

The Cardiovascular Risk of Young Women with Polycystic Ovary Syndrome: An Observational, Analytical, Prospective Case-Control Study

FRANCESCO ORIO, JR., STEFANO PALOMBA, LETIZIA SPINELLI, TERESA CASCELLA, LIBUSE TAUCHMANOVÀ, FULVIO ZULLO, GAETANO LOMBARDI, AND ANNAMARIA COLAO

Department of Molecular and Clinical Endocrinology and Oncology (F.O., T.C., L.T., G.L., A.C.) and Internal Medicine (L.S.), University Federico II, 80131 Naples, Italy; and Department of Obstetrics and Gynecology, University of Catanzaro (S.P., F.Z.), 88100 Catanzaro, Italy

To evaluate the cardiovascular risk of polycystic ovary syndrome (PCOS), we investigated lipid profile, metabolic pattern, and echocardiography in 30 young women with PCOS and 30 healthy age- and body mass index (BMI)-matched women. PCOS women had higher fasting glucose and insulin levels, homeostasis model assessment score of insulin sensitivity, total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels, and TC/high density lipoprotein cholesterol (HDL-C) ratio and lower HDL-C levels than controls. Additionally, PCOS women had higher left atrium size (32.0 ± 4.9 vs. 27.4 ± 2.1 mm; $P < 0.0001$) and left ventricular mass index (80.5 ± 18.1 vs. 56.1 ± 5.4 g/m²; $P < 0.0001$) and lower left ventricular ejection fraction (64.4 ± 4.1 vs. $67.1 \pm 2.6\%$; $P = 0.003$) and early to late mitral flow velocity ratio (1.6 ± 0.4 vs.

2.1 ± 0.2 ; $P < 0.0001$) than controls. When patients and controls were grouped according to BMI [normal weight (BMI, >18 and <25 kg/m²), overweight (BMI, 25.1 – 30 kg/m²), and obese (BMI, >30 kg/m²)], the differences between PCOS women and controls were maintained in overweight and obese women. In normal weight PCOS women, a significant increase in left ventricular mass index and a decrease in diastolic filling were observed, notwithstanding no change in TC, LDL-C, HDL-C, TC/HDL-C ratio, and TG compared with controls. In conclusion, our data show the detrimental effect of PCOS on the cardiovascular system even in young women asymptomatic for cardiac disease. (*J Clin Endocrinol Metab* 89: 3696–3701, 2004)

THE POLYCYSTIC OVARY syndrome (PCOS) is one of the most common endocrine diseases in women, affecting up to 10% of women in reproductive age (1, 2). PCOS is characterized by chronic anovulatory cycles, oligo- or amenorrhea, hirsutism, and insulin resistance; obesity is also common (3–5). PCOS not only has a negative effect on fertility, but it is also considered a clear-cut plurimetabolic syndrome (2, 4, 6), being associated with type 2 diabetes mellitus, hypertension, and dyslipidemia (7–9). Insulin resistance is probably the major risk factor for the occurrence of cardiovascular (CV) disease (CVD) in PCOS (3).

The risk of coronary artery disease (10–12) and myocardial infarction (13) has been reported to be increased in patients with PCOS compared with regularly cycling women even if mortality because of circulatory disease does not seem to be increased (14–16). In PCOS women, endothelial and diastolic dysfunction have been shown and associated with both el-

evated androgen levels and insulin resistance (17, 18). Recently, together with classical CV risk factors, such as total (TC) and high density lipoprotein cholesterol (HDL-C) levels, obesity, homocysteine, and left ventricular (LV) hypertrophy (LVH) (19) have been shown to be independently associated with an increased CV risk. LVH is an important predictor of CV morbidity and mortality (20, 21), but determinants of LV mass (LVM) in nonhypertensive subjects are still incompletely understood (22–24).

The present study aims at further investigating the CV risk of young women with PCOS. We 1) studied the prevalence of LVH and altered diastolic filling and systolic performance by echocardiography, and 2) analyzed any potential relationship between cardiac and metabolic parameters, such as insulin secretion and lipid profile, in a selected cohort of 30 young women with PCOS.

Subjects and Methods

Subjects

Thirty young (<35 yr) women with PCOS and 30 age- and body mass index (BMI)-matched controls were enrolled in this pilot study. The controls were defined as age- and BMI-matched with cases when the number of years \pm age of cases and the BMI (kilograms per meter squared) of cases were less than to 2 yr and less than to 1 kg/m², respectively.

PCOS was defined according to clinical [Ferriman-Gallwey score, >8) (25) oligomenorrhea or amenorrhea > 6 months; biological LH/FSH ratio, >2 ; hyperandrogenism] and ultrasonographic (26, 27) findings. In Table 1 are shown the clinical and biochemical diagnostic features of the PCOS women.

The control group consisted of 30 healthy volunteer females with

Abbreviations: BMI, Body mass index; CV, cardiovascular; CVD, CV disease; DBP, diastolic blood pressure; E/A, maximal early diastolic flow velocity/maximal late diastolic flow velocity ratio; EDV, end-diastolic volume; ESV, end-systolic volume; FAI, free androgen index; HDL-C, high density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low density lipoprotein cholesterol; LV, left ventricular; LVEF, LV ejection fraction; LVH, LV hypertrophy; LVM, LV mass; LVMI, LV mass index; PCOS, polycystic ovary syndrome; PRL, prolactin; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

TABLE 1. Clinical and biochemical diagnostic features of the 30 PCOS studied women

Features	No. (%)
Anovulatory infertility	30 (100)
Normal FSH levels	30 (100)
Oligo/amenorrhea ^a	30 (100)
Clinical hyperandrogenism ^a	26 (86.7)
Hirsutism ^b	26 (86.7)
Acne	9 (30)
Biochemical hyperandrogenism ^a	15 (50)
T > 2 nmol/liter	12 (40)
A > 15 nmol/liter	11 (36.7)
DHEA-S > 10 μmol/liter	12 (40)
LH/FSH ratio >2	27 (90)
Polycystic ovary at TV-USG	24 (80)

T, Testosterone; A, androstenedione; DHEA-S, dehydroepiandrosterone sulfate; TV-USG, transvaginal ultrasonography.

^a NIH PCOS criteria.

^b As evaluated by Ferriman-Gallwey score.

regular menstrual cycles. Their healthy state was determined by medical history, physical and pelvic examination, and complete blood chemistry. The normal menstrual cycle was diagnosed after a 3-month prestudy period. During this period, all healthy women recorded in a daily diary the characteristics of their menses. A normal menstrual cycle was defined as cyclic uterine bleedings with a duration of 4–5 d and a frequency of 26–32 d/month. The quantity of blood flow was defined as normal subjectively by each woman and objectively using a serum hemoglobin assay. At the entry, the normal ovulatory state was confirmed by transvaginal ultrasonography and plasma progesterone levels during the luteal phase of the cycle.

Exclusion criteria for all subjects included age less than 18 or more than 30 yr, pregnancy, hypothyroidism, hyperprolactinemia, Cushing's syndrome, nonclassical congenital adrenal hyperplasia, and current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic and antiobesity drugs, or other hormonal drugs. The presence of hyperprolactinemia was excluded with a single assay of plasma prolactin (PRL) levels (normal, <25 ng/ml) (28). In women with a serum PRL levels greater than 25 ng/ml, hyperprolactinemia was excluded considering the average value of serum PRL assayed at 0800 h for three times every 15 min. Nonclassical congenital adrenal hyperplasia was excluded with a single measure of serum 17-hydroxyprogesterone levels (normal, <6.0 nmol/liter) (29).

Women with clinical and/or biochemical hyperandrogenism alone were excluded from the control group. None of the patients was affected by any neoplastic or cardiovascular disorder, and none of the women (PCOS and controls) had hypertension or used any drug during the 3 months preceding the study. None of the women had a BMI less than 18 kg/m².

The study was performed according to the guidelines of the Helsinki Declaration on human experimentation and was approved by the local ethics committee of University Federico II of Naples. All patients gave their written informed consent before the study.

Study protocol

According to a previous study protocol (30) all patients and controls were submitted to a three-step study.

Clinical study. Height, weight, BMI, waist to hip ratio, and measurements of heart rate, systolic (SBP) and diastolic (DBP) blood pressure were evaluated by standard methods. BMI was measured as the ratio between the weight and the square of the height. A BMI between 25 and 30 kg/m² was considered an index of overweight whereas a BMI greater than 30 kg/m² was considered an index of obesity (31). The waist to hip ratio was measured as the ratio between the waist, considered to be the smallest circumference of torso between the 12th rib and the iliac crest, and the circumference of the hip, considered as the maximal extension of the buttocks. All measurements were performed when the patients were in a standing position with relaxed abdomen, arms at their sides,

and joined feet (32). Blood pressure was measured in the right arm, with the subjects in a relaxed sitting position. The average of six measurements (three taken by each of two examiners) with a mercury sphygmomanometer was used.

Biochemical study. Fasting glucose, triglycerides (TG), TC, low density lipoprotein cholesterol (LDL-C) and HDL-C levels were measured by standard procedures in the morning between 0800 and 0900 h after an overnight fast and resting in bed during early follicular phase (d 2–5) of the spontaneous or progesterone-induced withdrawal bleeding. Samples were performed 10 min after needle insertion in duplicate and immediately centrifuged, and the serum was stored at –80 C until analysis. The TC/HDL-C ratio was also calculated for each woman (33). Hypertriglyceridemia was diagnosed when triglycerides levels were greater than 250 mg/dl (34), whereas hypercholesterolemia was diagnosed when total cholesterol levels were greater than 240 mg/dl (35). Impaired glucose tolerance was diagnosed after an oral glucose tolerance test (75 g glucose diluted in 250 ml saline solution, measuring blood glucose every 30 min for 2 h). In line with World Health Organization criteria, diabetes mellitus was diagnosed when fasting blood glucose levels were greater than 126 mg/dl in two consecutive determinations or 200 mg/dl or more 2 h after oral glucose; reduced glucose tolerance was diagnosed when blood glucose levels were 126–200 mg/dl 2 h after oral glucose (36). Fasting and glucose load-stimulated insulin levels were measured in patients and controls to estimate the insulin sensitivity; the homeostasis model assessment (HOMA) index, which is considered an index of insulin resistance (37), was also calculated.

Echocardiographic study. M-Mode, two-dimensional, and pulsed Doppler echocardiography studies were performed by one operator (L.S.), who was blind with respect to the presence of metabolic abnormalities or arterial hypertension, using ultrasound systems (Apogee CX, Interspec, Inc., Ambler, PA) with a 3.5-MHz transducer during at least three consecutive cardiac cycles. All patients were studied in the left lateral position after a 10-min resting period according to the recommendations of the American Society of Echocardiography (38). The following measurements were recorded on M-mode tracing: interventricular septum and LV posterior wall thickness. The frequency-normalized mean velocity of circumferential fiber shortening end-diastolic and end-systolic volumes (EDV and ESV) and ejection fraction [EF = EDV – ESV/EDV (%)] were estimated according to the Quinones method (39). The LV ejection fraction (LVEF) is normal when it is above 50%. The LVM was calculated by Devereux's formula according to Penn's convention with the following regression-corrected cube formula: LVM = 1.04[(ISV + LVID + PWT)³ – (LVID)³] – 14 g. LVH was diagnosed when LVM values, corrected for body surface area [LVM index (LVMi)], were 135 g/m² or greater in males and 110 g/m² or greater in females (40). Doppler studies provided indexes of ventricular filling that were derived from the mitral flow velocities curves, *i.e.* maximal early diastolic flow velocity (E; centimeters per second), maximal late diastolic flow velocity (A; centimeters per second), and the ratio between E and A curves (E/A; normal, >1).

Assays

Plasma LH, FSH, PRL, estradiol, progesterone, testosterone, Δ⁴-androstenedione, and dehydroepiandrosterone sulfate were measured by specific RIA as previously described (41, 42). Serum 17-hydroxyprogesterone levels were determined by RIA (Diagnostic Systems Laboratories, Webster, TX) with a sensitivity of 0.01 ng/ml and intra- and interassay coefficients of variation of 8.9% and 9.0%, respectively. SHBG levels were measured using an immunoradiometric assay, as previously described (28, 43). In each woman the free androgen index (FAI) was calculated using the following formula: testosterone (nmol/liter)/SHBG × 100 (44).

Serum insulin was measured by a solid phase chemiluminescent enzyme immunoassay using commercially available kits (Immunolite, Diagnostic Products Corp., Los Angeles, CA). Blood glucose levels were determined by the glucose oxidase method. Serum TC, HDL-C, LDL-C, and TG levels were measured with an autoanalyzer (Monarch 1000, Instrumentation Laboratory, Milan, Italy) using commercially available kits (IL TEST, Instrumentation Laboratory) as previously reported (45, 46). Serum LDL-C was evaluated using Friedewald's formula: TC – HDL-C – 1/5 TG (47).

Statistical analysis

Statistical analysis was performed using the SPSS 11.5.2.1 package (SPSS, Inc., Chicago, IL). Data were expressed as the mean \pm sd. Stepwise multiple linear regression analysis was performed to evaluate the relative importance of LVMi, as a dependent variable, against predictor variables: age, BMI, HOMA, FAI, lipid profile, SBP, DBP, and number of cigarettes smoked daily. Differences in physical activity and smoking habitus (percentage of women smoking) were evaluated using Mann-Whitney U test and χ^2 test, respectively. The other comparisons between patients and controls were performed using a *t* test for unpaired data. Significance was set at 5%.

Results

Clinical study (Table 2)

As expected, PCOS patients had significantly ($P < 0.05$) higher LH, testosterone, Δ^4 -androstenedione, and SHBG levels than controls. DBP and mean blood pressure were also significantly ($P < 0.05$) higher in the patients than in the controls, whereas SBP and heart rate were similar in the two groups. The endocrine parameters were in line with the diagnosis of PCOS in the patients group. In particular, the FAI was significantly ($P < 0.05$) higher in patients than controls.

Biochemical study (Table 3)

PCOS patients had significantly ($P < 0.05$) higher fasting glucose and insulin levels, HOMA, TC, LDL-C, and TC/HDL-C ratio, whereas HDL-C levels were significantly ($P < 0.05$) lower than control values. TG levels were similar in

TABLE 2. Demographic and endocrine profile in 30 young patients with clinical, ultrasonographic, and endocrine diagnosis of PCOS and 30 age- and BMI-matched controls

	PCOS	Controls	<i>P</i> ^a
Age (yr)	24.3 \pm 5.6	24.8 \pm 4.2	0.70
BMI (kg/m ²)	28.7 \pm 6.7	27.3 \pm 5.0	0.36
WHR	0.94 \pm 0.23	0.87 \pm 0.06	0.11
Physical activity score ^b	2.1 \pm 0.4	2.0 \pm 0.3	0.27
Smoking habitus			
No. of smokers (%) ^c	10 (33.3)	8 (26.7)	0.57
No. of cigarettes daily	4.2 \pm 1.3	5.6 \pm 1.4	0.15
HR (beats/min)	78.3 \pm 5.9	76.2 \pm 4.4	0.12
SBP (mm Hg)	112 \pm 3.0	110 \pm 3.8	0.6
DBP (mm Hg)	72 \pm 8.1	67.0 \pm 6.0	0.005
DP (mm Hg)	40.1 \pm 10.2	44.7 \pm 10.8	0.26
MBP (mm Hg)	84.9 \pm 8.3	80.5 \pm 5.7	0.04
Serum hormone levels			
FSH (IU/liter)	7.8 \pm 4.5	9.1 \pm 0.6	0.15
LH (IU/liter)	23.5 \pm 4.5	9.1 \pm 1.5	<0.0001
PRL (μ g/liter)	14.0 \pm 9.2	12.3 \pm 1.1	0.24
E ₂ (pmol/liter)	55.8 \pm 24.3	52.2 \pm 2.2	0.32
17-OH-P (nmol/liter)	2.8 \pm 3.5	0.7 \pm 0.2	0.005
T (nmol/liter)	2.4 \pm 1.3	0.5 \pm 0.2	<0.0001
A4 (nmol/liter)	4.1 \pm 1.9	1.0 \pm 0.3	<0.0001
DHEA-S (μ mol/liter)	4.4 \pm 1.3	4.0 \pm 1.0	0.17
SHBG (nmol/liter)	28.6 \pm 5.7	50.4 \pm 3.5	<0.0001
FAI (%)	8.6 \pm 5.0	1.0 \pm 0.5	<0.0001

WHR, Waist/hip ratio; HR, heart rate; DP, differential pressure; MBP, mean blood pressure; E₂, estradiol; 17-OH-P, 17-hydroxyprogesterone; T, testosterone; A, androstenedione; DHEA-S, dehydroepiandrosterone sulfate.

^a By unpaired *t* test except when indicated.

^b By Mann-Whitney *U* test.

^c By χ^2 test.

TABLE 3. Metabolic profile and cardiovascular risk factors in women with and without PCOS

	PCOS	Controls	<i>P</i>
Fasting glucose (mmol/liter)	5.3 \pm 2.6	2.6 \pm 0.6	<0.0001
Fasting insulin (pmol/liter)	12.9 \pm 5.2	2.3 \pm 0.9	<0.0001
HOMA	3.2 \pm 2.0	0.3 \pm 0.1	<0.0001
TC (mmol/liter)	4.2 \pm 0.5	3.5 \pm 0.4	<0.0001
LDL-C (mmol/liter)	2.3 \pm 0.4	1.8 \pm 0.3	<0.0001
HDL-C (mmol/liter)	2.5 \pm 0.5	2.9 \pm 0.3	<0.0001
TC/HDL-C ratio	1.7 \pm 0.4	1.2 \pm 0.4	<0.0001
TG (mmol/liter)	1.5 \pm 0.2	1.4 \pm 0.2	0.06

TABLE 4. Echocardiographic findings in PCOS and controls

	PCOS	Controls	<i>P</i>
LV diastolic diameter (mm)	46.0 \pm 3.9	42.9 \pm 1.7	0.1
LV systolic diameter (mm)	26.6 \pm 4.3	23.0 \pm 1.8	0.001
IST (mm)	8.3 \pm 1.2	6.7 \pm 0.8	<0.0001
LV posterior wall thickness (mm)	8.1 \pm 1.5	6.6 \pm 0.8	<0.0001
LVMi (g/m ²)	80.5 \pm 14.8	56.1 \pm 5.4	<0.0001
Left atrium size (mm)	32.0 \pm 4.9	27.4 \pm 2.1	<0.0001
Aorta size (mm)	28.9 \pm 3.5	28.0 \pm 1.3	0.1
LVEF (%)	64.4 \pm 4.1	67.1 \pm 2.6	0.003
Early to late mitral flow velocity	1.6 \pm 0.4	2.1 \pm 0.2	<0.0001

IST, Interventricular septum thickness.

patients and controls. Neither the patients nor the controls had hypercholesterolemia or hypertriglyceridemia.

Echocardiography study (Table 4)

Young women with PCOS had a cardiac size significantly ($P < 0.05$) increased compared with controls. They had also interventricular septum, LV posterior wall thickness, ESV, and LVMi significantly ($P < 0.05$) higher than controls. Two of 30 (6.7%) had LVH (>110 g/m²). Additionally, PCOS patients had significantly ($P < 0.05$) lower LVEF and E/A than controls, although all patients had normal LVEF, and two patients had abnormal E/A (6.7%).

When patients and controls were grouped according to BMI into three groups, namely subjects of normal weight (BMI, $>18 < 25$ kg/m²), overweight (BMI, 25.1–30 kg/m²), and obese (BMI, >30 kg/m²), it was observed that the majority of the differences in the metabolic profile and cardiac findings persisted (Table 5). As expected, there was a progressive impairment of metabolic profile and echocardiographic pattern from patients with normal weight to those with obesity (Table 5). Interestingly, normal weight PCOS women had a significant ($P < 0.05$) increase in LVMi and a decrease in diastolic filling, but no difference in TC, LDL-C, HDL-C, TC/HDL-C ratio, or TG, compared with controls. The other two groups had the same pattern described in the series of patients as a whole.

The final model of stepwise multiple linear regression analysis in PCOS patients showed that LVMi is linearly related only to HOMA (coefficient = 6.764; $\beta = 0.874$; $P < 0.0001$; constant = 58.647).

Discussion

The results of this prospective controlled study in selected young women with PCOS showed a significant impairment

TABLE 5. Main cardiovascular risk factors and echocardiographic findings in patients and controls according to BMI

	BMI 18–25 kg/m ²			BMI 25.1–30 kg/m ²			BMI >30 kg/m ²		
	PCOS	Controls	<i>P</i>	PCOS	Controls	<i>P</i>	PCOS	Controls	<i>P</i>
No.	12	12		6	6		12	12	
FAI (%)	9.1 ± 6.2	1.0 ± 0.5	<0.0001	10.8 ± 2.5	0.8 ± 0.5	<0.0001	7.1 ± 5.0	1.1 ± 0.4	<0.0001
Fasting insulin (pmol/liter)	9.0 ± 4.3 ^a	2.2 ± 0.8	<0.0001	10.3 ± 3.0 ^a	2.7 ± 1.0	<0.0001	18 ± 7.3	2.3 ± 1.0	<0.0001
HOMA	1.8 ± 0.8 ^b	0.3 ± 0.1	<0.0001	2.5 ± 1.2 ^a	0.3 ± 0.1	0.001	4.9 ± 3.7	0.3 ± 0.1	<0.0001
TC (mmol/liter)	3.6 ± 0.4	3.4 ± 0.3	0.180	4.6 ± 0.6	3.5 ± 0.5	0.006	4.8 ± 0.5	3.7 ± 0.4	<0.0001
LDL-C (mmol/liter)	2.0 ± 0.4	1.7 ± 0.3	0.142	2.3 ± 0.3	1.8 ± 0.2	0.007	2.5 ± 0.5	1.9 ± 0.4	0.004
HDL-C (mmol/liter)	2.4 ± 0.6	2.7 ± 0.3	0.136	2.5 ± 0.3	2.9 ± 0.2	0.022	2.6 ± 0.3	3.0 ± 0.4	0.011
TC/HDL-C ratio	1.5 ± 0.4	1.2 ± 0.3	0.050	1.8 ± 0.5	1.2 ± 0.4	0.045	1.8 ± 0.3	1.2 ± 0.5	0.002
TG (mmol/liter)	1.3 ± 0.2	1.2 ± 0.3	0.347	1.5 ± 0.3	1.4 ± 0.2	0.512	1.6 ± 0.2	1.5 ± 0.2	0.234
LVMi (g/m ²)	70.2 ± 19.1 ^a	56.2 ± 4.3	0.021	77.7 ± 8.2	56.3 ± 8.7	0.001	92.2 ± 14	55.8 ± 4.9	<0.0001
LVEF (%)	65.9 ± 3.4	67.7 ± 3.0	0.183	65.5 ± 4.8	66.2 ± 2.6	0.760	62.2 ± 3.7	66.7 ± 1.9	0.001
Early to late mitral flow velocity	1.7 ± 0.3	2.0 ± 0.1	0.003	1.4 ± 0.3	1.9 ± 0.1	0.003	1.5 ± 0.4	2.1 ± 0.1	<0.0001

^a *P* < 0.05 vs. PCOS patients with BMI greater than 30 kg/m².

^b *P* < 0.05 vs. PCOS patients with BMI of 25.1–30 and greater than 30 kg/m².

of glucose and lipid profile associated with an increased LVM and decreased LV performance and diastolic filling. Most of these abnormalities persisted even in young patients with normal weight, suggesting that the pathogenesis of cardiac abnormalities in PCOS is not only dependent on BMI. In fact, only in the patients was LVMi significantly correlated with both BMI and HOMA index.

PCOS women represent an intriguing biological model illustrating hormonal effects on cardiovascular risk. In fact, several findings indicate a relationship between heart disease and PCOS, *i.e.* dyslipidemia (9), insulin resistance (3, 7), increased LVM, and diastolic dysfunction (48, 49). PCOS as a putative cause of CVD is, however, still questioned, because definitive data to demonstrate a direct influence of PCOS on heart disease are still lacking (50–52). On the basis of the multiple findings linking CVD with PCOS, we designed this prospective controlled study to investigate different variables affecting heart structure and function. We selected a group of young patients to exclude any role of long-standing undiagnosed PCOS and investigated the early phases of the disease. To better understand the role of increased BMI frequent in PCOS, we included a group of lean patients and controls. This would allow us to detect cardiac abnormalities not related to overweight and obesity.

PCOS women were reported to have higher TG levels and lower HDL-C values (53). Because insulin is a major positive regulator of lipoprotein lipase that is involved in the pathway of HDL-C production, dyslipidemia is probably secondary to insulin resistance, although hyperandrogenism may affect lipoproteins and lipids independently of insulin levels and body weight (9). In our series we confirmed an unfavorable lipid profile; however, we did not find any increase in TG levels. Our young patients with PCOS had an increase in TC and a decrease in HDL-C levels as major findings associated with increased glucose and insulin levels and HOMA index. We also confirmed increased LVM and diastolic dysfunction in young PCOS women. Interestingly, these abnormal echocardiographic aspects were present even in the 12 normal weight women who did not show alterations in lipid profile. Furthermore, these young PCOS women showed greater LVMi than their age- and BMI-matched controls. Although it is well known that ventricular mass indexed for height is significantly higher in overweight than in

normal weight subjects (54), our PCOS women showed an increased LVMi that was not weight dependent. Therefore, PCOS could be considered an aggravating factor causing LVH and could play a role in the early cardiovascular disease in PCOS. Among the various echocardiographic parameters that were different between PCOS and controls, the increased LVMi in young PCOS patients has clinical importance, because it represents the main cause of both LVH and diastolic dysfunction in PCOS women, worsening from early to elderly age.

LVH is one of the several metabolic and cardiovascular risk factors associated with insulin resistance (55) and/or visceral obesity (56). In our series, there was a linear relation between LVMi and HOMA. Hyperinsulinemia is a predictor of coronary artery disease (57–60), and insulin resistance has been proposed as the key factor linking hypertension, glucose intolerance, obesity, lipid abnormalities, and coronary heart disease in an association called metabolic syndrome X (61). In fact, the increased LVM in PCOS women could be caused by an increase in blood pressure, even in the absence of hypertension (62). Indeed, in our series we found slightly increased mean blood pressure and DBP in PCOS women compared with controls.

In accord with previous studies (48, 49), we also report diastolic dysfunction in PCOS. Specifically, Tiras *et al.* (49) suggested that patients with PCOS have diastolic dysfunction; furthermore, no difference in E/A was observed between PCOS and control women. On the contrary, we showed both reduced ejection fraction of LV and E/A, suggesting impaired LV diastolic filling. However, whether the E/A ratio is an early predictor of diastolic dysfunction in PCOS remains to be determined. In addition, Prelevic *et al.* (63) reported that systolic flow velocity is lower in PCOS than in age-matched control women, and there is an inverse relationship between serum fasting insulin and LV systolic outflow parameters; furthermore, increased insulin levels in PCOS are associated with decreased cardiac flow (63).

Although we did not find any association between LVM or diastolic dysfunction and hyperandrogenism, cross-sectional data consistently showed a strong obesity-independent association of androgen excess in women with a cluster of CVD risk factors, including insulin resistance, dyslipidemia, and impaired fibrinolysis. It was therefore sug-

gested that the chronically abnormal hormonal and metabolic milieu found in women with PCOS, starting from adolescence, may predispose these women to premature atherosclerosis. Furthermore, based on calculated risk profiles, PCOS women were predicted to have a 7-fold increased relative risk for myocardial infarction; in fact, Birdsall *et al.* (11) showed significant associations between the presence of polycystic ovaries and the presence and severity of cardiovascular artery disease and a family history of myocardial infarction as well as with elevated levels of insulin and TG and lower levels of HDL-C (11).

Some findings of clinical studies showed that women with CVD were affected more frequently than controls by clinical symptoms of androgen excess, such as hirsutism and polycystic ovaries (3, 4, 50, 64). Because many women with PCOS are overweight, and most, if not all, are insulin resistant, it is a matter of debate whether these symptoms are secondary to obesity and insulin resistance or whether hyperandrogenism itself contributes to obesity, insulin resistance, and hyperinsulinemia.

Our findings suggest that young PCOS women have increased LVM and diastolic dysfunction, neither of which is weight dependent, demonstrating that PCOS women are candidates for early CVD. Additional studies are needed to better clarify the exact role of insulin resistance and/or hyperandrogenism in the CVD, particularly in the complex etiopathogenetic scenario of the increased LVM in young PCOS patients.

Acknowledgments

We are grateful to Dr. Francesco Manguso (Department of Clinical and Experimental Medicine, Gastroenterology Unit, "Federico II" University, Naples, Italy) for his invaluable assistance in statistical analysis. Received November 26, 2003. Accepted April 26, 2004.

Address all correspondence and requests for reprints to: Dr. Francesco Orio, Department of Molecular and Clinical Endocrinology and Oncology, University Federico II, Via S. Pansini 5, 80131 Naples, Italy. E-mail: francescoorio@virgilio.it.

References

1. Franks S 1995 Polycystic ovary syndrome. *N Engl J Med* 333:853–861
2. Scarpitta AM, Sinagra D 2000 Polycystic ovary syndrome: an endocrine and metabolic disease. *Gynecol Endocrinol* 14:392–395
3. Dunaif A 1997 Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 18:774–800
4. Lobo RA, Carmina E 2000 The importance of diagnosing the polycystic ovary syndrome. *Ann Intern Med* 132:989–993
5. Chang RJ, Nakamura RM, Judd HL, Kaplan SA 1983 Insulin resistance in nonobese patients with polycystic ovarian disease. *J Clin Endocrinol Metab* 57:356–359
6. Franks S 2001 Are women with polycystic ovary syndrome at increased risk of cardiovascular disease? Too early to be sure, but not too early to act! *Am J Med* 111:665–666
7. Ovalle F, Azziz R 2002 Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. *Fertil Steril* 77:1095–1105
8. Holte J, Gennarelli G, Berne C, Bergh T, Lithell H 1996 Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? *Hum Reprod* 11:23–28
9. Wild RA, Painter PC, Coulson PB, Carruth KB, Ranney GB 1985 Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 61:946–951
10. Cibula D, Cifkova R, Fanta M, Poledne R, Zivny J, Skibova J 2000 Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension, and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. *Hum Reprod* 15:785–789
11. Birdsall MA, Farquhar CM, White HD 1997 Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. *Ann Intern Med* 126:32–35
12. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy II PF, Fitzpatrick LA 2003 Prevalence and predictors of coronary artery disease calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:2562–2568
13. Dahlgren E, Janson PO, Johansson S, Lapidus L, Oden A 1992 Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet Gynecol Scand* 71:599–604
14. Talbott E, Guzik D, Clerici A, Berga S, Detre K, Weimer K, Kuller L 1995 Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler Thromb Vasc Biol* 15:821–826
15. Conway GS, Agrawal R, Betteridge DJ, Jacobs HS 1992 Risk factors for coronary heart disease in lean and obese women with the polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 37:119–125
16. Talbott E, Guzik DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH 2000 Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 20:2414–2421
17. Paradisi G, Steinberg HO, Hemphill A, Cronin J, Hook G, Shepard MK, Baron AD 2001 Polycystic ovary syndrome is associated with endothelial dysfunction. *Circulation* 103:1410–1415
18. Kelly CJG, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JMC 2002 Altered vascular function in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 87:742–746
19. Harjai KJ 1999 Potential new cardiovascular risk factors: left ventricular hypertrophy, homocysteine, lipoprotein(a), triglycerides, oxidative stress, and fibrinogen. *Ann Intern Med* 131:376–386
20. Levy D, Garrison RH, Savage DD, Kannel WB, Castelli WP 1991 Prognostic implication of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 322:1561–1566
21. Koren MJ, Devereux RB, Casale PN, Savane DD, Laragh JH 1991 Relation of the left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 114:345–352
22. Vaccaro O, Cardoni O, Cuomo V, Panarelli W, Laurenzi M, Mancini M, Riccardi G, Zanchetti A 2003 Relationship between plasma insulin and left ventricular mass in normotensive participants of the Gubbio study. *Clin Endocrinol (Oxf)* 58:316–322
23. de Simone G, Pisanis F, Contaldo F 2001 Link of nonhemodynamic factors to hemodynamic determinants of left ventricular hypertrophy. *Hypertension* 38:13–18
24. de Simone G, Devereux RB, Roman MJ, Halderman MH, Laragh JH 1994 Relation of obesity and gender to left ventricular hypertrophy in normotensive adults. *Hypertension* 23:600–606
25. Ferriman D, Gallwey JD 1961 Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 21:1440–1447
26. Fulghesu AM, Ciampelli M, Belosi C, Apa R, Pavone V, Lanzone A 2001 A new ultrasound criterion for the diagnosis of polycystic ovary syndrome: the ovarian stroma/total area ratio. *Fertil Steril* 76:326–331
27. Balen AH, Laven JSE, Tan S-L, Dewailly D 2003 Ultrasound assessment of the polycystic ovary: international consensus definitions. *Hum Reprod Update* 9:505–514
28. Orio Jr F, Palomba S, Colao A, Tenuta M, Dentico C, Peretta M, Lombardi G, Nappi C, Orio F 2001 Growth hormone secretion after baclofen administration in different phases of the menstrual cycle in healthy women. *Horm Res* 55:131–136
29. Azziz R, Zaccur HA 1989 21-Hydroxylase deficiency in female hyperandrogenism: screening and diagnosis. *J Clin Endocrinol Metab* 69:577–584
30. Colao A, Pivonello P, Spiezia S, Faggiano A, Ferone D, Filippella, Marzullo P, Cerbone G, Siciliani M, Lombardi G 1999 Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. *J Clin Endocrinol Metab* 84:2664–2672
31. 1983 Obesity. A report of the Royal College of Physicians. *J R Coll Physicians Lond* 17:5–65
32. Yanovski SZ 1993 A practical approach to treatment of the obese patient. *Arch Fam Med* 2:309–316
33. Castelli WP 1996 Lipid, risk factors and ischaemic heart disease. *Atherosclerosis* 124(Suppl):S1–S9
34. Consensus Conference 1984 Treatment of hypertriglyceridemia. *JAMA* 251:1196–1200
35. Expert Panel: Report of the National Cholesterol Education 1988 Program expert panel on detection, evaluation and treatment of high blood cholesterol in adults. *Arch Intern Med* 148:36–39
36. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197
37. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC 1985 Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419
38. Feigenbaum H 1979 Echocardiography, 2nd ed. Philadelphia: Lea and Febiger

39. Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters Jr WL, Ribeiro LG, Miller RR 1981 A new simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 64:744–753
40. Devereux RB, Lutas EM, Casale PN, Kligfield P, Eisenberg RR, Hammond IW, Miller DH, Reis G, Alderman MH, Laragh JH 1984 Standardization of M-mode echocardiographic left ventricular anatomic measurements. *J Am Coll Cardiol* 4:1222–1230
41. Orio Jr F, Palomba S, Colao A, Russo T, Dentico C, Tauchmanová L, Savastano S, Nappi C, Sultan C, Zullo F, Lombardi G 2003 GH release after GHRH plus arginine administration in obese and overweight women with polycystic ovary syndrome. *J Endocrinol Invest* 26:117–122
42. Orio Jr F, Lucidi P, Palomba S, Tauchmanová L, Cascella T, Russo T, Zullo F, Colao A, Lombardi G, De Feo P 2003 Circulating ghrelin concentrations in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:942–945
43. Orio Jr F, Palomba S, Di Biase S, Colao A, Tauchmanová L, Savastano S, Labella D, Russo T, Zullo F, Lombardi G 2003 Homocysteine levels and C677T polymorphism of methylenetetrahydrofolate reductase in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:673–679
44. Morley JE, Patrick P, Perry III HM 2002 Evaluation of assays available to measure free testosterone. *Metabolism* 5:554–559
45. Palomba S, Affinito P, Tommaselli GA, Nappi C 1998 A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. *Fertil Steril* 70:111–118
46. Palomba S, Affinito P, Di Carlo C, Bifulco G, Nappi C 1999 Long-term administration of tibolone plus gonadotropin-releasing hormone agonist for the treatment of uterine leiomyomas: effectiveness and effects on vasomotor symptoms, bone mass, and lipid profiles. *Fertil Steril* 72:889–895
47. Friedewald WT, Levy RI, Fredrickson DS 1972 Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502
48. Yarali H, Yildirim A, Aybar F, Kabakci G, Bukulmez O, Akgul E, Oto A 2001 Diastolic dysfunction and increased serum homocysteine concentrations may contribute to increased cardiovascular risk in patients with polycystic ovary syndrome. *Fertil Steril* 76:511–516
49. Tiras MB, Yalcin R, Noyan V, Maral I, Yildirim M, Dortlemmez O, Daya S 1999 Alterations in cardiac flow parameters in patients with polycystic ovarian syndrome. *Hum Reprod* 14:1949–1952
50. Amowitz LL, Sobel BE 1999 Cardiovascular consequences of polycystic ovary syndrome. *Endocrinol Metab Clin North Am* 28:439–458
51. Arslanian SA, Lewy VD, Danadian K 2001 Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and β -cell dysfunction and risk of cardiovascular disease. *J Clin Endocrinol Metab* 86:66–71
52. Legro RS 2003 Polycystic ovary syndrome and cardiovascular disease: a premature association? *Endocr Rev* 24:302–312
53. Wild RA 1995 Obesity, lipids, cardiovascular risk and androgen excess. *Am J Med* 98:27S–32S
54. De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH 1992 Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 20:1251–1260
55. McFarlane SI, Banerji M, Sowers JR 2001 Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metab* 86:713–718
56. Vetta F, Cicconetti P, Ronzoni S, Rizzo V, Palleschi L, Canarile G, Lupattelli MR, Migliori M, Morelli S, Marigliano V 1998 Hyperinsulinaemia, regional adipose tissue distribution and left ventricular mass in normotensive, elderly, obese subjects. *Eur Heart J* 19:326–331
57. Pyorala K 1979 Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care* 2:131–141
58. Welborn TA, Wearne K 1979 Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. *Diabetes Care* 2:154–160
59. Ducimentiere P, Eschwege E, Papoz L, Richard JL, Claude JR, Rosselin G 1980 Relationship of plasma insulin level to the incidence of myocardial infarction and coronary heart disease. *Diabetologia* 19:205–210
60. Fontbonne A, Charles MA, Thibault N, Richard JL, Claude JR, Warnet JM, Rosselin GE, Eschwège E 1991 Hyperinsulinemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15 year follow-up. *Diabetologia* 34:356–361
61. Reaven GM 1988 Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37:1595–1607
62. Zimmermann S, Phillips RA, Dunaif A, Finegood DT, Wilkenfeld C, Ardeljan M, Gorlin R, Krakoff LR 1992 Polycystic ovary syndrome: lack of hypertension despite profound insulin resistance. *J Clin Endocrinol Metab* 75:508–513
63. Prelevic GM, Beljic T, Balint-Peric L, Ginsburg J 1995 Cardiac flow velocity in women with the polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 43:677–681
64. Rajkhowa M, Glass MR, Rutherford AJ, Michelmores K, Balen AH 2000 Polycystic ovary syndrome: a risk factor for cardiovascular disease? *Br J Obstet Gynaecol* 107:11–18

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.