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Ovarian Morphology by Transabdominal Ultrasound Correlates With Reproductive and Metabolic Disturbance in Adolescents With PCOS

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Abstract

Purpose: To determine whether ovarian morphology imaged using transabdominal ultrasonography reflects clinical and metabolic features in adolescents with polycystic ovary syndrome (PCOS).

Methods: A retrospective pilot study was conducted in 33 adolescents (12–18 years) with PCOS as defined by hyperandrogenism and irregular cycles. Adolescents underwent the following assessments at a random time during the menstrual cycle: transabdominal ultrasonography, physical examination (height, weight, and systolic and diastolic blood pressure), fasting hormonal tests (free, percent free, and total testosterone, androstenedione, follicle stimulating hormone, luteinizing hormone), and metabolic tests (including an oral glucose tolerance test, fasting and 2-hour insulin and glucose, homeostatic model assessment of insulin resistance, and whole-body insulin sensitivity index). Ultrasound images were analyzed offline for ovarian area (OA), ovarian volume (OV), follicle number per cross section (FNPS), and follicle distribution pattern. Associations among endocrine and metabolic variables with sonographic features were assessed by Spearman's rank correlation coefficients and stepwise multiple linear regression.

Results: Total testosterone and androstenedione, but not free testosterone, or percent free testosterone, positively correlated with OA ($\rho = .515$, $\rho = .422$, respectively), OV ($\rho = .451$, $\rho = .382$), and FNPS ($\rho = .394$, $\rho = .474$). Luteinizing hormone:follicle stimulating hormone ratio

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also positively correlated with ovarian size (OA, ρ = .520 and OV, ρ = .409). Unexpectedly, body mass index (ρ = −.503) and fasting glucose levels (ρ = −.393) were inversely correlated with FNPS. Total testosterone was an independent predictor of FNPS, OA, and OV as judged by stepwise multiple regression analyses.

Conclusions: Some aspects of ovarian morphology in adolescents with PCOS using transabdominal ultrasonography associate with markers of reproductive dysfunction and provide rationale to further investigate how ovarian morphology may reflect concurrent metabolic dysfunction.

Keywords

Transabdominal ultrasonography; Ovaries; Adolescent; PCOS; Metabolism

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder imparting short- and long-term health risks for females. The appropriateness and ability to diagnose PCOS in adolescence is controversial, given the overlap of PCOS symptoms with the normal progression through puberty [1]. Several attempts have been made to develop internationally accepted criteria for PCOS in adolescents; however, limited data on the normative ranges of androgens, duration of cycle irregularity, and ovarian morphology during this developmental period hinder a consensus [1]. Some [2,3], but not all studies [4,5], which examined PCOS in adolescents have demonstrated an increased risk of reproductive and cardiometabolic abnormalities, which may follow these girls into adulthood [6]. Despite this uncertainty, there is growing support that early identification of and intervention for PCOS during the adolescent period is needed to obviate these potential long-term health risks.

Consideration of ovarian morphology to diagnose PCOS [7,8] and serve as an indicator of reproductive and metabolic disturbance has been evaluated in adults [9,10]. Modern, higher frequency transvaginal ultrasound systems (i.e., ≥8 MHz) have improved the ability to assess ovarian morphology in PCOS [8]. Further, the use of standardized approaches to evaluate ovarian morphology has greatly improved the reliability of these sonographic assessments [11]. Although not all studies have shown consistent associations among markers of ovarian morphology and reproductive and metabolic end points [12,13], use of older and poorer imaging technology, heterogeneous cohorts, and unreliable approaches to assessing ovarian morphology may have contributed to the variation in findings.

The utility of sonographic ovarian imaging to gauge reproductive or metabolic disturbance in adolescents with PCOS is only beginning to be explored, as the relevance of transabdominal ultrasonographic assessments of ovarian morphology in adolescents is not widely accepted [8,14]. Transabdominal ultrasonography (TAUS) utilizes lower frequency probes, is more susceptible to attenuation due to abdominal adiposity, and is believed to yield poorer quality images compared with transvaginal ultrasound (TVUS). However, recent studies employing newer ultrasound technology report follicle numbers [15] using TAUS and find no association between BMI and quality of the images [16,17]. Moreover, differences in ovarian morphology between adolescents with PCOS and/or hyperandrogenism and healthy controls have been detected using TAUS [4,16–18]. Therefore, it is plausible that ovarian morphology may not only be different in adolescents

with PCOS but also reflect severity of the symptomology in this condition [19]. This may be particularly helpful in identifying those adolescents with heightened risks for reproductive and metabolic comorbidities. To that end, the objective of this study was to test the hypothesis that ovarian morphology reflects the clinical and metabolic features of PCOS in adolescents.

Materials and Methods

Subjects

A retrospective analysis of data collected from a previous study evaluating glucose metabolism in adolescents with PCOS as defined in the 2006 Androgen Excess Society [20] was conducted. A subgroup of 33 adolescents was identified as having both ultrasound data and PCOS defined by the National Institutes of Health and did not meet exclusionary criteria. Briefly, participants were between ages 12 and 18 years and were recruited after being referred to the Multi-Specialty Adolescent PCOS Program at Yale University, School of Medicine from 2008 to 2010. PCOS was defined as having both [1] cycle irregularity and [2] clinical or biochemical evidence of hyperandrogenism. Irregular and/or infrequent menstruation that persisted at least 1.5 years post menarche or primary amenorrhea based on no menstruation at least 3 years post thelarche were used to define cycle irregularity [21]. Clinical hyperandrogenism was defined as the subjective presence of hirsutism and hyperandrogenemia was defined as a serum total testosterone >39 ng/dL, which is above the reference range for Tanner stage 5 on a commercial high-performance liquid chromatography mass spectrometry assay [20]. Adolescents had not used hormonal contraceptives or insulin sensitizers at the time of study participation. Biochemical screening was conducted to exclude for uncontrolled endocrinopathies, including nonclassical adrenal 21-hydroxylase deficiency, androgen-secreting tumors, hyperprolactinemia, and thyroid dysfunction, as described elsewhere [20].

Study procedures

Each participant underwent a complete history and physical examination by either a pediatric endocrinologist (T.S.B.), an endocrinologist (C.A.F.), or a pediatric gynecologist (B.W.R.) in a hospital clinic. Hirsutism was assessed by a clinician experienced in assessing hair growth using the modified Ferriman and Gallwey scoring system. Hirsutism data were missing for two participants. Ethnicity data were self-reported. The body weight of each subject was measured to the nearest .1 kg with a digital scale (Tanita TBF-310, Arlington Heights, IL). Blood pressure was measured using an automated device. Blood pressure was not obtained in one participant. A TAUS was performed by sonographers at the hospital clinic using either a Phillips M3 (73% of ultrasounds) or an HDI 5000 (23% of ultrasounds), with a C5–1 or C5–2 transabdominal probe. Fasting metabolic and hormonal workups were completed at a random time during the menstrual cycle between the hours of 0800 and 1000 and included a 2-hour 75-g oral glucose tolerance test with measurements of serum glucose and insulin concentrations at the 0-hour and 2-hour time points post glucose ingestion.

Ultrasound image assessment

Single cross-sectional images of each ovary were obtained in the transverse and sagittal planes. Ultrasound images were analyzed offline using Santesoft DICOM Editor (Emmanouil Kannellopoulus, Athens, Greece) for the following parameters by a single observer (H.V.): total number of antral follicles in the single plane (follicle number per cross section [FNPS]), ovarian area (OA), ovarian volume (OV), and follicle distribution pattern (FDP). The OA was estimated in the sagittal plane using the equation $\pi/3$ (transverse diameter) × (sagittal diameter). The OV was estimated using the following equation: $\pi/6$ (transverse diameter) × (anteroposterior diameter) × (longitudinal diameter). The FDP was determined on cross-sectional images that showed >9 follicles and had no follicles ≥10 mm [9]. The FDP was graded based on the following scale: (1) both ovaries have fewer than nine follicles; (2) one ovary has more than nine follicles which are scattered throughout the ovary (e.g., heterogeneous distribution pattern); (3) both ovaries have >9 follicles and a heterogeneous distribution pattern; (4) at least one ovary has more than nine follicles and has a peripheral distribution pattern; and (5) both ovaries have more than nine follicles and have a peripheral distribution pattern. Ovarian data are presented as a mean of both ovaries. When a dominant follicle (≥10 mm) or corpus luteum was detected, only the data from one ovary were reported. The investigator was blinded to the endocrine and metabolic status of the participants. Image quality was evaluated as a subjective assessment of the ability to visualize the contour of the ovary, resolution antral follicles, and degree of antral follicle clustering within the ovary. Right and left ovary image quality was evaluated as "poor," "partially visible," or "excellent." Eighteen percent (6/33) of the participants had subjectively poor image quality in both ovaries. FNPS was unable to be ascertained from both ovaries in three adolescents and FDP in two adolescents due to poor image quality.

Biochemical assays

As these data represent a subgroup analysis of a larger cohort [20], assay details have been reported elsewhere. Briefly, plasma glucose levels were determined by the glucose oxidation method, and insulin levels were determined using radioimmunoassay within the Yale Clinical Laboratories. All other hormones were analyzed by the commercial laboratory Esoterix, Inc (Austin, TX). Total testosterone and androstenedione were measured by high-performance liquid chromatography mass spectrometry. Serum free and percent free testosterone were determined by equilibrium dialysis. FSH and LH were determined by chemiluminescent assay. Esoterix Laboratory Services maintains an acceptable level of inter-assay variability at 15% and 20% for mass spectrometry and immune assays, respectively.

Data analysis

Descriptive statistics were tabulated for the clinical, endocrine, and ultrasonographic end points (median, 5th percentile, 95th percentile). BMI percentiles were derived from standard curves developed by the Centers for Disease Control (www.cdc.gov/growthcharts/). Glucose abnormalities were assessed per the American Diabetes Association 2016 guidelines. Impaired glucose tolerance was defined as a 2-hour glucose level of 140–199 mg/dL following a 75-g oral glucose tolerance test. Hypertension was defined using the guidelines

proposed by the Working Group on High Blood Pressure in Children and Adolescents [22]. Prehypertension was defined as systolic or diastolic blood pressure falling between the 90th and 95th percentiles for age, sex, and height. Hypertension was defined as the blood pressure exceeding the 95th percentile. Hypertension in adolescents 18 years of age were based on the Centers for Disease Control guidelines for blood pressure in adults [23]. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin concentration (μU/mL) multiplied by fasting glucose concentration (mg/dl) divided by 405, as previously described [24]. A normative HOMA-IR value was set at <4.39 for this study, which is two standard deviations above the mean for a population-based sample of adolescents, with normal fasting glucose and normal weight [25]. The whole-body insulin sensitivity index (WBISI) was calculated by a modified formula using fasting and 2-hour insulin and glucose values that showed good association with other measures of insulin sensitivity [26]. Because there are no known WBISI thresholds to define glucoregulatory status in adolescents, this metric was not used to assess metabolic status. Associations among FNPS, OV, OA, and FDP with clinical and metabolic parameters were assessed by Spearman rank correlation coefficients. Stepwise multiple linear regression analyses were conducted to determine which metabolic or endocrine variables that correlated with markers of ovarian morphology significantly predicted FNPS, OV, and OA. Significant predictors ($p < .05$) were retained in the final model. Analyses were performed using SPSS (v23). Significance was detected if $p < .05$. Based on a retrospective power calculation (GPower v3.1.9.2, Universität Kiel, Germany), this study had 80% power to detect a significant correlation of .40 and 55% power to detect signifi-cant correlations of .30.

Ethical considerations

The study was approved by the Yale School of Medicine Institutional Review Board. All interactions with human participants occurred at the multi-specialty adolescent program for evaluation of PCOS. Each subject signed an age-appropriate assent/consent form and a parent of each subject gave written informed consent.

Results

Clinical characteristics of the adolescents

The demographic, clinical, ultrasound, and metabolic characteristics of the participants are reported in Table 1. The median age of the adolescents was 15.5 years. Thirty had oligomenor-rhea or amenorrhea, whereas the remaining three adolescents had primary amenorrhea. All adolescents presented with clinical and/or biochemical hyperandrogenism, as per the inclusion criteria. Ninety percent were hirsute (28/31) and 48% had hyperandrogenemia (16/33), defined as elevated total testosterone. As a group, the median value of total testosterone was at the upper limit of the normal reference range. Median free and percent free testosterone were above the upper limits of normal. Elevated free testosterone was detected in 69% (22/33) of adolescents and 73% (24/33) had elevated percent free testosterone. The median value of androstenedione was within the normal reference range (Table 1).

Most of the adolescents were overweight or obese. Specifically, 18% (6/33) were overweight (85th–94th percentile) and 67% (18/33) were obese (>95th percentile of BMI for age). One adolescent (3%) exhibited impaired glucose tolerance based on an elevated 2-hour blood glucose following an oral glucose tolerance test, whereas 30% (10/33) of adolescents were judged as insulin resistant based on an elevated HOMA-IR. Twenty-five percent of adolescents were prehypertensive (8/32) and approximately 9% of adolescents were hypertensive (3/32).

Ultrasonographic characteristics of the adolescents

Ovarian size was variable with OA ranging from 1.88 to 9.94 cm^2 and OV ranging from 1.45 to 20.88 cm^3. Likewise, FNPS ranged from 2.5 to 22 follicles. Sixteen percent (5/31) of adolescents were classified as having a peripheral distribution of follicles in at least one ovary, whereas 32% (10/31) were classified as having a heterogeneous distribution pattern in at least one ovary. Fifty-one percent (16/31) of adolescents did not have the sufficient number of follicles in the cross-sectional images of either ovary to allow for a pattern designation (FNPS <9).

Associations among sonographic markers of ovarian morphology with clinical and metabolic features are presented in Table 2. Ovarian size was positively associated with total testosterone, androstenedione, LH, and LH:FSH ratio. FNPS was positively associated with total testosterone and androstenedione, whereas associations with LH:FSH ($p = .085$) and LH ($p = .064$) did not reach statistical significance. Additionally, FNPS negatively associated with BMI and fasting glucose (Table 2).

Using stepwise linear regression analyses, total testosterone, but not androstenedione or LH:FSH, was included in the final model and significantly predicted mean OA ($\beta = .045$, SE = .015, $p = .005$, $R^2 = .231$) and OV ($\beta = .120$, SE = .039, $p = .005$, $R^2 = .231$). Due to high collinearity between the LH:FSH and serum LH concentrations, only LH:FSH was included as a potential predictor in the model. In the case of FNPS, total testosterone, but not androstenedione, BMI, or fasting glucose, was a significant predictor identified by stepwise linear regression ($\beta = .109$, SE = .036, $p = .005$, $R^2 = .246$). In examination of the residuals and homogeneity of variance, an outlier was identified. To confirm robustness of the final models, the outlier was removed and final models re-fit which confirmed total testosterone as a significant predictor.

Discussion

The main objective of this study was to test the hypothesis that aspects of ovarian morphology assessed by TAUS would reflect the degree of reproductive and metabolic disturbance in a well-defined cohort of adolescents with PCOS. Our results partially supported this hypothesis. Ovarian size and FNPS positively correlated with total testosterone levels as well as its precursor, androstenedione. These findings agree with previous studies that showed larger OV in adolescents with PCOS [17,18,27] or hyperandrogenemia [16] versus healthy controls using TAUS. Regression analyses confirmed that total testosterone significantly predicts ovarian size and follicle number in adolescents with PCOS, consistent with the notion that ovarian hyperandrogenism is

the major source of androgen excess in adolescents with PCOS [28]. Larger ovarian size has also been noted in adolescents with irregular menstrual cycles compared with those with regular menstrual cycles [29–31]. Although the presence of PCOS was not formally evaluated in the studies evaluating ovarian morphology in irregularly cycling adolescents, longitudinal assessments [29] were also consistent, with ovarian size being reported in association with PCOS-like clinical symptoms. Furthermore, we showed that ovarian size correlated with LH levels and the LH:FSH. Given that LH is a key hormonal driver of ovarian androgen production, this study contributes to the growing evidence [19] that ovarian size and follicle numbers reflect reproductive dysfunction in adolescence, albeit some controversy exists [32]. We did not detect associations between free or percent free testosterone with either ovarian size or follicle number, in agreement with a previous study that reported no difference in OV, follicle number, or free testosterone between lean and overweight adolescents with PCOS [27]. Free testosterone concentrations change in part secondary to insulin-induced suppression of SHBG [33]. Positive associations between free testosterone and BMI [34] in adolescents suggest that elevated free testosterone may capture a metabolic origin of PCOS. As such, a biochemical marker that more directly reflects increased androgen production of an ovarian origin (such as total testosterone) would be expected to better associate with ovarian morphology compared to free testosterone.

A peripheral distribution pattern in at least one ovary was noted in 15% of adolescents, which is much less than previous reports of >80% [35,36]. Some have postulated that this morphological pattern reflects a more advanced state of reproductive dysfunction in women with PCOS [37]. Several reasons may explain the lower prevalence of peripherally distributed follicles in our cohort. First, we may have underestimated the prevalence of a peripheral distribution pattern by evaluating only a single cross-sectional slice of the ovary. Second, differences in inclusion criteria may have led to phenotypic variations among PCOS cohorts, thus limiting the appropriateness of comparisons among studies. Unlike others reporting a high incidence of peripherally distributed follicles [35,36], we did not use ovarian morphology as a diagnostic criterion for PCOS as our objective was to determine whether aspects of ovarian morphology, not the presence of polycystic ovaries, reflected the severity of the condition. Studies which prospectively recruit adolescents with ultrasonographic evidence of polycystic ovarian morphology as part of their inclusion criteria would be expected to report a higher incidence of polycystic ovarian features, such as a peripheral distribution pattern. To that end, we did note that the median FNPS and OV in our cohort was lower than the most recently proposed thresholds for polycystic ovarian morphology for women over 18 years (FNPS: 7.5 vs. 9 and OV: 7.6 vs. 10.0 mL) [7,8]. Given the differences in imaging technology (TVUS vs. TAUS) and developmental stage, the use of adult criteria to define polycystic ovaries in adolescents may not be wholly appropriate. To the best of our knowledge, thresholds for FNPS using TAUS in adolescents have not been proposed nor have recent studies compared agreement in ovarian end points using modern TVUS and TAUS. For these reasons, direct comparisons among adult and adolescent ultrasound studies are limited.

Few studies have evaluated whether ovarian morphology corresponds with metabolic features in adolescents. A positive association between measures of adiposity and OV has been reported [30], whereas others have shown no association, leaving this area of study

controversial [17]. We anticipated that metabolic derangements associated with obesity would correspond with increasing ovarian size and follicle number, given that insulin has been shown to augment the effects of gonadotropins in the ovary [38]. In contrast to our hypothesis, aspects of ovarian morphology (i.e., FNPS) were inversely correlated with BMI and fasting glucose levels and we noted no associations between ovarian size and metabolic features. There are a number of potential interpretations of these findings. First, differences in the diagnostic criteria for PCOS employed, as well as the small sample size of this study, may have contributed to the differences in findings across studies. Moreover, the mechanisms whereby metabolic consequences of obesity impede folliculogenesis are not well understood. BMI has been shown to be inversely associated with LH pulse amplitude and serum LH levels in adolescents [39] which could impair its trophic effects on ovarian folliculogenesis and result in fewer growing antral follicles. An inverse association between BMI and fasting glucose with follicle number may reflect this phenomenon. One additional explanation for the unexpected findings may relate to the duration of metabolic exposure. It is plausible that a longer duration of metabolic perturbation and/or a more severe reproductive phenotype is needed for the establishment of consistent associations between morphological and metabolic factors. That said, our interpretations must be tempered as we did not assess follicle number in the entire ovary or follicle diameter, which would have provided relevant information on the stages of antral follicle development. We previously showed in adult women with PCOS that associations among follicle number and aspects of metabolic status depend on follicle size [9]. Smaller follicles positively correlated with metabolic markers, whereas negative associations were apparent with larger follicles —consistent with a favorable metabolic environment promoting advanced follicular growth. Whether these relationships would manifest during adolescence is uncertain and merits further research. Last, we cannot exclude the possibility that these associations may also represent a limitation of TAUS to detect antral follicles with increasing adiposity. However, it should be noted that we and others [15,27] were able to resolve antral follicles as small as 1–2 mm in overweight adolescents, which is in line with a recent study demonstrating that the usability of ovarian ultrasound data by TAUS was not impacted by increasing BMI [17].

This study was strengthened by its use of an offline analysis of ovarian morphology which significantly improves reliability in evaluating ovarian morphology [11]. We also conducted a comprehensive evaluation of several clinical, hormonal, and metabolic features in our participants which enabled the use of a well-defined study cohort. However, this study represented a pilot evaluation of ovarian morphology in a subset of adolescents with PCOS and, hence, was limited by its small sample size and lack of control group. Although we confirmed that the associations between ovarian morphology with reproductive and metabolic status that we identified represented meaningful relationships (as judged by a power calculation), we cannot exclude the possibility that we may have missed moderate associations with other parameters. This study was also observational in nature; therefore, associations detected cannot address causality. Furthermore, ultrasounds were not conducted at a standardized stage of the menstrual cycle, which may have weakened some of the associations noted. Whereas antral follicle development has been well characterized in regularly cycling women [40], follicle dynamics in early reproductive life have not been established. For this reason, we are unable to fully anticipate the impact of menstrual

cycle stage on our findings. Last, our analyses were limited to images of a single cross-sectional view of the ovary obtained from one of two ultrasound machines. Our internal assessment of image quality showed no difference between machines (Fisher's exact test: Left ovary: $p = .580$; Right ovary: $p = .784$) supporting our use of images collected from both ultrasound systems. Future prospective studies will benefit from providing estimates of follicle population throughout the entire ovary as well as measurements of the stromal compartment where there is paucity of data using modern equipment in adolescents.

In summary, we report that some aspects of ovarian morphology relate to the degree of androgen production and gonadotropin secretion despite potential competing influences of metabolic factors on ovarian morphology during adolescence. This study supports the utility of TAUS to reflect reproductive disturbance in adolescents with PCOS and provides rationale to further explore the potential of ovarian morphology to serve as a biomarker of metabolic disturbance in large, well-controlled prospective studies. Research aimed at establishing best practices for the sonographic evaluation of ovarian morphology is needed to solidify a role for ovarian imaging in the evaluation of reproductive and metabolic status in adolescents.

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IMPLICATIONS AND CONTRIBUTION

This study demonstrates that ovarian morphology assessed by transabdominal ultrasound may reflect reproductive disturbance in adolescents and may therefore serve as a clinical marker to assess reproductive and metabolic disturbance in early reproductive life.

Table 1

Clinical, ultrasonographic, and metabolic characteristics of adolescents with PCOS

Marker	PCOS cohort	Expected values
Demographic		
Age	15.5 (12.1–18.3)	—
Ethnicity, n (%)		—
Hispanic n (%)	7/33 (21)	—
Non-Hispanic	24/33 (73)	—
Not reported	1/33 (3)	—
Race, n (%)		—
African American	1/33 (3)	—
Asian	1/33 (3)	—
Mixed	2/33 (6)	—
White	29/33 (88)	—
Diagnostic		
Total testosterone (ng/dL)	38 (20–88)	<39
Hirsute, n (%)	28/31 (90)	—
Cycle irregularity (days)		21–35d
Oligomenorrhea	26/33 (79)	
Amenorrhea	4/33 (12)	
Primary amenorrhea	3/33 (9)	
Reproductive		
Free testosterone (pg/mL)	7.6 (1.5–19)	<6.3[a]
Percent free testosterone (%)	2 (.6–3.0)	<1.4[a]
Androstenedione (ng/dL)	175 (59–338)	50–224[b]
LH (mIU/mL)	5.7 (.41–40)	.4–11.7[b]
FSH (mIU/mL)	4.4 (1.0–11.0)	1.0–9.2[b]
LH:FSH ratio	1.52 (.1–5.26)	—
Sonographic		
Mean OA (sag) (cm^2)	4.66 (2.15–8.01)	—
Mean OV (cm^3)	7.56 (2.87–20.54)	—
Mean FNPS	7.5 (3–18)	—
Peripheral distribution pattern, n (%)	5/33 (15)	—
Metabolic		
Body mass index (kg/m^2)	30.65 (19.61–45.03)	<85th percentile[c]
Fasting glucose (mg/dL)	84 (70–96)	<100[d]
2-h Glucose (mg/dL)	105 (66–139)	<140[d]
Fasting insulin (μIU/mL)	13 (3–61)	≤17[b]
2-h Insulin (μIU/mL)	92.5 (23–390)	15–53[b]

Marker	PCOS cohort	Expected values
HOMA-IR	2.45 (.51–12.08)	4.39[e]
WBISI	3.30 (.59–12.51)	—
SHBG (nMol/L)	23.5 (10–113)	36–125[b]
Systolic BP (mmHg)	116 (97–130)	<90th percentile[f]
Diastolic BP (mmHg)	69 (49–79)	<90th percentile[f]

Values are expressed as median (5th, 95th percentile).

BMI = body mass index; BP = blood pressure; FSH = follicle stimulating hormone; HOMA-IR = homeostatic model of insulin resistance; LH = luteinizing hormone; OA = ovarian area; OV = ovarian volume; PCOS = polycystic ovary syndrome; SHBG = sex hormone-binding globulin; WBISI = whole-body insulin sensitivity index.

[a] Normal range of assay determined by Esoterix Laboratory for adults (adolescent reference ranges not available).

[b] Normal range of assay determined by Esoterix Laboratory for adolescents.

[c] BMI percentile is determined based on age using Center of Disease Control growth charts.

[d] Glucose thresholds based on the American Diabetes Association 2016 Guidelines.

[e] Based on Lee et al. (2006).

[f] Based on U.S. Department of Health and Human Services Report (2005).

Table 2

Associations between ultrasonographic markers of ovarian morphology and reproductive and metabolic features in adolescents with PCOS

Marker	Mean OA	Mean OV	Mean FNPS	FDP
Reproductive				
Total T (ng/dL)	.515**	.451**	.394*	.089
Free T (ng/dL)	.282	.222	.072	−.054
Percent-free T	−.114	−.071	−.166	.024
Androstenedione (ng/dL)	.422*	.382*	.474**	.112
LH (mIU/mL)	.496**	.404*	.343	.122
FSH (mIU/mL)	.304	.303	.242	.131
LH:FSH ratio	.520**	.409*	.320	.033
Metabolic				
BMI (kg/m^2)	−.306	−.288	−.503**	−.281
Fasting glucose (mg/dL)	−.193	−.248	−.393*	−.315
2-h Glucose (mg/dL)	−.117	−.100	−.078	.002
Fasting insulin (μIU/L)	−.173	−.181	−.204	−.013
2-h Insulin (μIU/L)	−.215	−.197	−.168	−.081
HOMA-IR	−.205	−.213	−.242	−.048
WBISI	.186	.186	.208	.045
SHBG	.182	.178	.244	.019
Systolic BP(mmHg)	−.096	−.168	−.096	−.077
Diastolic BP(mmHg)	−.015	.050	.103	.202

Values are expressed as Spearman's rho.

BMI = body mass index; BP = blood pressure; FDP = follicle distribution pattern; FNPS = follicle number per cross section; FSH = follicle stimulating hormone; HOMA-IR = homeostatic model of insulin resistance; LH = luteinizing hormone; T = testosterone; OA = ovarian area; OV = ovarian volume; PCOS = polycystic ovary syndrome; SHBG = sex hormone-binding globulin; WBISI = Whole-Body Insulin Sensitivity Index.

* $p < .05$;

** $p < .01$ (levels of significance).