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The Diagnosis of Polycystic Ovary Syndrome during Adolescence

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Key Words

Hyperandrogenism · Ovarian hyperandrogenism · Ovary · Polycystic ovary syndrome · Puberty

Abstract

Background/Aims: The diagnostic criteria for polycystic ovary syndrome (PCOS) in adolescence are controversial, primarily because the diagnostic pathological features used in adult women may be normal pubertal physiological events. Hence, international pediatric and adolescent specialty societies have defined criteria that have sufficient evidence to be used for the diagnosis of PCOS in adolescents. ***Methods:*** The literature has been reviewed and evidence graded to address a series of questions regarding the diagnosis of PCOS during adolescence including the following: clinical and biochemical evidence of hyperandrogenism, criteria for oligoanovulation and polycystic ovary morphology, diagnostic criteria to exclude other causes of hyperandrogenism and amenorrhea, role of insulin resistance, and intervention. ***Results and Conclusion:*** Features of PCOS overlap normal pubertal development. Hence, caution should be taken before diagnosing PCOS without longitudinal evaluation. However, treatment may be indicated even in the absence of a definitive diagnosis. While obesity, insulin resistance, and hyperinsulinemia are common findings in adolescents with hyperandrogenism, these features should not be used to diagnose PCOS among adolescent girls.

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Introduction

Polycystic ovary syndrome (PCOS) affects 6–15% of women of reproductive age and accounts for 72–84% of adult hyperandrogenism [1–3]. The cause of PCOS is unknown, but considerable evidence suggests that it is a complex trait arising from heritable influences, nonheritable intra- and extrauterine environmental factors, variations in insulin resistance, alterations in steroidogenesis/steroid metabolism, and alternative adaptations to energy excess [4, 5].

The classic features in adult women include chronic anovulation associated with relative infertility, polycystic ovarian morphology, and hirsutism [6]. Intrinsic abnormalities in ovarian steroidogenesis may underlie this ovarian dysfunction in some [7, 8]. However, additional factors, such as insulin resistance and/or hyperinsulinemia, may play a major role. Hence, similar to diabetes, PCOS is not one disorder/disease [9].

Three international conferences have developed somewhat different but overlapping diagnostic criteria for adult women: the National Institutes of Health (NIH) conference criteria (1990), the Rotterdam consensus criteria (2003) (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004), and the Androgen Excess-PCOS Society consensus criteria (2006) [10–12]. The NIH criteria included hyperandrogenism, chronic anovulation, and exclusion of other causes of these symptoms [10]. The Rotterdam criteria are the broadest and include the features of the other definitions. They allow PCOS to be diagnosed with a combination of chronic anovulation and polycystic ovary morphology (PCOM) without hyperandrogenism [13–17].

The diagnostic criteria for PCOS in adolescence are controversial, primarily because the diagnostic pathological features used in adult women, e.g. acne, irregular menses, and PCOM, may be normal pubertal physiological events [18]. In the recently published Guideline for the Diagnosis and Treatment of Polycystic Ovary Syndrome [19], the Endocrine Society indicated that diagnostic criteria are unclear during adolescence. Hence, questions still exist regarding the features of PCOS in adolescence. How can one be certain that adolescent hyperandrogenemia is not a consequence of the lack of full synchrony of the hypothalamic-pituitary-ovarian axis during the prolonged anovulatory cycles typical of pubertal development rather than an early manifestation of PCOS? Whether adolescent androgen levels predict adult levels and, as such, whether adolescent hyperandrogenic anovulation accurately predicts adult PCOS is unclear. Since anovulatory cycles are common after menarche, it is unclear when persistence of adolescent oligomenorrhea becomes a significant clinical finding.

Insulin resistance and hyperinsulinemia are intrinsic to PCOS and are believed to exacerbate the hyperandrogenism and the reproductive and metabolic manifestations of PCOS in adolescents. At the present time, none of the current definitions of PCOS include obesity, insulin resistance, or hyperinsulinemia as a diagnostic criterion [1, 10–13, 18–20]. Therefore, insulin resistance and/or hyperinsulinemia should not be used to diagnose PCOS among adolescent girls.

To obtain consensus, the Pediatric Endocrine Society invited an expert group of representatives from the Androgen Excess-PCOS Society and stakeholder international pediatric and adolescent specialty societies with the goal of defining which criteria have sufficient evidence to be used for the diagnosis of PCOS in adolescents. The hierarchy of the evidence available in the literature assessed for this process was graded according to the AGREE criteria for evaluation of evidence as follows [1, 21]:

- Level A requires at least one randomized controlled trial (RCT) as part of a body of literature of overall good quality and consistency that addresses the specific recommendation.
- Level B requires the availability of well-controlled clinical studies, but no RCTs are available on the topics of recommendation.
- Level C requires evidence obtained from expert committee reports of opinions and/or clinical experiences of respected authorities, which indicates an absence of directly applicable clinical studies of good quality.

Question 1: What Are the Criteria for Clinical Evidence of Clinical Hyperandrogenism in the Adolescent Girl?

No consensus exists on the clinical criteria to reach the diagnosis of androgen excess in adolescence. In the absence of such consensus, the diagnosis of androgen excess should be considered in adolescents presenting with unwanted hair growth in a male-like pattern (hirsutism), moderate to severe inflammatory acne, and/or menstrual irregularities. Hirsutism is defined as excessive coarse sexual hair, i.e., terminal hair that develops in a male-like distribution [22–24].

All adult PCOS criteria consider hirsutism as evidence of clinical hyperandrogenism. Acne and seborrhea are common, but alopecia is rare in adolescence [25]. Hirsut-

ism reflects the interaction between circulating androgen concentrations, local androgen concentrations, and the apparent sensitivity of the pilosebaceous unit/hair follicle to androgens. The severity of hirsutism does not correlate well with circulating androgen concentrations [26]. Due to ethnic/genetic differences, hirsutism may be a less prominent feature of hyperandrogenism, as observed in some Asian populations [27]. Even though hirsutism is common among women with hyperandrogenism, the latter can occur in the absence of cutaneous manifestations [2, 3]. Idiopathic hirsutism is defined as hirsutism without hyperandrogenemia [22, 24, 28].

In adults, sexual hair growth is commonly graded by the semiquantitative Ferriman-Gallwey (FG) score. This scoring system has its limitations, which include different cutoff scores among racial/ethnic groups, its subjective nature, the lack of consideration of androgen-sensitive areas such as sideburns and the buttocks, and the failure to account for a locally high score that does not raise the total score to an abnormal extent (focal hirsutism) [22, 24]. It is important to realize that about half of otherwise asymptomatic mild hirsutism is not associated with hyperandrogenemia [22, 24]. However, mild or focal hirsutism may be a sign of hyperandrogenemia in young women when associated with other evidence of PCOS, i.e., menstrual irregularity [29–32].

Whereas hair growth is comparable in unselected White and Black women, women from China, Japan, Thailand, and other South Asian countries have less hair per unit skin [26, 30, 33–35]. One approach to defining hirsutism is using a FG score above the 95th percentile for the population, which is >8 in premenopausal adult White and Black women [24]. Hirsutism, similarly defined, is indicated by a score ≥9–10 in Mediterranean, Hispanic, and Middle Eastern women, ≥2 for Han Chinese women, and ≥5 in Southern Chinese women [36]. Nevertheless, using a cluster analysis, modified FG scores >3 were uncommon among an unselected group of adult White and Black women [37].

There are sparse normative data in early adolescence. Whether a different cutoff score should be used to define hirsutism in the young pubertal girl, at a stage when sexual hair is still developing, is unclear. Even if not associated with androgen excess, hirsutism can be devastating for an adolescent girl and often warrants cosmetic treatment [38, 39]. Upper lip scores of 3–4 were found in <3% of Black and White US adolescents, though scores of 1–2 rose in prevalence from 7.3% at <2 years after menarche to 28.2% at >2 years after menarche [40, 41].

Hirsutism must be distinguished from hypertrichosis, which is defined as generalized excessive vellus hair growth distributed in a nonsexual pattern, e.g., predominantly on forearms or lower legs. This hair growth is not due to androgen excess. It may be hereditary, is frequent among girls of Mediterranean or Mid-Eastern ethnic background, or may result from malnutrition or certain medications, e.g., phenytoin or cyclosporine [29].

Acne vulgaris may be the only pilosebaceous manifestation of hyperandrogenism [29]. While comedonal acne is common in adolescent girls, moderate or severe comedonal acne (i.e., 10 or more facial lesions) in early puberty or moderate inflammatory acne through the perimenarcheal years is uncommon (<5% prevalence) [42, 43].

Recommendations

(1) Isolated mild hirsutism should not be considered clinical evidence of hyperandrogenism in the early postmenarcheal years when it may be in a developmental phase (Level C).

(2) Moderate to severe hirsutism constitutes clinical evidence of hyperandrogenism (Level B).

(3) Girls with acne that is persistent and poorly responsive to topical dermatologic therapy should be evaluated for the presence of hyperandrogenemia before initiation of any medical therapies (Level C).

Question 2: What Are the Criteria for Evidence of Biochemical Hyperandrogenism in the Adolescent Girl?

The diagnosis of biochemical hyperandrogenism in symptomatic women with PCOS is based on documentation of elevated serum androgens using a reliable assay with well-defined normal ranges [20, 24]. Testosterone is the major circulating androgen. Measurements of total and/or free testosterone have been the most recommended hormone determinations to document hyperandrogenemia [20, 22, 24]. However, accurate determinations of total and free testosterone concentrations are often problematic [44]. The diurnal rhythm, stage of puberty, phase of menstrual cycle, and sex hormone-binding globulin (SHBG) concentrations are biological variables that influence testosterone concentrations. Methodological problems regarding testosterone determinations include the following: (1) inadequate assay sensitivity to measure low testosterone concentrations in children and women; (2) assay interference due to simultaneous presence of

other steroid molecules with similar structure; (3) lack of well-defined normative values; (4) binding of testosterone to SHBG and other proteins in the peripheral circulation, and (5) technical aspects of testosterone assays [24, 45–47].

Methods used to measure testosterone concentrations include radioimmunoassays, chemiluminescence immunoassays, gas chromatography-tandem mass spectrometry (GC-MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). A blinded comparison of three different methods using samples obtained from over 500 adult women showed poor precision at low levels and much variability between the three methods, which highlights the difficulties in accurately measuring testosterone concentrations [46]. Extraction steps to remove interfering substances have largely been eliminated from most automated analyzer methods for the direct measurement of testosterone, resulting in a lack of sensitivity and specificity [47]. The multichannel platform assays now commonly used by hospital laboratories are adequate for SHBG and dehydroepiandrosterone sulfate (DHEAS) assays. It is anticipated that the increasing availability of reproducible high-quality tandem mass spectrometry methods will improve access to reliable and accurate steroid assays. However, these assays are not yet readily available [48].

SHBG concentrations govern the fraction of testosterone that is free and, hence, bioavailable. Serum free testosterone (or the related bioavailable testosterone and free androgen index) is either calculated as the product of the total testosterone concentration times the free fraction computed from the SHBG concentration or directly determined by dialysis [49]. Free testosterone determined by equilibrium dialysis is presumed to be the most sensitive single test for the diagnosis of hyperandrogenemia [20, 24, 46, 48]. However, free testosterone assays are less well standardized than the total testosterone assay, which has limited their usefulness. The cost-effectiveness of routine assays of androgens other than testosterone has not been well studied, though androstenedione may be helpful in some populations [50].

The criteria used to define hyperandrogenemia in adolescent girls are confounded by developmental considerations. Testosterone levels have long been known to rise during puberty to reach a peak approximating adult levels within a few years after menarche [51–54]. However, testosterone levels increase as adolescent anovulatory cycles lengthen in both asymptomatic and symptomatic anovulatory schoolgirls [55–57]. Thus, there is uncertainty about whether mild hyperandrogenemia results as a normal perimenarcheal phenomenon. Additionally, how often adolescent hyperandrogenemia persists and predicts adult hyperandrogenemia is unclear [52].

In a study of unselected schoolgirls with oligomenorrhea, 4% had hirsutism and 57% had elevated testosterone levels [58]. Follow-up of these oligomenorrheic girls from 15 to 18 years showed that the body mass index (BMI) predicted ongoing menstrual abnormality better than androgen levels [52]. Follow-up of a different group of unselected healthy adolescents for 12 years showed tracking of androgen levels into adulthood; higher levels in adolescence were associated with lower fertility, suggesting evolving PCOS [59]. Serum free testosterone was not measured and testosterone concentrations were not re-measured, so the prevalence of hyperandrogenemia was possibly underestimated. In another series, hyperandrogenemia detected in girls with menstrual disorders frequently persisted over a 2- to 7-year follow-up period [60]. However, detailed data are not available regarding the accuracy of the prediction of ongoing hyperandrogenic anovulation from a single elevated testosterone level. Further, no data are available indicating how long hyperandrogenemia must continue to accurately predict persistence and development of PCOS in adulthood.

At this time, because of the variability in the results of testosterone assays and the limited data on the normal developmental fluctuations in testosterone levels during puberty, no clear cutoff testosterone concentrations can be given that pertain with certainty to the broad population. For these reasons, testosterone concentrations should be considered elevated when they are persistently greater than the adult female normative values according to assays performed by specialty laboratories with well-defined reference intervals. In general, for an assay using an extraction step, total testosterone concentrations >55 ng/dl are likely consistent with hyperandrogenism [18]. Gambineri et al. [61] defined hyperandrogenism during the follicular phase as total testosterone concentrations >42 ng/dl using a LC-MS/MS assay.

Recommendations

(1) Hyperandrogenemia needs to be defined based on the detailed characteristics of the testosterone assay used (Level A).

(2) Biochemical evidence of hyperandrogenism, as indicated by persistent elevation of serum total and/or free testosterone levels and determined in a reliable reference laboratory, provides the clearest support for the presence of hyperandrogenism in an adolescent girl with symptoms of PCOS (Level B).

(3) A single androgen level >2 SD above the mean for the specific assay should not be considered to be evidence of hyperandrogenism in an otherwise asymptomatic adolescent girl (Level C).

Question 3: What Are the Criteria for Evidence of Oligo-Anovulation in Adolescents?

Menstrual irregularity is common among adolescents and is generally the result of anovulatory cycles. Both are frequent in the first 2 years after menarche. Regular cycles (21–45 days) are established by the third year after menarche in approximately 95% of girls, but cycles can remain irregular until the fifth year. Both Metcalf et al. [62] and Apter [63] reported that anovulatory cycles can persist until nearly 5 years after menarche. These data, like earlier studies on variation in menstrual cycle length, indicate that complete maturation of the hypothalamic-pituitary-ovarian axis can take up to 5 years after menarche [64–67]. Despite the view that irregular menstrual cycles in the first 5 years are not a reason for clinical concern, more recent studies report that regular menstrual patterns can in fact be established within 6–12 months of menarche [68–70]. Indeed, after 6 years of follow-up, 59% of the adolescents who had presented with oligomenorrhea at the beginning of the study remained oligomenorrheic and fulfilled the criteria for PCOS [70].

Persistent oligomenorrhea was suggested as a requirement for the diagnosis of PCOS in adolescents by the Endocrine Society's recent PCOS clinical practice guidelines [19]. However, the definition of 'persistent oligomenorrhea' is uncertain. Carmina et al. [18] indicated that persistent oligomenorrhea should be defined as lasting at least 2 years prior to PCOS diagnosis. Rosenfield [54] concluded that PCOS should be considered when menstrual irregularity persists for ≥1 year. Southam and Richart [71] demonstrated that approximately 50% of girls with persistent oligomenorrhea or abnormal uterine bleeding for 1 year remained oligomenorrheic during an 8-year follow-up period.

To define persistent oligomenorrhea in the context of the known variation in the adolescent menstrual cycle, scrutiny of parameters for normal cycles in peripubertal girls is worthwhile. The median age at menarche, between 12 and 13 years, has remained relatively stable across well-nourished populations in developed countries [72]. Ninety percent of females are menstruating by 13.75 years of age, and 98% of females will have had menarche by age 15 years [54]. Although primary amenorrhea has traditionally been defined as no menarche by 16 years of age, 'many diagnosable and treatable disorders can and should be detected earlier, using the statistically derived guideline of 14–15 years of age' [73, 74].

Most normal cycles range from 20 to 90 days, even in the first gynecologic year [75–77]. It is statistically uncommon for girls and adolescents to remain amenorrheic for more than 3 months or 90 days regardless of the gynecologic age [64, 75]. The 5th and 95th percentiles for cycle length within the first gynecologic year are 18.3 and 83.1 days, respectively. With increasing gynecologic age, fewer females experience cycles exceeding 45 days. By 2 years after menarche, the 5th and 95th percentiles for the cycle length are 20.2 and 53.5 days, respectively; and by 3 years after menarche, the 5th and 95th percentiles are 20.6 and 43.6 days, respectively [64]. Legro et al. [69] found that over 90% of adolescent females have 10 or more menstrual cycles per year (average menstrual interval 36.5 days) 3 years after menarche. For some girls, irregular excessive menstrual bleeding, i.e., dysfunctional uterine bleeding, may be a manifestation of chronic anovulation.

The challenge for the clinician is the differentiation of adolescents with 'physiological adolescent anovulation' from those with true ovulatory dysfunction, particularly because evidence suggests that symptoms of PCOS can appear in the first years after menarche [70, 78]. Thus, the persistence of menstrual irregularities appears to be a good indicator of the possible underlying pathology with acknowledgement that the definition of persistence differs among experts. Accordingly, the persistence of oligomenorrhea (menstrual cycles longer than 45 days), secondary amenorrhea (absence of cycles for more than 3 months), or primary amenorrhea in girls with complete pubertal development and adult stature suggests the coexistence of androgen excess [71, 78].

Based upon the above evidence, we put forth the following recommendations for evidence of oligo-anovulation in adolescence. However, the clinical context with which a patient presents is the ultimate indicator for that individual patient. For example, a 15-year-old without menarche, who started thelarche 1 year prior, coupled with a family history of delayed puberty can likely be reassured and followed for further progression of puberty. Alternatively, a 13-year-old without menses, but who has facial hair, severe acne, a maternal history of PCOS, and advanced breast development for 3–4 years likely warrants further investigation.

Recommendations

(1) The majority of adolescents establish a menstrual interval of 20–45 days within the first 2 years after menarche. Menstrual intervals persistently shorter than 20 days or greater than 45 days in individuals 2 or more years after menarche are evidence of oligo-anovulation (Level B).

(2) A menstrual interval greater than 90 days is unusual even in the first year after menarche. As such, consecutive menstrual intervals greater than 90 days are rare and require further investigation regardless of years after menarche (Level B).

(3) Lack of onset of menses by age 15 years or by more than 2–3 years after thelarche regardless of chronologic age is statistically uncommon and warrants evaluation and consideration of diagnoses such as PCOS (Level B).

Question 4. What Are the Criteria for PCOM in an Adolescent Girl?

What Are the Ultrasonographic Criteria for a Polycystic Ovary?

What Are the Criteria for the Diagnosis of PCOM in Adults?

The association of polycystic ovaries with amenorrhea and hyperandrogenism was noted since the first clinical description of this entity. However, the inclusion of polycystic ovaries as a key diagnostic element of the syndrome has been controversial for adults. Using a transvaginal approach and 3D ultrasound examinations during the follicular phase of the menstrual cycle (cycle days 2–6), the Androgen Excess-PCOS Taskforce suggested that PCOM should be defined as follicle number per ovary >24 using transvaginal ultrasound imaging [79]. Moreover, a multifollicular pattern, which is defined by the presence of ≥6 somewhat larger follicles (4–10 mm) distributed across the ovary without increase in stromal tissue, should not be considered a pathological finding since it does not have a relationship with hyperandrogenism [18, 80, 81].

What Are the Criteria for PCOM in Adolescents?

The significance of ovarian morphologic findings in making a diagnosis of PCOS in adolescents is controversial due to physiological changes of the ovaries observed during the second decade of life and the high prevalence of this finding in adolescent girls. At the center of this controversy is the fact that the guidelines used to define PCOM overlap with the criteria for a multifollicular ovary especially when utilizing a transabdominal approach and follicle counts. The ovarian volume starts to increase with the onset of puberty, achieves maximum volume soon after (between menarche and age 16 years), and remains stable or decreases slightly thereafter [82–85]. Follicle number and size are also noted to increase with puberty, with a higher number of small follicles during adolescence and young adulthood and a decrease thereafter [84]. Isolated studies have also suggested the use of MRI or Doppler examination for the diagnosis of PCOM [85–88]. Dewailly et al. [79] concluded that, when using transabdominal ultrasonography, an ovarian volume >10 cm^3 should be used because follicle counts become unreliable with this methodology.

What Is the Prevalence of PCOM in Adolescents?

PCOM, variously defined, has been reported with a prevalence of 30–40% (range between 26 and 54%) and has been described in healthy girls [82]. Given this high prevalence of PCOM in nonhyperandrogenic girls, caution should be exercised when interpreting the ultrasound study to avoid generating unnecessary anxiety in the adolescent and her family. Hence, PCOM is an inconsistent finding and does not invariably predict the development of PCOS [82].

What Hormonal Findings Are Associated with Polycystic Ovaries?

The few reports that have evaluated the hormonal correlates of PCOM in healthy nonhirsute adolescents using transabdominal ultrasonography have found similar levels of androgens, insulin, and indexes of insulin sensitivity in girls with and without PCOM [80, 82]. PCOM has been related to birth weight; one study showed that hyperandrogenic girls with PCOM had higher birth weight and higher HOMA-IR [89].

Elevated anti-Müllerian hormone (AMH) levels have been a consistent hormonal finding associated with PCOM in healthy girls [90, 91]. AMH is produced by granulosa cells during the early stages of follicular development. AMH concentrations reflect the number of antral follicles and are often elevated in adult women with PCOS. Available data are inconsistent regarding the usefulness of AMH in the diagnosis of PCOS among adolescent girls [92–96].

Recommendations

(1) No compelling criteria to define PCOM have been established for adolescents. Until further research establishes definitive criteria, an ovarian volume >12.0 cm^3 (by formula for a prolate ellipsoid) can be considered en-

larged. Follicle counts should not be utilized to define PCOM in adolescents (Level B).

(2) Further, a multifollicular pattern, which is defined by the presence of large follicles distributed throughout the ovary, does not have a relationship with hyperandrogenism, is more common in adolescents, and should not be considered a pathological finding (Level C).

(3) Additionally, in healthy girls with regular menstrual cycles and without hyperandrogenism, PCOM does not indicate a diagnosis of PCOS (Level B).

(4) Abdominal ultrasound in adolescents, particularly obese girls, may yield inadequate information (Level C).

(5) AMH concentrations should not be used to characterize PCOM (Level B).

(6) Until better quality-consistent data are available, ovarian imaging can be deferred during the diagnostic evaluation for PCOS (Level C).

Question 5: What Diagnostic Procedures Are Appropriate in Adolescents to Exclude Other Causes of Hyperandrogenism and Amenorrhea?

All diagnostic criteria for PCOS include the proviso that other causes of androgen excess and amenorrhea have been excluded. The most frequent differential diagnosis is between PCOS and nonclassic forms of congenital adrenal hyperplasia (NCAH) because the phenotypic features are very similar [97, 98].

The most common form of CAH is 21-hydroxylase deficiency due to mutations in the *CYP21A2* gene. The reported prevalence for NCAH is 1 in 1,000 with an increased prevalence in specific ethnic groups [99]. Although rare, other disorders of steroidogenesis can be associated with a PCOS phenotype in adult women and premature pubarche in children [100, 101].

Cushing's syndrome, primary pigmented nodular adrenocortical disease, McCune-Albright syndrome, glucocorticoid resistance due to mutations in the glucocorticoid receptor gene, ovarian androgen-secreting tumors, thyroid dysfunction, hyperprolactinemia, and adrenal tumors can be associated with androgen excess [102–104]. Although adrenocortical tumors are rare in children, most present with clinical features due to excessive androgen secretion [105]. If androgen-secreting tumors are suspected, abdominal and pelvic ultrasounds should be used as first-line screening tests.

The approach to the differential diagnosis begins with a thorough medical history and physical examination. Bloodwork typically includes 17-hydroxyprogesterone (17-OHP), total testosterone, free testosterone, SHBG, androstenedione, and DHEAS. The clinical findings can guide additional hormone determinations such as thyroid function studies, gonadotropins, prolactin, and ACTH stimulation testing [97, 98]. For those with NCAH, ACTH-stimulated 17-OHP values usually exceed 1,500–10,000 ng/dl [106]. When molecular genetic testing is performed, mutations on both *CYP21A2* alleles are usually identified found when the stimulated 17-OHP exceeds 1,500 ng/dl [107].

Performing ACTH stimulation tests on all adolescent girls with suspected NCAH is not feasible. The use of follicular phase morning 17-OHP levels has been advocated. Morning 17-OHP values >200 ng/dl appear to detect most adult women with NCAH [108, 109]. Although morning 17-OHP concentrations (>200 ng/dl) have been reported as being more common in women with CAH (87%), over 20% of women with PCOS had elevated morning 17-OHP values [110]. Normal random 17-OHP values do not completely exclude the diagnosis of NCAH because the values may be normal when obtained later in the day. Genetic testing should not be used as the primary diagnostic tool for NCAH because of the complexity of the *CYP21A2* genetic locus [111].

Recommendations

(1) A thorough medical history, physical examination, and appropriate laboratory assessment are essential to provide the information necessary to exclude other disorders associated with androgen excess (Level A).

Question 6: What Is the Role of Insulin Resistance/Hyperinsulinemia in the Diagnosis of PCOS in Adolescents?

The high prevalence of insulin resistance and hyperinsulinemia among adolescent girls with PCOS is well recognized. Insulin resistance and hyperinsulinemia are intrinsic to PCOS in adults and adolescents, lean or obese. Hyperinsulinemia is believed to exacerbate the hyperandrogenism and the reproductive and metabolic manifestations of PCOS in adolescents. With the exception of one published recommendation, none of the current definitions of PCOS in adolescent or adult women include insulin resistance/hyperinsulinemia as a diagnostic criterion [1, 10–12, 18, 19, 112]. Rather insulin resistance and hyperinsulinemia should be viewed as warnings to investigate and treat comorbidities associated with PCOS such as pre-diabetes or type 2 diabetes (T2D).

Fasting insulin and 24-hour insulin concentrations as well as stimulated insulin responses to intravenous glucose are elevated in adolescent girls at risk for PCOS even after adjusting for BMI [113]. The insulin resistance of PCOS is inherent to the syndrome and is over and above that conferred by obesity, since obese adolescents at risk for PCOS had a 50% lower in vivo peripheral insulin sensitivity when measured by the hyperinsulinemic-euglycemic clamp and compared with BMI-, body composition-, and visceral adiposity-matched obese peers [114]. This insulin resistance is compensated by an increased insulin secretion [114]. Some nonobese adolescents with ovarian androgen excess and a history of premature pubarche and those with low birth weight and exaggerated adrenarche are also reported to have hyperinsulinemia and decreased IGFBP-1 starting in prepubertal years and during puberty [115–118]. In most patients, clinical features suggest insulin resistance. Thus, the measurement of fasting glucose-to-insulin ratios, i.e., HOMA, or the performance of a standard oral glucose tolerance test will suffice to establish hyperinsulinemia/insulin resistance [119]. Accordingly, clamp studies should be performed only in the research setting.

Overweight and obesity are common findings among adolescent girls with PCOS particularly in the US population [120]. The weight has an android distribution, and even nonobese adolescents with PCOS are reported to have twice as much abdominal fat as the reference population [121, 122]. Metabolic disturbances associated with insulin resistance such as the metabolic syndrome, impaired glucose tolerance, and type 2 diabetes are reported to occur at a relatively higher prevalence among obese adolescents with PCOS. This prevalence was independent of obesity in some studies but not in others [121–129].

There is increasing evidence for a link between insulin resistance/hyperinsulinemia and the androgen excess in adolescents with PCOS. In vitro and in vivo data in adults indicate that hyperinsulinemia plays an important role in ovarian androgen production [130, 131]. Observations suggesting that insulin resistance and/or hyperinsulinemia may be factors in the development of hyperandrogenism in adolescence include: (1) a population-based study from Australia of adolescents considered to have PCOS in which increased free testosterone concentration was the factor most predictive of insulin resistance, while menstrual irregularities and polycystic ovaries were not associated with insulin resistance [127]; (2) hCG-stimulated testosterone concentration was increased in the presence of insulin resistance/hyperinsulinism [132]; (3) weight loss, treatment with metformin, or treatment with rosiglitazone were associated with improved insulin sensitivity and attenuation of hyperandrogenemia in some studies [133–137]; and (4) among nonobese Catalan adolescents with a history of premature pubarche, exaggerated adrenarche, and low birth weight, treatment with metformin or rosiglitazone, either prior to puberty or during adolescence, was reported to attenuate hyperandrogenism [138]. Fetal growth restriction and low birth weight – conditions that increase the predisposition to insulin resistance – are reported to be associated with hyperandrogenemia in adolescents in some but not all studies [116, 139, 140]. Rapid postnatal catch-up growth and adiposity seem to increase the risk of excessive androgen secretion and precocious pubarche with a higher predilection to develop features suggestive of PCOS in adolescence [4, 140, 141]. Lastly, intractable childhood obesity with insulin resistance/hyperinsulinemia is reported as a precursor of PCOS in some adolescents [9, 142–145].

Recommendations

(1) Although prevalent among adolescents at risk for PCOS, insulin resistance and hyperinsulinemia should not be utilized as diagnostic criteria (Level B).

(2) Insulin resistance and hyperinsulinemia can be considered as indications to investigate and treat potential comorbidities (Level B).

Question 7: Does a Diagnosis of PCOS during Adolescence Provide an Opportunity for Meaningful Intervention? What Are the Risks of Overdiagnosis?

A timely diagnosis of PCOS leads to awareness of this lifelong condition associated with hormonal and possibly metabolic complications and provides an opportunity for meaningful intervention, e.g., healthy lifestyle counseling, testing for comorbidities, or medications [9, 146, 147]. Testing for comorbidities can include fasting glucose, fasting insulin, and lipid concentrations. For girls with polydipsia, polyuria, acanthosis nigricans, or obesity, consideration may be given to assessing glucose tolerance with an oral glucose tolerance test. Signs and symptoms suggestive of depression should prompt a referral for behavioral health evaluation.

Intervention trials in adolescents with PCOS have shown benefits with respect to decreased androgen levels [89, 148–151]. These trials have also shown improvements related to hirsutism, ovulation, quality of life, sleep, lipid profile, adipocytokine levels, and insulin resistance [148–160]. However, most trials have been limited by their short

duration (less than 6 months). Adequately powered, randomized, double blind, placebo-controlled trials are lacking. Longer duration trials (12 months or more) are very limited and are either open-labelled trials or lack placebo-controlled arms [133, 135, 161–163]. Fortunately, meta-analyses have shown that medications commonly used in the management of women and adolescents with PCOS have a low risk of severe adverse effects [160].

On the other hand, overdiagnosis of PCOS can lead to unnecessary labeling and unwarranted interventions. A diagnosis of PCOS can impact an adolescent's quality of life; this diagnosis can create early and unwarranted anxiety about future fertility for the young women and her family. It is crucial to re-evaluate all adolescents with features suggestive of PCOS. Overdiagnosis can also lead to an overuse of treatments such as metformin and oral contraceptive pills. There has been a steady increase in prescribing metformin over the last 10 years particularly in obese adolescent girls between 16 and 18 years, despite metformin being 'off-label' or unlicensed in many countries for the treatment of PCOS or obesity [162, 163].

Recommendations

(1) A timely diagnosis of PCOS in symptomatic adolescent girls is important for the initiation of appropriate screening and treatment (Level A).

(2) Validated diagnostic criteria supported by robust clinical and hormonal findings are needed to avoid overdiagnosis and unnecessary treatment in otherwise healthy normal girls without hyperandrogenism (Level C).

(3) Research evaluating long-term interventions using high-quality RCTs and lifelong follow-up of girls with PCOS diagnosed during adolescence would be ideal (Level C).

Summary

This paper represents the consensus of pediatric endocrine and adolescent medicine experts representing professional organizations dedicated to the care of adolescents and young women with disorders of androgen excess. PCOS is a common heterogeneous phenotype with features overlapping some features characteristic of normal pubertal development. The clinician needs to carefully balance the risks and benefits of labeling an adolescent girl as having PCOS versus simply stating that the diagnosis of this disorder cannot be confirmed during the adolescent years. Most importantly, the levels of evidence supporting our recommendations are largely clinical studies or expert opinion. Thus, there is clearly a need for careful prospective clinical investigations to better define the diagnostic criteria and most effective treatments for adolescent girls with PCOS.

Summary Recommendations

(1) The overlap between normal pubertal development and characteristic features of PCOS may confound an accurate diagnosis of PCOS among adolescent girls (Level A).

(2) Other disorders associated with irregular menses or hyperandrogenism need to be excluded from diagnostic consideration (Level A).

(3) Great caution should be taken before diagnosing PCOS in adolescent girls with clinical features of androgen excess such as hirsutism and biochemical hyperandrogenism if oligomenorrhea has not persisted for more than 2 years. These girls can be considered to be at risk for PCOS. To avoid misdiagnosing physiological pubertal changes as PCOS, deferred diagnostic labeling accompanied by frequent longitudinal re-evaluations of these girls considered to be at risk for PCOS is beneficial and prudent during adolescence (Level C).

(4) Even in the absence of a definitive diagnosis and the lack of an approved therapy for PCOS in adolescence, treatment options that both alleviate the current symptoms and decrease the risk for subsequent associated comorbidities are recommended (Level B).

(5) Although obesity, insulin resistance, and hyperinsulinemia are common findings in adolescents with hyperandrogenism, these features should not be used to diagnose PCOS among adolescent girls (Level A).

(6) Prospective longitudinal research studies will be helpful to understand the natural history for girls considered to be at risk for PCOS. Research evaluating long-term interventions using high-quality RCTs and follow-up of girls with PCOS diagnosed during adolescence would be ideal. Through such research studies, it is hoped that validated diagnostic criteria supported by robust clinical and hormonal findings can be established to facilitate timely diagnosis while preventing overdiagnosis and unnecessary treatment in otherwise healthy normal pubertal girls (Level C).

Appendix

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