

# Adolescent Girls with Polycystic Ovary Syndrome Have an Increased Risk of the Metabolic Syndrome Associated with Increasing Androgen Levels Independent of Obesity and Insulin Resistance

Andrea D. Coviello, Richard S. Legro, and Andrea Dunaif

Department of Medicine (A.D.C., A.D.), Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611; and Department of Obstetrics and Gynecology (R.S.L.), Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033

**Context:** Adult women with polycystic ovary syndrome (PCOS) have an increased prevalence of the metabolic syndrome (MBS). The prevalence of MBS is also increasing in adolescents.

**Objective:** Our objective was to test the hypothesis that the prevalence of MBS is increased in adolescent girls with PCOS compared with the general population and to determine the factors associated with an increased risk of the MBS in PCOS.

**Design and Setting:** We conducted a cross-sectional case-control study at academic medical centers with general clinical research centers.

**Participants:** Participants included 49 adolescent girls with PCOS and 165 girls from the Third National Health and Nutrition Examination Survey (NHANES III) adolescent population of similar age and ethnic background.

**Main Outcome Measure:** We assessed the prevalence of MBS according to currently proposed adolescent MBS criteria.

**Results:** Thirty-seven percent of adolescent girls with PCOS had MBS compared with 5% of NHANES III girls ( $P < 0.0001$ ). None of the girls of normal body mass index (BMI) had MBS, whereas 11% of overweight and 63% of obese girls with PCOS had MBS compared with 0 and 32% of NHANES III girls, respectively. Girls with PCOS were 4.5 times more likely to have MBS than age-matched NHANES III girls after adjusting for BMI (odds ratio, 4.5; 95% confidence interval, 1.1–17.7;  $P = 0.03$ ). The odds of having the MBS were 3.8 times higher for every quartile increase in bioavailable testosterone in girls with PCOS after adjusting for BMI and insulin resistance (odds ratio, 3.8; 95% confidence interval, 1.4–10.2;  $P = 0.008$ ).

**Conclusions:** Adolescent girls with PCOS have a higher prevalence of MBS than the general adolescent population. Hyperandrogenemia is a risk factor for MBS independent of obesity and insulin resistance. (*J Clin Endocrinol Metab* 91: 492–497, 2006)

**M**ETABOLIC SYNDROME (MBS) is a constellation of cardiovascular disease risk factors associated with insulin resistance (IR): glucose intolerance, dyslipidemia, hypertension, and central obesity (1). There is a growing appreciation that adolescents are at increasing risk for type 2 diabetes mellitus (DM) and the MBS as the prevalence of obesity increases in this population (2–4). Analogous to the situation in adults, the prevalence of the MBS increases with obesity, reaching prevalence rates as high as 50% among morbidly obese adolescents (4). Polycystic ovary syndrome (PCOS) is a leading cause of glucose intolerance and IR in adolescent girls, particularly those with obesity (5, 6). IR is associated with an increased prevalence of the MBS among both obese and Hispanic adolescents (7, 8). Because adoles-

cents with PCOS are as insulin resistant as their adult counterparts (5, 9), they would be predicted to be at increased risk for the MBS as well. Limited studies of the MBS in adult women with PCOS suggest that the prevalence is twice that of the general population (10, 11), even after controlling for the increased prevalence of obesity among affected women (12). There is intriguing evidence that this increased risk may be conferred not only by IR but also by hyperandrogenemia. Postmenopausal women with MBS have higher bioavailable testosterone (uT) levels than unaffected women (13), and women with PCOS who have MBS have higher testosterone levels than those without the MBS (10).

Pediatricians are increasingly concerned about the long-term health effects of childhood and adolescent MBS and believe that it may be associated with early cardiovascular disease in adulthood (14). Progress in defining the nature of the long-term cardiovascular risk is hampered by the lack of consensus on criteria for the diagnosis of the MBS in adolescents (15) as well as the lack of longitudinal studies with cardiovascular endpoints as opposed to surrogate markers. Cardiovascular event endpoints are difficult to target because of the long latency period between the onset of atherosclerosis and the first cardiovascular event. However, there is evidence from autopsy studies that atherosclerosis starts in childhood (14). Further-

First Published Online October 25, 2005

Abbreviations: BMI, Body mass index; CI, confidence interval; CV, coefficients of variation; DHEAS, dehydroepiandrosterone sulfate; DM, diabetes mellitus; HDLc, high-density lipoprotein cholesterol; HOMA-IR, homeostatic index of insulin resistance; IR, insulin resistance; LDLc, low-density lipoprotein cholesterol; MBS, metabolic syndrome; PCOS, polycystic ovary syndrome; T, testosterone; TG, triglycerides; uT, bioavailable T.

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

more, cardiovascular risk factors in childhood and adolescence have been shown to track with cardiovascular risk factors in adulthood (14, 16). Because PCOS is a common disorder, an increase in MBS among affected adolescents could have substantial public health implications.

We performed this study to investigate whether adolescent girls with PCOS had an increased prevalence of MBS compared with the general U.S. population of comparable age and to test the hypothesis that androgen excess was an independent risk factor for MBS in affected girls. In addition, we compared two sets of diagnostic criteria for MBS as part of this study.

## Subjects and Methods

The study protocol was approved by the Institutional Review Boards of the Feinberg School of Medicine, Northwestern University, Brigham and Women's Hospital, and The Pennsylvania State University College of Medicine. Written informed consent was obtained from all participants and/or their parent or legal guardian before participation in the study. Adolescent girls with a confirmed diagnosis of PCOS were studied as part of a larger ongoing nationwide study of women with PCOS and their family members. The criteria for the diagnosis of PCOS were 1) hyperandrogenemia defined as a total testosterone (T) more than 58 ng/dl (2 nmol/liter) and/or uT more than 15 ng/dl (0.5 nmol/liter) and 2) evidence of anovulation based on irregular menses (17, 18). All girls were at least 1 yr post menarche at the time of evaluation for PCOS based on symptoms that also included weight gain, hirsutism, and acne. Exclusion criteria included hyperprolactinemia, evidence of congenital adrenal hyperplasia or androgen-secreting tumors, and current use of medications known to alter reproductive hormones including hormonal contraceptives, insulin sensitizers, and antihypertensive medications. Only girls with the following data for determining the diagnosis of the MBS were included in the study: 1) fasting glucose, 2) fasting triglycerides (TG), 3) fasting high-density lipoprotein cholesterol (HDLc), 4) waist circumference measurement, and 5) blood pressure measurement. Forty-nine girls with PCOS met these criteria.

Height and weight were measured on the morning of testing. Body mass index (BMI) was calculated. BMI percentiles adjusted for age and gender were calculated using EpiInfo, version 3.3, provided by the Centers for Disease Control (Atlanta, GA). Waist and hip circumferences were measured as previously reported (5). Blood pressure was measured in the seated position in the right arm after a 30-min rest period. The average of three measurements taken 2 min apart was the reported blood pressure. A morning blood sample was taken after an overnight fast for measurement of glucose, insulin, T, SHBG, non-SHBG-bound or uT, dehydroepiandrosterone sulfate (DHEAS), lipid, and lipoprotein levels.

## Reference population

The prevalence of MBS in this group of adolescent girls with PCOS was compared with the prevalence in the female adolescent Third National Health and Nutrition Examination Survey (NHANES III) population. The NHANES III population was sampled from all U.S. households between 1988 and 1994 (19). All non-Hispanic white females aged 12–19 yr with complete information for determining the diagnosis of MBS were included in the study to match the profile of our adolescent PCOS population. Participants who fasted 8 or more hours before their blood draw were included. A total of 165 girls were identified in the NHANES III population who underwent physical and laboratory evaluations and met the above criteria. BMI percentiles adjusted for age and gender were calculated using EpiInfo (Centers for Disease Control, Atlanta, GA).

## Laboratory assays

All laboratory assays were done at the endocrine research lab of The Pennsylvania State University College of Medicine, the central research laboratory for this study. T, uT, DHEAS, SHBG, and insulin were assayed as previously reported (18). The T assay had intra- and interassay

coefficients of variation (CV) of 4 and 12%, respectively, and the uT assay had intra- and interassay CV of 3 and 6%, respectively, at a low-pool range. The DHEAS assay had intra- and interassay CV of 5 and 8%, respectively. The SHBG assay had intra- and interassay CV of 6 and 8%, respectively. Plasma glucose was determined by the glucose oxidase technique (20). Fasting total cholesterol, HDLc, and TG were assayed as previously reported (21). Low-density lipoprotein cholesterol (LDLc) was calculated using the Friedewald equation (22).

## Diagnostic criteria for MBS in adolescents

Waist circumference percentiles adjusted for age, gender, and race were determined using distributions in 9713 children and adolescents in NHANES III (23). Blood pressure percentiles were calculated adjusted for age, gender, and height. The diagnosis of elevated blood pressure in adolescents was a blood pressure equal to or greater than the 90th percentile and hypertension as blood pressure greater than the 95th percentile as defined by the National High Blood Pressure Education Program for Children and Adolescents (24). The diagnosis of MBS was determined using two different proposed sets of criteria for adolescents.

The first diagnostic criteria were those outlined by Cook *et al.* (2). Adolescents meeting three or more of the following criteria were diagnosed with MBS: waist circumference of at least 90th percentile for age and gender; systolic or diastolic blood pressure at least 90th percentile for age, height, and gender; fasting TG at least 110 mg/dl (90th percentile for age) and fasting HDLc no more than 40 mg/dl (10th percentile for age); and fasting glucose at least 110 mg/dl.

The second diagnostic criteria were proposed by de Ferranti *et al.* (3). Subjects meeting three or more of the following criteria were diagnosed with MBS: waist circumference more than the 75th percentile for age and gender; elevated blood pressure defined by either systolic or diastolic blood pressure greater than the 90th percentile for age, gender, and height; fasting TG at least 97.3 mg/dl and fasting HDLc less than 50.2 mg/dl; and fasting glucose at least 110 mg/dl.

## Statistical analyses

Log transformation was used as necessary to approximate the normal distribution for parametric analyses. Comparisons between groups were done with *t* test after testing for equality of variance and ANCOVA for adjusted comparisons. When assumptions for parametric tests were not met, the two-sample Wilcoxon rank-sum/Mann-Whitney test was used. Prevalence rates across subgroups were compared with  $\chi^2$  analysis including Cochran-Mantel-Haenszel statistics for composite odds ratios. The homeostatic index of IR (HOMA-IR) was calculated as follows:  $\text{HOMA-IR} = [\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mmol/liter)}] / 22.5$  (25).

Logistic regression was used to examine predictors of MBS and to adjust for IR, BMI, and SHBG. Adjustment for IR was done by stratification by HOMA-IR quartile. Stratification by BMI was done by percentile grouping adjusted for age: 1) normal, less than the 85th percentile; 2) overweight, 85–94th percentile; 3) obese, 95–97th percentile; and 4) severely obese, more than the 97th percentile. Relationships between lipids, androgens, and metabolic parameters were examined with Pearson correlation and Spearman-Rank correlation coefficients. Linear regression was used to examine predictors of uT, and  $\alpha$  was set at 0.05 for the purpose of determining statistical significance for all analyses. Statistical analyses were done with Stata 6.0 (StataCorp, College Station, TX) and SAS 9.12 (SAS Institute, Inc., Cary, NC). Data are presented as the untransformed mean  $\pm$  SD or proportion  $\pm$  SE.

## Results

A total of 78 adolescent girls were identified with confirmed PCOS, of which 49 (63%) had complete data for the diagnosis of MBS. There was no difference in age, age of menarche, weight, BMI, serum androgen levels, or SHBG between the 49 girls included in the study *vs.* the 29 girls excluded because of lack of complete information for diagnosis of MBS. The mean age of girls with PCOS was  $17 \pm 2$  yr (range, 14–19 yr) (Table 1). All 49 girls identified their ethnicity as white or non-Hispanic origin. Although three

**TABLE 1.** Characteristics of PCOS and NHANES III adolescent girls

	PCOS (n = 49)	NHANES III (n = 165)
Age (yr)	17 ± 2	15 ± 2 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	32 ± 9	23 ± 5 <sup>a</sup>
BMI percentile	84 ± 23	58 ± 26 <sup>a</sup>
Weight (kg)	88 ± 27	60 ± 15 <sup>a</sup>
Weight percentile	85 ± 22	61 ± 27 <sup>a</sup>
Androgens		
Total T (ng/dl)	75 ± 24	
uT (ng/dl)	29 ± 14	
SHBG (nmol/liter)	60 ± 48	
DHEAS (ng/dl)	2491 ± 1124	
Insulin sensitivity		
Fasting insulin (μU/liter)	28 ± 21	
HOMA-IR	6 ± 5	
Features of MBS <sup>b</sup>		
Waist circumference (cm)	94 ± 21	76 ± 13
Systolic blood pressure (mm Hg)	119 ± 14	104 ± 9 <sup>b</sup>
Systolic blood pressure percentile	65 ± 28	39 ± 26 <sup>c</sup>
Diastolic blood pressure (mm Hg)	73 ± 10	61 ± 10 <sup>b</sup>
Diastolic percentile	66 ± 25	37 ± 24 <sup>b</sup>
Fasting HDL (mg/dl)	42 ± 10	49 ± 11
Fasting triglyceride (mg/dl)	122 ± 75	91 ± 48
Fasting glucose (mg/dl)	86 ± 10	87 ± 25

Data represent mean ± SD.

<sup>a</sup> Comparison of mean value of NHANES III population with PCOS population; *P* < 0.001.<sup>b</sup> Comparison of mean value of NHANES III with PCOS population adjusted for age and BMI (ANCOVA); *P* < 0.001.<sup>c</sup> *P* = 0.02; unadjusted mean for each group presented in table.

girls (6%) had a previous diagnosis of hypertension, 10 girls (20%) were newly diagnosed with hypertension using pediatric diagnostic criteria (24). None of the girls had a previous diagnosis of DM. One (2%) was newly diagnosed with type 2 DM. Over half (55%) were obese as defined by a BMI equal to or greater than the 95th percentile, and an additional 18% were overweight defined as BMI equal to or greater than the 85th but less than the 95th percentile. Nineteen girls (38%) were severely obese (BMI greater than the 97th percentile). Only four (8%) met the criteria for severe obesity defined by Weiss *et al.* (4) as a BMI greater than 2.5 SD above the mean (>99.4th percentile).

The prevalence of MBS was 37% in this group of adolescent girls with PCOS compared with 5% of the NHANES III girls using the adolescent criteria proposed by Cook *et al.* (2) (Table 2). The prevalence of MBS was 47% using the de Ferranti *et al.* (3) criteria compared with 13% of the NHANES III girls. The de Ferranti criteria had a higher prevalence of adolescent girls who met the waist circumference and lipid

profile criteria as expected given the more liberal cutoff points (Table 2). The proportion with elevated blood pressure and fasting glucose were similar with both criteria. Although only one girl with PCOS met all five MBS criteria, 4% had no features of MBS with the de Ferranti criteria, and 25% had no features of MBS with the Cook criteria.

The prevalence of MBS increased with BMI in the PCOS and NHANES III groups with both sets of criteria (*P* < 0.001). However, the prevalence of MBS in the obese girls with PCOS was strikingly higher than the prevalence in the general obese adolescent population in NHANES III by Cook criteria, 63 ± 9% *vs.* 32 ± 10%, respectively (*P* = 0.03) (Fig. 1A). Overall, the risk of MBS was higher in girls with PCOS compared with the general population after adjusting for BMI (*P* = 0.01).

#### Age-matched analysis

Because the mean age of girls with PCOS was higher, 17 ± 2 yr compared with 15 ± 2 yr in the NHANES III girls, a second analysis was done in 127 girls in NHANES III aged 14–19 yr to match the age range of girls with PCOS. The prevalence of the MBS in this subset was not appreciably different from the original group of 165 girls aged 12–19 yr. The prevalence of MBS in the NHANES III population aged 14–19 yr was 3 ± 2% using the Cook criteria (2) and 12 ± 3% using the de Ferranti criteria (3). The smaller group of NHANES III girls did result in a loss of power to allow comparison of MBS prevalence within BMI strata; however, the overall trend was the same. The overall odds of having MBS was higher in girls with PCOS compared with the NHANES III population age 14–19 yr after stratifying by BMI [odds ratio (OR), 4.5; 95% confidence interval (CI), 1.1–17.7; *P* = 0.03].

#### Hyperandrogenemia (subanalysis in girls with PCOS)

The mean uT was higher in the adolescent girls with the MBS than in adolescent girls without the MBS (40 ± 3 *vs.* 23 ± 2 ng/dl; *P* < 0.0001). The difference in uT between girls with and without the MBS was significant (*P* = 0.001) after adjusting for HOMA-IR and BMI with regression modeling (total model: *P* = 0.0002, *R*<sup>2</sup> = 0.31). There was no significant difference in total T between groups (80 ± 23 *vs.* 72 ± 25 ng/dl; *P* = 0.2). SHBG was lower in the girls with MBS than those without MBS (33 ± 13 *vs.* 77 ± 53 nmol/liter; *P* < 0.01).

The relative odds of an adolescent girl with PCOS having MBS increased approximately five times for every quartile increase in uT (OR, 4.8; 95% CI, 2.1–11.2; *P* < 0.0001) and increased approximately four times for every quartile in-

**TABLE 2.** Prevalence of the MBS in girls with PCOS (n = 49) and in girls in NHANES III (n = 165)

MBS feature	Cook criteria			de Ferranti criteria		
	MBS criteria	PCOS [% (SE)]	NHANES III [% (SE)]	MBS criteria	PCOS [% (SE)]	NHANES III [% (SE)]
Waist circumference	≥90th percentile	47 (7)	13 (2) <sup>a</sup>	>75th percentile	65 (7)	29 (3) <sup>a</sup>
TG	≥110 mg/dl	49 (7)	26 (3) <sup>a</sup>	≥97 mg/dl	53 (7)	33 (4) <sup>a</sup>
HDLc	≤40 mg/dl	49 (7)	20 (3) <sup>a</sup>	<50 mg/dl	84 (5)	50 (3) <sup>a</sup>
Blood pressure	≥90th percentile	41 (7)	2 (1) <sup>a</sup>	>90th percentile	41 (7)	2 (1) <sup>a</sup>
Fasting glucose	≥110 mg/dl	2 (2)	0.4 (0.4)	≥110 mg/dl	2 (2)	0.4 (0.4)
MBS prevalence	≥3 of above	37 (7)	5 (2) <sup>a</sup>	≥3 of above	47 (7)	13 (3) <sup>a</sup>

Cook criteria refers to those proposed by Cook *et al.* (2); de Ferranti criteria were proposed by de Ferranti *et al.* (3).<sup>a</sup> Prevalence in girls with PCOS compared with girls in NHANES III; *P* < 0.05.

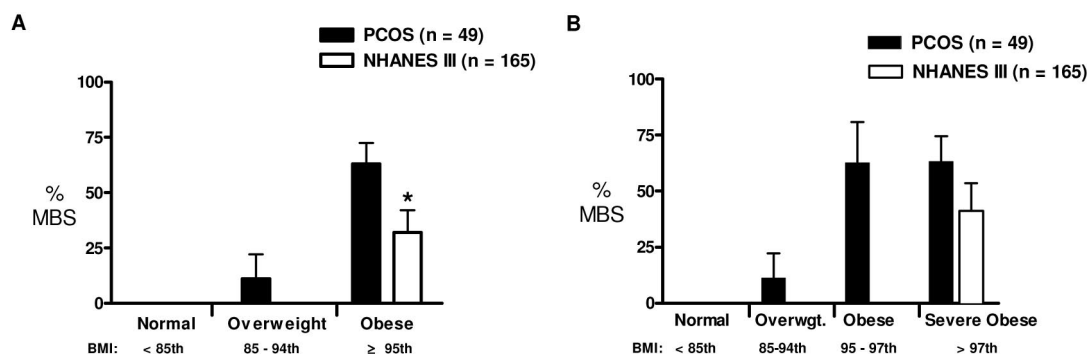


FIG. 1. A, The prevalence of MBS was higher in obese adolescent girls with PCOS compared with obese girls of similar age and ethnic/racial background in the NHANES III population using the Cook criteria ( $P = 0.01$ ). B, All of the MBS cases in the NHANES III population were in girls in the severely obese category, whereas MBS occurred in girls with lower BMIs in the setting of PCOS (overall trend,  $P = 0.01$ ). A similar pattern was seen with the de Ferranti criteria but was not statistically significant (data not shown). Columns are proportions with SE bars. Mean uT, T, and SHBG  $\pm$  SD for BMI brackets in B are as follows: normal, uT =  $21 \pm 9$  ng/dl, T =  $78 \pm 24$  ng/dl, and SHBG =  $105 \pm 63$  nmol/liter; overweight, uT =  $20 \pm 7$  ng/dl, T =  $50 \pm 15$  ng/dl, and SHBG =  $60 \pm 36$  nmol/liter; obese, uT =  $34 \pm 11$  ng/dl, T =  $82 \pm 18$  ng/dl, and SHBG =  $41 \pm 14$  nmol/liter; and severe obese, uT =  $38 \pm 16$  ng/dl, T =  $81 \pm 23$  ng/dl, and SHBG =  $37 \pm 22$  nmol/liter.

crease in uT after adjusting for HOMA-IR and BMI (OR, 3.8; 95% CI, 1.4–10.2;  $P = 0.008$ ) (Table 3). The prevalence of MBS increased with increasing uT quartile ( $P < 0.001$ ) (Fig. 2) and decreased with increasing SHBG quartile ( $P < 0.001$ ). The relative odds of having MBS increased approximately four times for every quartile increase in uT after adjusting for SHBG (OR, 3.8; 95% CI, 1.6–9.2;  $P = 0.003$ ). Girls with uT in the highest two quartiles were approximately 14 times more likely to have MBS than girls with uT in the lowest two quartiles after adjusting for IR and obesity (OR, 14.3; 95% CI, 2.0–100.5;  $P = 0.007$ ).

uT correlated positively with BMI percentile ( $\rho = 0.61$ ;  $P < 0.0001$ ), waist circumference ( $\rho = 0.54$ ;  $P = 0.0001$ ), fasting insulin ( $\rho = 0.39$ ;  $P = 0.005$ ), HOMA-IR ( $\rho = 0.37$ ;  $P = 0.008$ ), fasting TG ( $\rho = 0.34$ ;  $P = 0.02$ ), and systolic ( $\rho = 0.38$ ;  $P = 0.007$ ) and diastolic ( $\rho = 0.35$ ;  $P = 0.01$ ) blood pressure. uT did not correlate with fasting glucose but was negatively correlated with HDLc ( $\rho = -0.42$ ;  $P = 0.003$ ). SHBG correlated negatively with BMI percentile ( $\rho = -0.57$ ;  $P < 0.0001$ ), waist circumference ( $\rho = -0.56$ ;  $P < 0.0001$ ), fasting insulin ( $\rho = -0.42$ ;  $P = 0.003$ ), HOMA-IR ( $\rho = -0.42$ ;  $P = 0.003$ ), and uT ( $\rho = -0.70$ ;  $P < 0.0001$ ). HOMA-IR was positively correlated with BMI percentile ( $\rho = 0.59$ ;  $P < 0.0001$ ).

### Lipids

There was no significant difference in the prevalence of elevated LDLc or non-HDLc between girls with PCOS and

NHANES III girls. LDLc was in the borderline range ( $110\text{--}129$  mg/dl) in  $10 \pm 4\%$  of girls with PCOS compared with  $8 \pm 3\%$  of NHANES III girls (26) and in the at-risk range ( $\geq 130$  mg/dl) in  $17 \pm 5\%$  of girls with PCOS vs.  $18 \pm 4\%$  of NHANES III girls (27). Non-HDLc was greater than the 90th percentile for white females aged 12–17 yr in  $20 \pm 6\%$  of girls with PCOS compared with  $13 \pm 3\%$  of NHANES III girls (16). LDLc and non-HDLc were significantly correlated ( $\rho = 0.93$ ;  $P < 0.0001$ ) in the PCOS population.

The lipid profiles for adolescent girls with PCOS varied with MBS status. Mean fasting LDLc was higher in the group with MBS compared with those without MBS ( $109 \pm 22$  vs.  $94 \pm 25$  mg/dl;  $P = 0.03$ ) using the Cook adolescent MBS criteria. Mean HDLc was lower ( $36 \pm 5$  vs.  $45 \pm 11$  mg/dl;  $P = 0.0003$ ) and mean TG higher ( $176 \pm 86$  vs.  $90 \pm 43$  mg/dl;  $P < 0.0001$ ) in girls with MBS than those unaffected by MBS. Mean non-HDLc was higher in the girls with MBS ( $142 \pm 25$  vs.  $111 \pm 30$  mg/dl;  $P < 0.001$ ).

### Blood pressure

The prevalence of hypertension was greater in girls with PCOS compared with the NHANES III girls,  $27 \pm 6\%$  vs.  $1 \pm 1\%$ , respectively ( $P < 0.0001$ ). Girls with PCOS were also more at risk for hypertension with a blood pressure in the 90–95th percentile than the NHANES III girls,  $14 \pm 5\%$  vs.  $2 \pm 1\%$ , respectively ( $P < 0.0001$ ) (24).

**TABLE 3.** Logistic regression with MBS (Cook criteria) as dependent variable (n = 49 girls): estimating odds of MBS by uT quartile adjusting for HOMA-IR and BMI

	OR	95% CI	P
Relative odds of MBS by univariate risk factors			
uT quartile	4.8	2.1–11.2	<0.0001
SHBG quartile	0.3	0.2–0.7	0.002
Inverse SHBG quartile	3.0	1.5–5.9	0.002
HOMA-IR quartile	2.6	1.4–4.8	0.004
BMI percentile bracket <sup>a</sup>	3.8	1.8–8.2	0.001
Relative odds of MBS by uT quartile adjusted for the following risk factors:			
HOMA-IR quartile	4.8	1.8–12.4	0.001
BMI percentile bracket <sup>a</sup>	3.5	1.4–8.8	0.007
SHBG quartile	3.8	1.6–9.2	0.003
HOMA-IR quartile and BMI percentile bracket <sup>a</sup>	3.8	1.4–10.2	0.008

<sup>a</sup> BMI percentile brackets: <85th, 85–94th, 95–97th, and >97th.

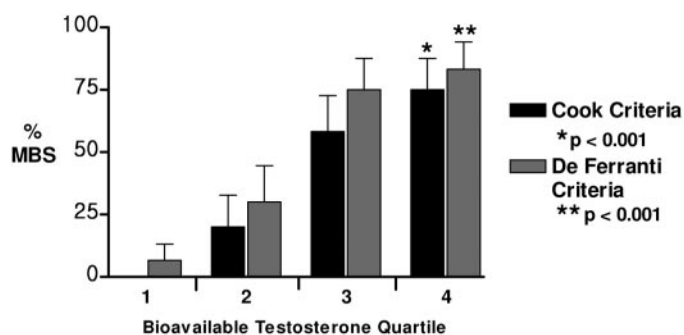


FIG. 2. The prevalence of the MBS increased with increasing uT quartile ( $\chi^2$  test for trend,  $P < 0.001$ ) with both sets of proposed criteria. The relative odds of having the MBS (Cook criteria) increased approximately five times (OR, 4.8; 95% CI, 2.1–11.2;  $P < 0.0001$ ) for every quartile increase in uT. Columns are proportions with SE bars. Mean uT  $\pm$  SD for each quartile is 1)  $16 \pm 4$  ng/dl, 2)  $24 \pm 2$  ng/dl, 3)  $30 \pm 2$  ng/dl, and 4)  $50 \pm 11$  ng/dl. Mean SHBG  $\pm$  SD for each quartile is 1)  $101 \pm 64$  nmol/liter, 2)  $53 \pm 18$  nmol/liter, 3)  $43 \pm 20$  nmol/liter, and 4)  $33 \pm 20$  nmol/liter. Mean T  $\pm$  SD for each quartile is 1)  $62 \pm 20$  ng/dl, 2)  $66 \pm 12$  ng/dl, 3)  $77 \pm 23$  ng/dl, and 4)  $97 \pm 22$  ng/dl.

### Discussion

Adolescent girls with PCOS have substantially increased risk for the MBS compared with the general female adolescent NHANES III population using either of the currently proposed criteria: 37 vs. 5% with the Cook criteria, respectively, and 47 vs. 13% with the de Ferranti criteria, respectively (2, 3). Although obesity and IR are significant risk factors for the MBS, hyperandrogenemia remained a significant predictor of the MBS after adjusting for both obesity and IR.

The Cook criteria were modified from the adult National Cholesterol Education Program Adult Treatment Panel III criteria by lowering the TG and HDLc cutoff points and using the 90th percentile for age and gender for waist circumference and the 90th percentile for age, gender, and height for blood pressure as cutoff points. The de Ferranti criteria were targeted to parallel the adult percentile cutoff points more closely, resulting in more liberal criteria. The difference between the Cook and de Ferranti criteria is largely because of the decrease in the waist circumference cutoff point from the 90th to the 75th percentile and the increase in the HDLc cutoff point from no more than 40 to less than 50.2 mg/dl in the de Ferranti criteria. The prevalence of elevated TG, elevated blood pressure, and fasting hyperglycemia was similar between the two sets of criteria (Table 2).

The increasing prevalence of MBS in children and adolescents has coincided with the rise in obesity as it has in adults (2, 28). The prevalence of MBS increased with BMI in the NHANES III population with both the Cook and de Ferranti criteria (2, 3) and has been estimated to be as high as 50% in a study of severely obese adolescents (4). Both BMI and waist circumference have been shown to be predictive of metabolic cardiovascular risk factors in children and adolescents (29). The rise in childhood obesity correlates with increased waist circumference, a good marker of abdominal visceral fat (14). Visceral adiposity is associated with IR, the primary pathophysiological mechanism thought to be responsible for the metabolic disturbances of MBS (1, 30, 31). Obesity is also a common feature of PCOS, affecting approximately 50–70% of adult women, with a fat distribution char-

acterized by increased central adiposity (32, 33). However, the high prevalence of MBS in these adolescent girls with PCOS cannot be accounted for by obesity alone. The prevalence of the MBS was similar in the obese (BMI, 95–97th percentile) and very obese (BMI, >97th percentile) girls, 62 vs. 63%, respectively (Fig. 1B).

Although the odds of having MBS increased significantly with both increasing HOMA-IR and BMI, the odds of having MBS increased approximately 4-fold for every quartile increase in uT independent of BMI and IR (Table 3). The increased risk of MBS associated with uT was also independent of SHBG. Treatment with flutamide, a nonsteroidal androgen receptor antagonist, has been shown to decrease central fat mass in obese women with PCOS (34) as well as in nonobese women and adolescent girls with PCOS in combination with metformin (35). There is evidence of an additive effect on the improvement of body composition, androgen levels, and IR when metformin and flutamide are used together (35, 36), suggesting an interaction between hyperandrogenemia, hyperinsulinemia, and obesity in the expression of the metabolic phenotype in PCOS. Interestingly, hyperandrogenemia has also been reported to be an independent risk factor for MBS in premenopausal women without PCOS (37) and has been associated with hyperinsulinemia, fasting hyperglycemia, and the metabolic syndrome in postmenopausal women as well (13). Androgen receptors have been identified on preadipocytes and adipocytes, and there is some evidence that intraabdominal fat development may be influenced by androgens (38). Androgens may contribute to MBS through mechanisms independent of or in synergy with central obesity and visceral adiposity.

The prevalence of hypertension was higher in the adolescent girls with PCOS compared with the NHANES III population, 27 vs. 1%, respectively (2). Adolescent girls with PCOS and abnormal glucose tolerance have a disruption of normal circadian blood pressure fluctuations that may be a precursor to the development of hypertension (9). Adolescent girls with PCOS and elevated blood pressure who meet criteria for MBS may represent a subset of girls with a more severe metabolic phenotype.

In addition to the lower HDLc and higher TG levels expected with MBS, the adolescent girls with PCOS and MBS in this study had significantly higher LDLc and non-HDLc compared with girls with PCOS without MBS. Elevated LDLc is characteristic of adult women with PCOS as well as sisters of women with PCOS who have hyperandrogenemia with normal menses (12, 21, 39). Treatment of adult women with the nonsteroidal androgen receptor antagonist flutamide has been shown to decrease fasting cholesterol and LDLc (12, 34, 40) and increase HDLc independent of obesity (40). Elevated LDLc and non-HDLc levels in adolescent girls with PCOS represent additional potential cardiovascular risk factors (16).

In summary, adolescent girls with PCOS appear to be at substantially increased risk for the MBS relative to adolescent girls in the general population. Hyperandrogenemia, in addition to obesity and IR, is an important risk factor for MBS in PCOS. These defects can be targeted with traditional therapy such as diet and exercise as well as with novel interventions with insulin sensitizers and antiandrogens. Early identification of MBS and intervention in adolescent girls with PCOS may

mitigate the associated metabolic effects and reduce the risk of developing diabetes and cardiovascular disease.

## Acknowledgments

Received July 26, 2005. Accepted October 17, 2005.

Address all correspondence and requests for reprints to: Andrea Dunaif, M.D., Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue, Tarry Building 15-709, Chicago, Illinois 60611-3008. E-mail: a-dunaif@northwestern.edu

This work was supported by the National Institutes of Health/National Institute of Child Health and Human Development through the National Cooperative Program in Infertility Research U54 HD34449, the Specialized Center of Research on Genes, Androgens, and Intrauterine Environment in PCOS P50 HD44405, K24 HD01476, and GCRC Grants M01 RR00048, M01 RR02635, and M01 RR 10732 and construction Grant C06 RR016499 to Pennsylvania State University.

## References

1. Ford ES, Giles WH, Dietz WH 2002 Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287:356–359
2. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH 2003 Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Arch Pediatr Adolesc Med* 157:821–827
3. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N 2004 Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation* 110:2494–2497
4. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S 2004 Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 350:2362–2374
5. Palmert MR, Gordon CM, Kartashov AI, Legro RS, Emans SJ, Dunaif A 2002 Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. *J Clin Endocrinol Metab* 87:1017–1023
6. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S 2002 Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 346:802–810
7. Cruz ML, Weigensberg MJ, Huang TT, Ball G, Shaibi GQ, Goran MI 2004 The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab* 89:108–113
8. Cruz ML, Goran MI 2004 The metabolic syndrome in children and adolescents. *Curr Diab Rep* 4:53–62
9. Arslanian SA, Lewy VD, Danadian K 2001 Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and  $\beta$ -cell dysfunction and risk of cardiovascular disease. *J Clin Endocrinol Metab* 86:66–71
10. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE 2004 Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 90:1929–1935
11. Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L 2003 Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. *Metabolism* 52:908–915
12. Sam S, Legro RS, Bentley-Lewis R, Dunaif A 2005 Dyslipidemia and metabolic syndrome in the sisters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 90:4797–4802
13. Golden SH, Ding J, Szklo M, Schmidt MI, Duncan BB, Dobs A 2004 Glucose and insulin components of the metabolic syndrome are associated with hyperandrogenism in postmenopausal women: the atherosclerosis risk in communities study. *Am J Epidemiol* 160:540–548
14. Cook S 2004 The metabolic syndrome: antecedent of adult cardiovascular disease in pediatrics. *J Pediatr* 145:427–430
15. Goodman E, Daniels SR, Morrison JA, Huang B, Dolan LM 2004 Contrasting prevalence of and demographic disparities in the World Health Organization and National Cholesterol Education Program Adult Treatment Panel III definitions of metabolic syndrome among adolescents. *J Pediatr* 145:445–451
16. Berenson GS, Srinivasan SR 2005 Cardiovascular risk factors in youth with implications for aging: the Bogalusa Heart Study. *Neurobiol Aging* 26:303–307
17. Zawadzki J, Dunaif A 1992 Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens J, Haseltine F, Merriam G, eds. *Polycystic ovary syndrome*. Boston: Blackwell Scientific; 377–384
18. Legro RS, Driscoll D, Strauss 3rd JF, Fox J, Dunaif A 1998 Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. *Proc Natl Acad Sci USA* 95:14956–14960
19. 1994 Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: programs and collection procedures. *Vital Health Stat* 1:1–407
20. Dunaif A, Finegood DT 1996  $\beta$ -Cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 81:942–947
21. Legro RS, Kusanman AR, Dunaif A 2001 Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 111:607–613
22. 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
23. Fernandez JR, Redden DT, Pietrobello A, Allison DB 2004 Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr* 145:439–444
24. 2004 The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114:555–576
25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC 1985 Homeostasis model assessment: insulin resistance and  $\beta$ -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419
26. O'Loughlin J, Lauzon B, Paradis G, Hanley J, Levy E, Delvin E, Lambert M 2004 Usefulness of the American Academy of Pediatrics recommendations for identifying youths with hypercholesterolemia. *Pediatrics* 113:1723–1727
27. Hickman TB, Briefel RR, Carroll MD, Rifkind BM, Cleeman JI, Maurer KR, Johnson CL 1998 Distributions and trends of serum lipid levels among United States children and adolescents ages 4–19 years: data from the Third National Health and Nutrition Examination Survey. *Prev Med* 27:879–890
28. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM 2004 Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA* 291:2847–2850
29. Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C, Berenson GS 2004 Body mass index, waist circumference, and clustering of cardiovascular disease risk factors in a biracial sample of children and adolescents. *Pediatrics* 114:e198–205
30. Reaven GM, Lithell H, Landsberg L 1996 Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 334:374–381
31. Grundy SM 1999 Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol* 83:25F–29F
32. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R 2002 Obesity and the polycystic ovary syndrome. *Int J Obes Relat Metab Disord* 26:883–896
33. Legro RS, Kusanman AR, Dodson WC, Dunaif A 1999 Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 84:165–169
34. Gambineri A, Pelusi C, Genghini S, Morselli-Labate AM, Cacciari M, Pagotto U, Pasquali R 2004 Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 60:241–249
35. Ibanez L, De Zegher F 2003 Flutamide-metformin therapy to reduce fat mass in hyperinsulinemic ovarian hyperandrogenism: effects in adolescents and in women on third-generation oral contraception. *J Clin Endocrinol Metab* 88:4720–4724
36. Ibanez L, Valls C, Ferrer A, Ong K, Dunger DB, De Zegher F 2002 Additive effects of insulin-sensitizing and anti-androgen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 87:2870–2874
37. Korhonen S, Hippelainen M, Vanhala M, Heinonen S, Niskanen L 2003 The androgenic sex hormone profile is an essential feature of metabolic syndrome in premenopausal women: a controlled community-based study. *Fertil Steril* 79:1327–1334
38. Dieudonne MN, Pecquery R, Boumediene A, Leneuve MC, Giudicelli Y 1998 Androgen receptors in human preadipocytes and adipocytes: regional specificities and regulation by sex steroids. *Am J Physiol* 274:C1645–C1652
39. Orio Jr F, Palomba S, Spinelli L, Cascella T, Tauchmanova L, Zullo F, Lombardi G, Colao A 2004 The cardiovascular risk of young women with polycystic ovary syndrome: an observational, analytical, prospective case-control study. *J Clin Endocrinol Metab* 89:3696–3701
40. Diamanti-Kandarakis E, Mitrakou A, Raptis S, Tolis G, Duleba AJ 1998 The effect of a pure antiandrogen receptor blocker, flutamide, on the lipid profile in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 83:2699–2705