Ultrasound features of polycystic ovaries relate to degree of reproductive and metabolic disturbance in polycystic ovary syndrome

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Objective: To reexamine associations between polycystic ovarian morphology (PCOM) and degree of symptomatology in polycystic ovary syndrome (PCOS) using a well-defined PCOS population, newer ultrasound technology, and reliable offline assessments of sonographic parameters.
Design: Cross-sectional observational study.
Setting: Academic hospital and clinical research unit.
Patient(s): Forty-nine women with PCOS as defined by hyperandrogenism and oligoamenorrhea.
Intervention(s): None.
Main Outcome Measure(s): Number of follicles per follicle size category, antral follicle count (AFC), ovarian volume (OV), follicle distribution pattern, stromal area, ovarian area, stromal to ovarian area ratio (S/A) and stromal echogenicity index (SI), total (TT), androstenedione, LH, FSH, cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, C-reactive protein, glucose, insulin, and hemoglobin A1C, menstrual cycle length, hirsutism score, body mass index (BMI), waist:hip ratio, and blood pressure.
Result(s): AFC, but not OV, was positively associated with TT ($\rho = .610$), androstenedione ($\rho = .490$), and LH:FSH ($\rho = .402$). SI was positively associated with androgen markers and LH:FSH, while S/A was negatively associated with these variables. Follicles ≤ 4 mm were negatively associated with various metabolic markers, whereas larger follicles (5–8 mm) showed positive associations. Stromal markers were not associated with cardiometabolic measures. LH:FSH best predicted follicles ≤ 4 mm, and BMI predicted 5- to 9-mm follicles. Dominant follicles ≥ 10 mm were best predicted by age.
Conclusion(s): AFC, and not OV, reflected the severity of reproductive dysfunction in PCOS. Associations among different sized follicles were consistent with recruitable sized follicles, which reflects the severity of metabolic dysfunction in PCOS. (Fertil Steril® 2015;103: 787–94. ©2015 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, ultrasound, follicle, metabolism, hyperandrogenism

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Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder that is characterized by the presence of enlarged ovaries with an abundance of small antral follicles distributed about a bright echodense stroma (1, 2). While the relevance of polycystic ovarian morphology (PCOM) to the diagnosis of PCOS has been debated (3), the most recent consensus criteria

for PCOS have included PCOM as a relevant marker (4–6). Whether PCOM predicts degree of symptomatology, response to treatment, and/or health risks in PCOS is uncertain. Of the studies that have reported associations among sonographic markers and clinical indices, most—but not all (7–15)—have noted positive relationships among androgens (7, 8, 10, 12–14, 16–23), gonadotropins (12, 13, 16, 19–21, 24), and menstrual cycle length (13, 22) with follicle counts, stromal area (SA), stromal echogenicity, and/or ovarian volume (OV). Associations with metabolic abnormalities are even less clear. There are reports of positive associations among follicle number, OV, and stromal features with markers of insulin resistance (10, 13, 15, 17–19, 23, 25). However, other investigators have found no such relationship (8, 11, 14, 18, 19, 21) or the opposite association (11). Because fewer studies have assessed associations with other cardiometabolic features (13, 14, 26) or have considered the impact of follicle size populations (23, 27), there are limited data on which features of PCOM inform severity or risk of chronic disease in PCOS.

Technical limitations leading to moderate to poor interobserver agreement when assessing PCOM may account for discrepancies among studies (28). We showed that systematic approaches are necessary to improve reliable sonographic assessments of PCOM (29, 30). Discrepant findings may also be due to inconsistencies in defining PCOM. Some researchers have used ultrasound criteria that were established in the 1980s (11, 12, 15, 16, 31), while others have used criteria supported by the 2003 Rotterdam consensus (17, 18, 21) or a variation of the two (20–22). We and others have provided evidence that these criteria are obsolete in light of advances in ultrasound technology (32–35). Finally, the PCOS populations studied to this point have been heterogeneous with little consideration of the potential influence of phenotypic variations in PCOS (6). The goal of the current study was to clarify the relationship among clinical, hormonal, metabolic, and sonographic features of PCOS using a well-defined clinical population, newer ultrasound technology, and reliable offline assessments of sonographic parameters.

MATERIALS AND METHODS

Subjects and Study Procedures

Forty-nine women diagnosed with PCOS by the National Institutes of Health (NIH) guidelines participated in the study (3). Participants were between ages 19 and 36 and had not used fertility medications, hormonal contraception, or insulin sensitizers in the 3 months before enrollment. Women with a history of ovarian surgery were excluded. Clinical assessments included an evaluation of menstrual cycle history to determine the extent of any menstrual cycle disturbance and/or duration of infertility as well as a physical exam to assess height, weight, waist and hip circumference, blood pressure, and the degree of terminal hair growth on nine regions of the body using the modified Ferriman-Gallwey scoring system (36). A transvaginal ultrasound scan was performed using a 9-MHz transvaginal transducer and an UltraSonix RP Scanner (version 2.3.5) to assess ovarian morphology. Ovaries were scanned from the inner to outer margins in both the sagittal and transverse planes. Digital recordings of the ultrasound scans were stored for offline image analysis. Fasting blood tests were performed to assess levels of gonadotropins, total and free androgens, and serum markers of the metabolic syndrome including lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]), C-reactive protein (CRP), and hemoglobin A1C (HbA1C). Fasting tests also included serum assessments for cortisol, PRL, thyroid hormones, DHEAS, and 17-hydroxyprogesterone to exclude for other endocrinopathy. Subjects had a 75-g oral glucose tolerance test performed after an overnight fast wherein glucose and insulin levels were measured at 0, 1, and 2 hours post–glucose ingestion. Some participants in this study were included in previous publications (30, 33, 37).

Clinical Definitions of PCOS Symptoms

PCOS was defined by the NIH criteria as having the following two symptoms: [1] oligo- or frank amenorrhea and [2] clinical or biochemical evidence of hyperandrogenism (3). Oligo- or frank amenorrhea was defined as a history of menstrual cycles longer than 38 days (38). Hyperandrogenism was defined as a modified hirsutism score ≥ 7 and/or total T (TT) levels ≥ 3.96 nmol/L, as described elsewhere (32).

Ultrasound Image Assessment

Ultrasound images of each ovary were analyzed offline using Santesoft DICOM Editor software (Emmanouil Kanellopoulus) for the following parameters: [1] total number of antral follicles in both ovaries (AFC), [2] total number of follicles per follicle size category, [3]OV, [4] ovarian area (OA), [5] SA, [6] ratio of SA to OA (S/A), [7] stromal index (SI), and [8] follicle distribution pattern (FDP).

Reliable follicle counts were achieved for each ovary by imposing a grid system onto the viewing window as described elsewhere (30). Sizes of individual follicles were based on the average of two orthogonal measurements that were made of the follicular antrum in the largest cross-sectional view. Based on an intraclass correlation coefficient analysis, the level of interobserver agreement for AFC by three observers was 0.84. OV was estimated using the equation: $\pi/6$ (transverse diameter) $\times$ (anteroposterior diameter) $\times$ (longitudinal diameter). The level of interobserver agreement for OV by three observers was 0.96. When all follicles in both the left and right ovary were <10 mm in size, a value for OV was designated as the mean recorded values of both ovaries. When a follicle ≥ 10 mm was present in a single ovary, the OV for the other ovary was used; and when present in both ovaries, the OV was excluded as per the method previously reported by Johnstone et al. 2010 (39).

A single investigator identified and evaluated the largest cross-sectional plane of each ovary to determine OA, SA, SI, and FDP. OA was measured by outlining the external limits of the ovary with electronic calipers. SA was measured by outlining the peripheral profile of the stroma, taking care to