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# Distinct Reproductive Phenotypes Segregate With Differences in Body Weight in Adolescent Polycystic Ovary Syndrome

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## Abstract

**Introduction:** Polycystic ovary syndrome (PCOS) is a heterogeneous clinical syndrome defined by hyperandrogenism and irregular menses. In adult women with PCOS, discrete metabolic and reproductive subgroups have been identified. We hypothesize that distinct phenotypes can be distinguished between adolescent girls who are lean (LN-G) and girls with obesity (OB-G) at the time of PCOS diagnosis.

**Methods:** Data were extracted from the CALICO multisite PCOS database. Clinical data collected at the time of diagnosis were available in 354 patients (81% with obesity) from 7 academic centers. Patients with body mass index (BMI) < 85th percentile for age and sex were characterized as lean (LN-G) and those with BMI percentile  $\geq$  95th percentile as obese (OB-G). We compared metabolic and reproductive phenotypes in LN-G and OB-G.

**Results:** Reproductive phenotypes differed between the groups, with LN-G having higher total testosterone, androstenedione, and LH levels, while OB-G had lower sex hormone binding globulin (SHBG) and higher free testosterone. Metabolic profiles differed as expected, with OB-G having higher hemoglobin A1c, alanine aminotransferase, and serum triglycerides and more severe acanthosis nigricans.

**Conclusion:** LN-G with PCOS had a distinct reproductive phenotype characterized by increased LH, total testosterone, and androstenedione levels, suggesting neuroendocrine-mediated ovarian androgen production. In contrast, phenotypes in OB-G suggest hyperandrogenemia is primarily driven by insulin resistance with low SHBG levels. These observations support the existence of distinct metabolic and reproductive subtypes in adolescent PCOS characterized by unique mechanisms for hyperandrogenemia.

**Key Words:** PCOS, adolescent, phenotypes, hyperandrogenism, obesity

Polycystic ovary syndrome (PCOS) is one of the most common endocrine conditions affecting females, with a prevalence in the range of 10% to 13% [1]. The clinical features of this heterogeneous complex genetic disorder include clinical and biochemical hyperandrogenism, ovulatory dysfunction, and hyperinsulinism/insulin resistance [2, 3]. PCOS is associated with significant metabolic and reproductive comorbidities including type 2 diabetes, metabolic syndrome, subfertility, and endometrial hyperplasia [2]. Despite its significant public health impact, uncertainty regarding the underlying

mechanisms of PCOS has limited the development of better treatments or more efficacious prevention approaches.

PCOS is a clinical phenotype characterized by a combination of clinical or biochemical hyperandrogenism, oligo-amenorrhea, and/or polycystic ovarian morphology, with the exclusion of confounding diagnoses, depending on the diagnostic criteria used [4–7]. PCOS is associated with varying risks for metabolic and reproductive comorbidities [8]. Despite the longstanding recognition of the heterogeneity of PCOS, treatment guidelines to date have not recommended

distinct treatment approaches across these differing phenotypes. Combination oral contraceptive pills remain the first-line pharmacologic treatment for PCOS based on current guidelines [1]. However, complimentary therapies to improve insulin sensitivity, support weight loss efforts, or improve clinical hyperandrogenism are also commonly used in the management of adolescent PCOS.

Obesity, hyperinsulinemia, and insulin resistance are common in individuals with PCOS [9-11]. Available data suggest that excess adiposity, hyperinsulinemia, and associated insulin resistance promote development of hyperandrogenemia and ovulatory dysfunction in some cases. Clinical observations suggest that interventions aimed at reducing excess weight and improving insulin sensitivity improve the reproductive features of PCOS in selected patients.

However, obesity is not a universal feature of the PCOS phenotype or a component of its diagnostic criteria. Previous studies have suggested roughly 50% of women with PCOS do not have overweight or obesity [12]. The literature on the metabolic phenotype in lean PCOS has been mixed, with some studies reporting increased insulin resistance and central obesity in these women [13, 14], while others contradict these findings [15-17]. Therefore, the significance of insulin resistance in the pathophysiology of PCOS in lean women remains unclear.

Among adolescent girls with PCOS, we hypothesize that distinct mechanisms may exist in girls who are lean (LN-G) compared to girls with obesity (OB-G). Elucidation of the features specific for each group is a critical step toward improvement in diagnosis and personalized treatment of this common condition. In this study, we investigated for clinically distinct metabolic and reproductive phenotypes in LN-G compared with OB-G at the time of PCOS diagnosis.

## Materials and Methods

### Data Collection

Data were extracted from the Clinical Adolescent polycystic Ovary syndrome (CALICO) database, a multisite adolescent PCOS database housed within Research Electronic Data Capture, a secure, HIPAA-compliant web-based application designed for data collection for research studies with data access at the University of Colorado. Retrospective clinical data was obtained from the electronic medical records (EMR) of 7 academic centers in the United States: Ann & Robert H. Lurie Children's Hospital of Chicago, University of Florida Health in Gainesville, Children's Mercy Hospital in Kansas City, John H. Stroger, Jr. Hospital in Chicago, Children's Hospital Los Angeles, Children's Hospital of Philadelphia, and Children's Hospital Colorado; all centers are large tertiary care centers. The EMR system from each site captures data from multiple affiliated pediatrics practices and therefore represents a wide range of patients from across the United States [18]. The institutional review boards at each site granted exemption and waiver of consent for this study.

Patient selection criteria for the initial EMR search included: patients 14 to 18 years of age at time of PCOS diagnosis with at least 2 office visits, with the diagnostic visit between July 1, 2013, and December 31, 2021, and PCOS identified using International Classification of Diseases-10 codes of "polycystic ovary syndrome" (E28.2), "androgen excess" (E28.1), or "irregular menses" (N92.6) [18]. From this initial cohort, manual data extraction was performed to confirm that

patients met criteria for inclusion in the final cohort. OB-G were defined by body mass index (BMI)  $\geq$  95th percentile and LN-G by BMI  $<$  85th percentile for age and sex at time of PCOS diagnosis [19]. PCOS diagnosis was confirmed using criteria recommended by the 2018 international evidence-based guideline criteria (1) biochemical hyperandrogenemia as evidenced by elevation in total testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEAS), or androstenedione levels; (2) irregular menses and ovulatory dysfunction as defined by menses  $<$ 21 days or  $>$ 45 days for those postmenarchal age 1 to 3 years,  $<$ 21 or  $>$ 35 days for those postmenarchal age 3+ years, or with primary amenorrhea by age 15 or  $>$ 3 years post thelarche; and (3) exclusion of any other cause for irregular menses or hyperandrogenism [7]. PCOS status was adjudicated by the board-certified pediatric endocrinologist site principal investigator for each site. Patients with the following conditions were excluded: type 1 diabetes or maturity-onset diabetes of the young; genetic forms of obesity, eg, Prader-Willi, Bardet Biedl; genetic conditions that may affect menses, eg, Turner syndrome; inflammatory conditions such as asthma or lupus requiring regular systemic steroids; past or current history of malignancy [18]. Trans male individuals receiving gender-affirming treatment with testosterone and patients taking hormonal contraception at the time of the diagnosis visit were also excluded [18]. Patients taking medications that can impact metabolic or reproductive phenotypes were excluded from the relevant analyses. These excluded participants included 28 OB-G and 4 LN-G on metformin, 3 OB-G on anti-hypertensives, 1 OB-G on a lipid-lowering medication, and 10 LN-G and 55 OB-G taking hormonal contraceptives.

Key demographic and diagnostic information at the time of PCOS diagnosis were collected [18]. Demographic information included age, race, and ethnicity. Medical information included birthweight, personal medical and surgical history, age of menarche, time since last menstrual period, and number of menses in the last 12 months. Data on family history of a first- or second-degree relative with PCOS, type 2 diabetes, obesity, or obstructive sleep apnea was also recorded. Information extracted from physical examinations included BMI value, percentile and Z-score for age and sex, systolic and diastolic blood pressure, hirsutism (Ferriman-Gallwey score), acanthosis nigricans, and acne. Severity of acanthosis nigricans was rated using the following scale: back of neck, barely visible (minimal, score 1) back of neck, obvious (mild, score 2), lateral sides of neck (moderate, score 3), circumferential (severe, score 4). Results of laboratory studies including hemoglobin A1C (HbA1c), alanine amino transferase (ALT), fasting lipid profiles, and reproductive hormones including free and total testosterone, LH, FSH, sex hormone binding globulin (SHBG), androstenedione, and DHEAS were tabulated. Due to recognized variability in the androgen assays represented in the database, androgen levels were normalized to the upper limit of normal provided by the published reference range of the measuring laboratory, as previously described [18]. We report these levels as percent of the upper limit of normal [18].

### Statistical Analysis

Data were log transformed when necessary to achieve normality of data distribution. Differences in categorical variables were compared using chi-square. Comparisons of continuous variables were made using an unpaired *t*-test or Mann-Whitney

if normalized data distribution was not achieved. As a secondary analysis, analysis of covariance adjusting for BMI z-score was performed to assess the impact of BMI on endpoint variables. Analyses were conducted in Prism 9 (GraphPad Software, San Diego, CA, USA) and SAS (SAS Institute, Inc., Cary, NC, USA). Data are reported as the mean  $\pm$  SD with the level of alpha set at .05.

## Results

Complete diagnostic data of 391 patients from 7 different sites were extracted from the database. Of these, 5 cases were excluded, as the subjects were >18 years old at the time of diagnosis. Seven cases were missing height and/or weight data, and 25 cases with BMI between the 85th and 95th percentile were also excluded, as they did not fulfill our inclusion criteria. The final cohort (n = 354) included 68 cases of LN-G and 286 cases of OB-G with PCOS (Table 1).

By definition, BMI was significantly higher in the OB-G group (Table 1). Age at diagnosis and age at menarche differed between the 2 groups; the OB-G group was younger and had experienced menarche earlier than the LN-G group (Table 1). However, post-menarchal age was comparable between the groups (Table 1). Reported ethnic backgrounds were also similar between the groups (Table 1).

LN-G had higher total testosterone, androstenedione, LH, and SHBG concentrations compared to OB-G (Fig. 1), while free testosterone concentrations were significantly higher in the OB-G group (Fig. 1). LH to FSH ratio was also higher in the LN-G ( $2.8 \pm 1.8$  LN-G vs  $1.8 \pm 0.8$  OB-G,  $P = .0008$ ). FSH and DHEAS did not differ between groups (FSH data not shown, DHEAS Fig. 1E). Additionally, Ferriman-Gallwey score and time from last menses to diagnosis did not differ (Table 1).

HbA1c was higher in the OB-G group, as were ALT and serum triglyceride levels, while high density lipoprotein levels were lower (Fig. 2). On clinical exam, the OB-G group demonstrated more severe acanthosis nigricans (Table 1). No differences were found between the groups for low density lipoprotein ( $P = .416$ , data not shown).

As a secondary analysis, we tested for differences in reproductive and metabolic phenotypes in LN-G and OB-G after adjusting for differences in BMI z-score. In this analysis, the difference in free testosterone was persistent ( $P = .005$ ), while there were no longer differences in total testosterone ( $P = .81$ ), DHEAS ( $P = .26$ ), androstenedione ( $P = .11$ ), LH ( $P = .48$ ), HbA1C ( $P = .32$ ), fasting insulin ( $P = .94$ ), triglycerides ( $P = .58$ ), high-density lipoprotein ( $P = .42$ ), total cholesterol ( $P = .99$ ), low-density lipoprotein ( $P = .37$ ), or ALT ( $P = .24$ ).

We evaluated the frequency of specific elevated androgen concentrations in LN-G and OB-G (Fig. 3). While no significant differences in the frequencies of high total testosterone concentrations were identified, elevated concentrations of DHEAS and androstenedione were observed more frequently in LN-G, while OB-G were more likely to have elevated free testosterone levels (Fig. 3).

## Discussion

PCOS is a complex, heterogenous, polygenic disorder [2]. We observed distinct metabolic and reproductive phenotypes in adolescent LN-G and OB-G at the time of diagnosis, supporting the hypothesis that diverse mechanisms are likely involved in the pathophysiology of PCOS. The reproductive phenotype in

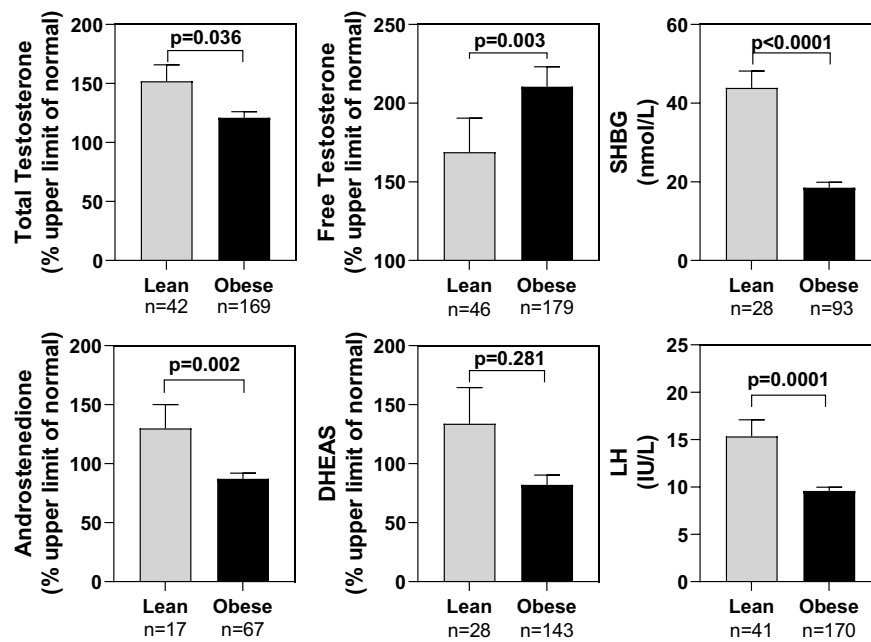
**Table 1. Participant demographics and physical characteristics at the time of diagnosis**

	Lean (LN-G) (BMI < 85th percentile) n = 68	Obese (OB-G) (BMI > 95th percentile) n = 286	P-value
No. of participants per institution			.02
DENVER	29	65	
CHOP	8	28	
FL	3	55	
KC	8	38	
CHLA	6	36	
CHI	7	32	
LURIE	7	32	
Age (years)	$15.8 \pm 1.3$	$15.3 \pm 1.5$	.031
BMI (kg/m <sup>2</sup> )	$22.6 \pm 3.4$	$36.1 \pm 5.6$	.001
Race/ethnicity (%)			.1765
White	63	58	
Black	13	18	
Hispanic	29	29	
Asian	10	4	
American Indian/ Alaskan Native	0	1	
Other/unknown	18	22	
Menarche age (years)	$12.1 \pm 1.6$ (n = 67)	$11.6 \pm 1.7$ (n = 270)	.018
Post-menarchal age (years)	$3.8 \pm 2.0$ (n = 67)	$3.8 \pm 1.9$ (n = 270)	.962
Last menses prior to diagnosis(months)	$5.5 \pm 8.3$ (n = 67)	$5.4 \pm 7.4$ (n = 279)	.746
Ferriman-Gallwey score	$6 \pm 7$ (n = 23)	$8 \pm 7$ (n = 70)	.541
Score (0-32)			
Acanthosis nigricans score (0-4) (%)	(n = 50)	(n = 241)	<.0001
None	74	21	
Minimal	14	13	
Mild	12	35	
Moderate	0	16	
Severe	0	15	
Systolic blood pressure (mmHg)	$112 \pm 11$ (n = 67)	$119 \pm 11$ (n = 265)	.96
Diastolic blood pressure (mmHg)	$66 \pm 8$ (n = 67)	$68 \pm 8$ (n = 265)	.96

Abbreviations: BMI, body mass index; LN-G, adolescent girls who are lean; OB-G, adolescent girls with obesity.

LN-G was characterized by increased LH, total testosterone, SHBG, and androstenedione concentrations and lower HbA1c, ALT, and triglyceride concentrations. In contrast, the phenotype in OB-G was characterized by lower SHBG and higher free testosterone levels. These discrete phenotypes for hyperandrogenemia in PCOS suggest the need for individualized treatment approaches in these distinct subgroups [7, 20].

PCOS has been long recognized as a heterogenous syndrome. The 1990 National Institutes of Health guidelines



**Figure 1.** Reproductive phenotypes in LN-G compared with OB-G at the time of PCOS diagnosis. LN-G had higher total testosterone (A), SHBG (C), androstenedione (D), and LH (F) concentrations, while OB-G had higher levels of free testosterone (B). DHEAS levels did not differ between the groups (E). Mean and SEM pictured. Abbreviations: DHEAS, dehydroepiandrosterone sulfate; LN-G, adolescent girls who are lean; OB-G, adolescent girls with obesity; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin.

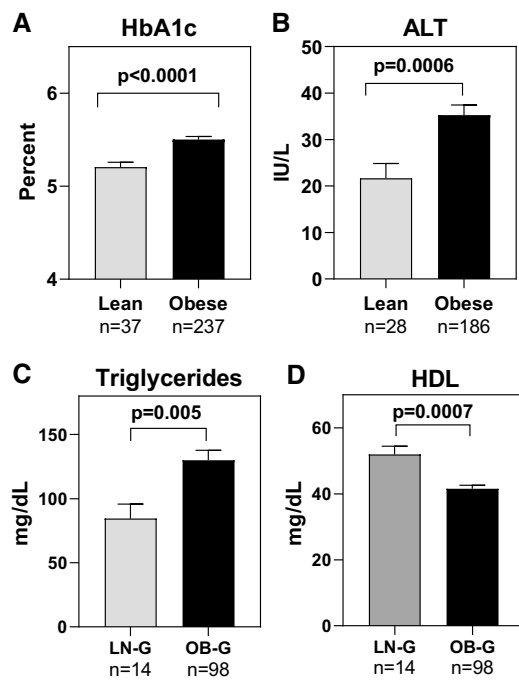
were the first to characterize the diagnostic features of PCOS. Subsequently, the 2003 Rotterdam ESHRE/ASRM Rotterdam and 2006 Androgen Excess-PCOS Society focused on the reproductive manifestations of PCOS [4-7]. Considering the different risk for comorbidities associated with these distinct phenotypes, efforts have been made to distinguish women who have a more metabolic profile from those with a more reproductive phenotype [8, 20]. Most of these efforts have used the presence or absence of specific diagnostic criteria as the framework to subgroup distinct subtypes rather than differences in biological mechanisms [8, 21, 22]. In addition, no formal recommendations for tailored treatment or screening recommendations have been established for women with these discrete phenotypes [7].

PCOS and obesity are closely associated, and excessive weight gain is likely a distinct risk factor for development of the syndrome in some girls. Mendelian randomization studies have provided further evidence for a causal role of obesity in the development of PCOS as genetic loci associated with obesity and central adiposity have been causally related to PCOS [23, 24]. These studies suggest that obesity augments the clinical features of PCOS. However, PCOS itself does not cause obesity. Clinical observations suggest that interventions aimed at reducing excess weight and improving insulin sensitivity improve the reproductive features of PCOS in selected patients.

The neuroendocrine phenotype in affected adult women with PCOS has been characterized by increased frequency of the GnRH pulse generator leading to preferential secretion of LH relative to FSH from the pituitary gland [2]. This increased circulating LH contributes to increased androgen production by ovarian theca cells [2]. Genome-wide association studies (GWAS) have reproducibly identified discrete loci within the region of genes critical to neuroendocrine functioning in the

pathogenesis of PCOS including the  $\beta$  subunit of FSH, the LH receptor, and the FSH receptor [2, 25-28]. We observed elevated LH levels in the LN-G, replicating an earlier finding that LH levels are higher in normal-weight girls with PCOS compared with girls with PCOS and obesity or obesity alone [29]. We hypothesize that this increased LH secretion contributes to the increased ovarian androgen production as manifested by high total testosterone and androstenedione levels in the LN-G. However, additional physiologic studies with LH pulse analysis or quantification of total LH production over time are needed to further study this hypothesis.

Recent studies in adult women have aimed to identify distinct subtypes within the PCOS population as a first step toward better appreciation of the pathophysiology of PCOS and, ultimately, more targeted therapies in these distinct groups. Using hierarchical cluster analysis in adult women with PCOS, Dapas et al presented evidence for a substantial impact of genetic susceptibility in the development of the leaner “reproductive” subphenotype [20]. The metabolic subphenotype was characterized by higher BMI, fasting insulin, and glucose concentrations, while the reproductive subphenotype was characterized by higher FSH, LH, and SHBG concentrations [20]. Further, GWAS analysis identified novel genetic loci associated with predominant reproductive or metabolic subgroup identity, with stronger statistical associations than those reported in previous PCOS GWAS studies [26, 28, 30]. Two of the genetic loci associated with the reproductive subphenotype mapped near genes with strong potential for biologic relevance in PCOS, including *PRDM2*, which encodes an estrogen receptor coactivator highly expressed in the ovary and pituitary, and *BMP1B*, an anti-Müllerian hormone receptor expressed in ovarian granulosa cells and gonadotropin-releasing hormone neurons [20]. There was 1 locus associated with the metabolic subphenotype, which



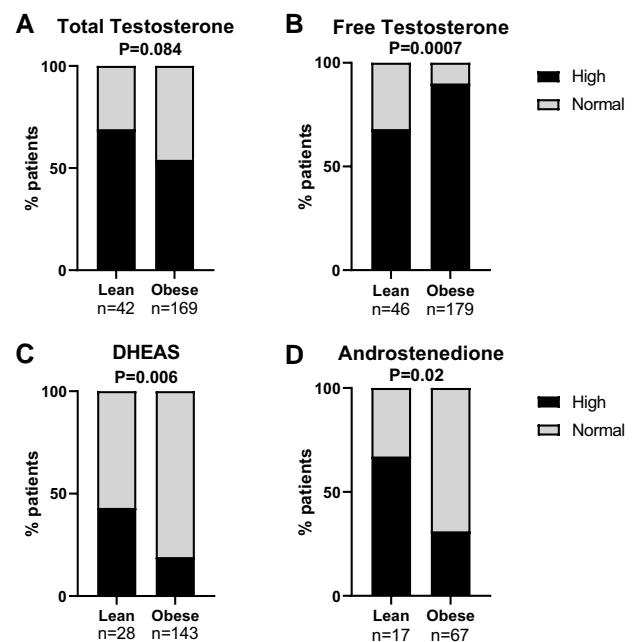
**Figure 2.** Metabolic phenotypes in LN-G compared with OB-G at the time of PCOS diagnosis. OB-G had higher HbA1C (A), ALT (B), and triglyceride levels (C), while LN-G had higher HDL levels (D). Mean and SEM pictured. Abbreviations: ALT, alanine transaminase; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; LN-G, adolescent girls who are lean; OB-G, adolescent girls with obesity; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin.

mapped to an intergenic region between *KCNH7*, which encodes a voltage-gated potassium channel, and *FIGN*, a microtubule-severing enzyme expressed in the pituitary gland and ovary [20]. Further studies including fine-mapping and functional experiments are necessary to confirm the pathogenic significance of these associations. However, the GWAS findings suggest that these subphenotypes are genetically and biologically relevant, with distinct genetic architecture, and represent a first step toward understanding the distinct mechanisms that produce these unique subtypes [20].

Studies in animal models have elucidated the potential ontogeny of neuroendocrine pathology in the development of ovarian hyperandrogenism and PCOS [31-34]. These pre-clinical studies have demonstrated that exposure to excess androgens or anti-Müllerian hormone in utero results in persistent ovarian hyperandrogenism and ovulatory dysfunction throughout reproductive age, presumably due to neuroendocrine mechanisms [31-34]. Further studies are needed to determine if these mechanisms apply to the leaner, more “reproductive” subphenotype in girls and women with PCOS.

Strengths of our study include the use of the CALICO registry with inclusion of a relatively large number of adolescents with PCOS. These data are from 7 different sites across the United States, thus including significant geographic diversity. These data also reflect the ethnic/genetic diversity of the United States at large with oversampling some traditionally underrepresented groups, eg, patients of Hispanic ethnicity.

This study also has limitations. Given the nature of a retrospective chart review, we were limited to the lab values obtained at the time of diagnosis, which resulted in some missing data. Of note, metabolic phenotype data was available from a larger percentage of OB-G compared to LN-G, which may have biased the



**Figure 3.** Frequency of elevated androgen levels in LN-G compared with OB-G at the time of PCOS diagnosis. There were no significant differences in the frequencies of high total testosterone levels between the groups (A). Elevated concentrations of free testosterone ( $P = .0001$ , A) were more common in OB-G. LN-G were more likely to have elevated levels of DHEAS ( $P = .020$ , C) and androstenedione ( $P = .009$ , D). Abbreviations: DHEAS, dehydroepiandrosterone sulfate; LN-G, adolescent girls who are lean; OB-G, adolescent girls with obesity; PCOS, polycystic ovary syndrome.

analysis for differences in metabolic phenotypes. These missing data were excluded from analysis. Additionally, some patients were taking medications at the time of their diagnostic visit, which precluded our ability to assess their metabolic and reproductive phenotypes. These participants were excluded from these relevant analyses. Again, this may have resulted in our inability to capture the most severely affected adolescents. In addition, while standardized assessment of reproductive hormones during the early follicular phase of the menstrual cycle would be preferred, this was not possible in the CALICO database, particularly considering the irregular menstrual cycles experienced by these patients. The data were from 7 different sites, each with different lab assays and multiple different providers. We controlled for the variance in lab values by analyzing the data as a percentage of the upper limit of normal for that assay; however, these lab variances could have affected the precision of the data. To reduce variability in diagnosis, PCOS criteria were confirmed for each patient by the pediatric endocrinologist site principal investigator, following the current guidelines for adolescents [7]. Finally, all 7 sites are tertiary referral centers, many with specific multidisciplinary PCOS clinics. An ascertainment bias likely exists because the identified patients tend to have more severe PCOS symptoms and comorbidities [8]. Prospective cross-sectional studies are needed to validate our findings. The absence of a non-PCOS obese group limits our ability to compare the OB-G group with obese girls without PCOS [29].

We have identified distinct metabolic and reproductive phenotypes in adolescent OB-G and LN-G at the time of PCOS diagnosis. These findings are comparable to the subgroups previously described in adult women with PCOS by cluster analysis. Hence, this study validates these subgroups previously identified in the more controlled research setting. This work contributes

to the framework for development of a more personalized approach in the care of adolescent girls with PCOS based on their unique phenotypes. Further studies are needed to elucidate the distinct biological mechanisms underlying these subtypes, which will be the next step toward development of more effective individualized management approaches.

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## Disclosures

M.G.C. is a consultant for Pollicy, Inc and Site PI for Amino Co, LLC and Eli-Lilly. S.F.W. is a member of the editorial board for the *Journal of the Endocrine Society*. Other authors have no disclosures to declare.

## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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