Cardiovascular disease risk in first-degree relatives of women with polycystic ovary syndrome

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Objective: To assess the risk of cardiovascular disease (CVD) in the parents of polycystic ovary syndrome (PCOS) patients using carotid intima medial thickness (CIMT) and brachial artery flow-mediated dilatation (FMD).
Design: Hospital-based case-control study.
Setting: Endocrine clinic of a medical institute in India.
Patient(s): Case group of 41 fathers and 45 mothers of PCOS patients (confirmed by Rotterdam's criteria) compared with 42 men and 44 women matched by age, sex and body mass index (BMI) as controls.
Intervention(s): CVD risk in parents of PCOS patients assessed via CIMT and FMD then correlated with various clinical and metabolic parameters.
Main Outcome Measure(s): Differences in CIMT and FMD between parents and controls.
Result(s): The CIMT was higher [0.6 (0.54–0.8) vs. 0.5 (0.45–0.55) mm] and brachial artery FMD was lower [11.9% (6.9%–16.2%) vs. 16.7% (13.5%–22.6%)] in the parents of PCOS patients as compared with the controls. Systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, and fasting and 2-hour plasma glucose were higher in the parents of the PCOS patients. The prevalence of CVD risk factors such as systemic hypertension, diabetes mellitus, abdominal obesity, the metabolic syndrome, and a family history of coronary artery disease in first-degree relatives was also higher in the parents of PCOS patients. The prevalence of diabetes was higher in the fathers of PCOS women, but other cardiovascular disease risk factors, CIMT, and FMD were comparable among the mothers.
Conclusion(s): The parents of PCOS patients have an increased CVD risk as evidenced by increased CIMT and low FMD. (Fertil Steril® 2016;105:1338–44. ©2016 by American Society for Reproductive Medicine.)
Key Words: Cardiovascular disease risk, carotid intima media thickness, flow-mediated dilatation, PCOS

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Cardiovascular disease (CVD) is the largest cause of mortality in India, accounting for one-fourth of all deaths in 2008 (1). The global burden of ischemic heart disease has also increased by 29% between 1990 and 2010 (2). Cardiovascular disease is expected to be the fastest growing chronic illness, at a rate of 9.2% annually, especially in the age group of 25 to 69 year olds (1). Every effort should be made to identify populations that are at risk of CVD in whom preventive measures can be implemented early, which would reduce the health and economic burden on the family and on society at large.

Women with PCOS have an increased prevalence of insulin resistance with hyperinsulinism, glucose intolerance, hypertension, dyslipidemia, and obesity (3). All these metabolic abnormalities confer an increased risk of CVD in patients with PCOS. In our previous study we showed that young women (18 to 35 years of age) with PCOS have evidence of early atherosclerosis, with a higher carotid intima media thickness (CIMT) (0.55 ± 0.09 mm vs. 0.40 ± 0.09 mm;

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$P=.0001$) and endothelial dysfunction with lower brachial flow-mediated dilatation (FMD) (9.39% ± 4.3% versus 13.8% ± 4.7%; $P=.0001$) as compared with controls matched by age and body mass index (BMI) (4).

There is familial clustering of PCOS phenotype and its associated metabolic abnormalities (5). First-degree relatives of PCOS patients have hyperinsulinemia and insulin resistance as evidenced by significantly higher fasting serum insulin and homeostasis model assessment for insulin resistance (HOMA-IR) (6). Mothers and fathers of PCOS patients have increased prevalence of glucose intolerance and type-2 diabetes compared with age- and BMI-matched healthy controls (7). First-degree relatives of PCOS patients also have a higher prevalence of systemic hypertension, obesity, and dyslipidemia as compared with the control group (8). A previous study has shown that fathers of women with PCOS have an elevated 10-year risk for CVD and a higher prevalence of heart attacks and strokes compared with the reference U.S. National Health and Nutrition Examination Survey (NHANES) population (9). Cardiovascular events occurred at an early age in the mothers of PCOS women, particularly in mothers who themselves had PCOS (10).

We hypothesized that with the added history of PCOS in the offspring, the parents of women with PCOS are likely to have a higher risk of CVD as well. We assessed the risk of CVD in the parents of women with PCOS via measurements of CIMT and brachial artery FMD, which are surrogate markers of early atherosclerosis and CVD. We correlated CIMT and FMD with various clinical and metabolic parameters.

MATERIALS AND METHODS

Study Design

This was a hospital-based case control study conducted in the endocrinology clinic of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, between November 2012 and November 2014. The fathers and mothers of all women with PCOS attending the endocrine clinic were given information regarding the study, and first 50 families who agreed to participate were recruited. Parents of 47 PCOS patients agreed to participate in the study.

The diagnosis of PCOS in the probands was made using the Rotterdam criteria (11). The prevalence of different phenotypes of PCOS according to the Rotterdam criteria in the probands (n = 47) were phenotype A 12 (25.5%), phenotype B 16 (34%), phenotype C 16 (34%), and phenotype D 3 (6.4%). Twenty-eight of the 47 PCOS patients satisfied the U.S. National Institutes of Health criteria of diagnosis. Forty-four of the 47 patients had hyperandrogenism. None of the patients with PCOS were consulting for metabolic health.

Parents who were >70 years old, had liver or renal failure, malignancy, or any acute medical illness in recent past (within 3 months) were excluded from the study. None of the parents of PCOS patients were being treated in the endocrine clinic for metabolic health. Controls matched for age, gender, and BMI (n = 86) were selected from hospital staff (22 of 86) and relatives of other clinic patients (64 of 86). The study was approved by the institutional ethics committee (ref. no. 2013-41-EMP-69), and written informed consent was obtained from all participants.

History and Anthropometric Evaluation

On the day of study, participant histories were recorded based on a predesigned form. The history included menstrual history, history of infertility, hypertension, diabetes mellitus, dyslipidemia, smoking, exercise, and family history of CVD (age of onset <55 years for men and <65 years for women). All participants underwent a detailed clinical examination, including clinical signs of hyperandrogenism noted in female relatives. Body weight (kg) was measured without footwear in light clothing, and height (cm) was measured without footwear or hats. The BMI was calculated and expressed as kg/m^2. The waist circumference (WC) was measured at the midpoint between the iliac crest and lower rib margin at the end of normal expiration, and the hip circumference was measured at the widest level of the greater trochanters. Blood pressure (BP) was recorded three times in a sitting position.

Biochemical Analysis

After an overnight fast of 8 to 10 hours, participants provided 10 mL of blood for glucose, lipid profile, high-sensitivity C-reactive protein (hsCRP), and hormone measurements followed by an oral glucose tolerance test with 75-g anhydrous glucose. A blood sample was drawn at the end of 2 hours for glucose and insulin. Sera were stored at −70°C until analysis. Serum total cholesterol (TC), high-density lipoprotein (HDL), and triglyceride (TG) concentrations were measured on the same day with an auto analyser (RX Imola; Randox Laboratories) using kits by the same company. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Blood glucose was determined using glucose oxidase method (Merckotest; Merck). Testosterone, sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin (PRL), 17-hydroxy progesterone (17-OHP), and dehydroepiandrosterone sulfate (DHEAS) were measured only in the women. The levels of FSH, LH, TSH, PRL, and SHBG were measured with an automated chemiluminescent immunoassay (Immulite 1000; Siemens Healthcare Diagnostics). Serum testosterone was measured by commercial radioimmunoassay kits (Immunotech; Beckman Coulter) with an analytic sensitivity 0.069 nmol/L, and intra-assay and interassay coefficient of variation of 5.6% and 15% respectively. DHEAS was measured by a commercial radioimmunoassay kit (Immunotech; Beckman Coulter) with an intra-assay and interassay coefficient of variation of 4.93% and 9.32%, respectively, and analytic sensitivity of 0.07 μmol/L. Insulin was measured by a commercial enzyme-linked immunosorbent assay kit (DRG Diagnostics GmbH) with a sensitivity of 1.76 μIU/mL and an intra-assay and interassay coefficient of variation of 1.8% and 6%, respectively. High-sensitivity CRP (hsCRP) was quantified by chemiluminescent immunoassay (Immulite 1000; Siemens Healthcare Diagnostics) with a sensitivity of 0.1 mg/L and an intra-assay and interassay coefficient of variation of 5% and 6.4%, respectively.

HOMA-IR was calculated by the formula: Fasting serum insulin (μIU/mL) × Fasting serum glucose (mmol/L)/ 22.5 and the metabolic syndrome was diagnosed using the International Diabetes Federation criteria (12). Systemic hypertension, impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus were defined by standard criteria (13, 14). Abdominal obesity was defined as waist circumference ≥90 cm for men and ≥80 cm for women (12).

CIMT and Brachial Artery FMD by Echo Doppler Examination

The protocols for measurement of CIMT and brachial FMD have been published previously elsewhere (4). The tests were performed after an overnight fast of 8 to 10 hours, and the participants were be asked to refrain from physical activity for 4 to 6 hours before the examination. For CIMT, longitudinal ultrasonographic scans of right and left carotid artery were obtained by echo color Doppler (General Electric) with a high resolution 10 MHz linear probe by a single operator (blinded to subject details). The intima media thickness of the posterior (far) wall of both common carotid arteries 1 cm proximal to the origin of the bulb were measured at the end of the diastole from the B-mode scan as the distance between the junction of the lumen and intima and that of the media and the adventitia (15). The mean CIMT for each side was calculated as the average of three measurements made in the right and left carotid arteries using electronic callipers. Measures from each side were averaged to produce an overall measure of CIMT.

Vascular reactivity or brachial FMD was studied in the dominant brachial artery with the use of a 10-MHz linear phased array ultrasound transducer by a single operator blinded to the participant's details. Blood pressure and electrocardiogram readings were monitored during the test. After obtaining baseline images of the brachial artery, a standard sphygmomanometer cuff was tied on upper arm and inflated to 40 mm Hg above systolic BP for 4.5 minutes to induce ischemia. The longitudinal scan was obtained from 30 seconds before to 2 minutes after cuff release. Measurement of the maximum diameter was taken 60 to 90 seconds after cuff release. Brachial FMD was expressed as the percentage change in the arterial diameter from baseline to maximum diameter after cuff deflation. All measurements were taken at end diastole coinciding with the R wave on electrocardiograph monitor (16).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range, whichever was appropriate. Frequencies and percentages were used for categorical data. Distribution of variables was checked for normality with Shapiro Wilk test. The clinical and biochemical variables were compared between parents of women with PCOS and the controls using an unpaired Student's *t*-test for normally distributed continuous data and the Mann-Whitney *U* test for non-normally distributed data. Pearson's chi-square test was used to assess the differences in the groups for categorical data. A Pearson correlation was performed to assess the relationship between CIMT and brachial FMD with clinical, metabolic, and hormone parameters. Variables showing a statistically significant correlation were entered into stepwise linear regression to assess the magnitude of their individual effect on CIMT and brachial FMD. Data were analyzed in the Statistical Package for the Social Sciences software (version 19.0, IBM SPSS Statistics). $P<.05$ was considered statistically significant.

RESULTS

Eighty-six first-degree relatives of PCOS patients (41 fathers and 45 mothers) were compared with 86 controls (42 men and 44 women) matched by age (50.4 ± 5.6 vs. 50.3 ± 5.7 years; $P=.850$) and BMI [25.9 (24.2–28.7) kg/m^2 vs. 25.7 (24.1–28.7) kg/m^2; $P=.861$]. Clinical and anthropometric data are shown in Table 1.

The parents of the PCOS patients had a higher systolic BP, diastolic BP, and higher waist–hip ratio (WHR) as compared with the controls. The fasting plasma glucose (FPG), 2-hour plasma glucose, LDL cholesterol, and postglucose insulin were also higher in the parents of PCOS patients (Table 2). Insulin resistance was higher in the parents as evidenced by a higher HOMA-IR value.

Among the cardiovascular risk parameters, the prevalence of systemic hypertension (26% vs. 12%; $P=.019$), diabetes mellitus (22% vs. 4.6%; $P=.001$), abdominal obesity (80% vs. 55%; $P=.000$), family history of coronary artery disease in first-degree relatives (21% vs. 9.%; $P=.033$) (see Table 1) and metabolic syndrome (64% vs. 30%; $P=.000$) were higher in parents of PCOS patients. Other risk parameters, including impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) [34 of 86 (39.5%) vs. 24 of 86 (27.9%); $P=.107$], LDL >130 mg/dL [25 of 86 (29.1%) vs. 21 of 86 (24.4%); $P=.49$], HDL <40/<50 mg/dL (men/women) [48 of 86 (53.9%) vs. 47 of 86 (54.65%); $P=.878$], triglycerides >150 mg/dL [27 of 86 (31.4%) vs. 25 of 86 (29%); $P=.740$], total cholesterol >200 mg/dL [26 of 86 (30.2%) vs. 24 of 86 (27.9%); $P=.737$], and hsCRP ($P=.954$), were comparable in parents and controls.

The CIMT was higher in the parents of women with PCOS [0.6 mm (0.54–0.8 mm) vs. 0.5 mm (0.45–0.55 mm); $P=.000$] and brachial artery brachial FMD was lower in parents [11.9 (6.9–16.2) vs. 16.7 (13.5–22.6); $P=.000$] as compared with controls (see Table 3).

Subgroup Analysis

Forty-one fathers were compared with 42 control men matched for age and BMI. Fathers of PCOS patients had a higher systolic BP, diastolic BP, and WHR compared with the controls (see Table 1). Fasting and 2-hour plasma glucose and insulin, any form of abnormality in glucose tolerance (27 of 41 vs. 9 of 42; $P=.000$), and HOMA-IR were also higher in the fathers (see Table 2). However, the lipid profile and hsCRP were comparable in both the groups. Among the cardiovascular risk factors, prevalence of systemic hypertension (24% vs. 7%, $P=.031$), diabetes mellitus (34% vs. 0%,

TABLE 1

Clinical parameters in parents of polycystic ovary syndrome patients and controls and in subgroups (fathers versus controls and mothers versus controls).

Parameter	Parents of PCOS (n = 86)	Controls (n = 86)	*P* value	Fathers of PCOS (n = 41)	Controls (n = 42)	*P* value	Mothers of PCOS (n = 45)	Controls (n = 44)	*P* value
Age (y)	50.4 ± 5.6	50.3 ± 5.7	.850	53.1 ± 5.1	52.9 ± 5.1	.898	47.9 ± 4.9	47.7 ± 5	.782
BMI (kg/m^2)	25.9 (24.2–28.7)	25.7 (24.1–28.7)	.861	25.6 ± 2.9	25.4 ± 2.9	.754	27.4 ± 4.4	27.4 ± 4.1	.992
Systemic hypertension	22/86 (26%)	10/86 (11.6%)	.019[a]	10/41 (24%)	3/42 (7%)	.031[a]	12/45 (27%)	7/44 (16%)	.216
Diabetes mellitus	19/86 (22%)	4/86 (4.6%)	.001[b]	14/41 (34%)	0/42 (0)	.00[b]	5/45 (11%)	4/44 (9%)	.227
Family history of CAD[c]	18/86 (21%)	8/86 (9%)	.033[a]	8/41 (19.5%)	4/42 (9.5%)	.196	10/45 (22%)	4/44 (9%)	.089
BP (mm Hg)									
Systolic	130 (120–136)	121 (110–128)	.000[b]	130 (122–136)	120 (110–130)	.001[b]	128 ± 14	121 ± 10	.013[a]
Diastolic	82 (80–88)	80 (78–82)	.000[b]	84 (80–88)	80 (70–82)	.000[b]	82 (80–86)	80 (78–82)	.002[b]
Waist–hip ratio	0.98 (0.91–1.01)	0.92 (0.89–0.97)	.000[b]	1 (0.96–1.03)	0.92 (0.88–0.97)	.000[b]	0.95 ± 0.06	0.93 ± 0.48	.05
Abdominal obesity (waist circumference)[d]	69/86 (80%)	47/86 (55%)	.000[b]	27/41 (66%)	8/42 (19%)	.00[b]	42/45 (93%)	39/44 (89%)	.439

Note: BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; PCOS = polycystic ovary syndrome.
[a] $P<.05$ for comparison between groups.
[b] $P<.01$ for comparison between groups.
[c] Age of onset <55 years for men and <65 years for women.
[d] Defined as waist circumference ≥90 cm for men and ≥80 cm for women.

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TABLE 2

Biochemical parameters in parents of polycystic ovary syndrome patients and controls, and in subgroups (fathers versus controls and mothers versus controls).

Parameter	Parents of PCOS (n = 86)	Controls (n = 86)	*P* value	Fathers of PCOS (n = 41)	Controls (n = 42)	*P* value	Mothers of PCOS (n = 45)	Controls (n = 44)	*P* value
FPG (mg/dL)	99 (83–112)	92 (78–103)	.031[a]	101 (82–121)	83 (72–95)	.003[a]	98 (83–109)	98 (84–111)	.857
2-h PG (mg/dL)	130 (107–176)	110 (91–136)	.001[b]	132 (102–222)	98 (86–110)	.000[b]	128 (113–153)	132 (109–145)	.837
Total cholesterol (mg/dL)	184 ± 36	175 ± 41	.103	173 ± 32	172 ± 45	.862	193 ± 37	177 ± 37	.039[a]
Triglycerides (mg/dL)	126 (93–161)	120 (80–154)	.228	123 (88–161)	116 (85–157)	.355	132 (95–157)	127 (75–153)	.470
LDL (mg/dL)	115 (86–136)	96 (76–127)	.016[a]	111 (85–127)	92 (69–133)	.263	118 ± 35	103 ± 29	.032[a]
HDL (mg/dL)	42 (36–51)	41 (33–51)	.542	40 (34–48)	41 (32–50)	.719	46 (37–53)	43 (33–54)	.349
Fasting insulin (μIU/mL)	12.7 (9.5–19.3)	11.5 (8.6–15.4)	.134	14.7 ± 6.9	10.3 ± 4.8	.001[a]	12.5 (9–19.7)	13.6 (10.2–18.6)	.556
Fasting C peptide (ng/mL)	5 (3.9–7.6)	4.7 (3.8–6.4)	.196	4.8 (4.2–7.1)	4.7 (3.8–6.3)	.373	5.2 (3.8–8)	4.7 (3.7–6.7)	.385
Postglucose insulin (μIU/mL)	43.6 (22.6–82.1)	18.2 (11.1–26.7)	.000[b]	37.6 (18.9–64)	14.1 (10.2–24.8)	.000[b]	59.8 ± 38.4	32.6 ± 25.7	.004[a]
HOMA IR	3.2 (2.1–5)	2.4 (1.7–3.9)	.019[a]	3.65 (2.2–5)	2.1 (1.3–2.6)	.000[a]	2.9 (1.7–5.1)	3.2 (2.3–5.1)	.361

Note: FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; HOMA IR = homeostasis model assessment for insulin resistance; 2-h PG = 2-hour post-OGTT plasma glucose; LDL = low-density lipoprotein cholesterol.
[a] $P<.05$ for comparison between groups.
[b] $P<.01$ for comparison between groups.

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TABLE 3

Cardiovascular disease risk parameters in parents of polycystic ovary syndrome patients and controls, and in subgroups (fathers versus controls and mothers versus controls).

Parameter	Parents of PCOS (n = 86)	Controls (n = 86)	*P* value	Fathers of PCOS (n = 41)	Controls (n = 42)	*P* value	Mothers of PCOS (n = 45)	Controls (n = 44)	*P* value
hsCRP (mg/L)	2 (0.8–4)	1.6 (0.8–4.7)	.973	1.09 (0.5–2.4)	1.3 (0.5–3.1)	.684	3.1 (1.6–5.2)	2.16 (1.1–7.8)	.884
Metabolic syndrome[a]	55/86 (63.9%)	26/86 (30.2%)	.000[b]	23/41 (56.1%)	7/42 (16.6%)	.000[b]	32/45 (71.1%)	19/44 (43.2%)	.008[b]
CIMT (mm)	0.6 (0.54–0.8)	0.5 (0.45–0.55)	.000[b]	0.7 (5.5–8.6)	0.5 (4.3–6)	.000[b]	0.6 (0.52–0.8)	0.5 (0.45–0.52)	.00[b]
FMD (% increase from baseline)	11.9 (6.9–16.2)	16.7 (13.5–22.6)	.000[b]	12.4 ± 6.5	16.9 ± 7.1	.003[b]	12.3 ± 6.1	19.6 ± 7.95	.00[b]

Note: CIMT = carotid intima media thickness; FMD = flow-mediated dilation; hsCRP = high-sensitivity C-reactive protein; PCOS = polycystic ovary syndrome.

[a] Diagnosed by IDF criteria.

[b] $P<.01$, for comparison between groups.

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P=.00), abdominal obesity (66% vs. 19%, *P*=.00), and the metabolic syndrome (56% vs. 17%, *P*=.000) were higher in fathers. Fathers of PCOS patients had a higher CIMT [0.7 mm (5.5–8.6 mm) vs. 0.5 mm (4.3–6 mm); *P*=.000] and lower brachial FMD [12.4% ± 6.5% vs. 16.9% ± 7.1%; *P*=.003] as compared with controls (see Table 3). The proportion of fathers who had diabetes was statistically significantly higher than the controls, so the data were reanalyzed excluding the values for fathers who had diabetes. Even then, the fathers had a statistically significantly higher BP, HOMA-IR, and abdominal obesity, and a higher prevalence of the metabolic syndrome as compared with controls. The CIMT was higher [0.6 mm (0.51–0.81 mm) vs. 0.5 mm (0.43–0.6 mm); *P*=.000], and the FMD was lower [13.2% (5.7%–19.7%) vs. 16.6% (11.9%–22.5%); *P*=.018] in the fathers without diabetes as compared with the controls (Supplemental Table 1, available online).

Forty-five mothers of PCOS patients were compared with 44 controls matched for age and BMI. The mothers of PCOS patients had a higher systolic BP, diastolic BP, WHR, TC, LDL cholesterol, and prevalence of the metabolic syndrome (71% vs. 43%; *P*=.008). Other parameters such as FPG, 2-hour plasma glucose, fasting insulin, and HOMA-IR were not different among the two groups (see Table 2). Cardiovascular risk factors such as systemic hypertension, diabetes mellitus, family history of coronary artery disease, abdominal obesity, and hsCRP were similar in the two groups. The frequency of postmenopausal women (53% vs. 51%; *P*=.84) as well as the androgen levels [testosterone (1.27 ± 1.56 nmol/L vs. 1.23 ± 0.59 nmol/L; *P*=.885) and DHEAS (2.13 ± 1.14 μmol/L vs. 2.78 ± 1.94 μmol/L; *P*=.057)] were also not different in the two groups. Mothers had a higher CIMT [0.6 mm (0.52–0.8 mm) vs. 0.5 mm (0.45–0.52 mm); *P*=.00] and a lower brachial FMD [12.3% ± 6.1% vs. 19.6% ± 7.95%; *P*=.00] compared with the controls (see Table 3).

We also analyzed whether the fathers had a worse metabolic and CVD risk profile as compared with mothers. The fathers had a higher prevalence of diabetes (34% vs. 11%; *P*=.010) as compared with the mothers. But all other metabolic parameters and CVD risk parameters, including CIMT and FMD, were comparable among fathers and mothers of PCOS patients (Supplemental Table 2, available online). The CIMT showed a positive correlation with age, WHR, systolic BP, diastolic BP, FPG, 2-hour plasma glucose, HOMA IR, and fasting and 2-hour postglucose insulin, but had a negative correlation with HDL. Brachial FMD had a negative correlation with age, WHR, systolic BP, and diastolic BP (Table 4). The CIMT and brachial FMD had a negative correlation. Stepwise linear regression showed systolic BP (*P*=.003), 2-hour postglucose insulin (*P*=.025), HDL cholesterol (*P*=.023), and 2-hour plasma glucose (*P*=.017) to be independent predictors of CIMT (adjusted $R^2 = 0.212$). Systolic BP was the only independent predictor of FMD (*P*=.004, adjusted $R^2 = 0.042$) (Supplemental Table 3, available online).

DISCUSSION

In this case control study, we assessed the CVD risk in parents of women with POCS using CIMT and brachial FMD. The

TABLE 4

Pearson's correlation between carotid intima media thickness and flow-mediated dilation with other parameters.

	CIMT		FMD	
Variable	Pearson's correlation coefficient	Statistical significance	Pearson's correlation coefficient	Statistical significance
Age	.267[a]	.000	−.169[b]	.027
BMI	.065	.396	.017	.829
Waist–hip ratio	.280[a]	.000	−.160[b]	.035
SBP	.315[a]	.000	−.218[a]	.004
DBP	.287[a]	.000	−.196[b]	.010
FPG	.180[b]	.018	.027	.722
2-h PG	.299[a]	.000	−.116	.131
TG	.097	.206	.030	.692
LDL	.064	.403	.035	.645
HDL	−.183[b]	.016	.134	.080
Fasting insulin	.119	.121	.08	.298
Postglucose insulin	.284[b]	.001	−.031	.726
HOMA IR	.173[b]	.023	.064	.401
hsCRP	.048	.528	.065	.397
CIMT	1	–	−.367[a]	.000
FMD	−.367[a]	.000	1	–

Note: BMI = body mass index; CIMT = carotid intima media thickness; DBP = diastolic BP; FMD = flow-mediated dilation; FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; HOMA IR = homeostatic measurement assessment-insulin resistance; 2-h PG = 2 hour plasma glucose; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

[a] $P<.01$ for comparison between groups.

[b] $P<.05$ for comparison between groups.

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CIMT was higher in both fathers ($P=.000$) and mothers ($P=.00$), indicating increased subclinical atherosclerosis as compared with the controls matched for age, sex, and BMI. Average CIMT was 0.2 mm and 0.1 mm higher in fathers and mothers, respectively, as compared with controls. Previous meta-analysis has shown that for each 0.1-mm increase in intima medial thickness of the common carotid artery, the age- and sex-adjusted relative risk increases by 10% to 15% for myocardial infarction and 15% to 18% for stroke (17). Translating this to our results suggests fathers had a 20% to 30% and mothers had 10% to 15% increased risk for myocardial infarction. Similarly, the increased risk for stroke was 30% to 36% for fathers and 15% to 18% for mothers compared with controls. Brachial FMD was lower in both fathers ($P=.000$) and mothers ($P=.00$), indicating higher degree of endothelial dysfunction as compared with controls. The average brachial FMD was 4.5% lower in fathers and 7% lower in mothers as compared with controls.

Previous meta-analysis of FMD and cardiovascular risk prediction has shown that the pooled overall CVD risk was 0.92 (95% confidence interval [CI], 0.88, 0.95) per 1% higher FMD (18). Both CIMT and brachial FMD measurements indicate that the parents of PCOS patients had a higher CVD risk similar to what has been seen in the probands (4). To our knowledge ours is the first study to assess CVD risk in the parents of women with PCOS using CIMT and FMD. The only other study in literature using FMD showed that brothers of women with PCOS of Asian origin had endothelial dysfunction, elevated insulin resistance, and dyslipidemia, increasing their risk of CVD (19).

There have been studies assessing risk of CVD using traditional risk factors such as obesity, hypertension, or diabetes in first-degree relatives of PCOS women. Atiomo et al. (20) reported that a history of CVD was more common in relatives of women with PCOS, same as in family members of the parents in our study, but they gave no clarification about who the relatives were or the type of CVD. Hunter et al (21) evaluated first-degree male relatives of 60 PCOS patients based on a questionnaire and found that brothers could be at a higher risk of CVD because of high cholesterol and weight problems. But the CVD risk was similar in the fathers of PCOS patients and controls. The limitations of the study were inconsistent diagnosis of PCOS, and none of the probands or first-degree relatives were examined or investigated for confirming the response given in the questionnaire. Yilmaz et al. (6) showed that the prevalence of CVD risk factors such as any glucose tolerance abnormality, systemic hypertension, or the metabolic syndrome was more prevalent in the fathers and mothers of PCOS patients. Fathers in our study had similar findings, and mothers had higher blood pressure and an increased prevalence of the metabolic syndrome. Parents in the Yilmaz study had higher fasting insulin, HOMA-IR, and area under the curve for insulin as compared with controls (6). In our study, the fasting insulin and HOMA-IR were higher in fathers but were similar in mothers compared with controls. This could be because in the Yilmaz study the controls were chosen if they had no family history of diabetes or CVD, contrary to our control group. We purposely did not exclude controls who had a history of diabetes or CVD because then the parents would have been compared with a more biased group than the general population.

Whether this increased risk assessed by traditional risk factors or surrogate markers eventually leads to increased CVD events, deaths, or all-cause mortality is not clear. Recent reports suggest that this may be true. In the study by Cheang et al (10) in 182 mothers of PCOS patients based on a questionnaire, cardiovascular events were more common among those who had probable PCOS, and cardiovascular events occurred at an early age in mothers who themselves had PCOS. But in this study no comparison was made with a control population. In the study by Taylor et al. (9) in 180 fathers and 211 mothers of women with PCOS, the fathers had an elevated 10-year risk for CVD using the Framingham risk score (11.5% vs. 9.9%; $P=.03$) and also had a higher prevalence of heart attack and stroke compared with the reference NHANES population (heart attack: 11.1% vs. 5.3%, $P=.0001$; stroke: 3% vs. 1%, $P=.002$). But this was not the case for the mothers of PCOS patients. In contrast, a recent study by Louwers et al. (22) in 946 mothers and 902 fathers of PCOS patients noted a statistically significant excess mortality (standardized mortality ratio 1.5; 95% CI, 1.15–1.92) in mothers $\geq$60 years old compared with the general Dutch population. Mothers with diabetes had a two times mortality risk compared with control women with diabetes (relative risk 2; 95% CI, 1.19–3.41).

The CIMT showed a positive correlation with WHR, systolic and diastolic BP, FPG, 2-hour plasma glucose, HOMA-IR, and postglucose insulin. All these risk factors and the metabolic syndrome were higher in the fathers of PCOS patients, which might have contributed to an increased CIMT in the fathers compared with the controls. The mothers had higher systolic BP, diastolic BP, and postglucose insulin, and a higher prevalence of the metabolic syndrome, which could explain the increased CIMT in mothers compared with controls. Brachial FMD had a negative correlation with WHR, systolic BP, and diastolic BP. All these were higher in fathers whereas mothers had increased systolic BP and diastolic BP as compared with controls. These might have contributed for the lower FMD observed in both fathers and mothers as compared with controls.

The strengths of our study were a well-defined homogenous cohort of cases who were compared with controls matched for age, sex, and BMI. The CIMT and FMD were measured in all patients by a single examiner who was blinded to patient details (with an intraobserver coefficient of variation of 6% for CIMT and 4.9% for FMD). The limitations were small sample size and other cardiovascular risk markers such as homocysteine and adiponectin were not measured.

In conclusion, both fathers and mothers of PCOS patients have a higher CVD risk as evidenced by a significantly higher CIMT and a lower brachial FMD as compared with controls matched for age, sex, and BMI. But whether these CVD risk markers will lead to higher CVD events in parents of PCOS requires long follow-up observation of this group. Because PCOS has a peripubertal onset, the parents of these women are not at an age where CVD events are high. But they are a target group for early screening and surveillance for CVD as preventive strategies can be instituted to avoid future CVD events.

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SUPPLEMENTAL TABLE 1

Comparison of clinical, metabolic, and cardiovascular disease risk profile between fathers of polycystic ovary syndrome patients and controls after excluding the effect of diabetes.

Parameter	Fathers (n = 27)	Controls (n = 42)	*P* value
Systolic BP (mm Hg)	130 (120–135)	120 (110–129.5)	.006[a]
Diastolic BP (mm Hg)	80 (80–89)	80 (70–80)	.000[a]
Waist hip ratio	0.99 (0.94–1.03)	0.92 (0.87–0.97)	.000[a]
2-h plasma glucose (mg/dL)	108 (96–128.5)	97.4 (86–108)	.011[b]
Fasting insulin (μIU/L)	13.8 ± 5.6	10.2 ± 4.9	.002[a]
Postglucose insulin (μIU/L)	44.7 (18–95)	14.1 (10–29)	.000[a]
HOMA IR	2.66 (2.03–4.1)	2.03 (1.21–2.6)	.002[a]
Metabolic syndrome	12/27 (44%)	7/42 (17%)	.012[b]
CIMT (mm)	0.6 (0.51–0.81)	0.5 (0.43–0.6)	.000[a]
FMD (%)	13.2 (5.7–19.7)	16.6 (11.9–22.5)	.018[b]

Note: BP = blood pressure; CIMT = carotid intima media thickness; FMD = flow-mediated dilation; HOMA IR = homeostasis model assessment for insulin resistance; PCOS = polycystic ovary syndrome.

[a] $P < .01$.

[b] $P < .05$.

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SUPPLEMENTAL TABLE 2

Comparison of various clinical, metabolic, and cardiovascular disease risk parameters between fathers and mothers of polycystic ovary syndrome patients.

Parameter	Fathers (n = 41)	Mothers (n = 45)	*P* value
Systemic hypertension	10/41	12/45	.809
Diabetes mellitus	14/41 (34%)	5/45 (11%)	.010[a]
IGT/IFG	13/41	21/45	.156
Obese/overweight	34/41	38/45	.159
Systolic (mm Hg)	129 ± 12	128 ± 14	.927
Diastolic (mm Hg)	84 ± 7	84 ± 6	.962
Waist hip ratio	0.98 ± 0.16	0.95 ± 0.06	.327
Fasting plasma glucose (mg/dL)	109 ± 42	96 ± 19	.073
2-h plasma glucose (mg/dL)	132 (102–222)	128 (113–153)	.622
Fasting C peptide (ng/mL)	4.8 (4.2–7.1)	5.2 (3.8–8)	.765
Fasting insulin (μIU/L)	14.7 ± 6.9	15 ± 9.2	.909
Postglucose insulin (μIU/L)	37.6 (19–64)	48.5 (28–89)	.095
HOMA IR	3.91 ± 2.2	3.71 ± 2.8	.724
Metabolic syndrome	23/41	32/45	.148
hsCRP	1.07 (0.55–2.35)	3.07 (1.68–4.88)	.001[b]
CIMT (mm)	0.71 ± 0.2	0.63 ± 1.55	.053
FMD (%)	12.4 ± 6.5	12.27 ± 0.61	.957

Note: CIMT = carotid intima media thickness; FMD = flow-mediated dilation; HOMA IR = homeostatic model assessment-insulin resistance; hsCRP = high sensitivity C reactive protein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; PCOS = polycystic ovary syndrome.

[a] $P < .05$ for comparison between groups.

[b] $P < .01$ for comparison between groups.

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SUPPLEMENTAL TABLE 3

Final model of stepwise linear regression to assess independent predictors of carotid intima media thickness and flow-mediated dilation.

Dependent variable	Independent variables	Standardized β	*P* value	Adjusted R^2
CIMT	SBP[a]	0.254	.003	0.212
	2-h PG[b]	0.202	.017	
	Postglucose insulin[b]	0.183	.025	
	HDL[b]	−0.183	.023	
FMD	SBP[a]	−.218	.004	0.042

Note: Variable entered into regression for CIMT: age, waist–hip ratio, systolic BP, diastolic BP, fasting plasma glucose, 2-h PG, HDL, postglucose insulin, and HOMA IR. Variable entered into regression for FMD: age, waist–hip ratio, systolic and diastolic BP. BP = blood pressure; CIMT = carotid intima media thickness; FMD = flow-mediated dilation; HDL = high-density lipoprotein cholesterol; 2-h PG = 2-hour plasma glucose; SBP = systolic blood pressure.

[a] $P < .01$.

[b] $P < .05$.

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