The Diagnosis of Polycystic Ovary Syndrome in Adolescents

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abstract

Consensus has recently been reached by international pediatric subspecialty societies that otherwise unexplained persistent hyperandrogenic anovulation using age- and stage-appropriate standards are appropriate diagnostic criteria for polycystic ovary syndrome (PCOS) in adolescents. The purpose of this review is to summarize these recommendations and discuss their basis and implications. Anovulation is indicated by abnormal uterine bleeding, which exists when menstrual cycle length is outside the normal range or bleeding is excessive: cycles outside 19 to 90 days are always abnormal, and most are 21 to 45 days even during the first postmenarcheal year. Continued menstrual abnormality in a hyperandrogenic adolescent for 1 year prognosticates at least 50% risk of persistence. Hyperandrogenism is best indicated by persistent elevation of serum testosterone above adult norms as determined in a reliable reference laboratory. Because hyperandrogenemia documentation can be problematic, moderate-severe hirsutism constitutes clinical evidence of hyperandrogenism. Moderate-severe inflammatory acne vulgaris unresponsive to topical treatment is an indication to test for hyperandrogenemia. Treatment of PCOS is symptom-directed. Cyclic estrogen-progestin oral contraceptives are ordinarily the preferred first-line medical treatment because they reliably improve both the menstrual abnormality and hyperandrogenism. First-line treatment of the comorbidities of obesity and insulin resistance is lifestyle modification with calorie restriction and increased exercise. Metformin in conjunction with behavior modification is indicated for glucose intolerance. Although persistence of hyperandrogenic anovulation for ≥2 years ensures the distinction of PCOS from physiologic anovulation, early workup is advisable to make a provisional diagnosis so that combined oral contraceptive treatment, which will mask diagnosis by suppressing hyperandrogenemia, is not unnecessarily delayed.

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www.pediatrics.org/cgi/doi/10.1542/peds.2015-1430

DOI: 10.1542/peds.2015-1430

Accepted for publication Jun 25, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The author has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: The author's research related to this article was supported in part by the *Eunice Kennedy Shriver* National Institutes of Child and Human Development/National Institutes of Health through cooperative agreement (U54-041859) as part of the Specialized Cooperative Centers Program in Reproduction and Infertility Research, HD-39267, and RR-00055 and UL1RR024999 from the National Center for Research Resources. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

POTENTIAL CONFLICTS OF INTEREST: The author has indicated he has no conflicts of interest to disclose.

Polycystic ovary syndrome (PCOS) is the most common cause of chronic hyperandrogenic anovulation and the single most common cause of infertility in young women.[1] It is also a risk factor for metabolic syndrome-related comorbidities and for impaired well-being and mortality.[2] Considerable evidence suggests that PCOS has diverse causes, arising as a complex trait with contributions from both heritable and environmental factors that affect ovarian steroidogenesis.[3,4] Insulin-resistant hyperinsulinism, in part related to coexistent obesity, is the most common nonsteroidogenic factor. The complex interactions generally mimic an autosomal dominant trait with variable penetrance: the disorder is correlated in identical twins[5]; about half of sisters are hyperandrogenic, and half of these also have oligo-amenorrhea and thus PCOS[6,7]; and polycystic ovaries appear to be inherited as an autosomal dominant trait.[7,8] Three percent to 35% of mothers have PCOS,[9,10] and metabolic syndrome prevalence is high in parents and siblings.[11–13]

Primary functional ovarian hyperandrogenism (FOH) accounts for the vast majority of PCOS. Ovarian androgenic function tests show that most have 17-hydroxyprogesterone hyperresponsiveness to gonadotropins in the absence of a steroidogenic block (typical FOH) and subnormal dexamethasone-suppressibility of testosterone; a minority have only the latter abnormality (atypical FOH)[1,14] A related adrenal androgenic hyperresponsiveness to adrenocorticotropin (primary functional adrenal hyperandrogenism) is often associated with FOH: it is the sole source of androgen in a small PCOS subset.

The syndrome was first described by Stein and Leventhal.[15] Over the past 25 years, internationally accepted diagnostic criteria have been developed for adults based on various combinations of otherwise unexplained hyperandrogenism, anovulation, and a polycystic ovary, which are all encompassed by Rotterdam consensus criteria.[16–18] These criteria generate 4 phenotypes, which fall on a spectrum of decreasing specificity and severity in Table 1.[1]

These diverse criteria have been problematic when applied to adolescents. Anovulatory cycles are frequent in adolescents. The common signs of adult hyperandrogenism are less reliable in adolescents than in adults: hirsutism is in a developmental phase, and acne vulgaris is common. Testosterone serum levels rise during anovulatory cycles; there is a paucity of reliable norms for androgen levels in adolescent girls, and the extent to which adolescent hyperandrogenism predicts adult hyperandrogenism is unclear. Furthermore, polycystic ovary morphology by adult standards is common in normal adolescents.

Recent Endocrine Society clinical guidelines suggest that adolescent PCOS be diagnosed using the National Institutes of Health–based criteria of otherwise unexplained hyperandrogenism and persistent anovulatory menstrual abnormality.[19] Because the evidence presented to support this conclusion was meager, the Pediatric Endocrine Society invited representatives of international pediatric, adult, and reproductive endocrinology, adolescent medicine, and adolescent gynecology subspecialty societies to appoint experts to define appropriate criteria for the diagnosis of PCOS in adolescence. Their consensus supported the criteria of persistent hyperandrogenic oligo-anovulatory menstrual abnormality based on age- and stage-appropriate standards, as summarized in Table 2.[4] The purpose of this review is to use these consensus criteria as a point of reference to address common misconceptions that stand as a barrier to the early diagnosis and treatment of PCOS.

TABLE 1 Diagnostic Criteria for PCOS in Adults[a]

1. Phenotype 1 ("classic PCOS")[b]
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Evidence of oligoanovulation
   c. Ultrasonographic evidence of a polycystic ovary
2. Phenotype 2 (essential National Institutes of Health Criteria)[†]
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Evidence of oligo-anovulation
3. Phenotype 3 ("ovulatory PCOS")[b]
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Ultrasonographic evidence of a polycystic ovary
4. Phenotype 4 (nonhyperandrogenic PCOS)
   a. Evidence of oligoanovulation
   b. Ultrasonographic evidence of a polycystic ovary

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[a] Rotterdam criteria; all involve exclusion of other causes of hyperandrogenism and anovulation.

[b] Androgen Excess–PCOS Society recognizes only hyperandrogenic phenotypes.

TABLE 2 Diagnostic Criteria for PCOS in Adolescents

Otherwise unexplained combination of:

1. Abnormal uterine bleeding pattern
   a. Abnormal for age or gynecologic age
   b. Persistent symptoms for 1–2 y
2. Evidence of hyperandrogenism
   a. Persistent testosterone elevation above adult norms in a reliable reference laboratory is the best evidence
   b. Moderate-severe hirsutism is clinical evidence of hyperandrogenism
   c. Moderate-severe inflammatory acne vulgaris is an indication to test for hyperandrogenemia

Based on Witchel S, Oberfield S, Rosenfield R, Codner E, Bonny A, Ibáñez L, et al. The Diagnosis of Polycystic Ovarian Syndrome during Adolescence *Horm Res Pediatr.* 2015;83 (6):376–389.

EVIDENCE OF AN ABNORMAL DEGREE OF ANOVULATION IN ADOLESCENTS

Physiologic adolescent anovulation is a well-known phenomenon: the greater length of menstrual cycles and greater degree of menstrual irregularity in adolescents than adults is due to their higher frequency of anovulatory cycles.[4,20–24] However, there is a widespread misconception that any degree of amenorrhea or menstrual irregularity is acceptable. Rather, normal adolescent menstrual cyclicity differs only slightly from that of reproductive-age adults: cycles shorter than 19 days or longer than 90 days are abnormal at any stage, 75% of menstrual cycles range from 21 to 45 days during the first postmenarcheal (gynecologic) year, and 95% of girls achieve 21- to 40-day adult menstrual cyclicity by their fifth gynecologic year.

Thus, most adolescent anovulation is asymptomatic, with cyclic menstrual bleeding usually occurring at 21- to 45-day intervals even in the first postmenarcheal year (Fig 1). This paradox arises because immature cyclic ovarian function is usually occurring during these intervals.[23,24] Most normal adolescent menstrual cycles that are not normally ovulatory by standard criteria have hormonal evidence of luteal insufficiency (Fig 1), which signifies antecedent ovulation with immature corpus luteum formation.[24] Serum hormonal changes during normal adolescent menstrual cycles confirm that substantial but immature cyclic follicular

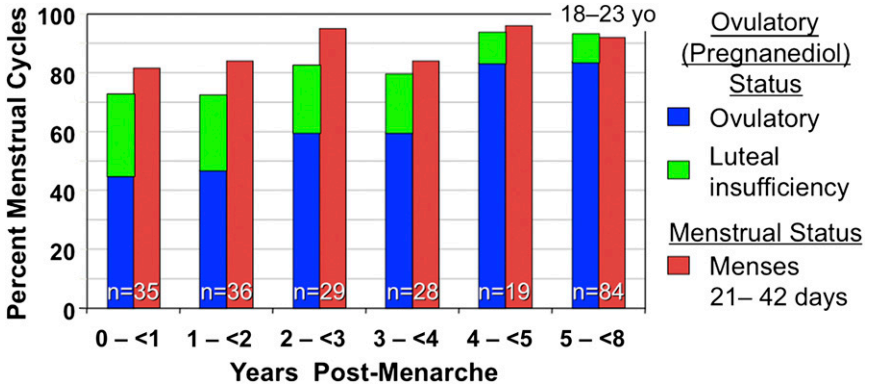

FIGURE 1

Comparison of the percent of menstrual cycles that are 21 to 45 days' duration (red) and percent of menstrual cycles that are ovulatory (blue) by postmenarcheal age through young adulthood. Ovulation was determined by normalcy of urinary pregnanediol glucuronide in weekly samples collected during last 12 days of each menstrual cycle; cycles with clearly detectable but subnormal pregnanediol are designated here as having luteal insufficiency (green). It can be seen that most of the cycles that are not ovulatory had sufficient cyclic follicular activity to generate an immature corpus luteum, which indicates antecedent ovulation, rather than being truly anovulatory as the investigators had labeled them. Data from Metcalf et al.[24]

development occurs in such girls and some aluteal adolescents.[23,25]

An abnormal menstrual bleeding pattern ("symptomatic adolescent anovulation") is almost always the result of anovulatory cycles and cause for concern if persistent.[3,23] The various manifestations of an abnormal degree of adolescent anovulation, that is, uterine bleeding patterns that occur in <5% of adolescents, are summarized in Table 3. Symptomatic adolescent anovulation has an overall long-term persistence rate of approximately one-third (Fig 2).[26]

However, the risk for ongoing anovulation is greater for hyperandrogenemic anovulatory adolescents than for nonhyperandrogenemic ones. Among girls evaluated for abnormal menstrual bleeding without clinical signs of hyperandrogenism, approximately half have elevated androgen levels.[27,28] Reevaluation of such patients has shown that hyperandrogenemia resolves in approximately half and that PCOS is the single most common cause of residual ongoing menstrual disorder.[29–32] Furthermore, in the presence of clinical evidence of hyperandrogenism, for example, hirsutism or serious acne, hyperandrogenic oligo-anovulation (ie, PCOS) persisted for ≥3 years in ≥80%.[31,33] Indeed, in a small series of adolescents with elevated free testosterone and documented FOH, follow-up showed that all still had PCOS as young adults.[33] Thus, the actuarial curve describing the prognosis for symptomatic anovulation seems to comprise 2 components: 1 for hyperandrogenemic cases, half of which persist, and another for nonhyperandrogenemic cases, few of which persist (Fig 2). The transient cases are due to physiologic anovulation. The persistent hyperandrogenemic cases are mostly PCOS, and the persistent nonhyperandrogenic cases have some form of hypogonadism.

In summary, uterine bleeding at intervals more frequent than 19 days or less frequent than 90 days is abnormal even in the first postmenarcheal year (Table 3). In the absence of clinical evidence of an endocrine disorder, persistent abnormal menstrual bleeding for 1 year carries an approximately 50% risk of ongoing menstrual irregularity, and approximately half of the ongoing cases will have PCOS. However, if clinical evidence of PCOS is present, such as hirsutism, the risk of ongoing hyperandrogenic menstrual abnormality is high.

CLINICAL AND BIOCHEMICAL EVIDENCE OF HYPERANDROGENISM IN ADOLESCENTS

The development of sexual hair (terminal hair that develops in a malelike pattern) and most sebaceous glands is dependent on androgen.[34] Hirsutism is considered clinical evidence of hyperandrogenism and equivalent to biochemical evidence of hyperandrogenism in all adult criteria for PCOS (Table 1) because documentation of hyperandrogenemia can be problematic.[35] However, this criterion is controversial because mild hirsutism is due to ethnic or familial factors rather than hyperandrogenemia half of the time, in contrast to moderate-severe hirsutism, which is usually due to hyperandrogenemia.[36] On the other hand, hyperandrogenemia is variably accompanied by hirsutism: little more than half of hyperandrogenemic PCOS patients are hirsute.[1]

Clinical Evidence of Hyperandrogenism

Hirsutism is defined as excessive sexual hair.[4,35] Sexual hair growth is commonly graded by the Ferriman-Gallwey score (Fig 3): a total score of 8 to 15 defines mild hirsutism, 16 to 24 moderate hirsutism, in the general US adult population.[35]

Hirsutism must be distinguished from hypertrichosis, which is defined as generalized excessive vellus hair growth distributed in a nonsexual pattern, for example, predominantly on forearms or lower legs. This hair growth is not due to androgen excess. It may have an ethnic/hereditary, basis or may result from malnutrition or certain medications, such as phenytoin or cyclosporine.

TABLE 3 Types of Abnormal Uterine Bleeding Found in Adolescent PCOS

Descriptor	Definition
Primary amenorrhea	Lack of menarche by 15 y of age or by 3 years after the onset of breast development[a]
Secondary amenorrhea	Over 90 d without a menstrual period after initially menstruating
Oligomenorrhea (infrequent AUB)	Postmenarcheal year 1: average cycle length >90 d (<4 periods/y)
	Postmenarcheal year 2: average cycle length >60 d (<6 periods/y)
	Postmenarcheal years 3–5: average cycle length >45 d (<8 periods/y)
	Postmenarcheal years ≥6: cycle length >38–40 d (≤9 periods/y)
Excessive anovulatory AUB†	Menstrual bleeding that occurs more frequently than every 21 d (19 d in yr 1) or is excessive (lasts >7 d or soaks >1 pad or tampon every 1–2 h)

Modified and reproduced with permission from Rosenfield RL. Clinical review: Adolescent anovulation: Maturational mechanisms and implications. *J Clin Endocrinol Metab.* 2013;98:3572–3583. AUB, abnormal uterine bleeding.

[a] Bone age of 15 y may be substituted for chronologic age in girls with earlier-than-average age at puberty onset.

[b] Encompasses frequent, intermenstrual, heavy, and/or prolonged AUB. Formerly termed "dysfunctional uterine bleeding."

The meager normative data that exist in adolescence suggest that an adult level of hirsutism is achieved by 2 years after menarche or 15 years of age[37,38]: upper lip scores of 3 to 4 increased over the course of puberty to reach an adult prevalence of <3% in Black and White US adolescents by the second postmenarcheal year (Fig 4).

Acne, rather than hirsutism, may be the only pilosebaceous manifestation of hyperandrogenism.[39] Comedonal acne is common in adolescent girls, but inflammatory acne that is moderate or severe (ie, >10 facial lesions, Table 4) is uncommon during the perimenarcheal years.[40] Girls with acne that is persistent and poorly responsive to topical dermatologic therapy are ordinarily treated by combined oral contraceptive (COC) pills, which lower ovarian androgen production, or the systemic retinoid Accutane.[41] Because COC therapy thus masks the hyperandrogenism of underlying PCOS, it is recommended that patients with moderate-severe inflammatory acne unresponsive to topical treatments be assessed for hyperandrogenemia before instituting systemic medical treatments.

Biochemical Evidence of Hyperandrogenism

Documentation of hyperandrogenism requires reliable assays with well-defined normal ranges.[4,42,43]

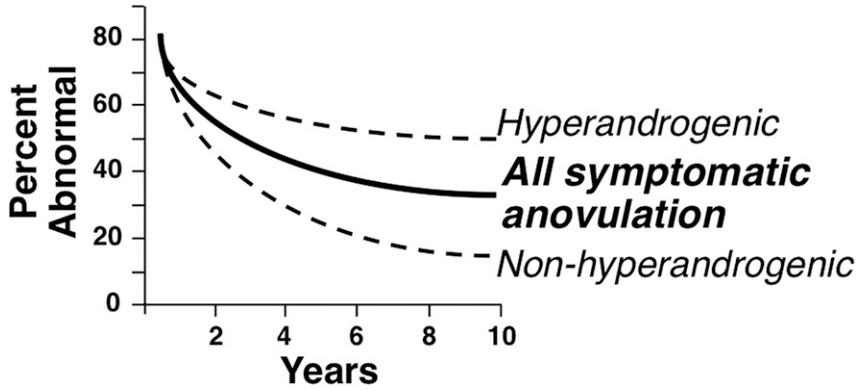

FIGURE 2

Probability that an adolescent with symptomatic anovulatory symptoms will have ongoing menstrual abnormality. "All symptomatic anovulation" curve represents the data of Southam et al.[26] "Hyperandrogenic" and "Nonhyperandrogenic" curves are hypothetical, based on data discussed in the text. Hyperandrogenic cases are predominantly a mix of physiologic anovulation and PCOS, with PCOS persisting. Nonhyperandrogenic cases are a mix of physiologic anovulation and hypogonadal cases, ranging from primary hypogonadism through hypothalamic amenorrhea to hypogonadotropic hypogonadism, with hypogonadal cases persisting.

Measurements of total and/or free testosterone are recommended to initiate documentation of hyperandrogenemia.[35,44] Elevated serum free testosterone is the single most sensitive indicator of hyperandrogenemia because the bioactive portion of the serum testosterone is the free fraction. Sex hormone binding globulin (SHBG) serum concentrations govern the fraction of testosterone that is free; they are lowered by obesity and androgen excess itself. The cost-effectiveness of routinely measuring more androgens than total and free testosterone has not been documented, although androstenedione may be considered[45] and dehydroepiandrosterone sulfate (DHEAS) is widely used to assess adrenal hyperandrogenism. Although dihydrotestosterone generated in target tissue mediates most testosterone effects, its serum level is of little diagnostic value.[36]

However, accurate determinations of total and free testosterone concentrations are often problematic. Diurnal rhythm, phase of menstrual cycle, and SHBG concentrations are biological variables that influence total testosterone concentrations. Methodological problems regarding testosterone determinations abound. Most notably, the multichannel platform assays now commonly used by hospital laboratories lack sensitivity, specificity, and accuracy for testosterone, although they are good for SHBG and DHEAS measurement. Some direct assays of total testosterone are also inaccurate, but others are as accurate as the postchromatographic radioimmunoassays that have been available only through specialty laboratories or the tandem mass spectrometry methods that are beginning to supplant them.[14,46,47] The reliable free testosterone assays calculate the free testosterone concentration as the product of the total testosterone and the fraction

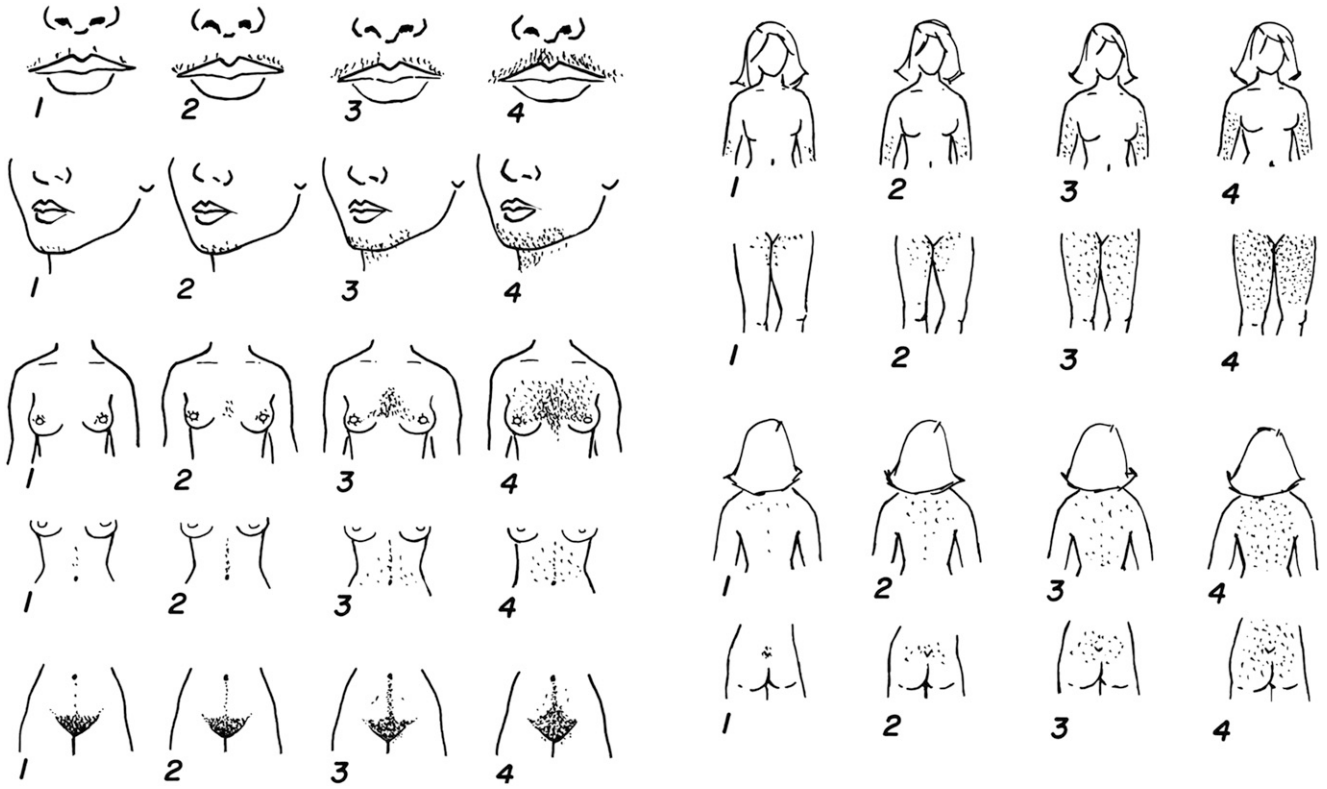

FIGURE 3
Ferriman-Gallwey hirsutism scoring system. Each of the 9 body areas most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score. Generalized hirsutism (score ≥8) is abnormal in the general US and UK populations, whereas locally excessive hair growth (score <8) is a common normal variant. The normal score is lower in Asian populations and higher in Mediterranean populations.[4] Reproduced with permission from Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, et al. Evaluation and treatment of hirsutism in premenopausal women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrin Metab.* 2008;93:1105–1120.[35]

that is free from SHBG binding (free testosterone = total testosterone × percent free testosterone).[48] The most common methods calculate percent free testosterone from the SHBG concentration or determine the percent free testosterone by dialysis. Free testosterone assays are less well standardized than total testosterone assays, which has limited their usefulness.

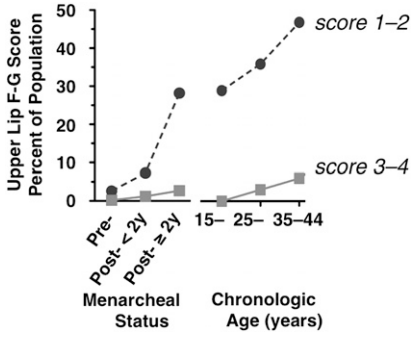

FIGURE 4
Upper lip hirsutism scores(Ferriman-Gallwey) in adolescents and adults. Data in relation to menarcheal stage from Lucky et al[38]; data in relation to age from Ferriman and Gallwey.[37] Young adult FG scores are normally achieved 2 years after menarche.

The criteria used to define hyperandrogenemia in adolescent girls are confounded by developmental considerations. However, shortly after menarche, serum testosterone of adolescents attains adult levels (Fig 5).[1,4] Thus, adult testosterone levels are an appropriate criterion on which to base a diagnosis of hyperandrogenemia.

However, testosterone levels increase as adolescent anovulatory cycles lengthen.[4] Thus, the few available data suggest that prolonged physiologic anovulation accounts for the half of hyperandrogenemic anovulatory cycles that resolve during adolescence, as discussed in the previous section.[29–33]

In summary, biochemical evidence of hyperandrogenism, as indicated by persistent elevation of serum total and/or free testosterone levels above adult norms and determined by a reliable reference laboratory, provides the clearest support for the presence of hyperandrogenism in an adolescent girl with symptoms of PCOS. In most such laboratories, the upper limit approximates 55 ng/dL for total testosterone and 9 pg/mL for free testosterone. However, an elevated androgen level should not be considered evidence of hyperandrogenism in an otherwise asymptomatic adolescent with anovulatory symptoms unless the hyperandrogenemia and anovulation persist. In the absence of the availability of reliable androgen assays, moderate-severe hirsutism

TABLE 4 An Acne Scoring System for Adolescents[a]

Severity	Comedonal Lesions[b]	Inflammatory Lesions[c]
Mild	1–10	1–10
Moderate	11–25	11–25
Severe	>25	>25

Based on Lucky AW, Biro FM, Simbartl LA, Morrison JA, Sorg NW. Predictors of severity of acne vulgaris in young adolescent girls: Results of a five-year longitudinal study. *J Pediatr.* 1997;130:30–39; Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131(suppl 3):S163–186; Deplewski D, Rosenfield RL. Role of hormones in pilosebaceous unit development. Endocr Rev. 2000;21:363–392.

[a] Face, chest, shoulders, and back may be graded separately.

[b] Open ("blackheads") or closed ("whiteheads") comedones (>1 mm diameter).

[c] Pustules, papules (≤5 mm) and nodules (>5 mm). Scarring should be noted separately.

constitutes clinical evidence of hyperandrogenism. Moderate-severe inflammatory acne vulgaris unresponsive to topical medications is an indication to test for hyperandrogenemia.

THE QUANDARY OF POLYCYSTIC OVARY MORPHOLOGY IN ADOLESCENCE

Histopathologically, the polycystic ovary is characterized by an excessive number of small antral follicles that are arrested before the preovulatory stage of development (which accounts for the polycystic appearance), ovarian enlargement, capsular thickening, and thecal-stromal hyperplasia and luteinization.[1] Ultrasonographically, polycystic ovary morphology (PCOM) has been defined in adults by consensus criteria as an ovary with a volume >10.0 mL by a simplified formula or a small antral follicle (2–9 mm diameter) count ≥12 per ovary.[17,49] However, it has become apparent that these criteria are problematic in young adults, particularly because the newer high-definition vaginal imaging techniques show that small antral follicle counts up to 24 are normal.[50,51]

Adult PCOM criteria are especially problematic when applied to adolescents. For one thing, an accurate antral follicle count cannot be defined by the abdominal ultrasonographic approach necessary in virginal adolescents.[51] For another, even if an accurate follicle count is obtained by magnetic resonance imaging, the adult criteria for PCOM overlap with criteria for a multifollicular ovary, which is defined by the presence of ≥6 follicles of 4- to 10-mm diameter without increase in ovarian volume and is known to be a normal variant unrelated to hyperandrogenism.[4] Furthermore, although data vary considerably, current data suggest that ovarian volume is slightly larger in adolescents than in adults.[1,4] Consequently, one-third to half of normal adolescents meet adult criteria for PCOM.[52] Until further research establishes definitive criteria, current evidence suggests that a mean ovarian volume >12 cc (or single ovary >15 cc) be considered enlarged in adolescents.[1,4,52]

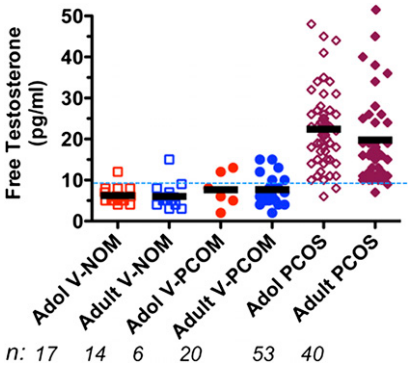

FIGURE 5

Free testosterone plasma levels in normal postmenarcheal adolescent and adult female volunteers with normal ovarian morphology (V-NOM) compared with those with polycystic ovary morphology (V-PCOM) and PCOS. V-NOM and V-PCOM were healthy eumenorrheic females with no clinical signs of androgen excess. Data on these subjects were previously reported,[1] but PCOM in adolescents has been redefined here as mean ovarian volume >12.0 mL, consistent with current consensus. Adolescents (Adol), 1 year postmenarcheal to 17.9 years of age, were similar to 18- to 39-year-old adults in each group. The free testosterone upper limit reference range (dotted line = 97th percentile = 9.3 pg/mL) was based on pooled adolescent and adult V-NOM, after excluding 1 outlier whose level was >3.0 SD from the mean of the entire group. V-PCOM had significantly higher free testosterone than pooled V-NOM (P = .03). Elevated levels were found in 2 of 6 adolescent and 4 of 30 adult volunteers with PCOM. To convert to pmol/L, multiply free testosterone by 3.47.

PCOM is variably related to hyperandrogenism in adults.[1] On one hand, it is absent in 5% to 20% of adult PCOS.[1,18,53] On the other, PCOM is a common finding among healthy women. Many of these women have mild PCOS features, that is, irregular menstrual cycles and/or hirsutism. When care has been taken to exclude those with such symptoms, approximately one-quarter of apparently normal adults with PCOM have mild subclinical androgenic ovarian dysfunction that is in the PCOS range (Fig 6); it has been postulated that these are carriers of PCOS or at risk for PCOS.

In summary, the uncertainty about appropriate criteria for PCOM in adolescents is too great to use PCOM as a diagnostic criterion in adolescents.

THE ROLE OF INSULIN RESISTANCE AND METABOLIC SYNDROME IN THE DIAGNOSIS OF PCOS

Insulin resistance out of proportion to that conferred by obesity is variously reported in one- to two-thirds of PCOS subjects.[54–56] Obesity prevalence likewise varies widely among populations, averaging approximately 50%.[57] The insulin resistance of PCOS seems to be associated with increased abdominal fat depots independent of BMI,[58] and superimposed excess adiposity further increases all fat depots and insulin resistance.[55,59]

Metabolic syndrome, a cluster of glucose abnormalities, central (android) obesity, hypertension, and dyslipidemia, is the variable result of insulin resistance interacting with obesity and age.[60,61] Its prevalence is highest in obese subjects.[4] It is present in ~25% of adolescents with PCOS.[11,62–64] The comorbidity of

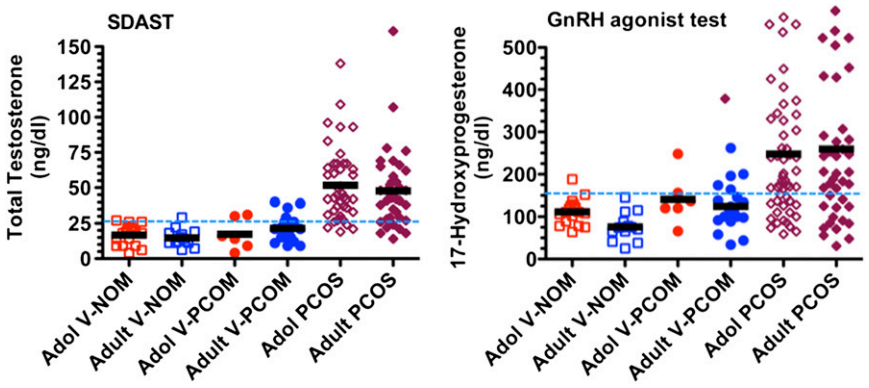

FIGURE 6

Ovarian androgenic function test results in normal postmenarcheal adolescent and adult female volunteers with normal ovarian morphology compared with those with polycystic ovary morphology and PCOS. Same groups as in Fig. 5. Adolescents (Adol) were similar to adults in each group. Dexamethasone 0.25 mg/m^2 orally was administered at 12 PM, and testosterone was measured 4 hours later (4 PM). This was followed shortly by administration of leuprolide acetate 10 μg/kg subcutaneously; 17-hydroxyprogesterone was sampled 20 to 24 hours later, 4 hours after a repeat 12 PM dexamethasone dose. Elevated total testosterone (>26 ng/dL) in response to a short dexamethasone androgen-suppression test (SDAST) or elevated 17-hydroxyprogesterone (>152 ng/dL) in response to a postdexamethasone gonadotropin-releasing hormone agonist (GnRHag) test indicate functional ovarian hyperandrogenism with 95% specificity and 68% concordance. Among the 93 PCOS patients, SDAST was abnormal in 85% (73% with abnormal GnRHag test), GnRHag test in 66% (92.5% with abnormal SDAST), and one or the other in 91%. Among volunteers with PCOM, 4 of 6 adolescents and 8 of 30 adults, including all with baseline elevation of free testosterone, had either an abnormal SDAST or GnRHag test result that is in the lower PCOS range. To convert to nanomole per liter, multiply total testosterone by 0.347 and 17-hydroxyprogesterone by 0.0303.

metabolic syndrome makes PCOS a risk factor for the early development of type 2 diabetes mellitus, sleep-disordered breathing, and ultimately, the threat of cardiovascular disease.

The insulin resistance of PCOS primarily involves insulin's glucose-metabolic effects.[65] Other insulin actions are unaffected in PCOS, with resultant compensatory insulin-resistant hyperinsulinism. The compensatory hyperinsulinemia accounts for acanthosis nigricans and synergizes with gonadotropins to aggravate ovarian androgen excess.[66] Severe insulin-resistant hyperinsulinemia causes pseudo-Cushing's syndrome and pseudo-acromegaly.[67]

In summary, although insulin resistance and obesity are commonly associated with PCOS, they are not necessarily present and so are not diagnostic criteria.[4] However, the presence of obesity and/or signs of insulin-resistant hyperinsulinism such as acanthosis nigricans should alert the physician to the possibility of PCOS and its metabolic syndrome–related comorbidities.

DIAGNOSTIC PROCEDURES TO EXCLUDE NON-PCOS CAUSES OF HYPERANDROGENIC ANOVULATION

PCOS consensus criteria all consider the disorder to be a diagnosis of exclusion. Although the differential diagnosis of PCOS is fairly long (Table 5),[68] most disorders other than physiologic adolescent anovulation are uncommon to rare. All guidelines recommend screening for nonclassic congenital adrenal hyperplasia (NCCAH), which is the most likely disorder to mimic PCOS although it accounts for only ~5% of hyperandrogenic anovulation.[4,19] Otherwise, guidelines differ on specific recommendations for approaching the workup. Most recommend screening for hypothyroidism because it causes menstrual irregularity and coarsening of hair (rather than true hirsutism[69]). Some recommend screening all hyperandrogenic women for hyperprolactinemia; most endocrinologists find it to be rare, but it has been reported in as many as 16% of young women presenting with PCOS symptoms.[69,70] Other disorders are undeniably rare, including the only life-threatening disorder in the differential diagnosis, androgen-secreting tumor, the prevalence of which is 0.2%. The central adiposity and hirsutism of PCOS often raise concern for Cushing's syndrome, which rarely presents as PCOS. Some rare disorders are clinically subtle early on but easy to screen for (eg, insulin-like growth factor-I for acromegaly).

The approach to the differential diagnosis begins with a thorough medical history and physical examination. Because PCOS is but 1 of many causes of anovulation and only approximately half of hyperandrogenic patients have cutaneous signs of hyperandrogenism, the initial evaluation often includes determination of the serum gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[3,23] Low LH suggests a hypogonadotropic disorder of neuroendocrine origin, whereas high FSH suggests primary ovarian failure. A pregnancy test is indicated in any sexually mature teenager with amenorrhea.

The initial endocrinologic hyperandrogenism workup typically includes serum total testosterone, free testosterone, SHBG, DHEAS, and an early morning serum 17-hydroxyprogesterone level. Beyond that, the workup is individualized. For patients for whom cost is a major consideration, a minimalist approach is reasonable in which the clinical findings guide additional hormone determinations such as thyrotropin, prolactin, insulin-like growth factor-I, and serum or urinary cortisol. For others, economy of time justifies initiating studies with this full endocrine screening panel. Clinical or

TABLE 5 Causes of Androgen Excess in Adolescents

A. Physiologic adolescent anovulation
B. Functional gonadal hyperandrogenism
  1. PCOS/primary functional ovarian hyperandrogenism (common form of PCOS)
  2. Secondary functional ovarian hyperandrogenism
    a. Virilizing congenital adrenal hyperplasia
    b. Ovarian steroidogenic blocks
    c. Insulin resistance syndromes
    d. Acromegaly
    e. Epilepsy ± valproic acid therapy
  3. Disorders of sex development
  4. Pregnancy-related hyperandrogenism
C. Functional adrenal hyperandrogenism
  1. PCOS/primary functional adrenal hyperandrogenism (uncommon form of PCOS)
  2. Virilizing congenital adrenal hyperplasia
  3. Other glucocorticoid-suppressible adrenal hyperandrogenism
    a. Hyperprolactinemia
    b. Cortisone reductase deficiency
    c. Apparent dehydroepiandrosterone sulfotransferase deficiency
  4. Glucocorticoid-nonsuppressible adrenal hyperandrogenism
    a. Cushing's syndrome
    b. Glucocorticoid resistance
D. Peripheral androgen metabolic disorders
  1. Obesity
  2. Idiopathic
  3. Portohepatic shunting
E. Virilizing tumors
F. Androgenic drugs

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laboratory findings or patient preferences may dictate a more complete endocrinologic evaluation for rare disorders (Table 5) in some cases.[3,71]

The 8 AM 17-hydroxyprogesterone level requires interpretation; normal random values do not completely exclude NCCAH because of marked diurnal variation. An 8 AM value >200 ng/dL (6.0 nmol/L) is suggestive of NCCAH, although it is also compatible with recent ovulation or tumoral hyperandrogenism.[72] This cutoff displayed 92% to 98% sensitivity in detecting NCCAH[73,74] and 12% to 25% specificity in discriminating it from PCOS.[75,76] Thus, unless the 17-OHP level achieves a diagnostic level (>1000 ng/dL = 30 nmol/L), an adrenocorticotropic hormone test is recommended to confirm the diagnosis of NCCAH.[74]

Pelvic ultrasonography is seldom necessary for diagnosis because criteria for PCOM in adolescence are uncertain, as discussed earlier. However, it is indicated if clinical findings are suggestive of a virilizing tumor (eg, rapid progression, clitoromegaly, pelvic mass, or a total testosterone level >200 ng/dL) or disorder of sex development. In the absence of tumor, ultrasonography can be reassuring evidence that the "cysts" of PCOS are not tumor-related.

Currently the only certain way to differentiate the hyperandrogenemia of PCOS from that of physiologic adolescent anovulation is by the persistence of PCOS into adulthood. This is particularly problematic in cases with otherwise asymptomatic, but hyperandrogenemic, adolescents with abnormal menstrual bleeding patterns: the data reviewed here indicate that approximately half of these will remit and the other half persist as PCOS. The distinction is less problematic in cases with menstrual irregularity with symptomatic hyperandrogenism, that is, moderate-severe hirsutism or inflammatory acne: the foregoing data reviewed here indicate that the great majority (perhaps all) will persist as PCOS.

It may be possible to make the distinction between PCOS and physiologic adolescent anovulation early by testing ovarian androgenic function to diagnose the presence of FOH.[33] Further research will be necessary to test this possibility. Two kinds of tests are available (Fig 6). A dexamethasone androgen-suppression test is the most sensitive, but least specific, of these tests: elevated testosterone post-dexamethasone indicates a nonadrenal source, which is usually ovarian. The more specific test determines whether 17-hydroxyprogesterone hyperresponds to gonadotropins (indicative of typical FOH): this involves administering either a test dose of gonadotropin-releasing hormone agonist or of human chorionic gonadotropin and determining the 17-hydroxyprogesterone level 20 to 24 hours later.

Making a positive diagnosis of FOH by testing ovarian androgenic function also makes possible another distinction that is seldom made but has practical implications: determining whether PCOS is due to simple obesity, a category of PCOS considered "pseudo-PCOS." Excess adiposity itself suppresses ovulation (via LH suppression) and causes hyperandrogenemia (via adipose tissue formation of testosterone from androstenedione).[77] Neither an ovarian nor adrenal source of hyperandrogenism was demonstrable by ovarian androgenic function tests in ~10% of our PCOS cases (National Institutes of Health criteria), and the great majority of these were obese.[1,14,78] These cases were generally characterized by mild elevation of serum free testosterone, normal total testosterone, normal LH, and normal ovarian volume.

A fasting lipid panel and oral glucose tolerance test are advisable for early detection of diabetes mellitus and metabolic syndrome in PCOS patients with obesity or family risk factors. Obese PCOS patients should also be screened for sleep-disordered breathing. Evaluation for metabolic syndrome should also be considered in primary relatives in view of the familial component(s) of PCOS.

PRINCIPLES OF TREATMENT OF ADOLESCENT PCOS

The treatment of PCOS is symptomatic and is individualized according to patient complaints and goals. The main considerations in treating adolescent PCOS are menstrual irregularity, cutaneous manifestations

of hyperandrogenism, and the comorbidities of metabolic syndrome.

Cyclic administration of estrogen-progestin in the form of combined COC pills is the first-line medical treatment of most adolescents.[23,79] COCs normalize endometrial cycling, thereby protecting against endometrial carcinoma, and inhibit ovarian function, thereby normalizing serum androgens. These actions make them optimal both for treating abnormal uterine bleeding and as adjuncts to cosmetic and topical treatments for hirsutism and acne. Progestin monotherapy is the major alternative to COCs for the control of menstrual irregularity for those opposed to or with contraindications for (eg, thromboembolic risk) COCs. However, hyperandrogenism antagonizes the effects of female hormones on the neuroendocrine system and endometrium, so irregular bleeding may persist and androgens are not well suppressed.

Comorbidities related to obesity and insulin resistance require separate management consideratons.[19,80,81] Lifestyle modification with calorie restriction and increased exercise is paramount, but sustained weight loss is difficult to achieve. Insulin-lowering treatments, whether weight reduction or drug treatment, have an ~50% probability of improving menstrual cyclicity but a negligible effect on hirsutism. Well-controlled studies indicate that metformin monotherapy offers no advantage over lifestyle modification with regard to weight reduction or menstrual frequency. Since it may have additive clinical and biochemical effects, metformin is most effective in combination with a behavioral weight-reduction program.[82–84] The only clear indication for metformin is abnormal glucose tolerance. Other applications require further evaluation.[85] More detailed discussion of these treatments and higher-tier patient management considerations can be found elsewhere.[3,68,71]

DISCUSSION

Consensus has recently been reached by international pediatric subspecialty societies that otherwise unexplained persistent hyperandrogenic anovulation using age- and stage-appropriate standards are appropriate diagnostic criteria for PCOS in adolescents (Table 2).[4] Two aspects of these criteria warrant further discussion.

The consensus group urged great caution before labeling hyperandrogenic adolescents as having PCOS if the menstrual abnormality has not persisted for 2 years or more. Before that point in time, they recommended that such girls be considered to be "at-risk for PCOS" (ie, assigned a provisional diagnosis) to avoid misdiagnosing physiologic pubertal changes as PCOS. They coupled this recommendation with one for frequent longitudinal reevaluations. These recommendations place a high value on the accuracy of diagnosis.

Notably, the recommendations specify that initiation of a diagnostic workup should not be unnecessarily delayed. Workup within 2 years may be necessary so that medical treatment that would mask hyperandrogenemia and anovulatory symptoms, particularly COCs, is not unnecessarily delayed. Thus, initiation of diagnostic testing is advisable within 1 year if treatment is required to control abnormal menstrual bleeding or comorbidities or if symptoms suggestive of PCOS coexist (eg, development of hirsutism, moderate inflammatory acne resistant to topical therapy, acanthosis nigricans). Excessive uterine bleeding may mandate emergency evaluation early in the course. Primary amenorrhea should be evaluated when recognized.

The practitioner should also recognize that menstrual abnormalities may not be the chief complaint. Indeed, anovulatory symptoms may not be the initial symptom but may emerge a year or more after presentation for obesity, hirsutism, or acanthosis nigricans.[33] Thus, these complaints should trigger consideration of an early appropriate workup. If PCOS is suspected in such a patient, specific ovarian androgenic function testing to document FOH may be particularly helpful.

In adolescents in whom a provisional diagnosis of PCOS has been made, the recommendation for longitudinal reevaluation requires withdrawing COC for ~3 months when the patient is gynecologically mature (eg, at graduation from high school) to determine persistence of hyperandrogenic anovulation; this maneuver should be coupled with contraceptive counseling because the infertility of PCOS is relative, not absolute.

ACKNOWLEDGMENTS

The helpful suggestions of Drs Laura Torchen and Christine Yu are appreciated.

ABBREVIATIONS

COC: combined oral contraceptive
DHEAS: dehydroepiandrosterone sulfate
FOH: functional ovarian hyperandrogenism
LH: luteinizing hormone
NCCAH: nonclassic congenital adrenal hyperplasia
PCOM: polycystic ovary morphology
PCOS: polycystic ovary syndrome
SHBG: sex hormone binding globulin

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