Gonadal dysfunction in morbidly obese adolescent girls

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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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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,