

WEIGHT CHANGE AND ANDROGEN LEVELS DURING CONTRACEPTIVE TREATMENT OF WOMEN AFFECTED BY POLYCYSTIC OVARY

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Objective. The aim of this study was to investigate the effect of oral contraceptive Diane 35 (ethinylestradiol + cyproteroneacetate – EE/CPA) which is widely used in the treatment of PCOS in Europe, on body weight, lipid levels and endocrine parameters in non-obese women with PCOS.

Subjects and methods. Nineteen PCOS women were examined in the early follicular phase of menstrual cycle, blood samples for the estimation of cholesterol (C), HDL cholesterol (HDL-C), triglycerides (TG), testosterone (T), androstenedione (A), dehydroepiandrosterone sulfate (DHEAS) and sex hormone binding globulin (SHBG) were taken before the start of treatment with Diane 35 and again after 7 ± 3.8 months of treatment with Diane 35. Body weight (W) was recorded at the time of both examinations.

Results. After the treatment with Diane 35 the levels of W ($p < 0.05$), total C ($p < 0.05$), TG ($p < 0.004$) and SHBG ($p < 0.0001$) increased significantly. In addition, significant negative correlation between SHBG levels before treatment and increase of W after Diane 35 was found ($r = -0.56$; $p < 0.02$). Increase of W correlated negatively with T before treatment ($r = -0.58$; $p < 0.02$) and positively with the change in T level after treatment ($r = 0.50$; $p < 0.05$).

Conclusions. Increase of body weight in a significant number of PCOS-affected women was seen after treatment with Diane 35 and it is assumed to blunt ameliorating effects of this treatment on androgen levels. Considering our findings, we conclude that the treatment with CPA/EE can result in significant weight gain ameliorating positive effects of the treatment on androgen levels. These findings could underline the necessity of the finding new therapeutical options for PCOS, besides contraception. Studies concerning body composition during contraceptive treatment in PCOS would be also useful in the future.

Key words: Polycystic ovary syndrome – Cyproterone acetate – Androgen – Lipid levels – SHBG – Insulin resistance

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder. Among the important features modifying the clinical picture of PCOS, is obesity. Many authors still consider hormonal contraception as the first line of PCOS treatment, since it ameliorates hormonal disturbances (androgen production, LH hypersecretion) and improves oligo/amenorrhoea and skin manifestations of hyperandrogenemia eg. (BURKMAN 1995). Such beneficial effects could be equivocal in some patients, as recently a negative impact of pre-existing obesity on androgen levels after

treatment was described (CIBULA et al. 2001). Studies concerning the impact of obesity on hormonal manifestations of PCOS either found a negative effect of obesity on androgen levels (CIAMPELLI et al. 1999) or not (GOLLAND et al. 1993). One of the well-known untoward side-effects of contraceptive pills is the weight gain occurring in a remarkable proportion of patients (REGIDOR et al. 2000). Nevertheless, little is known about the possible interrelations between weight changes and endocrine manifestations of PCOS during contraceptive treatment.

The aim of the present study was to investigate the effect of oral contraceptive Diane 35 (ethinylestradiol + cyproteroneacetate-EE/CPA), which is widely used in the treatment of PCOS in Europe, on body weight, lipid levels and endocrine parameters in non-obese women with PCOS.

Subjects and methods

Protocol of the study. Nineteen women fulfilling the diagnostic criteria of polycystic ovary syndrome (oligo/amenorrhoea, hyperandrogenemia and clinical manifestation of either acne or hirsutism) attending the Outpatient Department of Institute of Endocrinology during 2 years were consecutively enrolled into the study. The age of patients was 24.3 ± 4.3 years. They were either slim or mildly overweighted (the average weight was 66.3 ± 13.5 kg). Cholesterol, HDL cholesterol, triglycerides, SHBG, testosterone, androstenedione and dehydroepiandrosterone sulfate DHEAS were measured in serum obtained before treatment in the early follicular phase (day 1-7, 7-8.30 a.m.) – (stage 0). Afterward, on the first day of next menstrual cycle, the treatment with Diane 35 has been started with maintenance for 7 ± 3.8 months. Subsequently, the blood tests were performed again between 25th and 28th day (stage 1) with the same parameters followed as in the stage 0. In both stages, the blood was collected in the fasting state. Institutional Ethical Committee approved the study.

Laboratory methods. DHEAS was measured using RIA kits from Immunotech (Marseille, France). Testosterone (T) was determined by standard RIA using anti-testosterone-3-carboxymethyloxime: BSA antiserum and testosterone-3-carboxymethyloxime-tyrosylmethylester- ^{125}I as a tracer; the intra-assay and inter-assay coefficients of variation were 7.2 % and 10 % respectively, and the sensitivity was 0.21 nmol/l. Androstenedione (A) was determined using standard RIA with anti- androstenedione-6-(O-carboxymethyloxime):BSA antiserum and ^3H androstenedione as a tracer; the intra-assay and inter-assay coefficients of variation were 8.1 % and 10.2 % respectively, and the sensitivity was 0.39 nmol/l. Sex hormone binding globulin (SHBG) was estimated using the IRMA method (Orion, Espoo Finland). Blood glucose was determined by an enzymatic method (Lachema, Brno, Czech Republic). Total cholesterol and triglycerides were determined enzymatically (reagents from Boehringer Mannheim, Germany, using a Cobas Mira S autoanalyzer,

Hoffman-La Roche, Basel, Switzerland); HDL-cholesterol was determined using the same method after precipitation.

Statistical evaluation. Index of free testosterone was calculated as $100 \times \text{T} / \text{SHBG}$. For the comparison of changes in different parameters before and after treatment, paired t-test was used. If the data were non-homogeneous or non-Gaussian, Wilcoxon's paired test was applied. The data are shown as mean \pm SD. Null hypotheses of statistical tests were evaluated at the 95 % level of significance ($p < 0.05$). For evaluation of the mutual relationships between changes (before treatment – after treatment) of individual parameters, Spearman rank correlations were used. If the p-value was less than 0.05, the correlation was considered as significant. The tests were performed using the statistical software STATGRAPHICS Plus 3.0 (Manugistics, Rockville, MA, USA).

Results

Body weight, lipids and endocrine parameters. When comparing all subjects before and after treatment, the body weight significantly increased ($p < 0.05$). In 9 patients the increase in body weight (average of 3.4 kg; range 1.0 to 8.5 kg) was observed, while in the rest of 10 patients no significant change in weight was observed. As to lipid spectrum, total cholesterol ($p < 0.05$) and triglycerides ($p < 0.004$) increased significantly. Trend towards increased levels of HDL cholesterol ($p = 0.11$) was found after treatment (Table 1).

Testosterone levels did not change significantly; although a slight decreasing tendency was indicated. SHBG levels increased significantly after the treatment ($p < 0.0001$), which implies that index of free testosterone significantly decreased ($p < 0.0001$). A decreasing tendency in the DHEAS levels appeared ($p = 0.14$). No change in androstenedione levels was observed (see Table 2).

In women with a weight gain, significantly lower testosterone (2.0 ± 0.44 vs. 2.85 ± 0.6 nmol, $p < 0.01$) and lower SHBG level (33 ± 10 vs. 56 ± 20 nmol/l, $p < 0.05$) was found the treatment as compared to women with the stable body weight.

Correlation analysis. Table 3 shows a significant negative correlation between SHBG levels before treatment and increase in the body weight after Diane 35 was found ($r = -0.56$; $p < 0.02$). Increase in body weight correlated negatively with testosterone levels before treatment ($r = -0.58$; $p < 0.02$). On the other hand, an in-

Table 1
Weight and lipid levels in PCOS women before and after treatment with Diane 35 (values are given as mean \pm SD)

	Before treatment	After treatment	p<
Weight (kg)	66.3 \pm 13.5	68.7 \pm 13.6	0.038
Cholesterol (mmol/l)	4.25 \pm 0.93	5.17 \pm 1.18	0.0295
HDL cholesterol (mmol/l)	1.33 \pm 0.31	1.45 \pm 0.35	0.07
Triglycerides (mmol/l)	0.78 \pm 0.30	1.28 \pm 0.38	0.004

Table 2
Steroid hormone and SHBG levels in PCOS women before and after treatment with Diane 35 (values are given as mean \pm SD)

	Before treatment	After treatment	p<
Testosterone (nmol/l)	2.49 \pm 0.74	2.05 \pm 0.81	NS
SHBG (nmol/l)	43.4 \pm 18.0	199.2 \pm 60.9	0.00001
Index of free testosterone	6.6 \pm 3.07	1.18 \pm 0.76	0.000004
Androstenedione (nmol/l)	8.07 \pm 4.80	6.54 \pm 2.49	NS
DHEAS (mmol/l)	8.20 \pm 3.21	6.02 \pm 2.57	0.09

crease in body weight correlated positively with the increase in testosterone after treatment ($r=0.50$; $p<0.05$). Change in body weight did not correlate with the change in any of the lipid parameters. Nevertheless, the increase in cholesterol levels strongly positively correlated with the increase in triglycerides ($r = 0.89$; $p<0.005$). We observed a positive relationship of borderline significance between decrease in the ratio of HDL cholesterol /cholesterol and increase in testosterone ($r =0.63$, $p=0.07$). Strong and significant negative relationships between the changes in cholesterol and DHEAS levels before treatment ($r = -0.76$; $p<0.05$) as well as between the changes triglyceride levels and DHEAS levels before treatment ($r= -0.73$; $p<0.05$) were found.

Discussion

As shown in the present study, the treatment with CPA/EE resulted in significant ameliorating effects on the index of free testosterone and a significant increase in SHBG levels, in agreement with others (FALSETTI et al. 1995, 2001; GOLLANG et al. 1993; PRELEVIC et al. 1990). We observed a significant increase in triglycerides and in total cholesterol and trend towards increase in HDL cholesterol. This is in accordance with other authors (CREATSAS et al. 2000, FALSETTI et al. 1995, PRELEVIC et al. 1990, VEXIAU et al. 1990). Side-effects of hormonal contraception on lipid levels result from

the combination of triglyceride elevation with that of HDL cholesterol as caused by estrogens and, on the other side, in a decrease in HDL cholesterol caused by relative androgenic properties of accompanying gestagen (DARNEY 1995).

The relationship between weight gain during CPA/EE treatment and SHBG levels before treatment is of interest, considering that SHBG is a marker of insulin sensitivity (NESTLER 1993). Probably more insulin-resistant PCOS women have a greater tendency to accumulate weight. Weight gain correlated positively with the change in plasma testosterone. Thus, the weight gain during CPA/EE treatment blunted the positive effect on plasma androgens. This appears a novel finding. In obese PCOS women, only nonsignificant changes in plasma androgens levels after combined oral contraceptives were found as compared to lean PCOS women (CIBULA et al. 2001).

Long-term effects of hormonal contraceptives on the natural history of PCOS are mostly unknown up to date. A retrospective study (PASQUALI et al. 1999) in 16 PCOS women using contraceptives for years reported a decrease in body mass index as well as in the waist to hip ratio and an increase in HDL cholesterol without significant changes in triglycerides or total cholesterol when compared to 21 women who did not use any medication. Unfortunately, other similar studies concerning especially the body composition are lacking.

Table 3:
Spearman's correlations between body weight (W), SHBG, testosterone (TESTO), cholesterol (CHOL), HDL-cholesterol (HDL), triglycerides (TG) and DHEAS before and after treatment with DIANE

difference in W									
-0,5597 19 0,0176	SHBG before treatment								
0,5015 19 0,0334	-0,0588 19 0,803	difference in TESTO							
0,2843 11 0,3687	-0,1818 11 0,5653	0,2545 11 0,4209	difference in CHOL						
-0,0792 9 0,8227	0,1333 9 0,7061	-0,35 9 0,3222	-0,0167 9 0,9624	difference in HDL					
0,4422 11 0,162	-0,4273 11 0,1766	-0,0727 11 0,8181	0,8909 11 0,0048	-0,05 9 0,8875	difference in TG				
-0,1667 15 0,5327	0,2451 17 0,3269	-0,1626 15 0,5428	-0,7667 9 0,0301	-0,3214 7 0,4311	-0,7333 9 0,0381	difference in DHEAS			
-0,0792 9 0,8227	0,2 9 0,5716	-0,6333 9 0,0732	-0,6 9 0,0897	0,65 9 0,066	-0,5333 9 0,1314	0,3214 7 0,4311	difference in HDL/ CHOL		
-0,5804 19 0,0138	0,3626 22 0,0966	-0,6839 19 0,0037	-0,3736 11 0,2375	-0,0502 9 0,8871	-0,2961 11 0,349	-0,1778 17 0,4769	-0,569 9 0,1075	TESTO before treatment	

Considering our findings, we conclude that treatment with CPA/EE can result in significant weight gain ameliorating positive effects of the treatment on androgen levels. These findings could underline the necessity of finding new therapeutical options for PCOS, besides contraception. Studies concerning body composition during contraceptive

treatment in PCOS would be also useful in the future.

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