Gonadal dysfunction in morbidly obese adolescent girls

Vivian Chin, M.D.,[a] Marisa Censani, M.D.,[a] Shulamit Lerner, M.D.,[a] Rushika Conroy, M.D.,[a] Sharon Oberfield, M.D.,[a] Donald McMahon, M.S.,[b] Jeffrey Zitsman, M.D.,[c] and Ilene Fennoy, M.D., M.P.H.[a]

[a] Division of Pediatric Endocrinology, Department of Pediatrics, [b] Department of Medicine, and [c] Department of Surgery, Columbia University Medical Center, New York, New York

Objective: To describe gonadal dysfunction and evaluate polycystic ovary syndrome (PCOS) and its association with metabolic syndrome (MeS) among girls in a morbidly obese adolescent population.
Design: In a cross-sectional study of 174 girls, height, weight, waist circumference, Tanner stage, reproductive hormones, carbohydrate and lipid markers, drug use, and menstrual history were obtained at baseline. Exclusion criteria were menarcheal age <2 years, hormonal contraceptive or metformin use, Tanner stage <4, and incomplete data on PCOS or MeS classification.
Setting: University medical center outpatient clinic.
Patient(s): Ninety-eight girls ages 13–19.6 years, Tanner 5, average body mass index of 46.6 kg/m^2, menarche at 11.4 years, and average menarcheal age of 5 years.
Intervention(s): None.
Main Outcome Measure(s): Polycystic ovary syndrome and MeS.
Result(s): Ninety-eight girls were divided into four groups: PCOS by National Institutes of Health criteria ($PCOS_N$, n = 24), irregular menses only (n = 25), elevated T (≥55 ng/dL) only (n = 6), and obese controls (n = 43). Metabolic syndrome by modified Cook criteria affected 32 girls or 33% overall: 6 of 24 $PCOS_N$, 7 of 25 irregular menses only, 4 of 6 elevated T only, and 15 of 43 obese controls. Polycystic ovary syndrome by National Institutes of Health criteria and its individual components were not associated with MeS after adjusting for body mass index.
Conclusion(s): Unlike obese adults, $PCOS_N$ and its individual components were not associated with MeS in the untreated morbidly obese adolescent population. (Fertil Steril® 2014;101: 1142–8. ©2014 by American Society for Reproductive Medicine.)
Key Words: Metabolic syndrome, polycystic ovary syndrome, bariatric surgery, morbid obesity

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Polycystic ovary syndrome (PCOS) is a condition of anovulation, clinical or biochemical hyperandrogenism, and/or polycystic ovaries and is the most common endocrinopathy of reproductive-aged women, affecting 5%–7% by the strictest criteria. Obesity increases this risk: 25% of overweight and obese women, rising to as high as 35% of morbidly obese women, are affected with PCOS (1–3). Metabolic syndrome (MeS) refers to a constellation of risk factors such as insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein (HDL) cholesterol, and increased low-density lipoproteins (LDLs) (4). Metabolic syndrome and its components increase an individual's overall risk for type 2 diabetes, cardiovascular disease (CVD), and mortality due to CVD (5, 6). Women with PCOS often have CVD, and it is unclear whether this risk is due to the increased prevalence of MeS. Metabolic syndrome affects 43%–50% of women with PCOS, compared with approximately 25% of the general population (7–10). Studies have shown that MeS prevalence in adult women with PCOS is two to three times higher than in control women after adjusting for body mass index (BMI) (9, 11, 12).

Morbidly obese adolescents often have multiple comorbidities, including hypertension, obstructive sleep apnea, hyperlipidemia, type 2 diabetes, metabolic syndrome, hepatic steatosis, and depression. However, gonadal dysfunction in the morbidly obese group has not been well studied. A literature search revealed few reports with mention of amenorrhea, irregular menses, hirsutism, and PCOS among adolescent girls in bariatric surgery programs (13–16). The childhood

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Reprint requests: Ilene Fennoy, M.D., M.P.H., Columbia University Medical Center, 622 West 168th Street, PH 5E-522, New York, New York 10032 (E-mail: if1@cumc.columbia.edu).

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obesity rate is alarmingly high, and identification of PCOS and MeS as cardiovascular risk factors in childhood should be considered because 77% of overweight children remain overweight as adults (17). Childhood MeS status has been shown to predict the risk for MeS in adulthood as well as type 2 diabetes in 25–30 years (18). Metabolic syndrome affects 8.6% of children, but the rate is much higher, nearly 30%, in overweight adolescents (19, 20). Although the relationship between PCOS and MeS has been well studied and verified in adults, it is not as well defined in adolescents. Some reports show that MeS affects 10.8%–37% of adolescent girls with PCOS, whereas others report that PCOS does not confer additional risk for MeS (21–23). Like adult women, adolescents with PCOS are insulin resistant, and PCOS may be able to predict MeS on the basis of this mechanism (24, 25). The objective of this study is to describe gonadal dysfunction and to determine whether PCOS can predict MeS in a group of adolescent girls with morbid obesity being evaluated for bariatric surgery.

MATERIALS AND METHODS

The study was approved by the institutional review board at Columbia University Medical Center. Written informed consent was obtained from all participants and their parents or legal guardians before enrollment. All authors have no known or perceived conflicts of interest. All adolescent girls who were being evaluated for bariatric surgery in the Center for Adolescent Bariatric Surgery program at Columbia University Medical Center had baseline measures taken. Height, weight, waist circumference (WC), blood pressure (BP), Tanner stage, reproductive hormones, carbohydrate and lipid markers, drug use, and menstrual history were obtained. Height, weight, WC, and BP were measured as previously reported (26). Laboratory values were performed after an overnight fast between the hours 8:00 AM and 10:00 AM, with hormonal assays performed at Esoterix, Inc., a specialized endocrine laboratory that measures insulin by immunochemiluminometric assay, total and free T and sex hormone–binding globulin (SHBG) by high-performance liquid chromatography tandem mass spectrometry by equilibrium dialysis, and LH and FSH by electrochemiluminometric assay. Glucose, lipids, liver function tests, and basic metabolic panel were performed at the laboratory of New York Presbyterian Hospital. The homeostatic index of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5 (27). A 2-hour oral glucose tolerance test was performed using the standard 75 grams of glucose. Area under the curve for glucose (AUC-G_{120}) and insulin (AUC-I_{120}) was calculated using the trapezoidal rule and four data points at 0, 30, 60, and 120 minutes (28). Height percentile, weight percentile, BMI percentile, and BMI *z*-score adjusted for age and sex were calculated using EpiInfo, version 3.5.3, provided by the Centers for Disease Control and Prevention. Blood pressure percentile adjusted for height and sex was calculated according to The Fourth Report using an online calculator from Uptodate.com (29).

Diagnosis of PCOS and MeS

Diagnosis of PCOS defined by National Institutes of Health (NIH) criteria ($PCOS_N$) was made if both criteria were met: [1] clinical or biochemical hyperandrogenism (total T $\geq$55 ng/dL) and [2] oligomenorrhea with fewer than eight cycles per year or amenorrhea (30). Clinical hyperandrogenism, which included signs like acne or hirsutism, was not systematically recorded, but when present was used in the diagnosis of $PCOS_N$. Girls with previous history of PCOS without confirmation of NIH criteria were not classified in the $PCOS_N$ group. Other endocrinopathies were excluded. Diagnosis of MeS defined by the modified Cook criteria is fulfilled if three of the following five were met: [1] fasting blood glucose $\geq$100 mg/dL, modified to the 2003 American Diabetes Association criterion, [2] triglycerides (TG) $\geq$110 mg/dL, [3] HDL $\leq$40 mg/dL, [4] WC $\geq$90th percentile for ethnicity, age, and sex, and [5] systolic or diastolic BP $\geq$90th percentile for age, height, and sex (20).

Only girls with complete data on menstrual history, total T values, fasting blood glucose, TG, HDL, WC, and BP were included in the study. All girls were at least 2 years postmenarche. Girls who did not have complete data, were <2 years postmenarcheal age, Tanner staging <4, or treated with hormonal contraceptives like oral contraceptive pills or intrauterine device or insulin-sensitizing agents like metformin for any reason were excluded.

Statistics

Group comparisons of multiple means were performed using analysis of variance, and adjustment for multiple means comparisons was performed using Scheffe's test. Fisher's exact test was performed for tests of proportions. SAS software was used (SAS Institute). An α level of 0.05 or less was considered statistically significant. Logistic regression modeling was used to examine predictors of metabolic syndrome using PCOS and its individual components as independent variables after adjusting for BMI.

RESULTS

A total of 174 girls were enrolled in the Center for Adolescent Bariatric Surgery program at Columbia University Medical Center from 2006 to 2013. After exclusion of 29 girls with missing data, 7 girls with menarcheal age <2 years, 1 girl with Tanner 3 staging, 16 girls taking metformin, 16 girls taking hormonal contraceptive, and 7 girls taking both, data from 98 girls were analyzed. They were divided into four groups: $PCOS_N$ (n = 24), irregular menses only (IM, n = 25), elevated T only (ET, n = 6), and obese controls (OC, n = 43).

Ninety-eight girls, ages 13 to 19.6 years, mean age 16.4 years (SD 1.3 years), Tanner 5, with an average BMI of 46.6 kg/m^2 (SD 7.3 kg/m^2) and average menarcheal age of 5 years (SD 1.7 years) were included in the study. They were predominantly Caucasian (42 of 98) and Hispanic (32 of 98); the rest were identified as African American (19 of 98), Asian (1 of 98), and other/unknown (4 of 98). Twenty-four of 98 (24.5%) were diagnosed with PCOS by NIH criteria, 25.5% (25 of 98) had irregular menses only, 6% (6 of 98) had elevated T only,

and 44% (43 of 98) were obese controls. All four groups were similar in their chronological age, weight, and age of menarche (Table 1). Body mass index was significantly higher in the IM group compared with the OC group (49.8 vs. 44.4 kg/m^2, P=.03). Menarcheal age was greater in $PCOS_N$ than in OC (5.9 vs. 4.7 years, P=.03). For MeS components, all four groups were similar in their HDL, TGs, systolic and diastolic BP percentile, WC, and fasting glucose. Measures of insulin resistance (HOMA-IR, HgbA1c, AUC-I_{120}, fasting insulin) and metabolic parameters (total cholesterol and LDL, aspartate aminotransferase (AST), alanine aminotransferase (ALT)), as well as hormonal values (LH, FSH, E_2, SHBG) were similar in all four groups. The $PCOS_N$ group had the highest AUC-G_{120} of 130.4 mg/dL/min compared with the OC group, with a level of 109.4 mg/dL/min (P=.018). As expected, total T levels were significantly different between groups, with ET having the highest mean T of 67 ng/dL, followed by $PCOS_N$ with mean T of 60.9 ng/dL, compared with IM and OC groups with lower T levels of 32.2 and 31.9 ng/dL, respectively (P<.0001). Free T was also elevated in $PCOS_N$ compared with IM and OC (11.5, 5.4, and 5.2 pg/mL, respectively, P<.0001). Metabolic syndrome by modified Cook criteria affected 32 girls or 33% overall, affecting 25% of $PCOS_N$, 28% of IM, 67% of ET, and 35% of OC, which is statistically similar among all groups (Fig. 1, P=.27).

To answer the question whether PCOS status can predict MeS status, three models were created by logistic regression analysis (Table 2). To model MeS, the dependent variable, we used PCOS components (irregular menses and T separately) as independent predictors while controlling for BMI in model 1 and model 2, respectively. In model 3, PCOS status itself was used as an independent predictor of MeS while controlling for BMI. Neither irregular menses in model 1 (odds ratio [OR] 0.4, confidence interval [CI] 0.16–1.04) nor T levels in model 2 (OR 1.07, CI 0.38–2.99) were significant predictors of MeS after adjusting for BMI. In model 3, PCOS status (OR 0.59, CI 0.19–1.63) itself was not a significant predictor of MeS after adjusting for BMI.

DISCUSSION

The identification of adolescents with PCOS is often difficult, owing to the transient and physiologic nature of features such as irregular menses and polycystic ovary morphology, in addition to difficulty in interpretation of clinical and biochemical evidence of hyperandrogenism. Three diagnostic

TABLE 1

Clinical, metabolic, and hormonal values by group expressed as mean (SD).

Parameter	$PCOS_N$ (n = 24)	IM (n = 25)	ET (n = 6)	OC (n = 43)	*P* value
Clinical characteristic					
Age range (y)	13–19.6	14–19.3	14.7–17.8	14.2–18.9	
Mean age (y)	16.8 (1.4)	16.0 (1.3)	16.0 (1.2)	16.5 (1.2)	.18
BMI (kg/m^2)	47.5 (8.3)	49.8 (9.2)	46.6 (7)	44.4 (4.6)	.03[a]
Weight (kg)	125.5 (22)	134.0 (22)	123.8 (19)	124.0 (17.8)	.23
Age menarche (y)	10.8 (1.6)	11.2 (1.6)	11.3 (0.8)	11.8 (1.1)	.056
Menarcheal age (y)	5.9 (1.9)	4.8 (1.8)	4.7 (1.8)	4.7 (1.5)	.03[b]
MeS (%)	25	28	67	35	.27
HDL (mg/dL)	44.7 (8)	42.5 (6)	45.3 (9)	43.2 (7)	.68
TG (mg/dL)	101.1 (39)	93.4 (38)	87 (23)	98.9 (49)	.85
Systolic BP%ile	62.3 (28)	61.7 (32)	76.2 (23)	65.4 (28)	.70
Diastolic BP%ile	73.5 (25)	78.2 (19)	74.3 (20)	70.0 (19)	.46
WC (cm)	131.5 (15)	137.8 (14)	128.2 (13)	130.4 (13)	.16
Fasting glucose (mg/dL)	88 (27)	84.3 (6)	85.7 (6)	86.9 (10)	.85
Other metabolic and hormonal values					
HOMA-IR	3.6 (2.5)	2.9 (2)	3.1 (1)	2.8 (3)	.70
HgbA1c (%)	5.7 (1)	5.6 (0.4)	5.8 (0.6)	5.5 (0.4)	.42
AUC-G_{120}(mg/dL/min)	130.4 (46)	120.9 (16)	125 (23)	109.4 (15)	.018[b]
AUC-I_{120} (μIU/mL/min)	57.1 (52)	65.7 (49)	58.2 (16)	39.9 (25)	.07
Fasting Insulin (μIU/mL)	16.1 (12)	13.7 (8)	14.9 (7)	13 (14)	.81
Cholesterol (mg/dL)	169.3 (24)	160.2 (28)	166.8 (36)	160 (31)	.57
LDL (mg/dL)	104.5 (22)	98.8 (24)	104 (39)	96.8 (26)	.66
AST (U/L)	18.8 (5)	19.7 (7)	16.7 (3)	16.5 (4)	.07
ALT (U/L)	21.3 (14)	20.8 (9)	15.5 (5)	16.7 (8)	.16
LH (mIU/mL)	8.2 (6)	6.1 (3)	8.7 (3)	9.9 (15)	.63
FSH (mIU/mL)	5.4 (2)	5.3 (2)	5.6 (2)	5.4 (3)	.99
E_2 (ng/dL)	18.5 (20)	14.1 (15)	47.2 (36)	28.9 (48)	.19
T (ng/dL)	60.9 (22)	32.2 (10)	67 (16)	31.9 (12)	<.0001[b,c,d,e]
Free T (pg/mL)	11.5 (7)	5.4 (2)	9.3 (5)	5.2 (2)	<.0001[b,c]
SHBG	30.3 (27)	27.0 (14)	42.2 (18)	27.0 (12)	.24

Note: Values expressed as mean (SE) except for MeS, expressed as percent. Analysis for group comparisons done with analysis of variance with the exception of MeS, which used Fisher's exact test.
[a] IM vs. OC.
[b] $PCOS_N$ vs. OC.
[c] $PCOS_N$ vs. IM.
[d] ET vs. IM.
[e] ET vs. OC.

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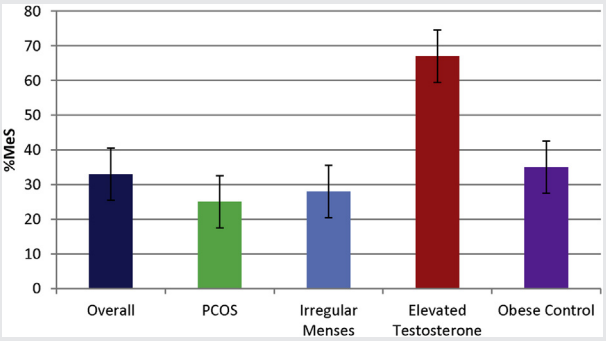
FIGURE 1



Prevalence of metabolic syndrome by group (percentage affected, with SE bars, *P*=.27).

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criteria for PCOS exist: 1990 NIH criteria, Androgen Excess Society criteria, and the Rotterdam criteria. The NIH criteria require anovulation/oligomenorrhea and clinical or biochemical hyperandrogenism, whereas the appearance of polycystic ovaries is not required for the diagnosis of PCOS. The Androgen Excess criteria require hyperandrogenism/hyperandrogenemia and one additional criterion, whereas the Rotterdam criteria do not specify which two of the three must be met.

Although menstrual irregularity in adults indicates anovulation of clinical significance, a feature in all three diagnostic criteria for PCOS, this is less dependable in adolescents. During the first 2 years after menarche, anovulatory cycles are common, affecting approximately 50% of the cycles while the hypothalamic–pituitary–ovarian (HPO) axis matures (31). Maturation of the HPO axis occurs as FSH secretion rises and pulsatility of LH is established, and frequency increases to adult patterns by Tanner stages 4 to 5 (32). Approximately 95% of the ovulatory cycles reach the 21–45 day range, with periods lasting 2–7 days in the third year after menarche (33). van Hooff et al. (34) found that more than half of the girls studied in his population cohort with oligomenorrhea at age 15 years remained so at age 18 years, and elevated LH, DHEAS, and T levels were strong predictors for persistent oligomenorrhea (34). This suggests that oligomenorrhea and anovulatory cycles that persist past 2 years after menarche are associated with PCOS. Roe et al. (22) studied a group of adolescents with PCOS according to Androgen Excess Society criteria and found that 98% of the girls reported menstrual irregularity, followed by acne, hirsutism, and weight gain. One must also take into account the age of menarche: the earlier the onset of menarche, the shorter the expected duration of oligomenorrhea due to anovulatory cycles (35). In our study, the average menarcheal age was 5 years.

Acne, a common complaint among adolescents, may resolve or improve over time. Hickey et al. (36) reports that 70% of adolescent girls had signs of mild to severe acne, which were not associated with elevated levels of free T. Establishment of clinical hyperandrogenism in adolescent girls with hirsutism is problematic because the Ferriman-Gallwey scoring system is standardized primarily on white women, mostly aged >24 years (37). Variable degrees of hirsutism among different ethnicities and differing sensitivity to androgens also make establishment of clinical hyperandrogenism difficult (38). According to Lucky et al. (38), upper lip hair is a very common complaint among black adolescent girls 2 years after menarche, affecting 49% vs. 9% of white subjects, and was not associated with elevated levels of T. It has been suggested that progressive hirsutism is the best clinical marker for PCOS (39). Establishment of biochemical hyperandrogenism is also fraught with difficulty owing to variable sensitivities of hormonal assays, limitations due to lack of normative data, and diurnal variations in detection of T (11). In 2007 the Endocrine Society released a position statement recommending that total T detection should be completed with sensitive assays such as chromatography/mass spectrometry rather than direct immunoassays, in conjunction with well-established references values (11, 40). Carmina et al. (41) have suggested using a threshold total T value as high as >2 SD above the mean or >55–59 ng/dL during the hours of 8:00 AM to 10:00 AM during the follicular phase to define hyperandrogenism for PCOS. Use of free T is generally not recommended in girls, owing to lack of sufficient normative data.

Sonographic evidence of polycystic ovarian morphology is difficult to interpret in adolescents and can be found in as many as 40% of healthy girls without pathology 2 years after menarche (42). Physiologically, ovarian volume is low during the prepubertal period and reaches maximum volume and antral follicle count during menarche, followed by a progressive decline in size and follicle number until menopause (43). These natural changes over time make the appearance of polycystic ovaries difficult to interpret because many normal healthy girls have been found to satisfy the criteria of ovarian volume >10 mL or more than 12 2–9-mm follicles for polycystic ovary morphology (42, 44). Adding to the difficulty is the limited use of transvaginal ultrasonography in virginal patients and the difficulty in obtaining high-quality transabdominal images in overweight and obese adolescent girls (45). In an Australian-based population study, polycystic ovarian morphology was of limited use in the diagnosis of PCOS in adolescents because only 35% met the criteria for abnormal ovarian morphology or size (36). There are suggestions by various groups to redefine the threshold mean ovarian

TABLE 2

Logistic regression models for MeS prediction.

Model	OR	CI	*P* value
Model 1 for MeS			
Irregular menses	0.40	0.16–1.04	.059
BMI	0.48	0.26–0.92	.027
Model 2 for MeS			
T	1.07	0.38–2.99	.894
BMI	0.60	0.33–1.08	.087
Model 3 for MeS			
PCOS	0.59	0.19–1.63	.287
BMI	0.57	0.31–1.04	.068

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volume according to different imaging modalities. Mean ovarian volumes of 5.6 mL for transabdominal and 6.74 mL for transvaginal ultrasounds were suggested as new threshold values with good accuracy for polycystic ovary morphology (46, 47). Given all these limitations and the large body habitus of our subjects, with an average WC of 132 cm, transabdominal pelvic ultrasound scans were not routinely performed in our subjects. Additionally, polycystic ovarian morphology is not a requirement to satisfy NIH criteria.

To the best of our knowledge, this study is the first to examine gonadal dysfunction in morbidly obese adolescent girls. Twenty-five percent of our untreated morbidly obese adolescents were affected by $PCOS_N$, which is slightly lower than what is expected in the adult population, whereas 28% had irregular menses only without any evidence of clinical or biochemical hyperandrogenism, and 6% had elevated T >55 ng/dL only and no evidence of menstrual irregularity.

Adolescents with PCOS have higher rates of insulin resistance than normal controls. Impaired glucose tolerance, an indicator of insulin resistance, affects between 10% and 30% of adolescents with PCOS, according to several studies (23, 24, 48). The gold standard used to assess reduced sensitivity to insulin is the euglycemic hyperinsulinemic clamp, but high costs and impracticality limit its use in clinical practice (49). Therefore, an oral glucose tolerance test is frequently used. A 75-g glucose load performed on all our subjects revealed that the AUC-G_{120} was significantly higher for the $PCOS_N$ group than for the OC group, despite no differences in AUC-I_{120}, HgbA1c, or HOMA-IR. Both groups had statistically similar BMI values. Perhaps this difference in glucose reflects deteriorating insulin sensitivity given that girls in the $PCOS_N$ group may have had the disease process for a few years. These results are consistent with the increased risk for insulin resistance in girls with PCOS.

We found no association between PCOS and MeS in the bariatric population among those without treatment and no clustering of PCOS components with MeS, which is contrary to adult data and a few previously published pediatric reports. Coviello et al. (21), using the National Health and Nutrition Examination Survey III cohort, described girls with PCOS diagnosed by NIH criteria as being 4.5 times more likely than control girls to have MeS even after adjusting for BMI; however, the presence of PCOS was not verified in the control group. Similarly, Roe et al. (22) identified 10% of girls with PCOS by Androgen Excess Criteria who had MeS, compared with 1.7% in girls without PCOS. However, the study was limited by the use of BMI as a surrogate for WC in the diagnosis of MeS and the use of controls who had some features of PCOS but not the full phenotype (22). In a study of girls with PCOS and their parental MeS status, it was found that MeS was threefold higher than expected for obesity status in girls with PCOS (12). On the other hand, among overweight and obese adolescents, PCOS status did not confer increased risk of MeS, regardless of the definition of MeS used (23). These differing conclusions may be explained by lack of consensus in defining MeS among adults and adolescents (50). For adults, MeS criteria have been defined by various groups, such as the World Health Organization, National Cholesterol Education Program Adult Treatment Panel (ATP) III, and the European Group for the Study of Insulin Resistance. In pediatrics, the modified Cook criteria, de Ferranti criteria, and International Diabetes Federation criteria have been used (20, 51–53). In adults, the ATP III definition is frequently used, incorporating features such as insulin resistance, central obesity, dyslipidemia, and hypertension without requiring any one be a key feature (54). In 2003, Cook modified the adult ATP III criteria for children; these criteria are widely used in the study of MeS in children, including this study. It remains difficult to conclusively determine whether there is an association between PCOS and MeS, given differing criteria used to define MeS among adults and adolescents.

Adding to the inconsistencies is the heterogeneity of PCOS. All three diagnostic criteria were used in various studies to describe the association between PCOS and MeS. According to Welt et al. (55) and Robinson et al. (56), those who met the NIH criteria were the most metabolically abnormal, whereas those who met Rotterdam criteria, with PCO morphology and ET or PCO morphology and IM were less insulin resistant and had lower BMI. Polycystic ovary syndrome based on differing diagnostic criteria is a heterogenous syndrome with varying metabolic dysfunction (55, 56).

Ethnic differences in PCOS phenotype have been studied and may explain the variable association between MeS and PCOS among the pediatric population (57). A majority of studies finding a positive association between PCOS and MeS had participants from the United States who were mainly of Caucasian background (9, 11, 58). In northern California, Hispanic women with PCOS were more likely to be obese and have type 2 diabetes than Caucasian and black women, respectively (59). Our study's participants varied in ethnicity, the majority being of Caucasian and Hispanic background. We expected our morbidly obese group to be more metabolically abnormal than previously studied groups consisting of mainly Caucasian women with lower average BMI. However, the prevalence of MeS was comparable to the prevalence among adult women studied. In a study of 394 women with PCOS by Ehrmann et al. (58), MeS was found to be 13.7 times more likely in the top BMI quartile compared with those in the lowest quartile. In our study, BMI of all subjects was greater than the 99th percentile, but only 33% of the group overall had MeS, and only 25% of $PCOS_N$ were affected. The prevalence of PCOS and MeS may not be accurate owing to exclusion of girls already treated with OCPs and/or metformin. Some girls who came in with a diagnosis of PCOS remained excluded from data analysis owing to inability to confirm the diagnosis while receiving treatment. However, OCPs were also started for reasons other than for PCOS, such as for contraception or for regulation of menses, including problems such as dysfunctional uterine bleeding. Girls who were treated with metformin without a confirmed documentation of impaired fasting glucose or impaired glucose tolerance while receiving treatment also remained excluded. The effect of exclusion of these girls on our data analysis is unknown, and we cannot presume that these girls were more metabolically unhealthy or severely

affected, other than the fact that they were taking metformin and/or OCPs for unknown reasons.

The mechanism behind the association between PCOS and MeS frequently has been cited to be insulin resistance and abdominal obesity. In women with PCOS, hyperinsulinism acts synergistically with LH within the theca cells of the ovary to cause increased synthesis of T (60). Between 50% and 60% of women with PCOS are affected by an increase of abdominal subcutaneous and visceral fat depots known as android body fat distribution (BFD), regardless of BMI (61). There is evidence to suggest that insulin resistance may be a consequence of android BFD, as well as the possibility that android BFD can both be a cause and effect of hyperandrogenemia (61). This suggests that central adiposity and insulin resistance play prominent roles in PCOS.

In girls with PCOS, age of menarche has been reported to be earlier or later than in controls, owing to various factors. Some girls with PCOS who report histories of premature pubarche may have early menarche, but other girls who present with primary amenorrhea are later diagnosed with PCOS (62, 63). According to Carroll et al. (64), among girls with $PCOS_N$, BMI and age of menarche are negatively correlated but were not different from controls, with average age of menarche of 12.72 vs. 12.5 years (64). In the same study, chromosome 6 rs7759938-T variant was found to be associated with earlier age at menarche in women with PCOS. In our study, average age of menarche trended in the $PCOS_N$ group as the earliest at 10.7 years ($P=.056$). Not surprisingly, the menarcheal age was the highest in the $PCOS_N$ group at 5.9 years, compared with 4.8, 4.7, and 4.7 years in the IM, ET, and OC groups, respectively. Given the younger age of menarche and the highest postmenarcheal age in the $PCOS_N$ group, the presence of oligomenorrhea is likely more indicative of anovulation than of an immature HPO axis.

In conclusion, in the adolescent bariatric population untreated with oral contraceptive pills and/or metformin, prevalence of $PCOS_N$ was 24.5%, whereas 25% of this group had MeS. Overall, 33% of the untreated morbidly obese adolescent girls had MeS. Metabolic syndrome and its individual components were not associated with PCOS status in the morbidly obese adolescent population, contrary to adult data. Although descriptions of gonadal function are rare in this group, this study is the largest adolescent bariatric group assessed to date. Further investigation is warranted to clarify the relationship between obesity and gonadal dysfunction in the morbidly obese adolescent.

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