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Original article

Anti-Müllerian Hormone in Obese Adolescent Girls With Polycystic Ovary Syndrome

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A B S T R A C T

Purpose: Anti-Müllerian hormone (AMH) is proposed as a biomarker of polycystic ovary syndrome (PCOS). This study investigated: (1) AMH concentrations in obese adolescents with PCOS versus without PCOS; (2) the relationship of AMH to sex steroid hormones, adiposity, and insulin resistance; and (3) the optimal AMH value and the multivariable prediction model to determine PCOS in obese adolescents.
Methods: AMH levels were measured in 46 obese PCOS girls and 43 obese non-PCOS girls. Sex steroid hormones, clamp-measured insulin sensitivity and secretion, body composition, and abdominal adiposity were evaluated. Logistic regression and receiver-operating characteristic curve analyses were used, and multivariate prediction models were developed to test the utility of AMH for the diagnosis of PCOS.
Results: AMH levels were higher in obese PCOS versus non-PCOS girls (8.3 ± .6 vs. 4.3 ± .4 ng/mL, $p < .0001$), of comparable age and puberty. AMH concentrations correlated positively with age in both groups, total and free testosterone in PCOS girls only, abdominal adipose tissue in non-PCOS girls, with no correlation to in vivo insulin sensitivity and secretion in either groups. A multivariate model including AMH (cutoff 6.26 ng/mL, area under the curve .788) together with sex hormone–binding globulin and total testosterone exhibited 93.4% predictive power for diagnosing PCOS.
Conclusions: AMH may be a useful biomarker for the diagnosis of PCOS in obese adolescent girls.

IMPLICATIONS AND CONTRIBUTION

Anti-müllerian hormone (AMH) concentrations in obese adolescent girls with polycystic ovary syndrome (PCOS) are almost twice as high as non-PCOS peers and correlate positively with age and testosterone. The AMH cutoff for diagnosing PCOS is 6.26 ng/mL in these obese girls, and the odds of having PCOS increases 47% for one-unit increase in AMH.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting females of reproductive age. PCOS is characterized by menstrual dysfunction, clinical and/or biochemical hyperandrogenism, with or without polycystic ovaries (PCO), and insulin resistance [1]. Given the heterogeneous nature of this condition, various combinations of clinical, biological, and ultrasonographic criteria have been proposed for the diagnosis of PCOS in adult women [2,3] and adolescent girls [1,4].

Obesity is a rapidly growing threat with significant associations between excess body fat and reproductive endocrinology and menstrual cycles in adult women and adolescent girls [5]. In adolescents, as puberty progresses, menstrual dysfunction appears in up to 40% of severely obese adolescents [6]. Moreover, some data show that androgen levels are elevated in obese girls

Conflicts of Interest: The authors have no conflicts of interest to disclose.

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compared with normal weight girls across puberty [7]. Against this backdrop of increasing rates of obesity, difficulties arise in distinguishing obesity-related dysfunction from PCOS-related abnormalities. In 2004, PCO evaluated by ultrasonography was added as a diagnostic measure to the Rotterdam PCOS criteria [3]. In addition, there has been a growing interest to test the utility of anti-Müllerian hormone (AMH) as a biomarker/predictor for PCO and/or PCOS [8,9].

Due to the significant correlation between AMH and antral follicle count (AFC) in women with and without PCOS [9–11], AMH was introduced as a surrogate measure of PCO, in addition to being a biomarker of PCOS because of its associations with other criteria of PCOS including oligomenorrhea and hyperandrogenism [12–14]. A recent meta-analysis suggested a 4.7 ng/mL as an optimal AMH concentration for diagnosing PCOS, based mostly on adult studies (only one pediatric study was included), with AMH cutoff levels ranging from 2.8–8.4 ng/mL [8]. Data with respect to the diagnostic utility of AMH in adolescents with PCOS particularly in obese adolescents are sparse [15–20]. Therefore, the purpose of this study was: (1) to investigate AMH levels in obese adolescent girls with PCOS in comparison to obese girls without PCOS; (2) to assess the relationship of AMH to sex steroid hormone profile, adiposity measures, and insulin resistance, a major metabolic component of PCOS; and (3) to examine the optimal AMH cutoff and the multivariable prediction model to predict PCOS in obese girls.

Materials and Methods

Patients

Data from 46 girls with a diagnosis of PCOS (5 overweight and 41 obese, age 14.9 ± .2 years, body mass index [BMI] 37.7 ± 1.1 kg/m^2 [mean ± standard error]), recruited from the PCOS Center at Children's Hospital of Pittsburgh, were compared with 43 girls without PCOS (12 overweight and 31 obese, age 14.4 ± .2 years, BMI 33.1 ± 1.1 kg/m^2) who participated in our NIH-funded K24 grant investigating insulin resistance in childhood, some of whose data, unrelated to AMH, have been published [21–23]. Eligible PCOS patients and their families were informed about the study while being evaluated in the PCOS center and given the opportunity to participate shortly after their diagnosis and before pharmacologic therapy was initiated. In addition, flyers were posted in the medical campus, pediatricians' offices, and city bus routes for interested individuals to contact us to learn about the study and assess eligibility. Consistent with our previous publications [21–25], the diagnosis of PCOS was made based on the presence of clinical signs and symptoms of hyperandrogenism and/or biochemical hyperandrogenemia after excluding other causes of hyperandrogenemia according to the NIH and the Endocrine Society Clinical Practice Guidelines [1]. Specifically, PCO morphology was not included in the PCOS criteria used for adolescents [26], which is different from other criteria such as the Androgen Excess Society or the Rotterdam. Recently, the Pediatric Endocrine Society recommended that no compelling criteria to define PCO morphology have been established for adolescents [4]. Inclusion criteria were: (1) PCOS diagnosis as previously mentioned; (2) age 10–20 years and postmenarche; and (3) BMI ≥ 85th percentile for age and sex. Girls who were previously diagnosed with systemic or psychiatric disease and were taking any medications that impact carbohydrate or lipid metabolism (oral contraceptive pills, metformin, anti-epileptics, antipsychotics, statins, and fish oil) were excluded. The study was approved by the Institutional Review Board of the University of Pittsburgh, and written informed parental consent and child assent were obtained from all participants before any research participation in accordance with the ethical guidelines of Children's Hospital of Pittsburgh.

Procedures

All procedures were performed at the Pediatric Clinical and Translational Research Center of Children's Hospital of Pittsburgh. All participants underwent medical history, physical examination, and hematologic and biochemical tests. Height and weight were assessed to the nearest .1 cm and .1 kg, respectively, and used to calculate BMI. Pubertal development was assessed using Tanner criteria [27]. Fasting blood samples were collected for determination of sex hormone profile including total and free testosterone, sex hormone–binding globulin (SHBG), estradiol, and dehydroepiandrosterone sulfate (DHEAS).

Body composition was evaluated with dual-energy X-ray absorptiometry with measurement of total body fat mass and percent body fat. Abdominal total adipose tissue, subcutaneous adipose tissue, and visceral adipose tissue were assessed by either computed tomography (CT) at L4-5 intervertebral space or magnetic resonance imaging (MRI) [28,29]. The switch from CT to MRI was imposed by the study section during the competitive grant renewal. However, there is a strong correlation (r = .89–.95) and good agreement between CT and MRI for the measurement of abdominal adipose tissue [30].

Metabolic studies

All participants underwent a 2-hour oral glucose tolerance test to assess glucose tolerance status [22,25]. Obese girls with PCOS and without PCOS were admitted twice within a 1- to 4-week period to the Pediatric Clinical and Translational Research Center for a hyperinsulinemic-euglycemic clamp, to assess in vivo insulin sensitivity, and a hyperglycemic clamp, to assess insulin secretion, performed in random order [22,24,25]. Each clamp evaluation was performed after a 10- to 12-hour overnight fast.

Fasting hepatic glucose production was measured before the start of the hyperinsulinemic-euglycemic clamp, with a primed (2.2 μmol/kg) constant infusion of [6,6-$^2H_2$] glucose at .22 μmol/kg/min for a total of 2 hours as described [22,24]. After the 2-hour baseline isotope infusion period, in vivo insulin sensitivity was evaluated during a 3-hour hyperinsulinemic (80 mU/m^2/min)-euglycemic clamp [22,24,25]. First- and second-phase insulin secretion was assessed during a 2-hour hyperglycemic (225 mg/dL) clamp as described previously [22,24,25]. Plasma glucose was increased rapidly to 225 mg/dL by a bolus infusion of dextrose and maintained at that level by a variable rate infusion of 20% dextrose for 2 hours, with frequent measurement of glucose and insulin concentrations.

Biochemical measurements

Total testosterone was measured by high-pressure liquid chromatography-tandem mass spectroscopy and DHEAS by radioimmunoassay in dilute serum after hydrolysis (Esoterix Inc., Calabasas Hills, CA). Free testosterone was measured by equilibrium dialysis and SHBG by immunoradiometric assay. Serum