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Effects of two different oral contraceptives on homocysteine metabolism in women with polycystic ovary syndrome

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Abstract

Purpose: This study was conducted to evaluate the effects of two different oral contraceptives (OCs) on homocysteine (Hcy) metabolism in 20 women with polycystic ovary syndrome (PCOS).

Methods: Women were randomLy allocated to receive either the biphasic OC containing 40/30 μg ethynylestradiol (EE)+25/125 μg desogestrel (DSG; $n=10$) or the monophasic OC containing 35 μg EE and 2 mg cyproterone acetate (CPA; $n=10$). Investigations were performed before and after 6 months of treatment. Fasting vitamin B_{12}, folate, Hcy and insulin sensitivity (SI), and glucose utilization independent of insulin (Sg), by the minimal model method, were evaluated.

Results: Folate and vitamin B_{12} were not significantly modified by either OC. EE/DSG decreased SI (2.53±0.35 vs. 1.68±0.45; $p<.05$), without modifying Hcy (9.54±0.7 μmol/L vs. 9.18±0.6 μmol/L). EE/CPA improved SI (1.47±0.38 vs. 3.27±0.48; $p<.04$) and decreased Hcy (9.8±1.9 μmol/L vs. 7.9±0.9 μmol/L; $p<.05$). This study indicates that in women with PCOS, EE/CPA, but not EE/DSG, improves IS and decreases fasting Hcy.

Keywords: Homocysteine; Insulin sensitivity; Polycystic ovary syndrome; Contraceptive; Desogestrel; Cyproterone acetate

1. Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive disorder characterized by hyperandrogenism and chronic anovulation. The ultrasound polycystic ovary morphology is consistent with, but not essential for, the diagnosis of the syndrome [1].

Although its etiology is still uncertain, PCOS is associated with impaired glucose tolerance, type 2 diabetes, obesity, dyslipidemia and cardiovascular disease [2]. Furthermore, insulin resistance and resultant hyperinsulinemia are the most important metabolic disturbances of PCOS, as they may contribute to premature coronary artery disease [3]. In accordance with the described association of insulin resistance and high levels of homocysteine (Hcy) [4,5], women with PCOS are reported to have an elevation of Hcy [4].

Hyperhomocysteinemia is a recognized risk factor for atherosclerosis, independent of other classic risk factors [6]. Elevated Hcy induces an increase in oxidative stress in vascular endothelium, activates platelets [7,8], impairs artery blood flow and stimulates vascular smooth muscle cell proliferation [9].

Oral contraceptives (OCs) are frequently used for the clinical management of women with PCOS. A few studies have shown that OCs do not modify the levels of Hcy in normal women [10,11], but no study was performed in women with insulin resistance, as are the women with PCOS.

This study evaluated the effect of two different OCs on Hcy metabolism of women with PCOS.

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2. Materials and methods

Twenty lean young women with PCOS, who had not received OCs or active endocrine and metabolic treatments for at least 8 months, were enrolled in the study. Each woman gave her informed consent to the study, which was previously approved by our local ethics committee and institutional review board. Polycystic ovary syndrome was defined by (i) ovarian hyperandrogenism (elevated levels of total testosterone, free testosterone or androstenedione); (ii) persistent amenorrhea or oligomenorrhea (less than six bleeding episodes per year) of perimenarchal onset; (iii) association with at least one of the following alterations: ultrasound evidence of polycystic ovaries, LH/FSH ratio greater than 1, Ferriman and Gallwey hirsutism score greater than 10 [12].

Following a computer-generated list of randomization, each woman was assigned to receive either a biphasic OC containing, for the first 7 days, 40 μg ethynylestradiol (EE)+25 μg desogestrel (DSG) and for the subsequent 14 days, 30 μg EE+125 μg DSG (Gracial, Akzo-Nobel, Oss, The Netherlands; $n=10$), or a monophasic OC containing 35 μg EE and 2 mg cyproterone acetate (CPA; Diane 35, Schering, Berlin, Germany; $n=10$). During the study, the women were requested not to modify their lifestyles or dietary habits.

Insulin sensitivity (SI) and glucose utilization independent of insulin (Sg) were investigated by a frequently sampled intravenous glucose tolerance test (FSIGT) [13,14]. A diet containing at least 200 mg/day of carbohydrates was prescribed for the 3 days preceding the investigation. After a 24-h low-protein diet and overnight fast, each woman was hospitalized at 0700. Women were maintained at bed rest. Two polyethylene catheters were placed in two antecubital veins and were kept patent by a slow infusion of saline solution. One catheter was used for intravenous glucose or insulin administration, and the other for blood collection. At 0900, glucose (0.3 g/kg) was injected over 1 min intravenously, followed 20 min later by an intravenous insulin bolus (0.03 U/kg). Samples of arterialized blood were collected at −5, 2, 4, 8, 20, 22, 30, 40, 60, 70, 100, 180 min after the glucose load. Blood samples were collected in tubes and placed on ice. Blood was immediately centrifuged. An aliquot of serum was immediately tested for glucose levels, whereas another aliquot was immediately frozen at −25°C until assayed. Insulin sensitivity and Sg were calculated by the minimal model method [14]. SI is expressed as units$\times 10^{-4}$ per minute$\times$micro-units per milliliter and Sg as units$\times 10^{-4}$ per minute. Folate, vitamin B_{12} and Hcy were assayed in samples collected prior to the glucose load. Investigations were performed at baseline, during the early follicular phase (4–7 days after spontaneous or progestin-induced menstruation), and during the first 7 days of the sixth month of treatment.

Serum Hcy was measured by a high-performance liquid chromatography method (BIO-RAD, Munich, Germany) with a fluorimetric detection. The assay had a sensitivity of 0.5 μmol/L and intra- and interassay coefficient of variation (CV) of 3.8% and 6%, respectively. A simultaneous radioimmunoassay kit (simulTRAC-SNB, ICN Pharmaceuticals, Orangeburg, New York) was used to measure serum concentrations of vitamin B_{12} and folate. The sensitivity was 75 pg/mL for vitamin B_{12} and 0.6 ng/mL for folate. The intra-assay CV was 11.2% for vitamin B_{12} and 4.1% for folate, whereas interassay CV was 12.3% and 7.1%, respectively. Glucose was determined by the glucose oxidase method. Insulin was measured by RIA, using commercially available kits (Biodata, Guidonia Montecelio, Rome, Italy). The intra- and interassay CV were 6.2% and 7%, respectively, and the sensitivity was 2 μU/mL.

Between-group comparisons were performed using the Student's *t*-test. Within-group comparisons were performed using the *t*-test for paired data. A value of $p<.05$ was

Table 1
Mean (±SE) age, body mass index (BMI), waist-to-hip ratio (WHR), glucose, insulin, SI, Sg, homocysteine, vitamin B_{12} and folate in women with polycystic ovary syndrome before and after 6 months of therapy with the biphasic OC containing EE+DSG (40/30 μg EE+25/125 mg DSG) or the monophasic combination of EE+CPA (35 μg EE+2 mg CPA)

	EE/DSG			EE/CPA		
	Before	During	p value	Before	During	p value
Age (year)	22.7±0.7			21.8±0.8		
BMI (kg/m^2)	23.5±1.9	22.5±1.4	NS	22.6±0.9	21.1±0.6	NS
WHR	0.7±0.02	0.7±0.02	NS	0.7±0.01	0.7±0.01	NS
Glucose (mg/dL)	84.5±2.9	85.2±2.4	NS	81.4±3.6	78.1±2.0	NS
Insulin (μU/mL)	15.7±1.1	19.6±1.1	<.01	17.9±2.4	18.7±2.9	NS
SI	2.53±0.35	1.68±0.45	<.05	1.47±0.38	3.27±0.48	<.04
Sg	0.023±0.002	0.032±0.004	<.04	0.03±0.003	0.026±0.004	NS
Homocysteine (μmol/mL)	9.54±0.7	9.18±0.6	NS	9.8±1.9	7.9±0.9	<.05
Vitamin B_{12} (pg/mL)	511±83	410±80	NS	664±74	471±92	NS
Folate (ng/dL)	5.0±0.7	6.2±1.0	NS	6.47±1.5	6.4±0.95	NS

p by paired *t*-test before vs. during, within each group.