.03	0.47 ± 0.04	**<0.05**

Data are presented as mean ± SD

SBP systolic blood pressure, *hsCRP* high sensitive C-reactive protein, *FMD* flow mediated dilatation, *NMD* nitrate-mediated dilatation, *CIMT* carotid intima media thickness

were not statistically significant ($p > 0.05$). Also hs-CRP levels did not change compared with baseline ($p > 0.05$). There was a reduction in FMD, however, it did not reach statistical significance ($p > 0.05$). Whereas the mean CIMT values increased significantly after 6 months ($p < 0.05$). Progression rate was 0.02 ± 0.01 mm and 0.03 ± 0.01 mm for right and left CIMT, respectively. There was not any significant correlation between CIMT, FMD, NMD or any metabolic parameters ($p > 0.05$).

After splitting the data according to BMI scores, 27 patients were normal weight (BMI < 25) and 13 were overweight (BMI > 25). At baseline systolic blood pressure and hsCRP levels were significantly higher among

overweight patients ($p < 0.05$). Also HDL levels and G/I were lower in the overweight group ($p < 0.05$). Evaluation of the splitted data revealed that, lipid profile parameters were significantly deteriorated after 6 months among normal-weight patients (Table 3). On the contrary, only TG levels among lipid parameters increased in overweight patients ($p < 0.05$). Although there was a reduction of FMD in all patients, this reduction reached a statistical significance in overweight group ($p < 0.05$) (Table 3).

Discussion

PCOS increases the risk of cardiovascular diseases and metabolic disorders [16, 17]. Concomitant disturbances such as obesity, dyslipidemia, and insulin resistance create a suspicion of the exact independent roles of these factors in future cardiovascular events. In order to control additional cardiovascular risk factors, we excluded the patients with such metabolic abnormalities except obesity in our study.

Currently, OCPs are the first-line treatment modality in PCOS due to their improving effects on menstrual irregularity and hyperandrogenism. Hence we preferred to evaluate cardiovascular risk factors of PCOS patients under treatment with OCP. In the literature, there are conflicting reports about the cardiovascular effects of OCPs on PCOS patients [18, 19]. Some of these reports support the beneficial effects of OCPs on cardiovascular system in PCOS patients [20, 21]. However, in a recent meta-analysis, it was suggested that OCPs may have negative effects on cardiovascular events in healthy individuals and these effects may be aggravated in case patient and has an increased cardiovascular risk factor such as PCOS [5, 7].

Endothelial dysfunction is recognized as an initial step in the development of atherosclerosis and it can be detected by reduced FMD [22]. PCOS was associated with impaired FMD in some previous reports [12, 13, 23]. In our study, there was a tendency of reduction in FMD, which was even significant among overweight patients ($p < 0.05$). This result suggests that the reduction of FMD in PCOS patients was a progressive event during the 6-month long follow up. According to the findings in the literature, OCPs seem to have neutral or negative effects on endothelial function among healthy individuals [24, 25]. However, some studies have reported controversial results. According to these studies, OCPs have deteriorating, neutral and improving effects on endothelial function among PCOS patients [18, 19, 21]. However, in the study of Mancini et al., hypocaloric diet was prescribed to the patients in addition to OCPs and a significant weight reduction was observed after the treatment. Therefore, it may be concluded that life style implementation may hinder the negative effects of

Table 3 Comparison of metabolic and cardiovascular parameters within normal and overweight patients before and after the treatment

Parameter	Normal weight			Overweight		
	Baseline	After treatment	p	Baseline	After treatment	p
BMI (kg/m^2)	20.99 ± 2.10	20.87 ± 2.44	>0.05	32.4 ± 5.45	32.6 ± 6.10	>0.05
Glucose/insulin ratio	21.61 ± 14.27	21.42 ± 14.60	>0.05	10.07 ± 5.28	10.21 ± 5.06	>0.05
HOMA	1.59 ± 1.54	1.50 ± 1.18	>0.05	3.16 ± 3.86	2.41 ± 1.89	>0.05
Total cholesterol (mg/dL)	174.85 ± 41.31	193.88 ± 40.42	**<0.05**	180.62 ± 33.50	179.11 ± 18.40	>0.05
HDL (mg/dL)	57.93 ± 13.02	60.00 ± 17.33	>0.05	43.69 ± 7.47	41.67 ± 8.39	>0.05
LDL (mg/dL)	99.73 ± 31.78	111.31 ± 33.05	**<0.05**	111.45 ± 23.81	104.16 ± 18.24	>0.05
Triglyceride (mg/dL)	88.89 ± 68.46	100.08 ± 36.38	**<0.05**	126.85 ± 42.37	165.11 ± 57.45	**<0.05**
hsCRP (mg/L)	1.81 ± 1.24	3.12 ± 2.66	>0.05	6.46 ± 4.62	5.69 ± 3.14	>0.05
FMD (%)	19.04 ± 9.57	16.84 ± 8.44	>0.05	18.21 ± 8.86	16.16 ± 5.83	**<0.05**
NMD (%)	32.97 ± 10.62	31.53 ± 11.93	>0.05	27.46 ± 11.77	26.16 ± 4.90	>0.05
CIMT (mm) (right)	0.43 ± 0.02	0.45 ± 0.04	**<0.05**	0.45 ± 0.03	0.48 ± 0.03	**<0.05**
CIMT (mm) (left)	0.43 ± 0.03	0.46 ± 0.04	**<0.05**	0.44 ± 0.03	0.47 ± 0.03	**<0.05**

Data are presented as mean ± SD

BMI body mass index, *WHR* waist to hip ratio, *HOMA* homeostasis model assessment, *HDL* high density lipid, *LDL* low density lipid, *SBP* systolic blood pressure, *hsCRP* high sensitive C-reactive protein, *FMD* flow mediated dilatation, *NMD* nitrate-mediated dilatation, *CIMT* carotid intima media thickness

treatment or natural progression of PCOS. In our study, endothelial function seems to be deteriorated after the 6-month follow up. In addition, the significant alteration, which was observed particularly in the overweight group, supports the previous reports, which emphasize the independent role of obesity in cardiovascular risk [26, 27].

CIMT is a validated sensitive and specific non-invasive marker of the early preclinical phases of systemic atherosclerosis and an increased CIMT is an independent predictor of the occurrence of major cardiovascular events later in life [8]. It has also been determined that women with PCOS exhibit increased CIMT [11]. However, there is limited data on the alteration rate of CIMT in PCOS patients subjected to follow-up. Only in a recent study, non-significant tendency toward a decrease in CIMT was reported with EE/CPA treatment [20]. The remarkable aspect of the study was that a diet and physical activity were prescribed to all patients in addition to the ongoing treatment. Contrary to that study, our results revealed that, both right and left CIMTs were significantly increased after 6 months in both the normal weight and the overweight groups. The significant change in CIMT might have resulted from increased lipid since endothelial dysfunction and increased IMT coexist with abnormal lipid profile [28]. Furthermore, in a recent study, a CIMT progression rate of 0.015 ± 0.024 mm per year was reported among healthy young women [29]. However, in our study, the increment in CIMT in our PCOS patients was 0.03 ± 0.01 mm at the end of 6 months, which is four times higher than that in the healthy young women of that study. The progression of these cardiovascular risk parameters in a short period of

time indicates the importance of close follow-up in PCOS patients. However, further studies are required to elucidate the effect of life style implementation on CIMT in PCOS patients.

In our study, except HDL, all lipid profile components were elevated significantly in the normal-weight patients while only TG levels were significantly elevated in the overweight patients. Although HDL levels seem to be elevated in normal-weight group, this increment did not reach statistical significance. In the literature, the potential impact of OCPs on lipid profile and the exact effect of OCP-induced lipid changes on cardiovascular system remain unclear. The estrogenic component of OCPs elevates TG and HDL levels dose-dependently, whereas their progestogenic effect on lipid levels depends on the progestin type [30]. However, there is not any direct evidence about the progestogenic effect on lipid metabolism since there is no study regarding the effect of progestogen-only oral contraceptives on the lipid profile of women with PCOS [31]. Different type of OCPs which include drospirenone, desogestrel and norethindrone have also been studied in women with PCOS regarding to their effects on lipid profile [32–34]. Increased TG and TC levels were mostly seen in these studies [32–34]. As to the results of the studies, which used EE/CPA as OCP; include the following: elevation of TC, TG, and LDL levels [35] elevation of only TG levels [18] and no significant alteration in lipid levels [36, 37]. The interesting result of our study was the higher deterioration of lipid profile in the normal-weight patients than in the overweight ones.

In previous studies, a CRP greater than 3 mg/L was accepted to be correlated with CVD [10]. Furthermore, OCPs and obesity were found to increase hs-CRP levels in healthy populations and PCOS patients in some researches [38–40]. In agreement with those reports, mean hCRP levels were above 3 mg/L at the baseline evaluation, in our study. Moreover, there was a tendency toward increment in hCRP after 6 months. However, that increase did not reach statistical significance.

Upon evaluation of baseline hormone values, all patients exhibited hyperandrogenemia. At the end of the treatment, the clinical and laboratory findings of our patients revealed a significant decrease in hyperandrogenemia in both the groups. In the current literature, most study results indicate hyperandrogenemia as a main factor of cardiovascular deterioration [12, 41, 42]. Furthermore, in a recent study, amelioration of excess androgen was recommended for cardiovascular prevention [43]. These findings suggest that OCPs may improve cardiovascular status. However, contrary to these findings, a positive correlation between FAI and FMD in overweight PCOS patients was also demonstrated in a previous study [44]. They suggested a positive cardioprotective effect of endogenous DHEAS in patients with PCOS which indicates that, hyperandrogenism may have a protective role against endothelial dysfunction. [44]. Similarly, the deterioration of cardiovascular risk parameters in our PCOS patients was not prevented by amelioration of hyperandrogenemia. Additionally there was no significant correlation between alteration rate of androgens and CIMT. Hence the potential beneficial cardiovascular effects of androgen amelioration might be influenced by hyperlipidemia in OCP prescribed PCOS patients.

We also evaluated glucose metabolism. Insulin resistance was not detected in our patients according to the HOMA criteria defined by a previous study on PCOS patients [45]. Hence insulin resistance was not a factor contributing to cardiovascular risk in our study population. Furthermore, we did not observe any deterioration in glucose metabolism after 6 months, which supports some of the previous reports [37, 46].

As a conclusion, CIMT, an indicator of early atherosclerosis, and FMD, a finding of endothelial dysfunction, seem to be deteriorated after the 6-month follow-up of PCOS patients who were prescribed to OCP containing cyproterone acetate. As the study was conducted with only one type of pill, it may not be concluded that the deterioration is because of cyproterone acetate, therefore additional studies with different type of OCPs are also necessary. In addition, the progression of these cardiovascular risk parameters in a short period of time indicates the importance of close follow-up in PCOS patients. These findings revealed that OCPs may not be protective against the progression of cardiovascular risk parameters. Thus, some additional treatment modalities such as life style implementation may be added to treatment especially in overweight PCOS patients. Long-term studies with larger populations are needed to confirm these findings.

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