

Evidence for Association Between Polycystic Ovary Syndrome and Premature Carotid Atherosclerosis in Middle-Aged Women

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Abstract—Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder characterized by obesity, hyperandrogenism, and insulin resistance. An adverse lipid profile has also been observed in PCOS-affected women, suggesting that these individuals may be at increased risk for coronary heart disease at a young age. The objective of the present study was to evaluate subclinical atherosclerosis among women with PCOS and age-matched control subjects. A total of 125 white PCOS cases and 142 controls, aged ≥ 30 years were recruited. Collection of baseline sociodemographic data, reproductive hormone levels, and cardiovascular risk factors was conducted from 1992 to 1994. During follow-up (1996 to 1999), these women underwent B-mode ultrasonography of the carotid arteries for the evaluation of carotid intima-media wall thickness (IMT) and the prevalence of plaque. A significant difference was observed in the distribution of carotid plaque among PCOS cases compared with controls: 7.2% (9 of 125) of PCOS cases had a plaque index of ≥ 3 compared with 0.7% (1 of 142) of similarly aged controls ($P=0.05$). Overall and in the group aged 30 to 44 years, no difference was noted in mean carotid IMT between PCOS cases and controls. Among women aged ≥ 45 years, PCOS cases had significantly greater mean IMT than did control women (0.78 ± 0.03 versus 0.70 ± 0.01 mm, $P=0.005$). This difference remained significant after adjustment for age and BMI ($P<0.05$). These results suggest that (1) lifelong exposure to an adverse cardiovascular risk profile in women with PCOS may lead to premature atherosclerosis, and (2) the PCOS-IMT association is explained in part by weight and fat distribution and associated risk factors. There may be an independent effect of PCOS unexplained by the above variables that is related to the hormonal dysregulation of this condition. (*Arterioscler Thromb Vasc Biol.* 2000;20:2414-2421.)

Key Words: cardiovascular risk factors ■ polycystic ovary syndrome ■ subclinical atherosclerosis ■ carotid intima-media wall thickness ■ B-mode duplex ultrasonography

Polycystic ovary syndrome (PCOS), a reproductive endocrine disorder characterized by chronic anovulation, hyperandrogenism, hyperinsulinemia, and obesity, may represent one of the largest unique groups of women at high risk for the development of early onset coronary heart disease.¹ PCOS affects $\approx 5\%$ of all women.² Over the past decade, it has been reported that women with PCOS exhibit an increase in coronary heart disease risk factors, including decreased levels of HDL cholesterol (HDLc), elevated levels of LDL cholesterol (LDLc) and triglycerides, increased prevalence of hypertension and insulin resistance, and abnormalities in the coagulation and fibrinolytic pathways.³⁻¹⁴ This profile is similar to the metabolic cardiovascular syndrome (syndrome X), which represents a clustering within an individual of hyperinsulinemia, mild glucose intolerance, dyslipidemia, and hypertension.¹⁵

Epidemiological studies in middle-aged and elderly populations have demonstrated greater carotid intima-media wall

thickness (IMT) in association with an adverse cardiovascular risk profile, including higher levels of LDLc and triglycerides, increased abdominal adiposity, higher systolic blood pressure, and hyperinsulinemia. These characteristics are similar to those observed in PCOS.¹⁶⁻²² Carotid arteriosclerosis assessed by B-mode ultrasound has been shown to be a reliable measure of generalized atherosclerosis and has been positively associated with the prevalence and incidence of stroke and myocardial infarction.²³⁻²⁹ Hence, carotid ultrasound is an important tool that can be used to further characterize the cardiovascular risk in the PCOS population.

In a previous report, we presented detailed information on cardiovascular risk factors in the largest group of PCOS cases (244 women) and controls (244 women) studied to date.^{3,30} Compared with control women of similar age, women with PCOS exhibited significantly increased body mass index (BMI), LDLc, waist-to-hip ratio, fasting insulin, and systolic blood pressure and significantly lower levels of HDLc.

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Risk profiles were also compared across 4 specific age groups: 19 to 24 years, 25 to 34 years, 35 to 44 years, and ≥ 45 years. After adjustment for BMI, hormone use, and insulin levels, women with PCOS had substantially higher LDLc and total cholesterol levels than did controls in each age group <45 years. After the age of 45, however, little difference was noted in risk factors between groups. Because weight is recognized as a major determinant of coronary heart disease risk, a further comparison of LDLc and other risk factors was made between cases and controls stratified by age (<40 and ≥ 40 years) and BMI (<26 and ≥ 26 kg/m²). In the group aged <40 years, LDLc levels were significantly higher among both thinner and heavier PCOS cases compared with controls of similar body habitus, suggesting a PCOS effect independent of BMI in these younger women. In the group aged ≥ 40 years, however, no difference in LDL levels was observed between cases and controls with stratification by BMI.³⁰

Subsequently, Guzick et al³¹ conducted a pilot study in this high-risk cohort to evaluate the development of subclinical atherosclerosis as evidenced by greater carotid IMT. Sixteen PCOS cases, aged ≥ 40 years, with a current testosterone level >2 nmol/L, and 16 age-matched normally cycling controls were recruited from the original study population to undergo duplex carotid scanning. Cases demonstrated a significantly higher mean carotid IMT than did controls (0.68 versus 0.62 mm, respectively; $P=0.03$). However, no significant difference in the prevalence of carotid plaque was evident between cases and controls.

The present study seeks to extend our investigation of subclinical atherosclerosis in our PCOS population of white women aged ≥ 30 years. We hypothesized that women with PCOS would have greater carotid IMT and plaque than would controls and that the increase could be linked to the adverse metabolic profile observed in PCOS.

Methods

Subjects

Women with PCOS were originally identified from the practice records of physicians in the Division of Reproductive Endocrinology at Magee-Women's Hospital between 1970 and 1990. A clinical diagnosis of PCOS was made if there was (1) a history of chronic anovulation in association with (2) clinical evidence of androgen excess (hirsutism) or biochemical evidence of an elevated total testosterone concentration (>2.0 nmol/L) or with (3) a ratio of luteinizing hormone to follicle-stimulating hormone of >2.0 . Of the 278 such women who lived within 50 miles of the clinic, 244 agreed to a clinical assessment of hormonal and cardiovascular status. Voter registration tapes and household directories were used to identify 244 age-matched control women. Detailed data collection and laboratory methodologies have been previously published.³

The subjects were recruited from participants in our initial case-control study who were aged ≥ 30 years at the time of the follow-up clinic visit (1996 to 1999).³ A total of 147 PCOS cases and 136 controls participated in the most recent clinic assessment. The present analysis was confined to white women.

Carotid Ultrasound Protocol

A Toshiba SSA-270A scanner equipped with a 5-MHz linear array imaging probe was used. Sonographers scanned the right and left common carotid artery, carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. For each location, the sonographer imaged the vessel in multiple planes and then focused on the interfaces required to measure IMT and also on any areas of focal plaque. The best images were digitized for later scoring.

Trained readers measured the average IMT across 1-cm segments of the near and far walls of the distal common carotid artery, the far wall of the carotid bulb, and the internal carotid artery on both right and left sides. Measures from each location were then averaged to produce an overall measure of carotid IMT. A computerized reading program developed for the Cardiovascular Health Study and modified in Pittsburgh was used. Readers also scored the ultrasound images for plaque in the common carotid, carotid bulb, internal carotid, and external carotid. Plaque was defined as a distinct area protruding into the vessel lumen with at least 50% greater thickness than the surrounding areas. For each segment, the degree of plaque was graded as follows: 0, no plaque; 1, 1 small plaque $<30\%$ of vessel diameter; 2, 1 medium plaque between 30% and 50% of the vessel diameter or multiple small plaques; and 3, 1 large plaque $>50\%$ of the vessel plaque or multiple plaques with at least 1 medium plaque. The grades were summed across right and left carotid arteries to create an overall measure of the extent of focal plaque called the plaque index. The plaque index has been used as a measure of focal plaque for a number of years and has been found to be a valid and reproducible measure of carotid atherosclerosis in a number of populations.

Reproducibility of carotid IMT and the plaque index was assessed in 5 women who underwent 2 ultrasound examinations within 1 week. Two separate sonographers scanned these women; 2 readers also scored each scan. When accounting for sonographer and reader variation, the intraclass correlation was 0.86 for IMT and 0.96 for the plaque index.

Statistical Analysis

All statistical analyses were performed by using SPSS (version 10.0). Baseline risk factors collected during the 1992 to 1994 clinic visit were used to predict current IMT and carotid plaque evaluated by ultrasound during the 1996 to 1999 clinical assessment. Demographic, hormonal, and lipid data were available for analysis from the original sample as previously reported.³ Descriptive statistics, including measures of central tendency and dispersion, were computed for PCOS cases and controls and compared by use of a *t* test for independent samples for continuous data or a χ^2 test for categorical data. Nonnormally distributed continuous data were logarithmically transformed before performing statistical comparisons for triglyceride, insulin, and testosterone levels. The distribution of carotid IMT was also markedly skewed. Thus, a reciprocal exponential transformation was performed to normalize the distribution of carotid IMT for statistical comparisons and regression modeling. Because the reciprocal transformation results in β values that are in the opposite direction from the associations noted between the risk variables and the raw IMT, the β values were multiplied by -1 for ease of interpretation. Additionally, age- and BMI-adjusted means were estimated and compared for cardiovascular risk factors and IMT by use of a general linear model.

Linear regression modeling was used to identify the independent baseline cardiovascular risk factors that predicted IMT as the dependent continuous variable. The use of baseline rather than concurrent risk variables as predictors of subclinical atherosclerosis, a chronic disease outcome with a long latency, was selected as the most appropriate modeling strategy. Cardiovascular predictors explored in these analyses included age, BMI, waist-to-hip ratio, systolic and diastolic blood pressure, LDLc, HDLc, triglycerides, fasting insulin, total testosterone, smoking status, and hormone use. Additionally, stratification by age and BMI was used to better assess the potential confounding effect of obesity on IMT. All analyses were conducted by use of the linear regression module in SPSS. Regression models were constructed for the total population and for subgroups stratified by age <45 and ≥ 45 years.

Exploratory univariate regressions of carotid IMT with specific cardiovascular risk factors were conducted. In multivariate regression modeling, the effect of PCOS on carotid IMT independent of age, BMI, and those cardiovascular risk factors found to be significant in the univariate regression analysis was assessed.

Results

A total of 125 white PCOS cases and 142 controls underwent carotid ultrasonographic scanning. Baseline sociodemo-

TABLE 1. Baseline Sociodemographic and Reproductive Factors in PCOS Cases and Controls of Similar Age (1992–1994)

Variables	Cases (n=125)	Controls (n=142)	P
Age (as of 1992–1993), y	37.5±6.2	39.0±6.2	0.050
Education, y	14.4±2.0	14.6±2.0	0.401
Married, %	85.7	68.5	0.044
Current smoking, %	23.0	17.5	0.459
OCP/HRT, %	15.9	17.5	0.512
Surgical/other, %	8.8	9.1	0.918
Natural menopause, %	1.6	2.1	0.152
No. of pregnancies	1.8±1.9	2.2±1.7	0.082
No. of live births	1.0±1.1	1.9±1.5	<0.001

Values are mean±SD or percentage. HRT indicates hormone replacement therapy; OCP, oral contraceptive pill.

graphic and reproductive factors for PCOS cases and controls obtained during the initial clinic visit (1992 to 1994) are shown in Table 1. Cases and controls were similar in general characteristics. At baseline, however, PCOS cases were slightly younger than controls (37.5 years versus 39.0 years, respectively; $P=0.05$), and cases had fewer pregnancies.

Selected cardiovascular risk factors in the PCOS cases and controls are shown in Table 2. Significant differences were noted in several baseline characteristics, including mean BMI, waist-to-hip ratio, total cholesterol, HDLc, insulin, triglyceride levels, and systolic blood pressure. Diastolic blood pressure was not significantly different between groups, and LDLc was of borderline significance. Total testosterone and androstenedione levels were significantly higher in cases than controls. There was also a significant difference noted in the ratio of luteinizing hormone to

TABLE 3. Plaque Index Results for PCOS Cases and Controls

Plaque Index	Cases		Controls		P*
	n	%	n	%	
Total					
0	98	78.4	120	84.5	0.050
1	14	11.2	16	11.3	
2	4	3.2	5	3.5	
3+	9	7.2	1	0.7	
30–44 y					
0	66	84.6	75	91.5	0.607
1	8	10.3	5	6.1	
2	2	2.6	1	1.2	
3+	2	2.6	1	1.2	
≥45 y					
0	32	68.1	45	75.0	0.019
1	6	12.8	11	18.3	
2	2	4.3	4	6.7	
3+	7	14.9	0	0.0	

*By χ^2 test.

follicle-stimulating hormone. These results are similar to those reported for the total cohort of 244 cases and 244 controls.³ To control for possible confounding, age- and BMI-adjusted analyses were also carried out. Mean adjusted values for each of the biochemical parameters are also presented. The results were similar, except that systolic blood pressure and total cholesterol were no longer significantly different between cases and controls.

Twenty-seven of 125 cases (21.6%) had ultrasonographic evidence of atherosclerotic plaque compared with 22 (15.5%) control women ($P=0.050$, Table 3). Of the 27 cases with

TABLE 2. Selected Baseline Cardiovascular Risk Factors in PCOS Cases and Controls of Similar Age (1992–1994)

Variables	Cases (n=125)		Controls (n=142)		Unadjusted P
	Mean±SE	Adjusted Mean±SE	Mean±SE	Adjusted Mean±SE	
BMI, kg/m ²	30.1±0.7	NA	26.5±0.5	NA	<0.001
Waist/hip ratio	0.84±0.01	0.82±0.01	0.77±0.01	0.78±0.01*	<0.001
SBP, mm Hg	113.9±1.3	112.2±1.0	110.4±1.1	112.0±1.0	0.038
DBP, mm Hg	72.3±1.0	71.0±0.7	70.6±0.7	71.7±0.7	0.155
CHOL, mg/dL	196.5±2.7	195.2±3.0	188.3±2.9	189.2±2.7	0.042
LDLc, mg/dL	122.1±2.6	120.1±2.7	115.0±2.6	116.4±2.5	0.059
HDLt, mg/dL	50.1±1.3	51.6±1.2	56.8±1.2	55.5±1.1*	<0.001
HDL2, mg/dL	8.2±0.6	8.9±0.6	11.9±0.6	11.4±0.5*	<0.001
Insulin, μ U/mL	23.7±2.1	21.2±1.4	14.0±0.9	16.3±1.3*	<0.001
TRIG, mg/dL	124.1±7.7	119.2±5.7	82.2±3.7	87.0±5.4*	<0.001
Total T, nmol/dL	1.65±0.10	1.64±0.08	1.04±0.04	1.05±0.07*	<0.001
AD, ng/dL	208.8±12.4	209.2±9.9	158.5±6.6	158.8±8.9*	<0.001
LH/FSH	1.52±0.09	1.53±0.09	1.16±0.09	1.16±0.09*	0.005

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; CHOL, cholesterol; HDL2, HDL cholesterol subtraction of HDLt; TRIG, triglycerides; total T, total testosterone; AD, androstenedione; LH, luteinizing hormone; and FSH, follicle-stimulating hormone.

*Adjusted $P<0.001$.

TABLE 4. Carotid IMT Results for PCOS Cases and Controls

	Cases			Controls			P*
	n	Mean±SE IMT,* mm	Age-BMI Adjusted Mean (CI)	n	Mean±SE IMT,* mm	Age-BMI Adjusted Mean (CI)	
Total	125	0.70±0.01	0.70 (0.68–0.73)	142	0.68±0.01	0.67 (0.65–0.69)	0.299
30–44 y	78	0.65±0.01	0.65 (0.62–0.69)	82	0.66±0.01	0.64 (0.61–0.67)	0.565
≥45 y	47	0.78±0.03	0.77 (0.74–0.81)	60	0.70±0.01	0.71 (0.68–0.75)	0.005

*Statistical test performed on transformed variable.

plaque, 14 women had a plaque index of 1, 4 had a plaque index of 2, and 9 had a plaque index of ≥3. Among the controls, 16 women had a plaque index of 1, 5 had an index of 2, and 1 of the controls had an index of ≥3. Among women aged ≥45 years, the proportion with a plaque index of ≥3 was also markedly greater in PCOS cases than in controls (14.9% versus 0.0%, *P*=0.002).

No significant differences in carotid IMT were noted between cases and controls (*P*=0.299) in the total group (Table 4). In the group aged 30 to 44 years, no significant difference was noted in carotid IMT between PCOS cases and controls. Among women aged ≥45 years, PCOS cases had significantly greater IMT than did control women (0.78±0.03 versus 0.70±0.01 mm, respectively; *P*=0.005). A significant interaction was noted between PCOS and age in the extent of carotid IMT (*P*=0.031, Figure).

The mean BMI for PCOS cases and controls aged 30 to 44 years was not significantly different (29.0±0.86 and 27.1±0.73 kg/m², respectively; *P*=0.08). However, among cases and controls aged ≥45 years, a significant difference existed in mean BMI (31.9±1.3 and 25.8±0.69 kg/m², respectively; *P*<0.001). Hence, age- and BMI-adjusted IMT means were calculated (Table 4). Adjusted IMT averages were 0.77±0.02 mm (95% CI 0.74 to 0.81) and 0.71±0.02 mm (95% CI 0.68 to 0.75) for cases and controls aged ≥45 years, respectively. This difference in IMT remained statistically significant even after adjustment (*P*<0.05).

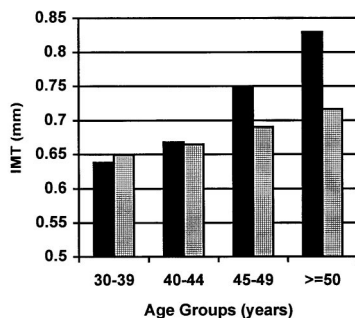
In the women aged <45 years, there was little evidence of any greater subclinical atherosclerosis in PCOS cases versus controls, regardless of BMI subgroup or case status (Table 5). In the group aged ≥45 years, higher BMI was associated with greater extent of carotid IMT among PCOS cases (0.75 versus 0.80 mm). The BMI effect is less evident in older control women (0.70 versus 0.72 mm). In the thinner subgroup aged ≥45 years, PCOS women (mean BMI 21.7 kg/m²) had a

0.05 mm greater IMT than was observed in thinner control women of similar BMI (22.7 kg/m²; 7.1% difference, *P*=0.219). Among women aged ≥45 years with a BMI ≥26 kg/m², a significant difference was noted in IMT between PCOS cases and controls (0.80 versus 0.72 mm, respectively; *P*=0.04). However, BMI was also higher among cases than controls (36.2 and 32.5 kg/m², respectively) in this subgroup. When analysis was restricted to women with a BMI <40 kg/m² to eliminate the body size difference between cases and controls (31.9 and 31.3 kg/m², respectively), although the numbers are smaller, the mean IMT remained greater in PCOS cases compared with controls (0.79±0.21 versus 0.72±0.10 mm, respectively; *P*=0.15).

Univariate linear regressions of IMT with selected cardiovascular risk factors are shown in Table 6. In the total group and in the group aged <45 years, several cardiovascular risk factors were found to be significantly associated with IMT, including age, BMI, diastolic and systolic blood pressures, waist-to-hip ratio, and triglycerides (*P*<0.05).

Conversely, in women aged ≥45 years, PCOS was a highly significant predictor of IMT (*P*=0.003). Of the traditional cardiovascular risk factors, BMI, LDLc, insulin, systolic blood pressure, and triglycerides were also significant predictors in this age group (all *P*<0.03). Hormone use and smoking status were not associated with IMT in the total group or in the age-stratified subgroups.

Multivariate linear regression models were carried out to assess the independent effect of PCOS on IMT adjusted for age, BMI, and cardiovascular risk factors found to be associated with IMT in the univariate analyses (LDLc, systolic and diastolic blood pressures, insulin, triglycerides, and waist-to-hip ratio). Results are presented in Table 7. In the total sample, after adjusting for age and BMI, PCOS was not a significant predictor of carotid IMT (*P*=0.337). Subsequent addition of the other cardiovascular risk factors in separate



(Cases = solid, Controls = hatched) (PCOS X age interaction *p* =.031)

Mean IMT in PCOS cases and controls by age (in 1999).

TABLE 5. Carotid IMT Levels in PCOS Cases and Controls Stratified by Age and BMI

	PCOS Cases		PCOS Controls		P
	n	Mean±SE IMT	n	Mean±SE IMT	
<45 y					
BMI <26	35	0.64±0.01	45	0.65±0.01	NS
BMI ≥26	42	0.67±0.01	36	0.67±0.01	NS
≥45 y					
BMI <26	14	0.75±0.04	41	0.70±0.01	0.219
BMI ≥26	33	0.80±0.03	19	0.72±0.02	0.040

BMI is missing for 1 case and 1 control.

TABLE 6. Univariate Linear Regression Results of IMT and Baseline CHD Risk Factors

	Total (n=267)			<45 y (n=160)			≥45 y (n=107)		
	β	SE	P	β	SE	P	β	SE	P
PCOS	0.068	0.064	0.290	-0.040	0.073	0.565	0.286	0.095	0.003*
BMI, kg/m ²	0.019	0.004	<0.001*	0.015	0.005	0.003*	0.021	0.006	<0.001*
Hormone use	0.025	0.085	0.766	-0.040	0.094	0.640	0.228	0.136	0.095
Smoking status	0.036	0.038	0.347	0.028	0.044	0.525	0.019	0.057	0.747
LDLc	0.016	0.001	0.120	0.001	0.001	0.512	0.004	0.002	0.016*
HDLt	-0.002	0.002	0.291	-0.003	0.003	0.240	-0.005	0.003	0.112
DBP, mm Hg	0.013	0.003	<0.001*	0.013	0.004	0.001*	0.009	0.005	0.081
SBP, mm Hg	0.012	0.002	<0.001*	0.11	0.003	<0.001*	0.008	0.003	0.015*
Insulin	0.141	0.045	0.002*	0.088	0.050	0.080*	0.225	0.073	0.003*
Waist/hip ratio	0.654	0.252	0.010*	0.897	0.389	0.022*	0.527	0.295	0.077
Age, y	0.036	0.005	<0.001*	0.029	0.009	0.002*	0.015	0.014	0.273
Total T	0.057	0.055	0.304	0.079	0.060	0.192	0.056	0.091	0.541
TRIG	0.211	0.055	<0.001*	0.169	0.070	0.017*	0.212	0.074	0.005*

IMT was measured in 1997–1999, and baseline risk factors were measured in 1992–1994.

*Significant at $P<0.05$.

models for the total group did not alter the PCOS-IMT relationship. Systolic blood pressure in the total sample was the only significant predictor of carotid IMT ($P=0.023$). Diastolic blood pressure and triglyceride levels were of borderline significance ($P=0.082$ and $P=0.078$, respectively). In the group aged <45 years, PCOS status was not significant in any model. Systolic and diastolic blood pressures were related to carotid IMT in this subgroup ($P<0.05$), and triglyceride level was of borderline significance ($P=0.066$).

In the group aged ≥ 45 years, PCOS was a significant predictor of IMT ($P=0.042$), independent of age and BMI. With the addition of LDLc, the association between PCOS and IMT became more significant ($P=0.024$). LDLc itself was a significant predictor in this older age group ($P=0.048$). LDLc and PCOS both exerted an independent effect on IMT independent of age and BMI. Similarly, with the addition of systolic or diastolic blood pressure or triglycerides in separate models, the PCOS-IMT relationship remained of borderline significance ($P=0.068$ to 0.088). Notably, the inclusion of log insulin or waist-to-hip ratio eliminated the significance of PCOS as an independent predictor of carotid IMT in the group aged ≥ 45 years (Table 7).

Discussion

PCOS is characterized by a clustering of risk factors (eg, greater body mass, waist-to-hip ratio, and fasting insulin levels and diabetes) that is associated with an adverse lipid profile and high blood pressure. Carotid artery wall thickness has been shown in numerous studies to be strongly associated with obesity, waist-to-hip ratio, and lipids.^{16–22} In the present study, carotid IMT was investigated as a potential marker of cardiovascular disease (CVD) risk in PCOS.

In the present study, a difference between PCOS cases and controls in carotid IMT was observed in older women (aged ≥ 45 years) but not in younger women. Because CVD is characterized by a long incubation period, the metabolic alterations observed in younger PCOS women

appear to translate into measurable carotid abnormalities by middle age. Moreover, PCOS and age appear to interact to adversely impact carotid wall thickness to a significantly greater degree than that observed with aging alone. Among 200 participants in the Healthy Women's Study (HWS) who underwent B-mode ultrasound of the carotid arteries, the mean IMT was 0.76 ± 0.11 mm, which is similar to that observed in our PCOS subgroup aged ≥ 45 years.¹⁸ However, the participants in the HWS were significantly older at the time of the carotid evaluation compared with the women with PCOS in this cohort (57.0 versus 49.6 years, respectively). This unfavorable influence of PCOS on carotid IMT in middle age is notable, inasmuch as the difference in lipid levels between PCOS cases and controls appears to narrow as women approach the menopausal transition.³⁰ From these data, one might speculate that longstanding exposure to an adverse cardiovascular profile among women with PCOS at an early age leads to premature subclinical atherosclerotic changes.

Further evidence in support of premature atherosclerotic changes in PCOS can be seen in the comparison of the proportions of cases and controls with a mean IMT of >0.75 mm. Bonithon-Kopp et al²⁰ proposed this definition of carotid IMT as a definition of subclinical disease. A total of 44.7% of the PCOS cases aged ≥ 45 years met this criterion for atherosclerosis compared with 15% of similarly aged controls ($P<0.001$).

In any attempt to evaluate the potential independent association of PCOS with CVD, obesity is a powerful confounding influence. Weight and BMI, as well as waist circumference, have been associated with increased subclinical atherosclerosis in several recent studies.^{21,22,32,33} In the present study as well, BMI was a powerful predictor of IMT, particularly in women with PCOS. In the stratified analysis, IMT was greater in thin and heavy women with PCOS compared with controls of similar size.

We also addressed the issue of which, if any, of the traditional cardiovascular risk factors could be "substituted"

TABLE 7. Multiple Linear Regression Models of Effect of PCOS Adjusted for Age, BMI, and Selected Risk Factors

	n	Total			<45 y			≥45 y		
		β	SE	P	β	SE	P	β	SE	P
PCOS	267	0.123	0.058	0.035*	-0.010	0.072	0.853	0.309	0.095	0.002†
Age		0.037	0.005	<0.001*	0.029	0.010	0.003*	0.021	0.013	0.107
PCOS	265	0.056	0.058	0.337	-0.050	0.071	0.495	0.206	0.100	0.042†
Age		0.037	0.005	<0.001*	0.031	0.009	0.001*	0.022	0.013	0.092
BMI		0.019	0.004	<0.001*	0.017	0.005	0.001*	0.017	0.006	0.008*
PCOS	265	0.052	0.058	0.368	-0.050	0.072	0.479	0.227	0.099	0.024†
Age		0.037	0.005	<0.001*	0.031	0.009	0.001*	0.020	0.013	0.124
BMI		0.018	0.004	<0.001*	0.017	0.005	0.001*	0.014	0.006	0.030
LDL		0.001	0.001	0.338	0.0002	0.001	0.815	0.003	0.002	0.048
PCOS	261	0.042	0.058	0.474	-0.060	0.071	0.383	0.174	0.101	0.088†
Age		0.033	0.005	<0.001*	0.030	0.009	0.002*	0.013	0.013	0.322
BMI		0.013	0.005	0.006*	0.008	0.006	0.221	0.016	0.007	0.037*
SBP		0.006	0.003	0.023*	0.009	0.003	0.007*	0.002	0.004	0.535
PCOS	261	0.048	0.058	0.417	-0.060	0.071	0.410	0.178	0.102	0.085†
Age		0.035	0.005	<0.001*	0.032	0.009	0.001*	0.014	0.013	0.287
BMI		0.015	0.005	0.001*	0.010	0.006	0.101	0.017	0.007	0.024*
DBP		0.006	0.004	0.082	0.010	0.004	0.033*	0.002	0.006	0.699
PCOS	265	0.035	0.059	0.556	-0.060	0.071	0.373	0.195	0.105	0.068†
Age		0.036	0.005	<0.001*	0.032	0.009	0.001*	0.021	0.013	0.113
BMI		0.015	0.004	<0.001*	0.014	0.005	0.011*	0.016	0.007	0.030*
TRIG		0.010	0.056	0.078	0.136	0.073	0.066	0.033	0.090	0.716
PCOS	263	0.032	0.059	0.596	-0.070	0.072	0.330	0.167	0.104	0.112
Age		0.035	0.005	<0.001*	0.032	0.009	0.001*	0.014	0.013	0.314
BMI		0.018	0.004	<0.001*	0.013	0.006	0.017*	0.018	0.006	0.007*
Waist/hip ratio		0.254	0.245	0.302	0.684	0.425	0.110	0.045	0.309	0.883
PCOS	236	0.036	0.062	0.564	-0.030	0.076	0.659	0.124	0.109	0.256
Age		0.036	0.005	<0.001*	0.035	0.010	0.001*	0.023	0.013	0.094
BMI		0.017	0.005	0.001*	0.013	0.007	0.044*	0.018	0.008	0.034*
Insulin		0.038	0.052	0.462	0.033	0.062	0.597	0.068	0.094	0.471

* $P < 0.05$; † $PCOS < 0.10$.

for PCOS to explain the apparent effect of this disorder observed in our older subgroup. When PCOS was entered as a univariate predictor of the transformed IMT variable, the regression coefficient was 0.286 ($P=0.003$). Controlling for age and BMI slightly altered the PCOS association ($\beta=0.206$, $P=0.042$). Additionally, adjusting for LDL, systolic or diastolic blood pressure, or triglycerides reduced the regression coefficient only slightly; the P value for PCOS as a predictor of IMT remained of borderline significance ($P=0.024$ to 0.09).

However, fasting insulin and waist circumference or waist-to-hip ratio appeared to attenuate the relationship of

PCOS and IMT, suggesting that at least part of the observed association of PCOS and IMT in middle-aged PCOS women may be driven by central obesity and hyperinsulinemia. Insulin enhances cholesterol transport into arteriolar smooth muscle cells and increases the proliferation and cholesterol synthesis of these cells.³⁴ Hyperinsulinemia has been found to be related to increased IMT in several previous studies.^{17,35} It is possible that the apparent association of PCOS with IMT may also be mediated by factors related to hyperinsulinemia and central obesity, such as plasminogen activator inhibitor-1, C-reactive protein, and tumor necrosis factor- α .^{13,14,36,37}

The major strengths of the present study include a well-characterized relatively large PCOS cohort of older and younger women as well as a 6- to 7-year follow-up from baseline risk factor measurement to subclinical disease assessment. These older PCOS women represent a unique group to monitor disease progression. However, study limitations exist. A longer period of follow-up is necessary, particularly in younger PCOS women, to confirm the progression of IMT as the cohort ages. In addition, subgroup analysis was limited by sample size considerations, especially in the group aged >45 years.

In clinical practice, women with PCOS are seen primarily for menstrual irregularity, androgen excess, and infertility. Treatment is traditionally targeted at the immediate presenting complaint. If the issues of menstrual dysfunction and infertility are resolved, these women may seek no further treatment. However, women with PCOS, because of the underlying pathophysiology (ie, aberrant sex-steroid hormone metabolism and insulin resistance) and/or associated elevated CVD risk factors, may be at high risk of CVD or cerebrovascular disease,³⁸ which may be prevented by pharmacological or nonpharmacological therapies. It is still not determined whether PCOS carries an increased risk of CVD above that due to obesity and body fat distribution and associated CVD risk factors. The results of the present study suggest that much of the excess risk may indeed be explained by the traditional known risk factors. To that end, weight control and physical activity may play an important role in risk management in PCOS. However, there may also be an independent effect of PCOS on IMT that may be mediated by low peak estradiol levels or hormonal dysregulation. Given the apparent increase of subclinical disease even in thinner PCOS cases, the use of insulin-lowering drugs in younger women with PCOS, reported in short-term studies to have a beneficial effect on endocrine parameters and lipid levels, should be investigated as a long-term means of reducing the later life risk of CVD.

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