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POLYCYSTIC OVARY SYNDROME: CLINICAL PRESENTATION IN NORMAL-WEIGHT COMPARED WITH OVERWEIGHT ADOLESCENTS

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Abstract

Objective—To characterize polycystic ovary syndrome (PCOS) in adolescents and determine whether a distinct clinical presentation differentiates normal-weight (NW) from overweight (OW) PCOS.

Methods—Retrospective chart review of patients seen in a tertiary care center from 1998-2008 who met the National Institutes of Health and/or Rotterdam criteria for PCOS (N = 211; NW = 43, OW = 168). We collected data on clinical features, biochemical markers, and ultrasound findings.

Results—Patient age ranged from 11.3 to 20.3 years (mean, 15.7 ± 1.7 years), and body mass index (BMI) from 17.4 to 64.2 kg/m^2 (mean, 31.7 ± 7.7 kg/m^2). Seventy-one percent of patients were Caucasian, 85% had irregular menses, 69% reported hirsutism, 18% had moderate to severe acne, 91% had a high free androgen index (FAI), and 8% had abnormal thyroid-stimulating hormone (TSH) levels. The BMI-standard deviation (SD) score was 0.1 ± 0.5 in NW and 3.4 ± 1.8 in OW girls. NW girls were older at diagnosis (16.4 ± 1.4 years vs. 15.5 ± 1.7 years; P = .0006) than OW girls, less likely to have a family history of obesity (22% vs. 65%; P<.0001), and less likely to have acanthosis nigricans (11% vs. 68%; P<.0001). NW girls were more likely to have polycystic ovaries on ultrasound (88% vs. 52%; P = .01) and a lower FAI (7.3 ± 4.5 vs. 17.4 ± 12.9; P<.0001). The BMI-SD score was negatively associated with sex hormone binding globulin (r_s = −0.52; P<.0001) and positively associated with FAI (r_s = 0.42; P<.0001).

Conclusion—NW girls are more likely to be older at diagnosis and have polycystic ovaries. Other differences in presentation between groups were attributable to differences in weight. NW PCOS is likely part of a continuous spectrum of clinical PCOS rather than a distinct entity.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder affecting 3 to 8% of women of reproductive age (1,2). Although signs and symptoms can manifest in adolescence, the

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DISCLOSURE

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diagnosis can be difficult. Menstrual irregularity and anovulation are not uncommon in the 2 years following menarche, and can be hard to differentiate from the oligoanovulation that characterizes PCOS (3). In addition, during puberty, adolescents have increased ovarian and adrenal steroidogenesis and relative hyperinsulinism (4), both of which are associated with PCOS.

There are several standards for the diagnosis of PCOS. These include the 1990 National Institutes of Health (NIH), 2003 Rotterdam, and 2006 Androgen Excess Society criteria. The NIH criteria include clinical or biochemical hyperandrogenism, oligo-ovulation, and exclusion of other disorders of hyperandrogenism (5). The Rotterdam criteria broaden the definition, requiring women to have at least two of the following: oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, and/or polycystic ovarian morphology (6). However, this definition includes a subgroup of women without hyperandrogenism and another subgroup with regular menses. To address this, the Androgen Excess Society refined the criteria to require women to have clinical or biochemical hyperandrogenism, ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and exclusion of other androgen excess or related disorders (7).

Although PCOS is commonly associated with excessive body weight and obesity, a lean phenotype also exists. Some studies have reported endocrine and metabolic differences between the overweight (OW) and lean phenotypes (8,9); however, most of these studies involved adult subjects. There is little information regarding the clinical presentation of PCOS in adolescents, and even less about features that differentiate OW and lean PCOS individuals in this younger population. The purpose of this study was thus to characterize PCOS in adolescents, and to determine whether a distinct clinical presentation differentiates normal-weight (NW) and OW PCOS patients.

METHODS

Study Design

We conducted a retrospective chart review of all adolescents with PCOS seen in a tertiary care outpatient center between 1998 and 2008. A total of 253 patients were initially identified with PCOS as either their primary or secondary diagnosis based on the ninth edition of the International Classification of Disease code for PCOS. The study was approved by the Partners HealthCare Institutional review board.

Study Population

During the study period, providers used both NIH and Rotterdam criteria to diagnose PCOS. Therefore, to be more inclusive, patients who met either the NIH (n = 199) or Rotterdam (n = 12) criteria for PCOS and had notes available from their initial outpatient visit were included in the study. Patients with a diagnosis of congenital adrenal hyperplasia or other reason for hyperandrogenism were excluded from the study. Data were obtained at baseline before patients started medical treatment for PCOS, and those patients with baseline laboratory data drawn while on oral contraceptives were not included in the biochemical analysis (n = 17). Patients were not excluded if some clinical or biochemical data were

unavailable. Of the 253 patients initially identified, 27 did not meet the diagnostic criteria for PCOS, 12 did not have data from their initial visit available, 2 had data from outside the study period, and 1 had congenital adrenal hyperplasia, resulting in a final population of 211 patients.

Clinical Features

The following self-reported clinical data were collected: race, ethnicity, history of hirsutism, irregular menses (defined as no menses for >6 months, a cycle interval >35 days but <6 months, or cycle length between 21 and 35 days, with more than a 4-day variation between cycles in individual subjects [10]), type 1 or 2 diabetes mellitus, thyroid dysfunction, hyperprolactinemia, as well as family history of PCOS and being overweight. Age at diagnosis was determined from clinical records. Body mass index (BMI), thyromegaly, acne, acanthosis nigricans, and clitoromegaly (defined as total clitoral length greater than 24.6 mm [11]) identified on physical examination were also recorded. To compare lean individuals with individuals that were not lean, OW was defined as a BMI >85th percentile for age and sex, while NW was defined as a BMI ≤85th percentile. Obese was defined as a BMI >95th percentile for age and sex. BMI percentile and BMI-standard deviation (SD) scores were calculated using Centers for Disease Control tables (12). Acne grade was defined as mild if the clinician stated it was mild or minimal in the physical exam; otherwise, if on physical exam the clinician stated it was moderate or severe, or described multiple locations, acne was graded moderate to severe.

The following laboratory data were collected: levels of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), free androgen index (FAI), 17-hydroxyprogesterone, dehydroepiandrosterone sulfate (DHEAS), prolactin, thyroid-stimulating hormone (TSH), and free thyroxine (T_4), and results from ovarian ultrasound completed transabdominally or transvaginally. Most ultrasound evaluations were completed at one center and were described as polycystic if there were 12 or more follicles in the 2 to 9 mm range per ovary, or an ovarian volume ≥10 mL per ovary. As most of our subjects had irregular menses at diagnosis, their menstrual phase at the time of the blood draw was unknown.

Due to the retrospective nature of this study, there was no uniform protocol followed by providers regarding which laboratory tests to obtain, resulting in the inavailability of androgen level data for some patients. Because a diagnosis of PCOS is based on evidence of clinical or biochemical hyperandrogenism, patients without androgen level data who had evidence of clinical hyperandrogenism were included in the study. Reference ranges for total testosterone, 17-hydroxyprogesterone, and DHEAS were also recorded, as these tests were sent to different laboratories. To accurately compare total levels of testosterone, 17-hydroxyprogesterone, and DHEAS, values are presented as multiples of the upper limit of normal based on gender and pubertal status rather than as absolute values (13). The FAI was calculated by multiplying the total testosterone level (ng/dL) by 3.47 and dividing by the SHBG level (nmol/L). The FAI was defined as elevated if it was >4, as per the reference values identified by the laboratory at Massachusetts General Hospital. The TSH level was

defined as abnormal if it was above or below the reference range identified by the laboratory.

Data Analysis

Data analysis was completed using JMP® statistical software (SAS Institute, Cary, NC). Analyses were performed using Student's *t* test for continuous variables, and Pearson's X^2 test for categorical variables. For cell sizes less than n = 5, the Fisher's exact test was used. For continuous variables where n was less than 30 or the data had a skewed distribution, the Wilcoxon test was used. The Spearman rank correlation was used to explore possible associations between BMI and FAI and SHBG.

RESULTS

All Subjects with PCOS

The characteristics of the 211 adolescents who met the study's inclusion criteria are summarized in Table 1. Seventy-one percent of the group self-identified as Caucasian, 6% as African American, 6% as Asian, 7% as belonging to more than one race, and 18% as other races. Nineteen percent (n = 40) of the adolescents were OW, and 61% (n = 128) were obese. Thirty-three individuals had a BMI-SD score between 0 and 1, 37 had a BMI-SD score between 1 and 2, and 127 had a BMI-SD score >2. All but 2 girls were postmenarchal, indicating that they were at Tanner stage IV or greater. The two premenarchal girls were Tanner stage V on exam, and presented with primary amenorrhea that self-resolved on follow-up. Only 20 girls had attained menarche less than 2 years before diagnosis; their data did not differ substantially from the group as a whole, and are thus not reported separately.

Laboratory data were obtained for 42 to 78% of the study population, depending on the specific test. TSH values ranged from 0.01 to 33.85 μU/mL, with 3 values above the 10 μU/mL level (12.64, 19.9, and 33.85 μU/mL) and 2 values below the 0.40 μU/mL level (each 0.01 μU/mL). In the 5 girls with abnormal TSH values, the PCOS diagnosis persisted after they received appropriate treatment. Six girls had a history of elevated prolactin level, but were diagnosed with PCOS as well (two had hyperprolactinemia with normal head magnetic resonance imaging scans, one had a previous history of hyperprolactinemia that had since resolved, two had microprolactinomas with elevated FAI even after the prolactin level had normalized, and one had a microprolactinoma with clinical signs of androgen excess). The results did not significantly change when data from these 6 patients were excluded. One girl had documented clitoromegaly with a negative work-up for other causes of hyperandrogenism, and was diagnosed with PCOS.

Normal-weight Versus Overweight PCOS

Characteristics of NW girls with PCOS (n = 43) and OW girls with PCOS (n = 168) are summarized in Table 2. Analysis of biochemical features showed that 81% of NW girls and 77% of OW girls had data available for total testosterone level, and 100 out of 211 (47%) had SHBG level data, enabling FAI calculation. NW girls had a lower FAI (n = 23; 7.3 ± 4.5 vs. 17.4 ± 12.9; $P<.0001$), likely due to higher SHBG levels in comparison with OW girls (n = 77; 42.6 ± 30.7 vs. 17.8 ± 10.6 nmol/L; $P<.0001$). Seventy-seven percent of the girls had

their testosterone level determined at the same institution (85% in the NW group, and 75% in the OW group). The proportion of girls with an LH to FSH ratio >3 did not differ between groups (data not shown).

The clinical characteristics of girls who had laboratory analyses performed were compared to those of girls who did not have laboratory analyses performed, and did not significantly differ (data not shown). BMI-SD scores were positively associated with FAI (r_s = 0.42; *P*<.0001), and negatively associated with SHBG level (r_s= −0.52; *P*<.0001). All analyses were repeated comparing NW girls with girls who had a BMI greater than the 95th percentile for age and gender, with similar results (data not shown).

DISCUSSION

This was a large, retrospective review of the presentation of PCOS in adolescents. The resulting data suggest that NW girls are more likely than OW girls to be diagnosed at an older age and have polycystic ovaries on ultrasound. OW girls are more likely to have a family history of excess weight/obesity, and to present with acanthosis nigricans and a higher FAI, features attributable to increased weight. Bekx et al (13) reviewed data for 70 girls between the ages of 11 and 22 years who were referred to a PCOS clinic, and noted that 84% were OW or obese, 70% had acne, and 60% had hirsutism. Bronstein et al (14) reviewed data for 58 girls ages 9 to 18 years (five of whom were premenarchal) with PCOS diagnosed based on Rotterdam criteria, and noted that 64% were OW or obese, 78% had acanthosis nigricans, 74% had acne, and 71% had hirsutism. Our larger study found similar OW and obesity rates and signs of clinical hyperandrogenism.

In contrast to Bronstein et al (14), who reported elevated total testosterone in 76% of their subjects, but similar to Bekx et al (13), who reported elevated total testosterone in 21% of adolescents with PCOS, we found that 27% of girls with PCOS had high total testosterone. This discrepancy may be attributable to differences in the number of very young girls in the studies. The study by Bronstein et al (14) included 15 girls ages 9 to 12 years, of whom 14 had high total testosterone, whereas our study had very few girls aged 9 to 12 years (n = 5). Conversely, when elevated androgens were defined as an elevated FAI, almost all adolescents in our study had a value greater than four. This suggests a sampling bias, given that biochemical evidence of elevated androgens (and particularly an elevated FAI) is a diagnostic feature of PCOS.

Accurate measurement of testosterone level in women is difficult because commonly used assays lack the accuracy and sensitivity necessary to detect the low concentrations found in females. Direct assays for total testosterone are not adequately standardized for women, and have limited accuracy at levels <300 ng/dL (15). Determination of total testosterone by radioimmunoassay after extraction and chromatography can be imprecise, and carries a risk of matrix effects. Measurement of testosterone by high-performance liquid chromatography/tandem mass spectrometry is accurate, but is not standardized and therefore not routinely used in clinical practice. The free testosterone analog-based assay is inaccurate, and is more an indicator of total testosterone than free testosterone (15-17). To address these limitations in our study, the total testosterone level was reported as multiples of the upper limit of

normal, and a FAI was calculated when data on SHBG level were available, which was the case for 47% of our study population. FAI correlates well with free testosterone determined by equilibrium dialysis, but is only as accurate as the total testosterone and SHBG assay from which it is derived (15,17).

The fact that abnormal thyroid function was only observed in the OW group is likely related to the association between mild hyperthyrotropinemia and obesity. Isolated hyperthyrotropinemia was found in 12.8% of obese children and adolescents in a study from Italy (n = 938), and appeared to reverse with weight loss (18,19). Grandone et al (18) also noted that obese children and adolescents have higher levels of free triiodothyronine (T3) (*P* = .03) compared to those with normal TSH. The explanation for this phenomenon is unclear, but leptin may play a role, as it has similar 24-hour patterns of variability as TSH (20). Interestingly, one study posited an association between a genetic variant of gonadotropin-releasing hormone receptor and serum thyroid concentration and insulin secretion in patients with PCOS, suggesting a possible link between these two disorders (21).

On average, in this study we found that NW girls were diagnosed later than OW girls. Since these girls were referred to a tertiary care center, this may have been due to a referral bias. The clinical suspicion for PCOS in the lean group may have been lower, leading to an older age at diagnosis.

In our study, a higher proportion of NW girls with PCOS had polycystic ovaries on sonogram than did OW girls. Silfen et al (8), who studied 33 adolescents (11 nonobese and 22 obese) with PCOS (defined as hyperandrogenism and oligomenorrhea or amenorrhea), reported that polycystic ovaries on ultrasound were more likely in the nonobese group than the obese group. Although we used the Rotterdam criteria for the diagnosis of PCOS for some of our patients, the small proportion of individuals meeting these criteria was similar in both groups, suggesting that NW individuals are more likely to present with polycystic ovaries on ultrasound. This finding may be confounded by the older age at presentation in the NW group (22) and limitations in imaging obese individuals. Furthermore, this may be nonspecific, as polycystic ovaries can occur in healthy women (23).

When comparing NW adolescents to OW adolescents with PCOS, we found that levels of testosterone, DHEAS, LH, and FSH did not differ between the groups, but the FAI was significantly higher, and levels of SHBG were significantly lower, in the OW group. Silfen et al (8) also reported no differences in testosterone and FSH levels in both obese and nonobese girls, but the obese group had significantly lower SHBG, resulting in a higher FAI, as was the case with our subjects. This finding suggests that FAI is a more sensitive marker for hyperandrogenism than total testosterone in the PCOS population (24). Of interest, LH and DHEAS levels were higher in the nonobese group in the study by Silfen et al (8). We speculate that our larger and more diverse sample may have contributed to the differences between our study and that report. Elevated ratios of LH to FSH have been shown in women with PCOS, and are inversely related to BMI (25). We did not find an inverse association between LH and BMI, likely because the LH level, which varies with menstrual cycle phase, was not drawn for all subjects during the same menstrual cycle phase (26), and because LH is released in a pulsatile manner, making a single measurement of LH level unreliable.

A correlation between FAI and BMI has been reported in studies of adults and peripubertal girls. Cupisti et al (27) compared 108 women with PCOS (59 patients with a BMI <25 vs. 49 patients with a BMI >25) and, similar to this study, showed that BMI is negatively correlated with SHBG level ($r_s = -0.479$; $P<.0001$). McCartney et al (28) found a similar correlation in a study of lean and obese peripubertal girls (28). Furthermore, when obese girls lose weight, androgen levels have been shown to decrease with the decrease in BMI (29). We suggest that in individuals at risk for developing PCOS, symptoms are more likely to be unmasked by obesity, which causes elevation of androgen levels and consequent neuroendocrine dysregulation. Thus, the obese and lean clinical presentations of PCOS likely represent a spectrum of one distinct entity that is exacerbated by weight gain. This highlights the need for increased vigilance across the weight spectrum, and particularly as weight goes up in adolescent girls, given that the risk of metabolic disorders associated with PCOS increases accordingly. This may be a particularly important issue in adolescence due to the physiologic insulin-resistant state associated with puberty, which may precipitate features of PCOS at a lower BMI than in adults. OW girls may need to be screened for other components of metabolic syndrome, for example, hemoglobin A1C, lipids, and liver enzymes. It will also be important to provide at-risk girls with treatment strategies, such as birth control pills and metformin, if lifestyle measures are ineffective.

This study has limitations inherent to a retrospective chart review. Although obese girls are more likely to have higher levels of insulin and greater insulin resistance, some studies have reported high insulin levels in lean adult PCOS patients as well (9,30). We were unable to compare fasting insulin and cholesterol levels in NW and OW girls with PCOS, as this was not a prospective study and there was no definitive protocol for laboratory evaluation of PCOS for all providers to follow. Routine clinical care of PCOS does not include assessing the fasting insulin level, and insulin level data are difficult to interpret in adolescents because of pubertal insulin resistance, which varies across pubertal stage. There may also be some bias associated with our biochemical data, as each practitioner independently decided which laboratory data should be gathered at the initial visit. Furthermore, our study population was predominantly Caucasian, making it difficult to generalize these data to other ethnic populations. Finally, this study was conducted at a tertiary care center, which may have introduced a referral bias, in that the girls referred to this center may have been more symptomatic than those not referred.

CONCLUSION

We report that NW girls with PCOS are more likely to be older at diagnosis and have polycystic ovaries on ultrasound than OW girls with PCOS. The older age at diagnosis in our NW group suggests that a higher index of suspicion may be necessary for earlier diagnosis of PCOS in NW girls with clinical evidence of hyperandrogenism. OW girls are more likely to have a family history of obesity than NW girls and are more likely to exhibit features associated with increased weight, such as acanthosis nigricans and a higher FAI. The positive association between BMI and FAI suggests that PCOS in NW girls is part of a continuous spectrum of clinical PCOS rather than a distinct entity. To better define PCOS in adolescents, more prospective data are needed regarding clinical presentation, biochemical markers, long-term outcomes, and response to treatment.

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Abbreviations

BMI	body mass index
BMI-SD	BMI-standard deviation
DHEAS	dehydroepiandrosterone sulfate
FAI	free androgen index
FSH	follicle-stimulating hormone
LH	luteinizing hormone
NIH	National Institutes of Health
NW	normal-weight
OW	overweight
PCOS	polycystic ovary syndrome
SHBG	sex hormone binding globulin
TSH	thyroid-stimulating hormone

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Table 1
Characteristics of the Study Population

Characteristic	Mean ± SD (range)	Total n[a]
Age (years)	15.7 ± 1.7 (11.3-20.3)	211
Years post-menarche	3.7 ± 2.0 (−0.4-10.6)	181
BMI mean (kg/m^2)	31.7 ± 7.7 (17.4-64.2)	211
BMI-SD score	2.7 ± 2.1 (−1.1-10.6)	211

Characteristic	% (n)	Total n[a]
Race	71 Caucasian (133)	187
	6 African American (12)	187
History of:		
Irregular menses	85 (176)	208
Hirsutism	69 (120)	173
Diabetes	1 (3)	211
Family history of:		
PCOS	33 (63)	190
Obesity/being overweight	57 (104)	183
Exam findings:		
Mild acne	53 (103)	196
Moderate-severe acne	18 (36)	196
Acanthosis nigricans	57 (106)	186
Biochemical findings:		
FAI >4[b]	91 (91)	100
Elevated testosterone[c]	26 (43)	164
Elevated 17-OHP[d]	23 (20)	88
Abnormal TSH	8 (11)	144
Polycystic ovaries on ultrasound	59 (46)	78

Abbreviations: BMI = body mass index; BMI-SD = BMI-standard deviation; FAI = free androgen index; 17-OHP = 17-hydroxyprogesterone; PCOS = polycystic ovary syndrome; TSH = thyroid-stimulating hormone.

[a] Reported value of less than 211 indicates data were not available for all individuals.

[b] FAI >4 reported as elevated by the Chemistry Laboratory of Massachusetts General Hospital.

[c] Testosterone level was divided by the upper limit of normal of the reference range provided by the laboratory, and was defined as elevated if the ratio was >1.

[d] 17-OHP level was divided by the upper limit of normal of the reference range provided by the laboratory, and was defined as elevated if the ratio was >1.

Table 2
Characteristics of Normal-weight Versus Overweight Girls with PCOS

Characteristic	Normal-weight Mean ± SD (range) (n)	Overweight Mean ± SD (range) (n)	*P* value
Age (years)	16.4 ± 1.4 (13.4-19.3) (43)	15.5 ± 1.7 (11.3-20.3) (168)	.0006
Years post-menarche	3.9 ± 1.7 (1.6-6.1) (36)	3.7 ± 2.1 (−0.4-6.5) (145)	NS
BMI-SD score	0.1 ± 0.5 (−1.1-0.9) (43)	3.4 ± 1.8 (0.6-10.6) (168)	<0.0001

Characteristic	Normal-weight (n/total) or (n)	Overweight (n/total) or (n)	*P* value
Non-Caucasian	24 (10/41)	30 (44/146)	NS
Rotterdam criteria only	7 (3/43)	5 (9/168)	NS
History of:			
Irregular menses	79 (34/43)	86 (142/165)	NS
Hirsutism	76 (29/38)	67 (91/135)	NS
Family history of:			
PCOS	26 (10/39)	35 (53/151)	NS
Obesity/being overweight	22 (8/36)	65 (96/147)	<.0001
Examination findings:			
Mild acne	46 (19/41)	54 (84/155)	NS
Moderate-severe acne	17 (7/41)	19 (29/155)	NS
Acanthosis nigricans	11 (4/36)	68 (102/150)	<.0001
Biochemical findings:			
FAI	7.3 ± 4.5 (23)	17.4 ± 12.9 (77)	<.0001
SHBG (nmol/L)	42.6 ± 30.7 (23)	17.8 ± 10.6 (77)	<.0001
Testosterone/ULN[a]	0.8 ± 0.3 (35)	0.9 ± 0.6 (129)	NS
DHEAS/ULN[b]	0.6 ± 0.3 (20)	0.6 ± 0.4 (70)	NS
17-OHP/ULN[c]	0.6 ± 0.5 (22)	0.8 ± 1.0 (66)	NS
LH/FSH ratio	1.8 ± 1.1 (37)	1.7 ± 0.8 (121)	NS
Prolactin (ng/mL)	11.0 ± 10.0 (32)	12.0 ± 12.7 (112)	NS
Abnormal TSH	0 (0/32)	10 (11/112)	NS
Polycystic ovaries on ultrasound	88 (14/16)	52 (32/62)	.01[d]

Abbreviations: BMI = body mass index; BMI-SD = BMI-standard deviation; DHEAS = dehydroepiandrosterone sulfate; FAI = free androgen index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; NS = not significant; 17-OHP = 17-hydroxyprogesterone; PCOS = polycystic ovary syndrome; SHBG = sex hormone binding globulin; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] Testosterone level divided by the ULN of the reference range provided by the laboratory (mean ± SD reported).

[b] DHEAS level divided by the ULN of the reference range for Tanner V provided by the laboratory (mean ± SD reported).

[c] 17-OHP level divided by the ULN of the reference range provided by the laboratory (mean ± SD reported).

[d] When data for girls meeting NIH criteria only were analyzed, $P = .0037$ for polycystic ovaries on ultrasound; otherwise *P* values were unchanged.