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PCOS

Cerebral artery hemodynamics in polycystic ovary syndrome

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Abstract

Objective. The aim of the present study was to investigate hemodynamic changes in the medial cerebral artery and also the internal carotid artery in young women with polycystic ovary syndrome (PCOS) and polycystic ovaries (PCO).

Methods. Twenty-eight patients with PCOS, 16 patients with PCO and 24 healthy control subjects were included in the study. Blood flow rate, pulsatility index and back pressure of both the medial cerebral artery and the internal carotid artery were determined by transcranial Doppler ultrasonography and the results compared between groups.

Results. There were no significant differences between the groups in bilateral medial cerebral artery and internal carotid artery blood flow rate, pulsatility index and back pressure.

Conclusion. Our results do not indicate whether the risk of cerebrovascular events will increase for PCOS patients in middle and advanced age, but do show that changes in cerebral hemodynamics are not likely in PCOS at an early stage.

Keywords: *Polycystic ovary syndrome, polycystic ovary, transcranial Doppler ultrasonography, cerebral artery hemodynamics*

Introduction

Polycystic ovary syndrome (PCOS) is characterized by various endocrine/metabolic disorders and related systemic findings in addition to polycystic ovaries (PCO) as determined by ultrasound. Menstrual disorders (oligo/amenorrhoea), infertility, obesity, hyperandrogenism (i.e., acne, hirsutism and alopecia) and insulin resistance are important findings accompanying PCOS [1]. Involvement of other systems, especially those related to endocrine and vascular abnormalities, has also been reported in PCOS patients.

It is speculated that the incidence of cardiovascular disease (CVD) and cerebrovascular incidents are increased in PCOS patients due to abnormalities in vascular structure and function [2–4]. However, hemodynamic studies in PCOS have concentrated almost exclusively on the pelvic vessels. The results of the few studies on vessels outside the pelvis suggest decreased flow over the aortic arch and increased resting forearm flow [5,6]. There are only a few studies on cerebrovascular structure and dynamics in PCOS patients. Guzick and colleagues observed a mild increase in the carotid intima and media thickness of middle-aged women with PCOS [7]. Another study investigating internal carotid artery (ICA) hemodynamics with Doppler ultrasound found lower pulsatility index (PI) values in young PCOS patients compared with controls [2]. The significance of this change in the ICA of young PCOS patients for cerebrovascular disease and how it affects the hemodynamics of intracranial vessels are not clear. Our aim in the present study was to determine the extent of intracranial vessel involvement in the early stages of PCOS by evaluating the medial cerebral artery (MCA) and ICA hemodynamics by transcranial Doppler ultrasonography (TCD) in young women with PCOS and PCO.

Materials and method

Twenty-eight PCOS patients and 16 PCO patients were included in the study, together with 24 healthy control subjects. They were examined between October 2004 and January 2005 at the Obstetrics and Gynecology Outpatient Department of Inonu University, Turgut Ozal Medical Faculty.

The 2003 revised Rotterdam criteria were used for selecting the PCOS patient group. The presence of at

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least two of the following criteria was necessary for the diagnosis of PCOS:

(1) Oligo- or anovulation.
(2) Clinical and/or biochemical signs of hyperandrogenism.
(3) Polycystic ovaries on ultrasound (or direct inspection).

Other etiologies for hyperandrogenism (such as congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumors) were excluded [8].

Thyroid disease, androgen-secreting neoplasm, Cushing's syndrome and 21-hydroxylase deficiency were first eliminated. Patients who smoked, those with systemic disease that could affect TCD results such as lung disease and anemia, patients with abnormal blood or routine biochemistry results and those who had used oral contraceptives (OC) or medication for ovulation induction within the past 6 months were excluded from the study. The control group consisted of 24 healthy women who menstruated regularly, had no symptoms or signs of hyperandrogenism, whose androgen levels were normal and had normal ovaries on an ultrasound examination.

We obtained approval from the Ethics Committee of our hospital before initiating the study. All subjects provided consent after they received information on the study.

Clinical parameters

Patients' medical history, drug history, menstrual history, number of pregnancies, OC usage or ovulation induction history, and family history of diabetes were obtained. Diastolic and systolic blood pressures were determined. Body mass index (BMI) was used to determine the degree of obesity and was calculated as body weight divided by the square of height (kg/m^2). Subjects with BMI <25 kg/m^2 were classified as non-obese, those with BMI $=$ 25–30 kg/m^2 as overweight, and those with BMI $\geqslant$ 30 kg/m^2 as obese [9]. The waist/hip ratio (WHR) was determined. Patients with a score of 8 with the modified Ferriman–Gallwey scoring were accepted as suffering from hirsutism [10]. Patients who had not menstruated for $\geqslant 6$ months were classified as amenorrheic ($n=1$, 1.5%) while those with a menstrual cycle >35 days were considered oligomenorrheic ($n=27$, 96.5%). All clinical evaluations were carried out by the same physician.

Biochemical parameters

Venous blood samples were obtained in the follicular phase, on the 2nd to 4th day of menstruation, at 08.00–10.00 hours following an 8 h fast. Measurements were performed on the 2nd to 5th day of menstruation following progesterone administration in oligomenorrheic and amenorrheic patients. The following parameters were determined from the blood samples provided by the patients: follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin (PRL), cortisol, dehydroepiandrosterone sulfate (DHEAS), total testosterone, sex hormone-binding globulin (SHBG), free androgen index (FAI), fasting glucose, fasting insulin, insulin resistance index (IRI), serum glutamic–oxaloloacetic transaminase, serum glutamic–pyruvic transaminase, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein (VLDL), total cholesterol, triglycerides, C-peptide, apolipoprotein A-I, apolipoprotein B and lipoprotein A. The fasting glucose/insulin ratio was used to calculate the IRI [11].

Pelvic ultrasonography

Pelvic ultrasonography was performed with an ATL Ultrasound (Bothell, WA, USA) HDI 3500 instrument using a 2–5 MHz abdominal probe (in virgin patients) or a 4–8 MHz transvaginal probe (in the five PCOS patients, four PCO patients and one control subject who were not virgins), with the patient in the lithotomy or supine position. Ultrasonographic imaging PCO criteria were the presence of $\geqslant 12$ follicles 2–9 mm in diameter in at least one ovary and/or ovarian volume of >10 ml [8]. The location in the ovary and stromal echogenicity of the follicles were not taken into consideration. The ultrasonography was repeated during menstruation in patients with follicles $\geqslant 10$ mm. If there were no follicles of this size, the ovarian volume was calculated with the formula [12]:

$$(4/3)\pi \times (\text{length}/2) \times (\text{width}/2) \times (\text{height}/2),$$

and follicles with a diameter of 2–9 mm were evaluated. The ultrasonographic evaluation of all cases was performed by the same physician.

Transcranial Doppler ultrasonography

The MultiDop X4 TCD-8 .01b DWL 2.54 g (DWL Elektronische Systeme GmbH) instrument and 2–4 MHz probes were used for the transcranial Doppler investigation. The subject was placed in the supine position; the head was hyperextended and turned to the side opposite to that to be examined for ICA imaging. The ICA was imaged about 2 cm distal to the carotid bifurcation in both submandibular regions with the 4 MHz. probe. MCA imaging was at 45–65 mm depth from both temporal windows using the 2 MHz probe with the patient at the supine position. The peak systolic velocity, end-diastolic velocity and mean velocity of both MCA and ICA were measured and PI values calculated automatically [2] as:

$$\text{PI} = (\text{peak systolic velocity} - \text{end-diastolic velocity})/\text{mean velocity}.$$

The back pressure was calculated using the PI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) [2] as:

$$\text{Back pressure} = \text{DBP} + (\text{SBP} - \text{DBP}) \times [1/3 - (1/\text{PI})].$$

All investigations were carried out by the same neurologist in a blinded manner.

Statistical analysis

Data are presented as mean $\pm$ standard deviation or median (minimum–maximum). Statistical significance was determined by Student's t test, analysis of variance and the Kruskal–Wallis test in group comparisons. Statistics also included the Mann–Whitney U test and χ^2 test as appropriate. Statistically significant differences were determined at the $p < 0.005$ level. All tests were performed using the SPSS statistical package (SPSS Inc., Chicago, IL, USA).

Results

The mean age of subjects was 21.46 ± 3.07 years (range 17–29 years) in the control group, 21.81 ± 2.99 years (18–30 years) in the PCO group and 22.61 ± 3.83 years (17–33 years) in the PCOS group; there was no statistically significant difference between the groups ($p = 0.657$). Moreover, there were no significant differences between groups with regard to BMI, WHR, systolic and diastolic blood pressures, and family history of diabetes mellitus.

However, comparing the biochemical results between groups, total testosterone, SHBG, FAI, LH and estradiol were found to be statistically significantly different in the PCOS group compared with the other two groups. There were no statistically significant differences between the groups in terms of FSH, PRL, DHEAS, total cholesterol, HDL-C, LDL-C, VLDL and triglyceride levels and IRI. The biochemical results are presented in Table I, together with the p values for the comparisons between groups.

When the patients were investigated with TCD, there was no statistically significant difference between the groups concerning the right and left MCA and ICA mean blood flow rate, PI and back pressure (Table II).

Discussion

To our knowledge, this is the first study in which the hemodynamic properties of the MCA have been investigated by TCD in women with PCOS and PCO. The results show that there was no difference in hemodynamic parameters such as blood flow rate, PI and back pressure in the MCA and also the ICA between these patients and the control group.

It is known that CVD risk factors such as obesity, dyslipidemia, glucose intolerance, diabetes and hypertension are encountered more frequently in PCOS patients, and the morbidity and mortality rates due to CVD are thought to be higher in these patients [13]. Risk factors do not necessarily equate with disease and/or events, and when approached by the more stringent requirement of cardiovascular events, i.e., when we take into consideration increased mortality, premature mortality or increased incidence of CVD such as stroke or myocardial

Table I. Biochemical results of the subject groups: controls, women with polycystic ovaries (PCO) and women with polycystic ovary syndrome (PCOS).

	Control group ($n = 24$)	PCO group ($n = 16$)	PCOS group ($n = 28$)	p Value
Total testosterone (ng/dl)	35.7 ± 22.3	30.8 ± 24.1	50.1 ± 20.3*	0.014
SHBG (nmol/ml)	56.4 (24–180)	54.6 (40–180)	37.9 (13–94)*	0.014
FAI (%)	2.1 (0–6.8)	1.8 (0.5–5.1)	4.6 (0–21.9)*	0.001
LH (mIU/ml)	5.24 ± 1.7	5.86 ± 1.7	10.1 ± 7.1*	0.002
FSH (mIU/ml)	7.5 ± 1.8	6.9 ± 1.7	6.9 ± 1.9	NS
Estradiol (pg/ml)	19 (19–213)	25.3 (19–41)	29.6 (19–315)**	0.049
PRL (ng/ml)	13.5 (6–25)	16.7 (5–42)	15.3 (7–42)	NS
IRI (mg/10^{-4} IU)	12.3 ± 3.5	15.5 ± 7.0	11.2 ± 6.6	NS
DHEAS (μg/dl)	248.7 ± 99.9	213.4 ± 102.6	238.4 ± 94.3	NS
Total cholesterol (mg/dl)	161 (122–230)	165 (140–237)	159 (111–232)	NS
HDL-C (mg/dl)	51 (33–59)	48.1 (32–77)	46 (33–93)	NS
LDL-C (mg/dl)	93 (50–160)	99 (75–146)	95 (27–158)	NS
VLDL (mg/dl)	14.6 (9–32)	17 (10–36)	15.6 (8–58)	NS
Triglycerides (mg/dl)	72.5 (43–162)	87.5 (49–180)	77 (41–289)	NS

SHBG, sex hormone-binding globulin; FAI, free androgen index; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin; IRI, insulin resistance index; DHEAS, dehydroepiandrosterone sulfate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein; NS, not significant; data are presented as mean $\pm$ standard deviation or median (minimum–maximum); *significant difference between the PCOS group and the other two groups; **significant difference between the PCOS group and the control group only.

Table II. Transcranial Doppler ultrasound results of the subject groups: controls, women with polycystic ovaries (PCO) and women with polycystic ovary syndrome (PCOS).

	Control group ($n=24$)	PCO group ($n=16$)	PCOS group ($n=28$)	p Value
Right medial cerebral artery				
V_{mean} (cm/s)	73.6 ± 9.8	74.8 ± 15.1	75.5 ± 13.4	NS
PI	0.77 ± 0.1	0.74 ± 0.13	0.79 ± 0.11	NS
Bp (mmHg)	29.05 ± 12.01	29.15 ± 17.40	33.00 ± 15.55	NS
Left medial cerebral artery				
V_{mean} (cm/s)	73.6 ± 10.9	71.1 ± 13	73.4 ± 12.3	NS
PI	0.77 ± 0.13	0.76 ± 0.11	0.78 ± 0.11	NS
Bp (mmHg)	27.46 ± 14.73	30.23 ± 18.61	32.24 ± 15.38	NS
Right internal carotid artery				
V_{mean} (cm/s)	17.6 ± 2.9	19.3 ± 3.4	18.7 ± 3.5	NS
PI	1.59 ± 0.28	1.51 ± 0.27	1.58 ± 0.3	NS
Bp (mmHg)	52.88 ± 11.88	52.94 ± 15.17	54.91 ± 12.41	NS
Left internal carotid artery				
V_{mean} (cm/s)	18.9 ± 4.2	18.1 ± 3.26	19.3 ± 3.9	NS
PI	1.61 ± 0.21	1.45 ± 0.25	1.55 ± 0.27	NS
Bp (mmHg)	53.50 ± 11.05	54.04 ± 13.30	54.42 ± 12.10	NS

V_{mean} (cm/s); s, second; mean blood flow rate; PI, pulsatility index; Bp, back pressure; NS, not significant, data are presented as mean ± standard deviation.

infarction, very few studies report that women with PCOS are unduly affected [14]. For example, although Wild and associates have reported an increased prevalence of cardiovascular risk factors in women with PCOS, they have not found a significant increase in mortality or morbidity due to coronary disease [15]. This may be due to protective factors against coronary disease in women with PCOS (such as prolonged exposure to unopposed estrogen or elevated levels of vascular endothelial growth factor) [15].

Most studies on CVD related to women with PCOS report indirect conclusions reached as a result of risk factor consideration [16,17]. The diagnostic criteria used for the two clinical conditions are different and there are limited studies on long-term follow-up of women with PCOS [14]. Most studies on women with PCOS involve small groups of premenopausal women with inadequate follow-up. The variability in study design and more importantly in the symptoms of PCOS leads to confusion.

The fact that there may be an increase in the incidence of cerebrovascular incidents in PCOS patients has been studied less often than that for CVD. The few studies on peripheral vascular structure and hemodynamics have found anomalies of vascular reactivity in the brachial and femoral arteries in addition to the ovarian arteries. Studies on cerebral vascular structure have reported changes or increase in the carotid vessel wall thickness [4,18], decreased viscoelasticity and abnormalities of the vessel tonus [2,3], but the clinical meaning and significance of these findings are not certain. It is thought that these changes are due to endothelial changes in the carotid arteries, as seen in the systemic arteries, caused especially by increased insulin resistance and that vascular tonus abnormalities arise as a result [2].

Reports of emergence of a disturbance in the carotid artery structure and hemodynamics after middle age in PCOS have indicated that they are due to the long-term effect of the main findings of PCOS [18]. We did not find any difference in early-stage hemodynamics of the ICA and MCA when patients with PCOS or other PCO patients were compared with control subjects.

In their TCD study in young women with PCOS and PCO, Lakhani and co-workers found low PI and low back pressure in the ICA which they thought might be due to decreased vascular resistance in the cerebral circulation and stated that this may increase the risk of cerebrovascular incidents in PCOS [2]. It is not known definitely why PI and back pressure in the ICA are lower in PCOS women. PI in the ICA may also be lower when estrogen levels are increased [19]. Similarly, arterial PI increases in postmenopausal women and estrogen administration decreases PI [20]. Some reports also suggest that estrogen levels have a protective effect on cerebrovascular incidents [21,22]. A closer look at the study by Lakhani and co-workers reveals that estradiol levels were significantly higher in PCOS patients than in the control group [2]. The PI and back pressure, which is a marker that is associated with PI and may signify decreased vascular tonus, may therefore be related to estradiol levels in their study and may decrease the risk of cerebrovascular incidents. Our TCD findings indicate that the intracranial and extracranial hemodynamics in young PCOS patients may be normal even if estrogen levels are high.

In conclusion, normal intracranial and extracranial vessel hemodynamics was found in young PCOS patients. This does not indicate whether the risk of cerebrovascular incidents will increase in middle and advanced age in PCOS patients, but does show that

changes in cerebral hemodynamics are not among the anomalies caused by PCOS at an early stage.

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