



FIRST OF A 4-PART E-SERIES

Polycystic ovary syndrome: Where we stand with diagnosis and treatment—and where we're going

➔ PCOS is one of the most common reproductive endocrine disorders of women—and one of the most impenetrable to understand and difficult to manage. Two experts tackle a long list of questions that your clinician–colleagues have been posing.

Steven R. Lindheim, MD, MMM, and Leah Whigham, PhD

Polycystic ovary syndrome, or PCOS, is a condition characterized by hyperandrogenism and chronic anovulation—the most common endocrinopathy in women of reproductive age, affecting at least 1 in every 15. Associated metabolic and health complications are significant and serious, and include obesity, insulin resistance, dyslipidemia, pancreatic β -cell dysfunction, type-2 diabetes, cardiovascular disease, endometrial cancer, sleep apnea, inflammation, and infertility. To the frustration of the medical community and patients, the exact cause (or causes) of PCOS remains largely unknown; making the diagnosis means, essentially, excluding disorders that mimic PCOS—including congenital adrenal hyperplasia, hyperprolactinemia, and thyroid disease. **PCOS is an enigma, in that it is a heterogeneous disorder, with the severity**

of clinical hyperandrogenism (hirsutism, acne, alopecia), obesity, and menstrual disturbance being considerably variable.

Furthermore, as many as 40% of women who have PCOS do not express classic signs of hyperandrogenism, making the diagnosis exceedingly challenging, particularly in the case of a patient of the lean (i.e., physical appearance) phenotype.

The picture is further confused. The appearance of polycystic-appearing ovaries (multiple tiny cysts) on ultrasonography (US) is noted in as many as 20% of women who have polycystic ovaries *without* evidence of androgen excess. The significance of this as an isolated finding on imaging in an otherwise normal woman is unclear. Some experts have described the presence of this finding as, again, signaling a cryptic or unexpressed form of PCOS or a prelude to the manifestation of signs of PCOS later.

The four parts of this article that will be posted here on the OBG MANAGEMENT Web site over coming months address questions that are often asked by clinicians about this challenging clinical entity. [*Editor's note:* Those four installments will, as they are published, be collected on a single Web page for ease of access.]

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Dr. Lindheim is Program Director, the Arizona Reproductive Institute, Tucson, AZ. He is an OBG MANAGEMENT Contributing Editor.

Dr. Whigham is Research Nutritionist, USDA Grand Forks Human Nutrition Research Center, Grand Forks, ND.

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Historical perspective

Q I'm confused. Going back to medical school, we were always taught that PCOS was an anatomic abnormality in which the ovary 1) produced excess androgens and 2) had a thickened covering, thus preventing ovulation. Today, PCOS has evolved into a seemingly complex entity. How did that transformation happen?

In its original description in the medical literature in the 1800s, PCOS was called *cystic oophoritis*.^{1,2} However, it wasn't until the early 1930s that Stein and Leventhal first diagnosed what was initially coined Stein-Leventhal syndrome, reporting their findings in 1935.³ Later, the condition was referred to as *polycystic ovarian disease*.

In 1945, Stein published a follow-up report in which he added excessive male-pattern hair growth and obesity to the list of described symptoms. Although other associated symptoms have been noted in women who have the syndrome, the four principal ones established by Stein and Leventhal between 1935 and 1945 are irregular menstruation, infertility, obesity, and hirsutism.

Evolution as a disorder. PCOS was, initially, thought to be an anatomic disorder that specifically involved the ovaries and their thickened capsules. By the 1960s, with the advent of the radioimmunoassay, researchers could measure hormone levels in women who had the disorder. Studies confirmed that PCOS was associated with 1) increased androgen production from the ovaries and 2) abnormal gonadotropin secretion. Specifically, luteinizing hormone (LH) stimulated excess ovarian androgen production. From a historical perspective, then, the view

of PCOS changed from anatomic disorder to, primarily, an endocrine disorder.

By the 1980s, clinical observations suggested a strong relationship between hyperinsulinemia and hyperandrogenism. The constellation of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN) was then called HAIR-AN syndrome. Dunaif described how insulin, acting through ovarian insulin growth-factor receptors as mediators in ovarian dysfunction, led to hyperandrogenism.⁴ Two mechanisms appeared to account for HAIR-AN syndrome:

- hyperinsulinemia induced by insulin resistance causes hyperandrogenism
- hyperandrogenism causes insulin resistance and hyperinsulinemia (acanthosis nigricans is considered to be an epiphenomenon caused by hyperinsulinemia).

In the late 1980s, Reaven theorized that central obesity (male-type, or apple-shaped, obesity), diabetes, and hypertension have a common cause in insulin resistance (IR) and impaired glucose tolerance (IGT).⁵ This constellation of symptoms, at first called *syndrome X*, is known today as *metabolic syndrome* and is an object of extensive scientific inquiry—especially because the combination of findings strongly predisposes an affected person to cardiovascular disease.

By 2000, PCOS was viewed more as a metabolic disorder, with an array of cardiac and metabolic risk factors (insulin resistance and glucose intolerance; hypertension; dyslipidemia; and dysfibrinolysis) that have been linked to a number of health disorders, including type-2 diabetes and atherosclerotic cardiovascular and cerebrovascular disease.

Today, diagnostic criteria for metabolic syndrome are at least three of these five findings:

- waist circumference, more than 35 inches
- triglycerides level, at least 50 mg/dL
- high-density lipoprotein-C level, greater than 50 mg/dL
- systolic BP, 130 mm Hg or higher, and diastolic BP, 85 mm Hg or higher
- fasting glucose level (after an oral glucose tolerance test) between 110 and 126 mg/dL or a 2-hour postprandial glucose level between 140 and 199 mg/dL, or both.

FAST TRACK

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In the next installment: The authors begin by taking on two common areas of questioning in the care of women who have PCOS:

- » "How is obesity defined and how is associated insulin resistance explained in the pathology of PCOS?"
- » "What is the prevalence of, and best way to screen for, insulin resistance?"

Prevalence

Q How prevalent is PCOS? Does prevalence vary if one considers clinical criteria, or biochemical criteria, or ultrasonographic criteria?

Data are scarce, making the prevalence of PCOS difficult to estimate—in part, because PCOS is a heterogeneous condition that can manifest with variable clinical evidence:

- hyperandrogenism—as either hirsutism, acne, or alopecia, or a combination of these signs
- menstrual or ovulatory dysfunction, or both
- overweight or obesity
- infertility
- insulin resistance and other metabolic abnormalities
- polycystic ovaries

Now that accepted diagnostic criteria for PCOS are in place, the prevalence rate of the syndrome will be easier to establish. In the discussion that follows, we attempt to establish estimates of prevalence based on histopathology, signs of clinical hyperandrogenism, and the US appearance of polycystic ovaries.

When PCOS is defined histopathologically (i.e., by the presence of polycystic ovaries at the time of oophorectomy or wedge resection), 1.4% to 3.5% of unselected women⁶ and 0.6% to 4.3% of infertile women⁷ have this syndrome.

When clinical criteria are used, prevalence varies with the clinical complaint. Hirsutism is usually a mark of increased ovarian or adrenal androgen production. Studies—including one in which more than 1,000 women were evaluated using the 1990 National Institutes of Health (NIH) criteria (see the next section)—suggest that, in fact, **more than 75% of hirsute women have PCOS.**^{8,9}

In the absence of frank hirsutism, when only unwanted facial hair is present, approximately 50% of these women meet the definition for having PCOS.¹⁰

Among women whose only complaint is acne, prevalence has been reported in as many as one-third (range, 19% to 37%, al-

though diagnostic criteria for PCOS were not well defined in these three studies).¹¹⁻¹³

Last, in women who had any manifestation of clinical hyperandrogenism by the 2003 Rotterdam criteria (hirsutism, acne, or alopecia, or a combination; again, see the next section), PCOS was diagnosed in 72%.¹⁴

When PCOS is defined by a finding of polycystic ovaries on US, prevalence varies by study settings. Polycystic ovaries are seen in 92% of women who have idiopathic hirsutism¹⁵; in 87% of women who have oligomenorrhea¹⁵; in 21% to 23% of randomly selected women^{14,16}; and in 23% of women who described themselves as “normal” and reported having a “regular” menstrual cycle.¹⁷ However, up to 25% of women with polycystic appearing ovaries may be entirely asymptomatic.¹⁸

In contrast, not all women who have an excess of androgens have polycystic-appearing ovaries¹⁹⁻²¹; this situation has been observed in 20% to 30% of young, healthy women.⁹

When biochemical parameters are used as diagnostic criteria, the prevalence of PCOS varies from 2.5% to 7.5%.²² In an unselected, minimally-biased population of women, overall prevalence of PCOS appears to be approximately 4.6%, although it could be as low as 3.5% and as high as 11.2%.²³

All these observations, findings, and criteria considered, it is generally accepted that PCOS is one of the most common reproductive endocrine disorders of women.

What are the diagnostic criteria for PCOS?

Q The diagnosis of PCOS is confusing; consensus statements seem to change over time. Can you clarify the confusion over definitions?

Since the original description in 1945 of the diagnostic criteria of PCOS—irregular menstruation, infertility, obesity, hirsutism—it’s become clear that this disorder is a heterogeneous condition. Some patients display classic symptoms; many have a mild variant.



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NIH seeks clarity. To further understand and study PCOS, it was essential to standardize the definition to facilitate collaborative clinical trials. In 1990, an NIH-sponsored consensus workshop attempted to standardize the criteria for making a diagnosis of PCOS.²⁴ This included a combination of:

- chronic anovulation
- clinical (hirsutism) or biochemical (or both) signs of hyperandrogenism
- exclusion of other causes (including thyroid dysfunction, hyperprolactinemia, and adult-onset congenital adrenal hyperplasia).

A diagnosis of PCOS did not, however, require that the ovaries have polycystic characteristics on US imaging. In contrast, the European definition of PCOS was a syndrome that included polycystic ovaries on US in conjunction with clinical or biochemical hyperandrogenism; oligomenorrhea or amenorrhea; and obesity.

International consensus sought. To foster agreement across borders, a joint workshop of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Endocrinology workshop was held in Rotterdam in 2003,^{25,26} resulting in an updated definition of PCOS. Ovarian morphology of multifollicular-appearing ovaries on US was recognized as an important component of the diagnosis; women who had clinical or biochemical hyperandrogenism in the face of a normal menstrual cycle could, therefore, have PCOS.

Workshop participants also agreed that a PCOS diagnosis required two of three criteria:

- oligo-ovulation or anovulation
- clinical or biochemical signs (or both) of hyperandrogenism
- polycystic ovaries on ultrasonography.

In addition, participants agreed that the exclusion of other causes of these findings—such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid dysfunction, and an elevated prolactin level—was still critical to the diagnosis. (Note: We'll discuss details of the diagnostic work-up for PCOS in a subsequent part of this article.)

The 2003 consensus meeting further described, in detail, US criteria by which to make a diagnosis of PCOS:

- at least 12 follicles in each ovary that are each 2 to 9 mm in diameter *or*
- ovarian volume greater than 10 mL.

These criteria do *not* apply to patients who are being treated with an oral contraceptive because their ovarian volume often appears smaller. In addition, having one ovary only that fits this definition was, and remains, sufficient to meet the US definition of PCOS. A so-called asymptomatic polycystic ovary—that is, positive US imaging in a woman who has regular cycles and a normal endocrine profile—should *not* be considered PCOS. ❌

In the next installment: The authors begin by taking on two common areas of questioning in the care of women who have PCOS:

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Ovarian morphology of multifollicular-appearing ovaries on US was recognized as an important component of the diagnosis

REFERENCES

1. Valisneri A. Storia della Generazione dell'Uomo, e degli Animali, se sia da' vermicelli spermatici, o dale uova. Venezia, Italy: Appreo Gio Gabriel Hertz; 1721.
2. Chereau A. Memoires pour servir a l etude des maladies des ovaries. Paris, France: Fortin, Masson & Cie; 1844.
3. Stein I, Leventhal M. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol.* 1935;29:181-185.
4. Dunaif A, Mandeli J, Fluhr H, Dobrjansky A.J. The impact of obesity and chronic hyperinsulinemia on gonadotropin release and gonadal steroid secretion in the polycystic ovary syndrome. *Clin Endocrinol Metab.* 1988;66(1):131-139.
5. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med.* 1993;44:121-131.
6. Vara P, Niemineva K. The Stein-Leventhal syndrome. *Ann Chir Gynaecol Fenn.* 1951;40(1):23-33.
7. Breteche J. Ovarian cysts and sclerocystic ovaritis in sterility. *CR Soc Fr Gynecol.* 1952;22(2):94-98.
8. Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Extensive clinical experience: relative prevalence of different androgen disorders in 950 women referred because of clinical hyperandrogenism. *J Clin Endocrinol Metab.* 2006;91(1):2-6.
9. Azziz R, Sanchez LA, Knochenhauer ES, et al. Androgen excess in women: experience with over 1,000 consecutive patients. *J Clin Endocrinol Metab.* 2004;89(2):453-462.
10. Souter I, Sanchez LA, Perez M, Bartolucci AA, Azziz R. The prevalence of androgen excess among patients with minimal unwanted hair growth. *Am J Obstet Gynecol.* 2004;191(6):1914-1920.
11. Vexiau P, Husson C, Chivot M, Brerault JL, Fiet J, Julien R et al. Androgen excess in women with acne alone compared

- with women with acne and/or hirsutism. *J Invest Dermatol.* 1990;94(3):279-283.
12. Borgia F, Cannavo S, Guarneri, Cannavo SP, Vaccaro M, Guarneri B. Correlation between endocrinological parameters and acne severity in adult women. *Acta Derm Venereol.* 2004;84(3):201-204.
 13. Timpatanapong P, Rojanasakul. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. *J Dermatol.* 1997;24(4):223-229.
 14. Clayton RN, Ogden V, Hodgkinson J, et al. How common are polycystic ovaries in normal women and what is their significance for the fertility of the population? *Clin Endocrinol (Oxf).* 1992;37(2):127-134.
 15. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J (Clin Res Ed).* 1986;293(6543):355-359.
 16. Farquhar CM, Birdsall M, Manning P, Mitchell JM. Transabdominal versus transvaginal ultrasound in the diagnosis of polycystic ovaries in a population of randomly selected women. *Ultrasound Obstet Gynecol.* 1994;4(1):54-59.
 17. Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries—a common finding in normal women. *Lancet.* 1988;1(8590):870-872.
 18. Swanson M, Sauerbrei EE, Cooperberg PL. Medical implications of ultrasonically detected polycystic ovaries. *J Clin Ultrasound.* 1981;9(5):219-222.
 19. Orsini LF, Venturoli S, Lorusso R, Pluchinotta V, Paradisi R, Bovicelli L. Ultrasonic findings in polycystic ovarian disease. *Fertil Steril.* 1985;43(5):709-714.
 20. el Tabbakh GH, Lotfy I, Azab I, Rahman HA, Southren AL, Aleem FA. Correlation of the ultrasonic appearance of the ovaries in polycystic ovarian disease and the clinical, hormonal, and laparoscopic findings. *Am J Obstet Gynecol.* 1986;154(4):892-895.
 21. Carmina E, Lobo R. Do hyperandrogenic women with normal menses have polycystic ovary syndrome? *Fertil Steril.* 1999;71(2):319-322.
 22. Futterweit W, Mechanick JI. Polycystic ovarian disease: etiology, diagnosis, and treatment. *Compr Ther.* 1988;14(11):12-20.
 23. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab.* 1998;83(9):3078-3082.
 24. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Hasseltine FP, Merriam GR, eds. *Polycystic ovary syndrome.* Boston, MA: Blackwell Scientific Publications; 1992:377-384.
 25. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1):19-25.
 26. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004;19(1):41-47.