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Diagnosis and Challenges of Polycystic Ovary Syndrome in Adolescence

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Abstract

Although the diagnostic criteria for polycystic ovary syndrome (PCOS) have become less stringent over the years, determination of the minimum diagnostic features in adolescents is still an area of controversy. Of particular concern is that many of the features considered to be diagnostic for PCOS may evolve over time and change during the first few years after menarche. Nonetheless, attempts to define young women who may be at risk for development of PCOS is pertinent since associated morbidity such as obesity, insulin resistance, and dyslipidemia may benefit from early intervention. The relative utility of diagnostic tools such as persistence of anovulatory cycles, hyperandrogenemia, hyperandrogenism (hirsutism, acne, or alopecia), or ovarian findings on ultrasound is not established in adolescents. Some suggest that even using the strictest criteria, the diagnosis of PCOS may not valid in adolescents younger than 18 years. In addition, evidence does not necessarily support that lack of treatment of PCOS in younger adolescents will result in untoward outcomes since features consistent with PCOS often resolve with time. The presented data will help determine if it is possible to establish firm criteria which may be used to reliably diagnose PCOS in adolescents.

Keywords

- polycystic ovary syndrome
- polycystic ovarian morphology
- type 2 diabetes mellitus

Polycystic ovary syndrome (PCOS) is a common endocrinopathy that by strictest definition affects 5 to 10% of women of reproductive age.[1] It is characterized by menstrual irregularity, hyperandrogenism, and polycystic ovarian morphology (PCOM) and is also associated with insulin resistance, obesity, and components of the metabolic syndrome (MetS).[2,3] PCOS often presents during adolescence, but the diagnosis in this age group is complicated by the overlap between the features of PCOS and physiologic findings observed during the normal progression of puberty.[4] Further, the diagnosis is difficult to make with certainty given the absence of universally accepted diagnostic criteria for adolescents.

Three distinct sets of diagnostic criteria have been suggested for the diagnosis of PCOS in adults. The National Institutes of Health Consensus Statement[1] proposed that PCOS be defined as menstrual irregularity (chronic anovulation or oligomenorrhea) and evidence of clinical or biochemical hyperandrogenism with the exclusion of other etiologies. The 2003 European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam criteria (ESHRE/ASRM)[5] broadened the diagnosis of PCOS, requiring two of three features: anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries by ultrasound (US). Finally, the Androgen Excess and PCOS Society[6] defined PCOS as hyperandrogenism with ovarian dysfunction or polycystic ovaries. Most recently, the NIH Evidence-Based Methodology Workshop on PCOS[3] recommended use of the 2003 Rotterdam criteria with identification of specific phenotypes within the diagnosis.

As stated, at present there is not a total agreement regarding definitive criteria for the diagnosis of PCOS in adolescents. We reviewed 73 papers published since 2006 where adolescents with PCOS were described (►**Table 1**).[7–79] Of interest, 22 studies used NIH, 42 used Rotterdam, and 8 used Androgen Excess Society (AES) or other criteria to

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Table 1 Review of diagnosis of PCOS in adolescents (2006–2013)[7–79]

• Number of studies: 69; case reports: 4
• Criteria used[a]
– NIH 22
– Rotterdam 42
– AES/other 8
– Not specified 7
• Nationality
– USA 30, Canada 1, Chile 2, France 1, Italy 4, Spain 2, Finland 1, Germany 2, England 1, Poland 1, Tunisia 1, India 7, Greece 2, Turkey 3, Iran 2, Saudi Arabia 1, China 5, Taiwan 1, Hong Kong 1, Korea 1, Australia 3, New Zealand 1
• Study size: 1–1,563 subjects
• Mean age of subjects
– 15.1–29.1 y: 64 studies
– < 25 y: 62 studies
• Time since menarche: 0.5–5 y (22/73 data available)

Abbreviations: AES, Androgen Excess Society; NIH, National Institute of Health, PCOS, polycystic ovary syndrome.
[a]Five of the above mentioned articles used multiple criteria.

diagnose PCOS, some using more than 1. Seven of the studies reviewed did not specify any diagnostic criteria used. Of these studies, 31 were from North America, 21 were from Asia, 14 were from Europe, 1 was from Africa, and 3 were from Australia and New Zealand. Only 22 of the studies mentioned number of years postmenarche of the subjects.

Further, the variability of diagnoses in and of PCOS poses various challenges. Use of different criteria can result in a different prevalence of PCOS, even within the same cohort.[43,44] Clearly, while early diagnosis in adolescents may allow for earlier treatment and prevention of PCOS-associated morbidity, premature diagnosis carries risks of psychological distress and unnecessary treatment.

Numerous studies have called into question the appropriateness of applying adult criteria to adolescents because the features of PCOS are often physiologic or transitory during normal puberty.[80,81] Thus, several adolescent-specific criteria have been proposed. Sultan and Paris[82] suggests requiring four out of five of the following: oligomenorrhea or amenorrhea at least 2 years postmenarche, clinical hyperandrogenism, biologic hyperandrogenism, insulin resistance, and polycystic ovary morphology, while Carmina et al[80] and the 2012 ESHRE/ASRM Consensus Workshop Group[83] propose defining PCOS in adolescents by the presence of all three of the 2003 ESHRE/ASRM criteria: hyperandrogenism, chronic anovulation, and polycystic ovaries.

This review will discuss the components utilized by the many suggested criteria to allow one to establish the diagnosis of PCOS in adolescents as well as the ongoing challenge and controversy related to this goal.

Hyperandrogenism

Hyperandrogenism is a hallmark of PCOS; the NIH and AES criteria both require clinical and/or biochemical hyperandrogenism for the diagnosis of PCOS in adults, while the Rotterdam criteria recognize a phenotype of PCOS without androgen excess.[1,5,6] This feature of PCOS is especially important given its reported association with metabolic dysfunction.[21,29,35] However, the physiologic rise in androgens that occurs during puberty makes hyperandrogenism difficult to define in adolescents. Furthermore, there is not yet a consensus regarding the preferred assay or reference values for assessing hyperandrogenemia in this age group.[84]

Clinical hyperandrogenism is defined by most adult PCOS diagnostic criteria as the presence of hirsutism, acne, or androgenic alopecia.[1,5] Hirsutism, as measured by the modified Ferriman-Gallwey (mFG) score, is recognized as the most reliable marker of clinical hyperandrogenism in women with PCOS.[83] In Caucasian and African American women, an mFG score of ≥ 8 is often used to define hirsutism in the diagnosis of PCOS,[70] and this cutoff has been used by numerous studies of PCOS in adolescents.[44] However, because of less cumulative time of exposure to androgens, this cutoff may require modification for use in adolescents.[85] In addition, expression of hirsutism in and of itself appears to have ethnic variability.[86,87]

Roe et al[70] recently reported that 65% of adolescents with PCOS presented with hirsutism, which is consistent with other studies that report a high prevalence.[40] The common finding of acne in healthy adolescents, which is as high as 69%,[44] precludes its utility as a specific marker of hyperandrogenism in PCOS. Hickey et al[44] found no relationship between acne score and free testosterone (T) level or PCOM. Finally, androgenic alopecia has not been studied widely in adolescents and does not appear to be important for the assessment of hyperandrogenism in this population.[88] Of the three markers of clinical hyperandrogenism, progressive hirsutism is considered the most useful in adolescents.[80,88]

Biochemical hyperandrogenism, a more objective measure of excess androgens, can be assessed using a variety of assays to test for serum levels of total testosterone (TT), free T, androstenedione, and dehydroepiandrosterone sulfate. The adult PCOS criteria provide little consensus and guidance as to which assay to use, albeit use of highly specific assays is increasingly being recommended.[89]

The 2007 Endocrine Society position statement about the utility, limitations, and pitfalls of measuring T[84] does not specifically discuss androgens in adolescents, but suggests the use of TT assays, as opposed to free T, when measuring androgens in children. The position statement also suggests the use of T assays that use extraction and chromatography techniques, instead of direct immunoassays, to maximize sensitivity and accuracy and also stresses the need for standardized assay-specific reference values. Because of diurnal and menstrual cycle variation of T, for consistency it is recommended to be measured between 08:00 and 10:00 hours during the follicular phase.[84]

More recently, liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been studied as a technique for measuring total T in adults[90,91] and adolescents.[92,93] Two groups[92,93] recently developed reference ranges for total T in adolescents using LC-MS/MS and determined this method to be sufficiently sensitive and precise to be used in adolescents. Both groups measured T between 8:00 and 10:00 AM, and one made separate cutoffs based on menstrual cycle phase. However, a comparison of radioimmunoassay and LC-MS/MS measurement of TT in women did not find a significant difference between the results of the two methods although "there is significant variability between LC/MS assays and poor precision with all assays at low T levels."[89]

Thus, while hirsutism appears to be an important clinical marker of hyperandrogenism in adolescents, and a common presenting sign of PCOS, some have argued that biochemical hyperandrogenism is a more reliable and consistent marker of hyperandrogenism in the diagnosis of PCOS in adolescents.[4,5] Both should be evaluated in the workup of an adolescent with suspected PCOS.

Menstrual Irregularity

Menstrual irregularity is an important feature of PCOS in adults and common in the presentation of PCOS in adolescents.[70] Chronic oligo-ovulation or anovulation are included in all adult diagnostic criteria for PCOS. However, menstrual irregularity and anovulation are common among healthy adolescents, making their use in the diagnosis of PCOS in this group difficult.

In a study of 200 healthy girls, Apter and Vikho[94] found that at least 55% of menstrual cycles were anovulatory during the first 2 years postmenarche. The percentage of ovulatory cycles increased with age, reaching 80% at 4 to 5.5 years of gynecological age. While menstrual irregularity is common, its persistence after 2 years after menarche is associated with PCOS. Nair et al[51] studied a cohort of 136 adolescent girls with confirmed menstrual irregularity; at 2 year follow-up, 51.5% continued to have menstrual irregularity and 36% were diagnosed with PCOS using the Rotterdam criteria. In their cohort, Roe et al[70] found that 98% of adolescents diagnosed with PCOS by the AE-PCOS criteria presented with menstrual irregularity—68.3% with oligomenorrhea, 27.7% with secondary amenorrhea, and 4% with primary amenorrhea.

There is evidence that greater menstrual irregularity is associated with a more severe PCOS phenotype and higher androgen levels.[5] Rachmiel et al[30] reported that adolescents with primary amenorrhea and PCOS have increased features of MetS and higher androstenedione compared with those with oligomenorrhea. A study of a Finnish cohort found that adolescent girls with menstrual irregularity had increased T, decreased sex hormone binding globulin, and an increased free androgen index.[54] van Hooff et al found that about half of 14 to 16 year olds with oligomenorrhea remained oligomenorrheic at 18 years; body mass index (BMI) and menstrual history, but not androgen and luteinizing hormone concentrations, were predictive of persistent amenorrhea.[95]

Although it is often difficult to distinguish physiologic adolescent anovulation from PCOS-related menstrual irregularity,[96] some have offered suggestions for how menstrual irregularity should be defined in adolescents and when it should be evaluated. Merino et al[88] suggested that adolescent ovulatory dysfunction should be considered with the absence of menstrual periods for longer than 90 days, or persistent cycles longer than 45 days. Rosenfield suggested evaluation for menstrual irregularity when adolescents exhibit abnormal menstruation for at least 1 year or if it is associated with other signs and symptoms.[96]

The high prevalence of anovulatory cycles and menstrual irregularity in adolescence has led some to recommend that oligoamenorrhea should persist for at least 2 years and that only then can PCOS be diagnosed in adolescents who are at least 2 years postmenarche.[5,40,80] Advocates of this proposal state that because of the high frequency of menstrual irregularity in healthy adolescent girls, the diagnosis of PCOS in adolescents should not be made on the basis of menstrual irregularity alone.[80,97]

It is interesting to speculate that although dysfunctional intermittent uterine bleeding in adolescents can be confused with normal cycling with long interval cycles, in fact, it may be that these adolescents are actually those who already have evidence of chronic anovulation. In addition, some authors suggest that measurement of progesterone is the most specific way to assess ovulation[98]; however this is usually impractical in a clinical setting.

Ovarian Morphology

PCOM is included in both the AES-PCOS and Rotterdam diagnostic criteria for PCOS, which define PCOM as 12 or more follicles of 2 to 9 mm or ovarian volume $> 10\ cm^3$ in at least one ovary.[5] Recently Dewailly et al actually suggested that the former threshold of greater than 12 follicles per ovary may even be too low and a count of 19 follicles would be needed for more accurate diagnosis.[99] In adults, transvaginal US is the standard imaging method used to evaluate ovarian morphology, however because it is inappropriate for use in virginal adolescents, transabdominal US (TA-US) is instead often used in younger patients. Polycystic ovaries are a common finding in healthy adolescents, making the use of PCOM as a diagnostic criterion for PCOS in adolescents difficult.[81]

Mortensen et al[9] reported that 54% of healthy eumenorrheic girls between 1.3 and 3.8 years postmenarche had polycystic ovaries on TA-US, with a significant correlation between ovarian size and gynecological age. This correlation between increasing age and decreasing ovarian volume has also been found in adults.[100] Several other studies of healthy adolescents found the incidence of PCO to be 33 to 35% by TA-US.[43,44,101] While up to half of healthy adolescents meet PCO criteria, a third of adolescents with PCOS do not.[96]

Furthermore, the limitations of TA-US present a challenge in using PCOM in the diagnostic criteria for adolescents. This method is less discriminating than transvaginal US and especially difficult to use in obese patients, who make up

about half of the PCOS population.[97] Transrectal US and magnetic resonance imaging (MRI) have been used in a few studies, but these methods may be less practical in a clinical setting.[97,102]

Several authors have argued for the need for adolescent-specific thresholds for mean ovarian volume (MOV) for use in the diagnosis of PCOS. New thresholds have been suggested by groups using different imaging modalities. Villa et al[53] found that a MOV threshold of 5.6 mL was 89% sensitive and 80% specific for diagnosing PCOS using TA-US, while Chen et al[103] reported that a cutoff of 6.74 mL maximized specificity and sensitivity in Chinese adolescents using transvaginal US. Another study found an average MOV of 15.1 in adolescents with PCOS compared with 5.9 in healthy controls using MRI. In a comparison of TA-US and MRI in 11 obese adolescents with PCOS, Yoo et al found that MOV was not significantly different between the two methods, but that the number of patients who met Rotterdam criteria for PCO was different between the US and MRI groups.[104]

The limitations of using US for the detection of PCO have led to interest in anti-Müllerian hormone (AMH) as a surrogate marker. AMH is a glycoprotein secreted by granulosa cells of growing follicles and has been found to correlate with the number of small antral follicles.[88] However, reports about the utility of AMH as a marker for PCO in adolescents have been mixed. Hart et al[36] found that while serum AMH is significantly higher in adolescents girls with PCO, AMH level had insufficient specificity and sensitivity for detecting PCO. Villarroel et al,[101] who studied adolescents with regular menstrual cycles, and Li et al,[39] who studied Chinese adolescents with PCOS, developed similar cutoffs for AMH to predict PCO with sensitivities of 64 and 61% and specificities of 89.8 and 70%, respectively. Eilertsen et al[105] reported that serum AMH has good accuracy for diagnosing PCOS in adults when it replaces PCOM as a criterion for PCOS diagnosis. Although more work remains to assess the use of AMH as a surrogate marker for PCO, it may prove useful as a component to aid in the diagnosis of PCOS.

Obesity, Insulin Resistance, and Metabolic Syndrome

PCOS is associated with metabolic abnormalities including insulin resistance, obesity, type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease, dyslipidemia, and the MetS.[2,4,106] There is evidence that these metabolic impairments begin as early as adolescence in women with PCOS. Although metabolic features are not included in the diagnostic criteria for PCOS, they are important to consider in adolescents given their implications on long-term health. At present, the molecular mechanisms responsible for the interactions between hyperandrogenism, obesity, and insulin resistance in PCOS are not fully understood.

Obesity is common in both adults and adolescents with PCOS. It is unclear whether PCOS predisposes women to obesity or whether obesity exacerbates PCOS.[107] Several studies show the prevalence of obesity in PCOS to be above 60%[108]; Glueck et al found that 73% of adolescents with PCOS had a BMI above the 95th percentile.[109]

While a large portion of adolescents with PCOS are obese, obesity likely does not fully explain the other metabolic features associated with PCOS. Impaired glucose tolerance (IGT), which is associated with insulin resistance and is a strong predictor for T2DM, cardiovascular disease, and premature mortality,[110] is found at an increased rate in adolescents with PCOS. Several studies of adolescents with PCOS have reported the incidence of IGT to be 10 to 30%.[34,37,79,111] Flannery et al[79] found that IGT occurred across the spectrum of BMI and Huang et al[37] found that when matched for obesity, PCOS is associated with increased risk for insulin resistance, hyperinsulinemia, and prediabetes. However, Hart et al[43] found that PCOS was not associated with insulin resistance after controlling for BMI, and Glueck et al found that when matched for age, PCOS subjects did not have significantly different insulin or lipid levels than healthy controls.[109] While IGT is the most common form of abnormal glucose metabolism found in adolescents with PCOS, impaired fasting glucose and T2DM have also been reported in this group.[1,56,79]

MetS, a group of risk factors that increase the risk for cardiovascular disease and diabetes, is also associated with PCOS. Up to 40% of adults with PCOS have MetS.[34] In adolescents, multiple sets of criteria are used to define MetS and the prevalence of MetS varies among different cohorts. Most studies, however, report an increased incidence of MetS in PCOS compared with control subjects.[21,41,52,70] Coviello et al[21] found that 35% of girls with PCOS had MetS compared with 5% of controls and that this difference could not be accounted for by obesity alone. The reported prevalence in other studies ranges from 10 to 60%.[41,52,70] Gleuck et al[109] found that a diagnosis of PCOS at age 14 was a significant independent determinant for MetS at age 24. However, in a cohort that included only obese and overweight participants, Rossi et al[34] reported that the prevalence of MetS did not differ significantly between PCOS and controls when matched for obesity, regardless of the definition of MetS used. Similarly, Huang et al[37] found that PCOS was not associated with an increased risk for MetS when matched for obesity in a Chinese adolescent cohort.

It has been proposed that the hyperandrogenism associated with PCOS contributes to the metabolic abnormalities discussed above. Fruzzetti et al[35] reported that hyperandrogenemia was an important risk factor for lipid alterations in adolescents with PCOS. Another study[21] found higher levels of free T in adolescents with MetS and reported that levels of the hormone were positively correlated with BMI percentile, waist circumference, and fasting insulin. Elevated systolic and diastolic blood pressures have also been shown to be related to androgen levels in girls with PCOS.[21,29] In a large prospective study of schoolgirls, Glueck et al[109] reported that low sex hormone-binding globulin was the only significant predictor of MetS and that women with MetS at 24 years of age were more likely to have had a top decile free T at age 14. However, Forrester-Dumont et al[50] found that metabolic profile was not affected by the degree of hyperandrogenism in girls with PCOS, instead, low HDL best explained the high prevalence of MetS. While most studies agree that obesity and MetS occur

more frequently in adolescents with PCOS compared with the general population, the role of hyperandrogenism in this association remains controversial.

This review will not focus on therapy, however many clinical investigators still suggest that weight loss and lifestyle changes should be the first line of therapy. Metformin and oral contraceptive pills are also considered as secondary treatments that can improve the symptoms of PCOS. However, medical treatment of a condition not fully diagnosed can result in premature use of pharmacologic agents. The issue of treatment of PCOS in the adolescent further underlines the need for consensus and further research about the diagnosis of PCOS in this group. The many points of overlap between physiologic puberty and the features of PCOS may continue to suggest that a more conservative approach to the diagnosis of PCOS in adolescents compared with adults is prudent.

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