AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ANDROGEN EXCESS AND PCOS SOCIETY DISEASE STATE CLINICAL REVIEW: GUIDE TO THE BEST PRACTICES IN THE EVALUATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME – PART 1

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EXECUTIVE SUMMARY

Polycystic Ovary Syndrome (PCOS) is recognized as the most common endocrine disorder of reproductive-aged women around the world. This document, produced by the collaboration of the American Association of Clinical Endocrinologists (AACE) and the Androgen Excess and PCOS Society (AES) aims to highlight the most important clinical issues confronting physicians and their patients with PCOS. It is a summary of current best practices in 2015.

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*The opinions represented in the **AACE/ACE Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome** are the expressed opinions of the Reproductive Endocrinology Scientific Committee of the American Association of Clinical Endocrinologists and the Androgen Excess and PCOS Society. AACE/ACE Disease State Clinical Reviews are systematically developed documents written to assist health care professionals in medical decision making for specific clinical conditions, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment of the authors was applied.*

This review article is a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

- PCOS has been defined using various criteria, including menstrual irregularity, hyperandrogenism, and polycystic ovary morphology (PCOM).

  General agreement exists among specialty society guidelines that the diagnosis of PCOS must be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological) and polycystic ovaries.

- There is need for careful clinical assessment of women's history, physical examination, and laboratory evaluation, emphasizing the accuracy and validity of the methodology used for both biochemical measurements and ovarian imaging.

  Free testosterone (T) levels are more sensitive than the measurement of total T for establishing the existence of androgen excess and should be ideally determined through equilibrium dialysis techniques. Value of measuring levels of androgens other than T in patients with PCOS is relatively low.

  New ultrasound machines allow diagnosis of PCOM in patients having at least 25 small follicles (2 to 9 mm) in the whole ovary. Ovarian size at 10 mL remains the threshold between normal and increased ovary size.

  Serum 17-hydroxyprogesterone and anti-Müllerian hormone are useful for determining a diagnosis of PCOS.

- Correct diagnosis of PCOS impacts on the likelihood of associated metabolic and cardiovascular risks and leads to appropriate intervention, depending upon the woman's age, reproductive status, and her own concerns. The management of women with PCOS should include reproductive function, as well as the care of hirsutism, alopecia, and acne.

Cycle length >35 days suggests chronic anovulation, but cycle length slightly longer than normal (32 to 35 days) or slightly irregular (32 to 35-36 days) needs assessment for ovulatory dysfunction. Ovulatory dysfunction is associated with increased prevalence of endometrial hyperplasia and endometrial cancer, in addition to infertility.

In PCOS, hirsutism develops gradually and intensifies with weight gain. In the neoplastic virilizing states, hirsutism is of rapid onset, usually associated with clitoromegaly and oligomenorrhea.

Girls with severe acne or acne resistant to oral and topical agents, including isotretinoin (Accutane), may have a 40% likelihood of developing PCOS.

Hair loss patterns are variable in women with hyperandrogenemia, typically the vertex, crown or diffuse pattern, whereas women with more severe hyperandrogenemia may see bitemporal hair loss and loss of the frontal hairline.

Oral contraceptives (OCPs) can effectively lower androgens and block the effect of androgens via suppression of ovarian androgen production and by increasing sex hormone–binding globulin.

Physiologic doses of dexamethasone or prednisone can directly lower adrenal androgen output.

Anti-androgens can be used to block the effects of androgen in the pilosebaceous unit or in the hair follicle. Anti-androgen therapy works through competitive antagonism of the androgen receptor (spironolactone, cyproterone acetate, flutamide) or inhibition of 5α-reductase (finasteride) to prevent the conversion of T to its more potent form, 5α-dihydrotestosterone. The choice of anti-androgen therapy is guided by symptoms.

- The diagnosis of PCOS in adolescents is particularly challenging given significant age and developmental issues in this group. Management of infertility in women with PCOS requires an understanding of the pathophysiology of anovulation as well as currently available treatments.

Many features of PCOS, including acne, menstrual irregularities, and hyperinsulinemia, are common in normal puberty. Menstrual irregularities with anovulatory cycles and varied cycle length are common due to the immaturity of the hypothalamic-pituitary-ovarian axis in the 2- to 3-year time period post-menarche. Persistent oligomenorrhea 2 to 3 years beyond menarche predicts ongoing menstrual irregularities and greater likelihood of underlying ovarian or adrenal dysfunction.

In adolescent girls, large, multicystic ovaries are a common finding, so ultrasound is not a first-line investigation in women <17 years of age.

Ovarian dysfunction in adolescents should be based on oligomenorrhea and/or biochemical evidence of oligo/anovulation, but there are major limitations to the sensitivity of T assays in ranges applicable to young girls.

Metformin is commonly used in young girls and adolescents with PCOS as first-line monotherapy or in combination with OCPs and anti-androgen medications. In lean adolescent girls, a dose as low as 850 mg daily may be effective at reducing PCOS symptoms; in overweight and obese adolescents, dose escalation to 1.5 to 2.5 g daily is likely required.

Anti-androgen therapy in adolescents could affect bone mass, although available short-term data suggest no effect on bone loss. **(Endocr Pract. 2015;21:1291-1300)**

Abbreviations:
17OHP = 17 hydroxyprogesterone; **5αR** = 5α-reductase; **AA** = androgenic alopecia; **AES** = Androgen Excess Society; **AMH** = anti-Müllerian hormone; **BMI** = body mass index; **CV** = cardiovascular; **DHT** = 5α-dihydrotestosterone; **FG** = Ferriman-Gallwey; **LH** = luteinizing hormone; **MetS** = metabolic syndrome; **MS** = mass spectrometry; **NIH** = National Institutes of Health; **OCP** = oral contraceptive; **PCOM** = polycystic ovary morphology; **PCOS** = polycystic ovary syndrome; **RIA** = radioimmunoassay; **SHBG** = sex hormone–binding globulin; **SPA** = spironolactone; **T** = testosterone

INTRODUCTION

The past decade of research into polycystic ovary syndrome (PCOS) has produced important new insights into the evaluation and treatment of this disorder. This document is intended as a guide, highlighting the most current clinical information that a health care provider can use in managing patients with this disorder. It is not intended as a guideline but is written in a question and answer format by experts in clinical practice.

DEFINING PCOS

The Rotterdam criteria for PCOS have been endorsed by the National Institutes of Health (NIH). However, Androgen Excess Society (AES) guidelines may correspond better to the pathogenesis of this disorder, as the AES emphasizes the importance of clinical and/or biochemical hyperandrogenism and placing less importance on

polycystic ovary morphology (PCOM). Table 1 lists a comparison of criteria for the diagnosis of PCOS. Nevertheless, there is a general agreement that the diagnosis of PCOS must be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries. Despite this consensus, many doubts remain for the clinician who has to establish the existence of the criteria. In this section, we will discuss the possible issues that must be solved by the clinician in defining PCOS.

Establishing Hyperandrogenism

1. What Androgens Should Be Measured?

The issue of which serum androgen should be measured for diagnosis of PCOS remains controversial. Ideally, assessments of free testosterone (T) levels are more sensitive than the measurement of total T for establishing the existence of androgen excess (1). That said, although free-T measurements require equilibrium dialysis techniques, many commercial laboratories use direct analogue radioimmunoassay (RIA), which is notoriously inaccurate (2,3). Consequently, if the clinician is uncertain regarding the quality of the free-T assay, it may be preferable to rely on calculated free T, which has a good concordance and correlation with free T as measured by equilibrium dialysis methods (4).

The value of measuring the levels of androgens other than T in patients with PCOS is relatively low. Although levels of dehydroepiandrosterone sulfate (DHEAS) are increased in about 30 to 35% of PCOS patients (5), its measurement does not add significantly to the diagnosis, and in the majority of the patients, free and total T are also increased (5,6). Indeed, it has been estimated that only 5% of patients with PCOS have an exclusive increase in DHEAS (5). Similarly, measurements of either 11β-hydroxyandrostenedione or androstenedione reportedly add only a few patients and are thus generally not needed in clinical use (7).

2. What Technology Should Be Standard?

Based on the experience of Centers for Disease Control laboratories (8), many commercial diagnostic laboratories have switched to mass spectrometry (MS) coupled with liquid chromatography (LC) (LC/MS) assays, which have high sensitivity and specificity and provide accurate results. Moreover, MS is the reference method at centers such as the National Institute of Standards and Technology and is considered to be the "gold standard" for measurement of a variety of compounds. It should be noted, however, that in PCOS, good RIA methods that incorporate purification provide similar results (9). Methods that do not involve purification should be avoided, as they tend to overestimate values of total T in an unpredictable manner and do not generate reliable results (10). As previously discussed, measurement of free T requires equilibrium dialysis techniques. If these techniques are not available, determination of the free androgen index may be preferred in clinical practice. In conclusion, the clinician should be aware of the methods used by the laboratory and should avail the services of laboratories using LC/MS assays or RIA with purification.

3. Are There Normative Data References, and Are Any Useful?

Using conventional RIAs with purification steps, normal values of T are generally lower than 60 ng/dL. Although no normative values for T in women measured using LC/MS technology are available, the greater specificity of MS assays would anticipate lower total T levels (e.g., <50 ng/dL). Although normal values with direct RIAs are much higher–up to 70 to 80 ng/dL and in some instances 100 ng/dL–these should be avoided, as it becomes very difficult to distinguish normal women from hyperandrogenic women.

Table 1
Criteria for the Diagnosis of Polycystic Ovary Syndrome
(Other Hormonal or Androgen Excess Conditions Being Previously Excluded)[a]

NIH/NICHD (must meet both criteria)	ESHRE/ASRM (Rotterdam criteria) 2004	Androgen Excess Society 2006
Includes all of the following:	Includes two of the following:	Includes all of the following:
• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism
• Menstrual dysfunction	• Oligo-ovulation or anovulation • Polycystic ovaries	• Ovarian dysfunction and/or polycystic ovaries

Abbreviations: ESHRE/ASRM = European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; NIH/NICH = National Institutes of Health/National Institute of Child Health and Human Disease.
[a] Adapted from *Clin Epidemiol*. 2014;6:1-13.

4. To What Extent Should Hirsutism, Acne, and Alopecia Be Discussed?

In adult women, hirsutism, alopecia, and acne are good substitutes of biochemical hyperandrogenism and should be considered as indicating a condition of excess androgen production. This is not, however, the case during adolescence, when acne is very common and often reversible, whereas alopecia is uncommon and generally has other causes. During adolescence, therefore, only hirsutism should be considered a substitute of biochemical hyperandrogenism (11).

Establishing Ovulatory Dysfunction

1. How Can Ovulatory Dysfunction Be Defined?

If cycle length is >35 days, it may be assumed that chronic anovulation is present and no special tests are needed. However, if cycle length is only slightly longer than normal (32 to 35 days), or if cycles are slightly irregular, ranging from 32 to 35 to 36 days, ovulation should be assessed. In addition, when the patients are hyperandrogenic (i.e., biochemical or clinical hyperandrogenism), the possibility that apparently normal cycles are anovulatory should be ruled out. Several studies have shown that 10 to 15% of hyperandrogenic women with apparently normal cycles are anovulatory (12,13). In contrast, the finding of anovulation is very uncommon in normoandrogenic women with normal menses.

Measurement of serum progesterone during the midluteal phase (days 21 to 22) is the best way to assess ovulation. Whereas progesterone levels >2.5 ng/mL may indicate ovulation, values ≥7 ng/mL are generally needed for regular luteal function (14). Some physicians have proposed using 3 consecutive luteal determinations with a total serum value of ≥15 ng/mL to indicate normal luteal function (15). Alternatives to progesterone measurement (e.g., basal body temperature charts, urinary luteinizing hormone [LH] kits or timed endometrial biopsies) may be used, but they do not give sufficient information about the luteal phase.

2. What Length of Menstrual Cycle Defines the Threshold for Oligomenorrhea?

In adult women, a cycle length of ≥35 days is the threshold for oligomenorrhea. During adolescence, the threshold is higher, and a cycle length up to 40 days may be considered normal, with longer menstrual cycles indicating oligomenorrhea.

3. What Are the Clinical Implications of Ovulatory Dysfunction in PCOS?

Infertility is, of course, the main clinical implication of ovulatory dysfunction in PCOS. However, ovulatory dysfunction in association with other characteristics of PCOS, such as obesity, is also associated with increased prevalence of endometrial hyperplasia and endometrial cancer (16). Oral contraceptive (OCP) treatment may be useful for reducing endometrial cancer in PCOS, but, in any case, prolonged absence of a menstrual cycle should be avoided. In the recent joint meeting of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine in Amsterdam, induction of menstrual flow was recommended when the duration of the menstrual cycle is >3 months (17).

Polymenorrhea and/or hypermenorrhea are relatively uncommon in PCOS, but when present, they may induce iron deficiency anemia. Again, in such patients, OCP therapy may be useful for reducing the risk of anemia. Altered quality of life is another consequence of PCOS, but this seems to depend more on obesity and hirsutism than on altered menstrual cycles (18). However, in particular patients, psychological disturbances may be linked to altered menstrual cycles, and this should be considered when deciding the treatment of a PCOS patient.

Establishing PCOM

1. What Is the Standard Technology for Evaluating Ovarian Morphology?

Ovarian morphology must be assessed by transvaginal ultrasound. Although transabdominal ultrasounds may be used in the case of young girls or patients from a particular cultural background, ovarian morphology assessment, and, in particular, calculation of the number of small follicles, are less accurate using this technique. In the past few years, rapid improvements in ultrasound technology have increased by at least 2-fold the number of small follicles that may be observed inside a single ovary, and the clinician should be aware that the results of ovarian sonography strongly depend on the sensitivity of the ultrasound. Recent guidelines from the AES have suggested that machines using new software for automatic follicle numbering and probes with a frequency of at least 8 mHz are needed for optimal evaluation of ovarian morphology (19).

2. Are There Any Evidence-Based Criteria for Defining PCOM by Ultrasound?

The existing Rotterdam guidelines suggest that PCOM is indicated by the presence of at least 12 follicles measuring 2 to 9 mm in the whole ovary or by the finding of increased ovarian size (>10 mL) (20). These criteria were based on a completely different ultrasound technology however, and the unjustified increase in diagnoses of PCOS that has arisen from their use in conjunction with new ultrasound technology indicates that they are no longer appropriate in the clinic (21,22). New AES guidelines, which are based upon a review of the data published using new ultrasound technology, have increased the threshold count of small ovarian follicles to 25 (19). When using the new ultrasound machines, therefore, diagnosis of PCOM

is possible in patients having at least 25 small follicles (2 to 9 mm) in the whole ovary. Ovarian size threshold has not been influenced by new technologies, and 10 mL remains the threshold between normal and increased ovary size. In certain populations and during adolescence or in aging, however, a different threshold for ovarian size may be needed (23).

It is now absolutely necessary for clinicians to know what technology is used for assessment of ovarian morphology in their patients. If the clinician is not sure about which ultrasound technology is used, the diagnosis of PCOM should not be based on follicle count but only on ovarian size and eventually, bearing in mind the assay problems, on anti-Müllerian hormone (AMH) values (see the "Reproductive and Genetic Issues in PCOS" section in Part 2 of this Disease State Clinical Review, to be published in the next issue of *Endocrine Practice*)

3. What Other Laboratory Tests Should Be Performed in Evaluating PCOS?

In addition to androgens and (eventually) progesterone, only assessment of serum 17-hydroxyprogesterone (17OHP) and AMH are useful for determining a diagnosis of PCOS. Because patients with nonclassic 21-hydroxylase deficiency may present as PCOS (hyperandrogenism, anovulation, and PCOM [24]), evaluation of serum 17OHP should be always included in a diagnostic study. In these patients, a finding of 17OHP >10 ng/mL indicates the existence of a 21-hydroxylase deficiency, whereas values between 2 and 10 ng/mL suggest the need of further testing with adrenocorticotropic hormone stimulus (24). Finally, elevated AMH values (>4.5 ng/mL) may be useful as a substitute for ovarian morphology when no accurate ovarian ultrasound is available (25).

HYPERANDROGENISM AND PCOS

1. When Are Hirsutism, Acne, and Alopecia Defined as Clinical Signs of Hyperandrogenism?

Hirsutism

Hirsutism is defined as excessive hair growth in women in a pattern consistent with androgen sensitivity. Hair growth in certain anatomic areas is driven by androgens, and the development of excessive body hair in these areas is a major clinical sign of hyperandrogenism. The hair type present in most women with a hormonal hyperandrogenic disorder is coarse, thickened, pigmented, and long and is called terminal hair. It differs from vellus hair, which is fine, soft, unpigmented, and present in areas where hair growth is not androgen dependent. Typically, the onset of hirsutism in PCOS follows menarche, although a minority of premenarche girls have earlier onset of pubic hair development and some degree of hirsutism. Although 25 to 33% of white women have terminal hairs on the upper lip and periareolar area, as well as linea alba areas, the hirsutism in PCOS and a variety of other hyperandrogenic disorders is more pronounced. The presence of substantial numbers of terminal hairs over the chin, neck, lower face, and sideburns (particularly if extending medially) indicates the presence of androgen excess. Similarly, excessive hair growth on the lower back, sternum, abdomen, shoulders, buttocks, perineal area, and inner thighs is considered abnormal. Several clinical assessment scales have been used in the grading of hirsutism. Although the Hatch modification of the Ferriman-Gallwey (FG) scale has been the most widely used, it is limited by its subjective nature and failure to include the sideburn, perineal, or buttock areas (26). In PCOS, hirsutism develops gradually and intensifies with weight gain, whereas the neoplastic virilizing states involve a fairly rapid onset of severe hirsutism, usually associated with clitoromegaly and oligomenorrhea.

It should be noted that ethnic differences in the number of hair follicles present and individual skin sensitivity of the pilosebaceous unit to androgens are major determinants of the presence of hirsutism, as well as acne and androgenic alopecia (AA) (27). This emphasizes the well-known fact that there are women with minimal or no hirsutism who may have increased serum T levels, whereas other women with significant hirsutism may have normal or only slightly increased androgen levels.

Acne

During adolescence, acne should not be considered a substitute of hyperandrogenism (11), although girls with severe acne or acne that is resistant to oral and topical agents, including isotretinoin (Accutane), may have a 40% likelihood of developing PCOS (28,29). When acne persists after adolescence or is exacerbated in the mid-20s or -30s, hyperandrogenemia is common, and acne may be considered a clinical sign of hyperandrogenism. Those presenting with acne alone may have serum free T levels as high as those seen in hyperandrogenic disease states, demonstrating hirsutism without acne (30).

Alopecia

In the normal hair cycle, the anagen or growth phase lasts for 2 to 3 years and accounts for 85 to 90% of scalp hairs. In the setting of androgen excess, androgen-sensitive hair follicles shorten during the anagen phase, resulting in miniaturization of the scalp hair, less scalp coverage, and alopecia. The pattern of hair loss in women with hyperandrogenism is variable. For example, although hair loss patterns in women with hyperandrogenemia typically involve the vertex, crown, or a diffuse pattern, women with more severe hyperandrogenemia may experience bitemporal hair loss and loss of the frontal hairline (31).

2. What Are the Best Treatment Options for Women With Hyperandrogenism?

Pharmacologic strategies to control the dermatologic symptoms of hyperandrogenism are aimed both at lowering androgen levels and controlling the effect of androgens at the tissue level. OCPs can effectively lower androgens and block the effect of androgens via suppression of ovarian androgen production and by increasing sex hormone–binding globulin (SHBG). Moreover, physiologic doses of dexamethasone or prednisone can directly lower adrenal androgen output, and anti-androgens can be used to block the effects of androgen in regulating the expression of target genes in the pilosebaceous unit or in the hair follicle. The mechanistic basis of anti-androgen therapy is competitive antagonism of the androgen receptor (spironolactone, cyproterone acetate, flutamide) or inhibition of 5α-reductase (5αR) (finasteride) to prevent the conversion of T to its more potent form, 5α-dihydrotestosterone (DHT). The choice of anti-androgen therapy is guided by which symptoms are most bothersome to the patient, as well as whether the androgens are thought to be primarily of ovarian or adrenal origin.

The mainstay of first-line therapy for all dermatologic symptoms of hyperandrogenism is OCP therapy. OCPs contain estrogen (almost exclusively ethinyl estradiol) and a progestin. A daily dose of 20 to 35 μg of ethinyl estradiol effectively suppresses pituitary-ovarian communication, thereby decreasing ovarian androgen production. Newer progestins have been developed with an emphasis on greater progestogenic and less androgenic effects. Although the ideal progestins to use in PCOS are those with the lowest androgenic profile, such as chlormadinone and drospirenone, these may induce a higher number of venous thrombosis events and may be contraindicated in patients with severe obesity. The androgenic symptoms that may be attenuated by OCP treatment include hirsutism and acne, primarily through the ability of OCPs to raise SHBG and lower free T levels. OCPs pass through the liver, causing increased synthesis of SHBG, and they may be more effective at controlling hirsutism and acne than transdermal or vaginal ring preparations. OCPs as monotherapy are not very effective in arresting mild to moderate alopecia or hirsutism and are preferably combined with an anti-androgen to achieve a better response when targeting hirsutism and alopecia.

Spironolactone (SPA) is the most commonly used androgen blocker in the United States. It is relatively effective in the treatment of all dermatologic signs of PCOS, in particular acne and hirsutism (32,33). In addition to being an aldosterone antagonist, it competes with DHT for binding to the androgen receptor, although its effect on the latter is minimal compared to DHT. SPA also has several other effects, including a moderate local blocking of 5αR activity, competing with androgens for binding to SHBG, blocking conversion of T to DHT in dermal papilla cells, and antagonizing the androgenic effect of DHT on the hair follicle. Its progestational activity may also reduce levels of gonadotropin-releasing hormone and LH, thereby attenuating the LH effect on androgen steroidogenesis. The dosage of SPA is 100 to 200 mg daily, given in 2 divided doses. Because SPA may induce hyperkalemia, serum potassium should be monitored. Although headaches and dizziness are relatively frequent, the patient should increase water and salt intake in hot weather. Intermenstrual spotting may occur in almost half of the women taking SPA as monotherapy, and breast discomfort, dry skin, and gastritis are also noted in some women on this drug. As with other anti-androgens, SPA has the potential for teratogenicity (specifically, inadequate masculinization of male genitalia), and its combination with a nonandrogenic OCP is recommended. Although flutamide and cyproterone acetate are potent anti-androgens, they are not available in the United States.

Finasteride is 5αR inhibitor available in the United States that has been shown to exert a 50 to 60% reduction in DHT levels. As such, it is an important therapeutic agent for AA at a daily dosage of 5 mg (34), which has been shown to effect a significant reduction in FG scores in the majority of women after 6 months of treatment (35). Treatment of hirsutism is targeted at reducing the production and bioavailability of T, as well as blocking target tissue androgen action. An assessment of the data indicates that the use of 5αR inhibition therapy should be considered when prior therapy with OCPs and SPA are relatively ineffective for severe hirsutism (36). The effects of 5 mg of finasteride for premenopausal women with AA are variably favorable, particularly when used with an ethinyl estradiol/drospirenone OCP (37). Although the limited literature has made it difficult to fully assess dutasteride, it appears to have a somewhat better success rate in the treatment of alopecia (38). Dutasteride reduces plasma DHT more significantly than finasteride, with a concomitant rise in plasma T of approximately 25% due to blockage of the conversion of T to DHT by inhibition both 5αR isoenzymes. Consequently, the aromatase pathway is enhanced, resulting in an increase in circulating estrogens. Finally, metformin is an alternative therapy for hirsutism in women with PCOS who have other indications for metformin use. Although it is useful for metabolic and glycemic abnormalities and for improving menstrual irregularities, metformin is less effective than anti-androgens in treating hirsutism or acne (36,39).

PCOS IN THE ADOLESCENT

1. What Makes the Diagnosis of PCOS Challenging in Adolescents? Is It Important to Differentiate PCOS at This Stage, or Is It Acceptable to Delay Diagnosis Until Adulthood?

Because PCOS commonly presents during adolescence, it is important to diagnose the condition as early as

possible to evaluate and treat metabolic and cardiovascular (CV) risks, as well as the psychologic and dermatologic issues. There are complicating factors in diagnosing PCOS in adolescent girls, and there is a distinct potential for both over- and underdiagnosis of the syndrome (40). On the one hand, many of the cardinal features of PCOS, including acne, menstrual irregularities, and hyperinsulinemia, are common issues in normal puberty and accordingly are difficult to distinguish from a true underlying disorder. On the other hand, diagnostic features such as hirsutism may not be fully realized in adolescent girls presenting earlier in the continuum. Furthermore, clinical definitions of excessive hair growth and biochemical parameters for hyperandrogenism are based upon standards and definitions derived from adults. As previously discussed, PCOS as defined by the AES criteria requires evidence of ovarian dysfunction (either based on clinical evidence of oligo/anovulation or PCOM on ultrasound) and either biochemical or clinical evidence of hyperandrogenism (1). In addition to excluding alternative causes of these issues, including thyroid, adrenal, and pituitary dysfunction, the definition of each of the AES parameters in adolescents presents specific obstacles. For example, menstrual irregularities with anovulatory cycles and varied cycle length are common due to the immaturity of the hypothalamic-pituitary-ovarian axis during the 2- to 3-year time period postmenarche. Moreover, hyperandrogenemia leading to acne and hirsutism could also be related to normal puberty rather than underlying PCOS, and hyperinsulinemia is a feature of normal puberty. PCOS may be a trigger when obesity and concomitant insulin resistance act to exacerbate otherwise normal hormonal changes of puberty.

In terms of defining ovarian dysfunction in adolescents, a widely accepted approach is to follow the patient clinically for 2 to 3 years postmenarche before beginning a thorough investigation for underlying PCOS (41). This is based on the knowledge that persistent oligomenorrhea 2 to 3 years beyond menarche predicts ongoing menstrual irregularities and offers a greater likelihood of uncovering true underlying ovarian or adrenal dysfunction. Adult ultrasound criteria for PCOM are not applicable to adolescent girls, in whom large, multicystic ovaries are a common finding due to the natural history of ovarian development at menarche. Parenthetically, there is a great deal of heterogeneity in ovarian morphology in adolescents, and there are therefore minimal normative data on which to base ultrasound criteria for PCOM in this population. For these reasons, ultrasound is not a first-line investigation in women <17 years of age, and ovarian dysfunction in adolescents should be based on oligomenorrhea and/or biochemical evidence of oligo/anovulation.

Defining clinical and biochemical hyperandrogenism in adolescents has its own set of challenges. The cornerstone of defining clinical hyperandrogenism in women is the presence of hirsutism, whereas acne and alopecia indicate a possibility of underlying hyperandrogenism. Acne has a high background prevalence in adolescents and may not be related to underlying PCOS. On the other hand, diffuse hirsutism and abnormal hair growth defined by an elevated FG score may not be fully manifested in adolescence. Furthermore, the FG scoring system was determined in adult women and is not applicable to younger, perimenarchal age groups. Due to these issues, biochemical evidence of hyperandrogenism is extremely important to evaluate in this group. As we have previously alluded, in adult women, there are major limitations to the sensitivity of T assays in ranges applicable to young girls, with no established normal ranges. The lower limit of normal T in young girls may be lower than in adult women. A recent Australian study defined the upper 5 and 10% levels of free T in an unselected population of girls at 1.3 and 1.0 ng/dL, respectively (42), with a median total T of 35 ng/dL. A study from the United Kingdom showed that total T and SHBG levels progressively increase and decrease, respectively, throughout puberty, resulting in higher free T. By Tanner stage 5, median T is reportedly 40.3 ng/dL, and SHBG is reportedly 43 nmol/L (40). Rising free T levels in puberty are in part secondary to a decrease in SHBG from physiologic hyperinsulinemia.

Because the signs and symptoms are heterogeneous in adolescents and may vary over time, the diagnosis of PCOS may be overlooked. However, adolescence is a crucial time for diagnosis because this is a time frame when many patients with PCOS start gaining weight. Adolescents should therefore be followed carefully to confirm a diagnosis of PCOS and reduce the frequency of later complications in the CV system and type 2 diabetes mellitus.

2. What Is the Role of Metformin in Adolescents with PCOS, and What Is the Optimal Timing and Dose?

Metformin is commonly used in young girls and adolescents with PCOS as first-line monotherapy or in combination with OCPs and anti-androgen medications (43). Metformin is currently used to target hyperandrogenemia and symptoms of androgen excess, to restore normal menses, to aid in weight reduction, and to intervene in metabolic parameters of insulin resistance, with the goal of preventing long-term metabolic and CV complications. In addition, a body of evidence supports the use of metformin to prevent or delay the progression to PCOS in high-risk prepubertal girls.

As in adult women, evidence supports the use of metformin in obese/overweight and lean adolescent girls to help reduce androgen excess and improve ovarian function (44). Many adolescents who do not want to be on an OCP may derive symptom benefit from metformin monotherapy. In a small randomized, placebo-controlled study of obese adolescents and baseline hyperinsulinemia, metformin significantly improved biochemical hyperandrogenemia, restored menses, and improved high-density lipoprotein

(HDL) cholesterol, although there were no improvements in insulin sensitivity measurements or weight loss (45).

The prevalence of metabolic syndrome (MetS) in adolescents with PCOS appears to be very high. A U.S. study using AES criteria to define PCOS reported a MetS prevalence of 10.8%, compared with 1.7% in those without PCOS (46). The study also reported a higher proportion of metabolic abnormalities in subjects with PCOS compared with adolescents without PCOS, even after excluding body mass index (BMI). Insulin resistance and the components of MetS are therefore important targets of therapy in adolescent girls with PCOS. A recent retrospective study compared the effects of metformin monotherapy and metformin with OCPs on lipids in overweight/obese adolescents with PCOS (47). In the monotherapy group, there was a significant decrease in BMI and improvement in total and low-density lipoprotein (LDL) cholesterol over the 10 months of treatment, with no significant changes in triglycerides (TGs). In the group taking metformin with an OCP, total and LDL cholesterol were not significantly altered, whereas there was a significant increase in HDL cholesterol and a trend toward an increase in TGs. Lean girls with PCOS may also benefit from metformin monotherapy. For example, a small study of 10 normal-weight girls with a history of precocious puberty and PCOS showed that metformin treatment decreased biochemical and clinical hyperandrogenism, improved cyclic menses, decreased hyperinsulinemia, and improved lipid profiles (48).

In lean adolescent girls, a dose as low as 850 mg daily may be effective at reducing PCOS symptoms, although in overweight and obese adolescents, dose escalation to 1.5 to 2.5 g daily is likely required (44). In terms of timing, certain studies have suggested that early intervention in high-risk prepubertal and early menarchal girls can prevent the metabolic and clinical sequelae of PCOS. It should be pointed out, however, that these results were obtained in a well-defined patient population of girls with low birth weight and history of premature pubarche (49,50).

3. Are Anti-Androgen Therapies Appropriate in Adolescents With PCOS? Are There Additional Concerns Regarding Bone and CV Health Associated with the Use of These Medications in Young Girls?

SPA and finasteride are often added to OCPs in adolescents with PCOS to more aggressively address the androgen excess symptoms of acne, hirsutism, and alopecia. A major risk of both of these medications is teratogenesis, and ongoing OCP use must be emphasized. Although the safety and efficacy of these medications has been studied in adult women, this has not been the case in adolescents, and there is a paucity of literature addressing their use in this population. Other anti-androgens, such as cyproterone acetate and flutamide, have been studied in the adolescent population with good efficacy and side effect profiles (51). A specific concern of anti-androgen therapy in adolescents is the effect on bone mass. A recent retrospective study of adolescents treated with metformin or metformin plus an anti-androgenic OCP and flutamide for at least 1 year found no differences between the groups with respect to BMI, abdominal fat composition, and insulin sensitivity. Similarly, there were no differences in bone density and bone geometry parameters measured using peripheral quantitative computed tomography (52). A recent small, prospective study of younger (mean age, 22 years), lean women with PCOS treated with an OCP containing ethinyl estradiol/drospirenone and SPA found a statistically significant increase in C-reactive protein and homocysteine levels after 6 months of this treatment, although there were no changes in insulin parameters or lipid profile (53).

DISCLOSURE

Dr. Neil F. Goodman is on the Speakers Bureau for Abbie. The other authors have no multiplicity of interest to disclose.

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