Commentary

# Perspectives on the International Recommendations for the Diagnosis and Treatment of Polycystic Ovary Syndrome in Adolescence

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A B S T R A C T

Recommendations have been provided for the diagnosis and therapy of polycystic ovary syndrome in adolescence from 3 international expert conferences 2015-2018. Despite agreement about essentials, differences among details of these recommendations have engendered confusion. This commentary provides perspective about the agreements and disagreements among these recommendations and how these recommendations relate to other guidance. It concludes with practice suggestions that align with these recommendations.
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Recommendations for the diagnosis and treatment of polycystic ovary syndrome (PCOS) in adolescence from 3 international expert conferences, representing all relevant subspecialties, have been published in the last 5 years: 2015,[1] 2017,[2] and 2018.[3,4] As a convener of the first conference, I consider these documents to be in agreement about essential matters. However, they are fairly dense and so some participants have attempted to render their content more accessible.[5,6] However, a recent review of adolescent PCOS begins from the premise of "lack of agreement around both diagnosis and management",[7] so confusion remains about the subject.

This purpose of this commentary is to provide perspective about the agreements and disagreements among these international recommendations and how they relate to other guidance, and to provide practice suggestions that align with these recommendations.

These conferences have established uniformity in diagnosis. All of the documents agree on the core diagnostic criteria for adolescent PCOS: otherwise unexplained evidence of ovulatory dysfunction, as indicated by menstrual abnormalities on the basis of stage-appropriate standards, and evidence of an androgen excess disorder ("hyperandrogenism"; Table 1). All 3 groups agree that polycystic ovary morphology cannot be used as PCOS diagnostic criteria in adolescents, as they are for adults,[8,9] because adolescent ovary morphology might normally be similar until 8 years after menarche. No guidelines accept obesity and insulin resistance as criteria. These criteria are likely to remain fundamentally unchanged until further research yields understanding of the environmental–molecular genetic interactions that cause PCOS.[10]

So what specifically might practitioners find confusing about diagnostic criteria? The clinical details regarding suitable evidence to satisfy these criteria differ somewhat among the documents.

The menstrual abnormalities that indicate ovulatory dysfunction during the immediate postmenarcheal years are not fully described by any one document: they include primary and secondary amenorrhea, oligomenorrhea, and "dysfunctional" (excessive) uterine bleeding (Table 2).[4,11–15] The bounds shown in Table 2 approximate the 5th-95th percentiles of the general population.

The adolescent PCOS recommendations differ in requiring the menstrual abnormality to persist for 1 year (2018)[3,4] vs 2 years (2015, 2017)[1,2] to diagnose PCOS. What the conferees struggled with is differentiating how long after menarche a menstrual abnormality should persist to avoid confusing PCOS with normal immaturity of the menstrual cycle (traditionally termed "physiologic adolescent anovulation," [PAA], although recently it was recognized that most of these "anovulatory" cycles are actually immature ovulatory cycles[5,16,17]). The degree of certainty is improved only modestly by waiting 2 years rather than 1 year to make a diagnosis. Available data suggest that if a symptomatic menstrual disturbance persists for 1 year, it will last into adulthood in approximately half of women; and if it persists for 2 years, it will last into adulthood in nearly two-thirds of women.[5]

The 2018 adolescent PCOS guidelines go so far as to define irregular menstrual cycles as normal in the first year postmenarche.[3] Although there is no doubt that menstrual irregularity is normally greatest during early puberty, guidance from the American Academy of Pediatrics and American College of Obstetricians and Gynecologists places limits on the normal range of irregularity.[12] The latter joint statement generally considers menstrual intervals to be

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**Table 1**
International Diagnostic Criteria for Polycystic Ovary Syndrome in Adolescents[1–4]

Otherwise unexplained combination of:

1. Abnormal menstrual pattern as evidence of ovulatory dysfunction
   A. Abnormal for age or gynecologic age, and
   B. Persistent symptoms for 1-2 years
2. Clinical and/or biochemical evidence of hyperandrogenism
   A. Hirsutism, especially if moderate-severe, is clinical evidence of hyperandrogenism
   B. Elevation of serum total or free testosterone by a specialty reference assay is biochemical evidence of hyperandrogenism

abnormal if outside of the bounds shown in Table 2.[11,12] They indicate that menses "90 days apart even for one cycle" and menses greater than 45 days apart, irrespective of postmenarcheal year, might warrant evaluation.

Fortunately, the 3 PCOS documents provide for a resolution of their differences: they agree that girls suspected of having PCOS within the first 1-2 years after menarche should be evaluated at that time. If tests are consistent with PCOS, the patient can be followed with a provisional diagnosis of "at risk for PCOS," as discussed further with respect to symptomatic treatment.

All of the PCOS groups grappled with the extent to which adolescent hirsutism and acne constitute clinical evidence of androgen excess on a par with accurate biochemical evidence of hyperandrogenism. Mild hirsutism is considered acceptable evidence according to 2018 criteria, like 2013 Endocrine Society PCOS guidelines,[9] whereas the 2015 and 2017 recommendations require moderate-severe hirsutism as a clinical criterion for evidence of hyperandrogenism. However, the 2018 Endocrine Society hirsutism guidelines recommend demonstration of hyperandrogenemia in women with all degrees of hirsutism. This was recommended partly because hirsutism and acne are variably expressed manifestations of hyperandrogenism: thus, there is no endocrine basis for hirsutism in a substantial minority (approximately half of those with mild hirsutism, one-third overall) of women; conversely hyperandrogenemia often exists without hirsutism or acne.[18]

Although severe comedonal acne is common in early teenage adolescent girls, moderate-severe inflammatory acne occurs in less than 5% of them.[1,5] However, the prevalence of hyperandrogenemia in them is undetermined, so the 2015 and 2017 criteria considered moderate-severe inflammatory acne an indication to test for biochemical hyperandrogenism. Without citing further data, 2018 criteria considered all severe acne in adolescents to constitute clinical evidence of hyperandrogenism.

All 3 sets of adolescent PCOS recommendations agree that investigation for biochemical hyperandrogenism be initiated by measuring serum total and/or free testosterone using specialty assays with well defined reference ranges. These determine total testosterone using postextraction/chromatography radioimmunoassay or tandem mass spectrometry and then calculate free testosterone using a separate assay for testosterone binding to serum proteins. Documentation of biochemical hyperandrogenism has been problematic because standard platform assays of testosterone give grossly inaccurate results. The 2013 Endocrine Society PCOS task force did not consider accurate assays to be widely available and so permit hirsutism to be a surrogate for hyperandrogenism. The 2018 Endocrine Society Hirsutism Task Force deemed accurate assays to currently be widely available and so recommended them as the gold standard for demonstration of androgen excess as the basis of hirsutism. The adolescent PCOS guidelines took different positions within this spectrum, as noted previously.

The 2015 PCOS report was alone in specifying that the androgen level be persistently elevated. This recommendation was made because mild hyperandrogenemia might be found in the prolonged anovulatory cycles of PAA.

The management of PCOS was specifically addressed by the 2017 and 2018 adolescent PCOS conferences. Their different perspectives about pharmacologic treatment reflect the multicultural views about adolescent contraception. Estrogen-progestin combined oral contraceptive pills (COCP) are the favored first-line treatment recommended in the United States for the management of menstrual abnormalities and hirsutism.[7] Both international groups endorsed this treatment when contraception is desired. Metformin is otherwise favored by the 2017 consortium, which emphasizes its promotion of ovulation, and improved weight control, insulin resistance, metabolic parameters, and androgen levels. However, androgen levels are not reduced sufficiently to significantly improve hirsutism,[18] and the results of the few randomized, double-blind, placebo-controlled trials of metformin in adolescence show less effectiveness on ovulatory function than the many 2017-cited open-label trials suggest.[19] Agreement is uniform that healthy lifestyle management is first-line therapy for management of the associated obesity and

**Table 2**
Abnormal Uterine Bleeding (AUB) in Adolescence

| Symptom | Definition |
|---|---|
| Primary amenorrhea | Lack of menarche by 15 years of age or by 3 years after the onset of breast development |
| Secondary amenorrhea | More than 90 days without a menstrual period, after previously menstruating |
| Oligomenorrhea (infrequent AUB) | Year 0 to 1 post menarche: average cycle longer than 60 days (fewer than 6 periods per year)<br>Year 1 to less than 3 post menarche: average cycle longer than 45 days (fewer than 8 periods per year)<br>Year 3 to perimenopause: average cycle longer than 38 days (fewer than 9 periods per year) |
| Excessive uterine bleeding* | Menstrual bleeding that is more frequent than every 21 days (19 days in year 1), or prolonged (lasts >7 days) or heavy (soaking pads or tampons sufficiently to interfere with quality of life) |

* Encompasses frequent intermenstrual, heavy, or prolonged abnormal uterine bleeding, "polymenorrhea," and "meno/metrorrhagia." Traditionally termed "dysfunctional uterine bleeding."
Adapted from Rosenfield[11] according to Teede et al,[4] American Academy of Pediatrics Committee on Adolescence et al,[12] Treloar et al,[13] and Munro et al.[14]

metabolic disturbances (ie, before and/or in conjunction with metformin therapy).

In summary, the differences in details among the international PCOS recommendations primarily reflect tension between the desirability of early diagnosis (ie, avoiding false negative results) vs the liabilities of mistaken diagnosis (ie, avoiding false positive results) and attitudes about adolescent contraception. These are issues not likely to be resolved easily, yet they are matters for every physician to consider in management of each case.

What then are the take-home, practice points for the clinician faced with an adolescent within 1-2 years of menarche who has a menstrual abnormality, hirsutism, and/or topical treatment-resistant acne?

First, PCOS must be considered in the general context of all causes of adolescent menstrual disturbances. A large percentage of early postmenarcheal menstrual disturbances will be due to PAA. However, if irregularities persist for 1 year, approximately half will be due to PAA and half due to ovulatory dysfunction and less frequent conditions like pregnancy, disorders of the genital tract, and coagulopathy.[12] Approximately half of the ovulatory disorders will be due to hyperandrogenism (including PCOS) and half due to hypogonadism (of which eating disorder, excessive exercise, or gonadal failure are the prime considerations).[5,12]

It would be impractical for the front-line practitioner to evaluate all early postmenarcheal girls for a single abnormal menstrual cycle. The following approach is suggested as a middle ground between potentially mislabeling a girl as having a disorder vs making an early diagnosis in those who have a condition.

If a girl is amenorrheic for 2 months, it would seem prudent to ascertain whether she is in general good health, has signs of PCOS, or is possibly pregnant. If that assessment is negative, she should be followed to see if the menstrual disturbance becomes normal soon. However, for example, if she remains amenorrheic for more than 90 days or if 2 successive periods are more than 2 months apart, laboratory screening would be reasonable.

A screening panel for the most prevalent disorders would include a pregnancy test, serum luteinizing hormone, and follicle-stimulating hormone, as well as a complete blood count, comprehensive metabolic profile, and erythrocyte sedimentation rate.

Measurement of total and/or free testosterone using a specialty assay would be indicated in a few circumstances if this screening panel is negative. One, if the menstrual disorder is persistent or requires prompt treatment with COCP, as for heavy bleeding. Two, if the menstrual abnormality coexists with hirsutism, topical treatment-resistant moderate-severe acne, obesity/acanthosis nigricans, or evidence of frank virilization. Eighty percent or more of adolescents with a menstrual abnormality and hirsutism will prove to have PCOS.[5] Three, if hirsutism or acne will require COCP treatment, even if there is no menstrual abnormality, because the PCOS ovulatory dysfunction might take years to present.[2,5]

PCOS accounts for a large proportion of all adolescent hyperandrogenism. It is a diagnosis of exclusion for which referral to a specialist is advisable. Nonclassic congenital adrenal hyperplasia, hyperprolactinemia, endogenous Cushing syndrome, thyroid dysfunction, and virilizing tumor must be ruled out to make the diagnosis with high certainty.

Symptomatic treatment, just as for PCOS itself, is indicated in early postmenarcheal girls “at risk of PCOS” to manage menstrual abnormality, hirsutism, acne, or obesity (2015, 2018). Such girls should be reevaluated for persistence of PCOS by the time they finish high school, after withdrawing treatment for 3 or more months.[5,6] Of course, withdrawal of contraceptive therapy should only be undertaken after ensuring that nonhormonal contraceptive precautions are taken because the infertility of PCOS is not absolute. If evidence of ovulatory dysfunction and hyperandrogenism persist, the diagnosis of PCOS is confirmed, and treatment is reinstituted with an eye toward the time when fertility treatment might be required.

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