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Raising threshold for diagnosis of polycystic ovary syndrome excludes population of patients with metabolic risk

Molly M. Quinn, M.D.,[a] Chia-Ning Kao, M.Sc.,[a] Asima Ahmad, M.D.,[a] Nikolaus Lenhart, B.S.,[a] Kanade Shinkai, M.D., Ph.D.,[b] Marcelle I. Cedars, M.D.,[a] and Heather G. Huddleston, M.D.[a]

[a] Department of Obstetrics, Gynecology and Reproductive Sciences, and [b] Department of Dermatology, School of Medicine, University of California–San Francisco, San Francisco, California

Objective: To characterize the population of patients excluded from a diagnosis of polycystic ovary syndrome (PCOS) when follicle number criteria are increased to 25 per ovary as suggested by the Androgen Excess and Polycystic Ovary Syndrome Society's recent task force.
Design: Cross-sectional study.
Setting: Tertiary academic center.
Patient(s): A total of 259 women with PCOS according to Rotterdam criteria who were systematically examined from 2007 to 2015, with 1,100 ovulatory women participating in the Ovarian Aging (OVA) Study as controls.
Intervention(s): Anthropometric measurements, serum testing, ultrasonic imaging, and comprehensive dermatologic exams.
Main Outcome Measure(s): Body mass index (BMI), waist to hip ratio (WHR), serum cholesterol, fasting glucose and insulin, follicle count per ovary, biochemical hyperandrogenemia, and hirsutism.
Result(s): Forty-seven of 259 women meeting the Rotterdam criteria (18.1%) were excluded from a diagnosis of PCOS when the follicle number criteria was increased to 25. These women had clinical evidence of hyperandrogenism (68.1%) and biochemical hyperandrogenemia (44.7%), although fewer reported oligoanovulation (26.8%). The excluded women had elevated total cholesterol, fasting insulin, and homeostatic model of insulin resistance (HOMA-IR) when compared with controls despite controlling for age and BMI.
Conclusion(s): The women excluded from the PCOS diagnosis by raising the threshold of follicle number per ovary to ≥ 25 continue to show evidence of metabolic risk. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Follicle number, insulin resistance, metabolic risk, PCOS

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Stein and Leventhal (1) first described a syndrome of oligomenorrhea, infertility, and bilaterally enlarged ovaries in 1935. Ten years later, obesity and hirsutism were identified as clinical features associated with the phenotype (2). Since that time, there has been increasing recognition of the widespread prevalence of the polycystic ovary syndrome (PCOS) and ongoing debate as to the most appropriate diagnostic criteria for the most common endocrinologic disorder of reproductive-age women (3–6).

After the 1990 National Institutes of Health conference on PCOS, it was proposed that patients meeting criteria for the diagnosis demonstrate both chronic anovulation and clinical and/or biochemical signs of hyperandrogenism with exclusion of other etiologies. It was subsequently recognized that women with polycystic ovaries and hyperandrogenism may have features of the syndrome despite regular menstrual cycles (7). As a result, the criteria for diagnosis were revised at

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Reprint requests: Molly M. Quinn, M.D., Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Reproductive Endocrinology and Infertility, University of California San Francisco School of Medicine, 550 16th Street, 7th Floor, San Francisco, California 94158–2519 (E-mail: molly.quinn@ucsf.edu).

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the 2003 Rotterdam Consensus. A diagnosis required two out of three criteria be met: oligo or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic-appearing ovaries (8).

In 2006, the Androgen Excess and PCOS Society (AE-PCOS) appointed a task force to review the medical literature and recommend a definition of PCOS. The task force concluded that PCOS should be defined by hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligoanovulation and/or polycystic ovaries), and the exclusion of related disorders (9, 10).

Although the description of "cystic," enlarged ovaries by Stein and Leventhal gave PCOS its name, histologic examination of tissue from ovarian wedge resections in women with PCOS has demonstrated an increase in the number of growing or graafian follicles measuring $<$10 mm in diameter (11, 12). Therefore, multifollicular ovaries are a more accurate descriptor of the clinical phenomena. The first adopted criteria for polycystic ovarian morphology arbitrarily described an ovary containing 10 or more follicles measuring 2–18 mm in diameter distributed around the ovarian periphery with increased amount of stroma using transabdominal ultrasound (13).

Polycystic ovarian morphology (PCOM) consists of stromal hypertrophy and follicular excess. The Rotterdam Consensus adopted follicle number criteria of at least 12 or more follicles measuring 2–9 mm on one ovary and/or ovarian volume of greater than 10 mL on median section (8, 14). These cutoffs come from a receiver operating characteristic (ROC) study in which a follicle number per ovary of 12 provided 99% specificity and 75% sensitivity for distinguishing women with PCOS compared with controls (15). Notably, in this study the controls who were ovulatory and nonhirsute but had polycystic-appearing ovaries were excluded.

However, recent studies have suggested that defining a threshold for follicular excess as 12 or more follicles in any ovary may be inappropriately low given its presence in 32% to 84% of young women without apparent increased health risk (16–18). This research led to a reevaluation of the follicle number criteria for PCOS with one ROC curve, cluster analysis suggesting a cutoff of 19 follicles, and another suggesting 26 follicles per ovary for distinction between women with and without PCOM (19, 20). Finally, the Androgen Excess Society convened a task force to define and describe the significance of PCOM, with the suggestion that $\geq$25 follicles per ovary is the most diagnostic of PCOM in the setting of newer ultrasound technology (21).

Infertility, irregular menses, or hyperandrogenic symptoms may drive a patient with PCOS to seek medical care, but it has long been recognized that patients with PCOS have increased risk factors for cardiovascular disease, including metabolic syndrome, prediabetes or type 2 diabetes mellitus, dyslipidemia, abdominal obesity, and hypertension. Thus, from a general health standpoint, the identification of PCOS in a patient may serve as an opportunity for evaluation, counseling, and treatment of risk factors for cardiovascular disease at an earlier time than if PCOS had not been identified. For this reason, there has been a clear recommendation for screening for cardiovascular disease risk factors in patients with PCOS (22).

Our study characterizes the population of women excluded from a diagnosis of PCOS given the recently proposed elevated follicle number threshold. Additionally, we sought to address whether raising the threshold follicle number for a diagnosis of PCOS impacts the identification of patients with elevated metabolic risk.

MATERIALS AND METHODS

This is a cross-sectional cohort analysis of patients enrolled from 2007 to 2015 in a PCOS research database as part of a prospectively designed research study. The participants presented for evaluation of symptoms suggestive of PCOS to a multidisciplinary specialty clinic at a tertiary referral center and were consecutively enrolled. The patients signed consent forms if they agreed to participate in a research database and tissue bank study. Approval was obtained from the University of California–San Francisco Committee on Human Research.

The control population was composed of participants in the Ovarian Aging (OVA) Study, a population-based cohort of 1,100 healthy, multiethnic ovulatory women between the ages of 25 and 45 who were not seeking treatment for fertility; the study was designed to investigate reproductive aging. Regular menstrual cycles were an inclusion criterion for participation and were established based on clinical history indicating ability to predict the start of menses within 5 days. Controls were recruited through Kaiser Permanente (KP) of Northern California, a large, integrated health-care delivery system providing medical care to 30% of the population of northern California, and all patients were evaluated at the same academic center. A requirement for inclusion in OVA was that all women self-identify as belonging to one of four racial/ethnic groups categorized as Caucasian (27%), Asian (27%), Hispanic (23%), or African-American (23%). Women who reported multiethnic origin were not enrolled. All controls had a body mass index (BMI), waist and hip ratio (WHR), and blood pressure measurements at an index visit between 2006 and 2010. Transvaginal ultrasounds for assessment of antral follicle count were performed on a Shimadzu SDU-450XL machine with variable transducer frequency of 4–8 mHz at the index visit, which was scheduled on the second, third, or fourth day of the menstrual cycle. Fasting glucose, insulin, and cholesterol levels were determined at the same commercial laboratory. The University of California–San Francisco's Committee on Human Research approved the OVA Study. Further details regarding the study design and methodology for OVA have been previously published (23, 24).

In the study population, the diagnosis of PCOS was made according to the 2003 Rotterdam criteria, which require two of three clinical signs or symptoms to be met: [1] oligomenorrhea or amenorrhea; [2] clinical and/or biochemical signs of hyperandrogenism; or [3] polycystic ovaries on ultrasound (8). Initially PCOM was defined as $\geq$12 follicles measuring 2–9 mm or an ovarian volume $>$10 mL in at least one ovary.