A rational approach to the diagnosis of polycystic ovarian syndrome during adolescence

Uma abordagem racional do diagnóstico da síndrome dos ovários policísticos na adolescência

Paulina M. Merino¹,², Ethel Codner¹, Fernando Cassorla¹

SUMMARY

Polycystic ovarian syndrome (PCOS) is a lifelong disorder characterized by hyperandrogenism and ovulatory dysfunction, with a wide spectrum of clinical symptoms and signs. Three different sets of diagnostic criteria have been established in order to define this disease in adult women, but there is controversy regarding the use of these criteria in adolescence. During puberty, the adult criteria for ovulatory dysfunction does not seem applicable, because an irregular menstrual pattern and a decreased ovulatory rate is a physiologic event during this period of life. Also, a higher prevalence of polycystic ovarian morphology (PCOM) may be observed during this period, so PCOM is not a useful criterion to define PCOS in young women. These findings suggest that a key factor to diagnose PCOS during adolescence is hyperandrogenism. In addition, since PCOM is not clearly associated with hyperandrogenism during this period of life, the term “polycystic ovarian syndrome” during adolescence creates confusion and may be misleading.

Keywords
Hyperandrogenism; hirsutism; polycystic ovarian syndrome; adolescence; diagnosis; puberty; polycystic ovarian morphology; menstrual irregularities; anti-Müllerian hormone

SUMÁRIO

A síndrome dos ovários policísticos (SOP) é uma desordem que afeta pacientes por toda a vida e é caracterizada por hiperandrogenismo e disfunção ovariana, com um amplo leque de sintomas e sinais clínicos. Três diferentes conjuntos de critérios diagnósticos foram estabelecidos para definir essa doença em mulheres adultas, mas existem controvérsias relacionadas ao uso desses critérios na adolescência. Durante a puberdade, o critério de disfunção ovariana usado em adultos não parece aplicável, porque um padrão menstrual irregular e uma menor taxa de ovulação são eventos fisiológicos nesse período da vida. Além disso, uma maior prevalência de morfologia ovariana policística (MOP) pode ser observada nesse período, de forma que a MOP não é um critério útil para se definir a SOP em mulheres jovens. Esses achados sugerem que o hiperandrogenismo é um fator-chave para o diagnóstico da SOP na adolescência. Além disso, como a MOP não está claramente associada com o hiperandrogenismo durante esse período da vida, o termo “síndrome dos ovários policísticos” durante a adolescência cria confusão e pode ser errôneo.

Descritores
Hiperandrogenismo; hirsutismo; síndrome dos ovários policísticos; adolescência; diagnóstico; puberdade; morfologia ovariana policística; irregularidades menstruais; hormônio antiMülleriano
INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine and metabolic disorder that affects 5% to 7% of women in reproductive age (1). It is a lifelong disorder with different clinical manifestations across the lifespan, but it is often diagnosed during late adolescence, with anovulation and hyperandrogenism. The prevalence of this disorder during adolescence has not been established, because the symptoms and signs that define this condition often overlap with the physiological changes of the reproductive axis that occur in normal girls during this period (2,3).

We will review the three sets of diagnostic criteria of PCOS, which have been developed for adult women, and we will discuss whether these criteria are applicable to adolescent girls.

DEFINITION

The first description of PCOS was made by Irving Stein and Michael Leventhal in 1935, who described 7 adult women with amenorrhea, hirsutism, obesity and ovaries with “bilateral cystic degeneration” (4). The presence of this ovarian pattern was central in the initial description of these patients and led to the name of the syndrome, but it was later found that other patients with more subtle forms of PCOS, exhibit variable clinical and laboratory findings. The heterogeneity of PCOS has led to multiple groups of experts trying to establish a better definition, based on solid scientific evidence and useful from a clinical point of view (Table 1).

During the last 20 years, three separate groups of experts have established three different sets of diagnostic criteria, based in the presence of ovulatory dysfunction, clinical and biochemical hyperandrogenism, and ultrasonographic features of polycystic ovaries as diagnostic elements. The presence of clinical or biochemical hyperandrogenism, is required by two of the three existing classifications in order to make the diagnosis of PCOS.

The first attempt to reach a consensus on the definition of PCOS was made by the National Institutes of Health (NIH), in the United States, which in 1990 organized a meeting of experts to establish the diagnostic criteria for this syndrome (5). At this conference, a questionnaire was sent to a large number of experts in order to define their diagnostic criteria for PCOS. The meeting involved 58 researchers, and PCOS was defined by those criteria with at least 40% agreement. The survey showed that hyperandrogenemia was mentioned by 64% of the participants, the exclusion of other conditions by 60%, menstrual dysfunction by 52% and clinical hyperandrogenism (HA) by 48% of the experts. Following these results, the consensus reached by the NIH concluded that PCOS should be defined as a clinical disorder characterized by clinical and/or biochemical hyperandrogenism associated with a menstrual disorder, and that to make an accurate diagnosis, other conditions such as Cushing syndrome, congenital adrenal hyperplasia and hyperprolactinemia should be excluded (5).

These criteria were used to diagnose PCOS primarily in the United States, because European experts rejected the exclusion of ultrasound as a diagnostic criteria. Thus, in 2003, a meeting of experts sponsored by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine met in the city of Rotterdam to review the available data regarding the diagnosis of PCOS in adult women.

This panel of experts introduced the concept that polycystic ovarian morphology (PCOM) detected by ultrasound should be considered as a diagnostic criterion, thus broadening the clinical spectrum of PCOS. The Rotterdam consensus defined PCOS as patients who met two of three criteria: clinical or biochemical hyperandrogenism, oligo-anovulation and PCOM. This definition added two new phenotypes to those described by the NIH Consensus: women with anovulation and PCOM without hyperandrogenism or hyperandrogenism, and PCOM with normal ovulatory cycles. The diagnosis of PCOS, however, in the latter group of patients who do not have hyperandrogenism, has led to significant controversy among endocrinologists (6).

Because of these difficulties in the diagnosis of PCOS, the Androgen Excess Society (AES) decided to appoint an expert panel to review the literature using criteria derived from “evidence-based medicine”. This panel of experts assessed the literature regarding the possible association of different phenotypes of PCOS with long-term morbidity. This consensus, which differs in the survey methodology employed by the NIH or by the meeting of experts in Rotterdam, observed that only the patients with clinical and/or biochemical hyperandrogenism have increased long-term metabolic and cardiovascular risk, and that therefore the diagnosis
of PCOS in adult women requires the presence of hyperandrogenism. The AES published in 2006 these new diagnostic criteria that require the obligatory presence of hyperandrogenism, with either PCOM or oligo/anovulation in order to make the diagnosis of PCOS (Table 1) (7,8). The three classifications of PCOS, which have been developed for adults, are consistent in that neither the presence of insulin resistance, nor increased LH/FSH concentrations, nor the presence of excess weight or obesity are diagnostic elements of PCOS. Also, all definitions agree on the need to exclude other conditions that could mimic this syndrome (8).

CRITERIA TO DIAGNOSE PCOS IN THE ADOLESCENT GIRL

The three different sets of diagnostic criteria established to define PCOS are based in studies performed in adult patients. During adolescence, many features of this syndrome can also be observed in normal girls as physiological stages related to the maturation of the hypothalamus-pituitary-ovarian axis.

Ovulatory or menstrual dysfunction

Oligomenorrhea in adult women is defined as the presence of less than 9 menstrual periods per year, or 3 cycles greater than 38 days during the past year, and amenorrhea is defined as cycles over 90 days (9). However, the presence of regular menstrual cycles in women with hyperandrogenism does not ensure the presence of ovulation, since 40% of these women have oligo-anovulation when laboratory tests are performed. Thus, the AES and Rotterdam groups suggested that ovulatory dysfunction in adult women must be documented by the measurement of progesterone on days 20 to 24 of the menstrual cycle. In adolescence, menstrual cycles are frequently longer, and anovulation is physiological, thus complicating the use of this criteria.

Table 1. Diagnostic criteria for PCOS according to different published definitions. Modified from Ethel Codner and Héctor F. Escobar-Morreale. Hyperandrogenism and polycystic ovary syndrome in women with Type 1 diabetes mellitus. J Clin Endocrinol Metab. 2007;92:1209-16.

<table>
<thead>
<tr>
<th>Definition/year</th>
<th>Diagnostic criteria</th>
<th>Possible phenotypes</th>
<th>Exclusion criteria</th>
<th>Clinical hyperandrogenism</th>
<th>Biochemical hyperandrogenism</th>
<th>PCOM</th>
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<td>NIH/1990</td>
<td>Requires the simultaneous presence of: 1) clinical and/or biochemical hyperandrogenism, and 2) menstrual dysfunction</td>
<td>1) Clinical and/or biochemical hyperandrogenism + menstrual dysfunction</td>
<td>Congenital adrenal hyperplasia, androgen secreting tumors, Cushing’s syndrome, hyperprolactinemia</td>
<td>Hirsutism, alopecia, acne</td>
<td>1) Total testosterone, 2) Free testosterone, 3) Androstenedione, 4) DHEAS</td>
<td>Not included</td>
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<td>Rotterdam/2003</td>
<td>Requires the presence of at least 2 criteria: 1) clinical and/or biochemical hyperandrogenism, 2) menstrual dysfunction, and 3) PCOM</td>
<td>1) Clinical and/or biochemical hyperandrogenism + oligoanovulation, 2) Clinical and/or biochemical hyperandrogenism + oligoanovulation + PCOM, 3) Clinical and/or biochemical hyperandrogenism +PCOM, 4) PCOM + oligoanovulation</td>
<td>Congenital adrenal hyperplasia, androgen secreting tumors, Cushing’s syndrome</td>
<td>Hirsutism, acne and androgenic alopecia?</td>
<td>1) Total testosterone, 2) Free androgen index or free testosterone, 3) DHEAS</td>
<td>At least one ovary with: 1) 12 or more follicles (2-9 mm in diameter) or 2) Ovarian volume &gt; 10 ml</td>
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<td>AES/2006</td>
<td>Requires the presence of hyperandrogenism, clinical and/or biochemical, and either 1) oligo-anovulation or 2) PCOM</td>
<td>1) Clinical and/or biochemical hyperandrogenism + oligoanovulation, 2) Clinical and/or biochemical hyperandrogenism + oligoanovulation + PCOM, 3) 1) Clinical and/or biochemical hyperandrogenism +PCOM</td>
<td>Congenital adrenal hyperplasia, androgen secreting tumors, androgenic/anabolic drugs, Cushing’s syndrome, syndromes of severe insulin resistance, thyroid dysfunction, hyperprolactinemia</td>
<td>Hirsutism</td>
<td>1) Total testosterone, 2) Free androgen index or free testosterone, 3) DHEAS, 4) Androstenedione</td>
<td>At least one ovary with: 1) 12 or more follicles (2-9 mm in diameter) or 2) Ovarian volume &gt; 10 ml</td>
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During the early postmenarche (PM) years, the menstrual cycles can last between 21 and 45 days (10). The characteristic menstrual regularity of the adult female (24-38 days) is usually reached several years following menarche. According to the AAP/ACOG, the persistent presence of cycles longer than 45 days, suggest the presence of ovulatory dysfunction in adolescent girls (11). There are some data, however, that the persistence of oligomenorrhea 3-5 years following menarche can be related to the appearance of signs suggestive of PCOS.

In a study of Chilean adolescents, the mean menstrual cycle length was 45.4 ± 24.8 days with 25% of ovulatory cycles in the first year following menarche. The mean duration of the cycles decreased to 32.6 ± 5.1 and 32.2 ± 4.7 in the third and fourth years after menarche, with an ovulatory rate of 37% and 45%, respectively. This ovulatory rate was documented by a salivary progesterone > 0.06 ng/mL, obtained on days 13, 18, 23, and 28 of each menstrual cycle (12). Thus, the measurement of serum progesterone on day 20-24 of the cycle to diagnose ovulation may be misleading.

Therefore, because of the lower ovulatory rate and longer menstrual cycles during this period of life, it is necessary to consider different criteria to diagnose PCOS during adolescence. We suggest that the absence of menstrual periods for periods exceeding 90 days, or by persistent cycles longer than 45 days suggest the presence of ovulatory dysfunction in an adolescent.

Hiperandrogenism (HA)

HA has been considered the most important sign of PCOS, because of its relationship to long-term metabolic and cardiovascular risk in adult women with PCOS (6). As previously mentioned, HA can be clinical or biochemical.

Clinical hyperandrogenism results from an excess or hypersensitivity to androgens, and may include hirsutism, seborrhea, acne and androgenic alopecia. The NIH and Rotterdam classifications consider hirsutism, acne and alopecia as signs of hyperandrogenism. In contrast, the AES classification only accepts the presence of hirsutism as a genuine marker of HA. During adolescence hirsutism is considered the best marker for HA. Acne is a common transient finding in normal adolescents, and alopecia is very uncommon in the pediatric population.

Hirsutism is the most specific sign of clinical HA, and is defined as an increase in terminal hair in androgen-dependent areas (upper lip, chin, upper and lower back, anterior chest, upper and lower abdomen, arms and thighs) (13,14). In order to define hirsutism, the modified Ferriman and Gallwey score has been proposed (15,16). Hirsutism is defined by a Ferriman score equal or greater than 8, which corresponds to the 95th percentile for European populations. Other studies in less hirsute populations have used a cutoff of 6 and in some cases even of 3 (17-19). The cutoff for defining hirsutism during adolescence may be lower, due to the short exposure to androgens. The Ferriman score in the Raine cohort showed that 92% of adolescents have a score below 5, and that 58% have a score of zero (20).

It is important to make the distinction of hirsutism with hypertrichosis, which is not considered a manifestation of androgen excess. Hypertrichosis is a frequent finding in prepubertal girls, and differs from hirsutism in the quality of the hair, and in its anatomic distribution in androgen and non-androgen-dependent sensitive areas. A study performed in Latin American girls suggests that hypertrichosis may be secondary to a slight increase in total testosterone, and an increase in peripheral 5α-reductase activity (21).

Acne is considered by the NIH and Rotterdam groups as a manifestation of androgen excess, but not by the AES. Overall, although acne affects 15% to 25% of PCOS patients, it is unclear whether the prevalence of acne is significantly increased in these patients compared to the general population (22). Acne may be considered as HA during adolescence in some situations, such as in the presence of persistent comedones in prepubertal girls, in cases of widespread severe acne, and in cases who lack a response to standard treatment (23).

Alopecia is very uncommon in the pediatric population. A recent retrospective series of 438 pediatric patients (boys and girls) demonstrated that androgenetic alopecia (AGA) is the cause of alopecia in 13% of children and 42% of adolescents. Of the 57 pediatric patients studied, 19 were female, and 32% were premenarchal. In this group of girls with AGA, 9 patients had the clinical diagnosis of classic PCOS, but only 4 had additional hirsutism (24). Androgenic alopecia affects only 5% of women with hyperandrogenism, and thus is not considered a diagnostic criterion for HA by the AES (25). In addition, when not associated with hirsutism or acne, alopecia is a non-specific sign, which may caused by other etiologies unrelated to hyperandrognism, like alopecia areata, which is the most common cause in the pediatric population (24).
Biochemical hyperandrogenism is accepted by the three classifications as a central element for the diagnosis of PCOS (Table 1). The three classifications are consistent that biochemical hyperandrogenism should be documented by measuring total testosterone, dehydroepiandrosterone sulfate (DHEAS), and free androgens, either by determining free testosterone or by calculation of the free androgen index. There is less consensus on whether to measure serum androstenedione, or free testosterone, which has significant methodological problems, because the determination of free testosterone by direct radioimmunoassay (RIA) may be inaccurate (8,26,27).

For these reasons, the Rotterdam consensus supports the calculation of the free androgen index (FAI) that correlates well with the levels of free testosterone measured by equilibrium dialysis, and has excellent sensitivity and specificity in women with PCOS (28). As with total testosterone, there is no consensus regarding the FAI cutoff point to diagnose hyperandrogenism (29). The variability in methods to measure total testosterone complicates the definition of an universal cutoff point to define biochemical hyperandrogenism in adult women, but there are some data that a high-quality RIA assay for total testosterone might be useful clinically, because it correlates well with gas (GC-MS) or liquid (LC-MS) chromatography-mass spectrometry (30-32).

During adolescence, serum testosterone concentrations are higher than during adulthood, reaching a peak during the second decade of life (33). The problem to define biochemical HA during adolescence is related to the physiological increase in androgen levels during puberty, which is associated with lower SHBG levels, thus increasing free androgens (29,34). The presence of signs of insulin resistance (higher waist circumference and lower SHBG) as well as hyperandrogenemia (increased FAI) has been associated with irregular menstrual cycles and with an hyperandrogenic phenotype in a group of Hispanic adolescents (34).

Other signs suggestive of hyperandrogenism in childhood and adolescence are early pubarche, and premature adrenarche (35). In these cases, it is important to exclude other sources of androgens, such as adrenal disorders (congenital adrenal hyperplasia and Cushing syndrome), virilizing tumors (ovarian, adrenal), and other endocrinopathies (acromegaly, HAIR-AN, thyroid disorders etc.).

Polycystic ovarian morphology

Polycystic ovarian morphology (PCOM) has been considered as an important element for the diagnosis of polycystic ovarian syndrome in adult women, by both the Rotterdam and AES groups (6,36). The definition of PCOM emanates from studies that looked for sonographic criteria which were associated with clinical hyperandrogenism, and with PCOS as defined by classic criteria in adult women (37,38). The Rotterdam Consensus defined PCOM as the presence of 12 or more follicles of 2 to 9 mm in diameter, and/or an ovarian volume greater than 10 ml in at least one ovary. The subjective aspect of the ovaries, their follicular distribution or the appearance of the stroma is not considered as important. The sensitivity and specificity of these cutoffs to diagnose PCOS in adult women has been assessed with transvagal ultrasound, that has better resolution than the transabdominal route, which is frequently used in adolescents (39).

A high prevalence of PCOM in healthy adolescents, with regular menstrual cycles and with no evidence of clinical hyperandrogenism, has been reported in the 30%-35% range (40-42), which is similar to the prevalence of 38% and 37% observed in adolescents with hyperandrogenism and or PCOS, respectively, but is lower compared to the prevalence of PCOM 90%-100% in adult women with PCOS (17). Thus, these findings suggest that PCOM during adolescence is not increased in hyperandrogenic adolescents compared to healthy girls, and is less prevalent in the former group compared to adult women with PCOS.

The hormonal profile associated with the presence of PCOM has shown that this condition, when observed in healthy girls with regular menstrual cycles, is not associated with insulin resistance or hyperandrogenism (40,43,44). However, Mortensen and cols. showed mild ovarian dysfunction in some girls with PCOM, which was not later confirmed by Codner and cols. (43,45).

There are some data that this ultrasonographic finding is frequent in young women and decreases with age (46-48). In adults, this sonographic finding may be present in 10% to 20% of healthy women with regular menstrual cycles and without clinical hyperandrogenism (49,50). Moreover, the presence of PCOM may change over time in the same patient. Our longitudinal study in healthy non-obese, non-hyperandrogenic adolescents between 2 and 4 years postmenarche showed that PCOM is present in 33% of girls at 2, 3 and 4 years
postmenarche (Figure 1, with permission) (43). Similarly, Adams and cols. showed a low concordance for PCOM over a five year follow-up in adult women (51).

Numerous studies have looked for a surrogate marker of PCOM in adult patients with PCOS. Anti-Müllerian hormone (AMH), a glycoprotein secreted by the granulosa cells of small, growing follicles, correlates with the number of small antral follicles (2 to 5 mm) observed by transvaginal ultrasound in adult women (52,53). AMH has also been considered a hallmark of polycystic ovarian syndrome (54). Villarroel and cols. (40), from our group, reported that girls with PCOM have higher AMH levels than girls without PCOM (72.5 ± 6.1 vs. 33.4 ± 2.6 pmol/L; P < 0.0001), and lower FSH levels (5.4 ± 0.3; 6.2 ± 0.2 mUI/ml; P < 0.036). AMH levels positively correlated with the 2-5 mm follicle number, and AMH levels above 60.15 pmol/L had a sensitivity and specificity of 64.0 and 89.8%, respectively, to diagnose PCOM by the Rotterdam criteria (AUC = 0.873). These data, together with the lack of hyperandrogenism or insulin resistance previously mentioned, suggest that PCOM in adolescent girls is a physiologic condition that may be linked to a large follicle mass. Future studies will evaluate the long-term consequences of high AMH levels and PCOM in healthy girls.

Thus, it is not clear whether PCOM is associated with HA during adolescence, and there is no consensus whether to include PCOM as a diagnostic criteria for PCOS in adolescent girls, because it may be part of normal ovarian physiology during this period (20).

**PREDISPOISING FACTORS**

Several authors have proposed that adult PCOS begins in childhood (55). Prenatal exposure to androgens, demonstrated in animal studies (56,57), and in daughters of PCOS mothers (58-60), suggest that these conditions are associated with an adverse metabolic profile during childhood and puberty, similar to that seen in PCOS, and with higher AMH levels. Other predisposing factors may include low birth weight, premature pubarche, use of some drugs, type 1 diabetes, obesity and insulin resistance (61).

The prevalence of obesity is increasing in childhood and adolescence. Weight gain during adolescence carries a higher risk for early puberty, obesity and estrogen-dependent disease later in life, including polycystic ovary syndrome and breast cancer (62). A study regarding the association of obesity and hyperandrogenemia during the pubertal transition in 41 obese and 35 normal-weight peripubertal girls, showed that BMI correlates with total testosterone, SHBG, and free testosterone (P < 0.0001). The correlation of BMI with free testosterone is maintained after adjustment for age, pubertal stage, insulin, LH, and dehydroepiandrosterone sulfate levels (63).

Insulin resistance (IR) has been implicated in the pathophysiology of PCOS, and has been associated with hyperandrogenism, possibly caused by increased secretion of androgens by the theca cells and reduced hepatic production of sex hormone binding globulin (SHBG) (64). Evaluation of IR by measuring insulin and HOMA are not part of the diagnostic criteria for PCOS in adult women. In addition, during adolescence there is a degree of IR which appears to be physiological, so these criteria to diagnose PCOS are not very useful during puberty.

It has been observed that androgen levels are related to the metabolic syndrome, increased abdominal fat and abnormal pro-inflammatory and hemostatic agents (65,66). The altered metabolic profile observed in girls with PCOS is multifactorial and can be secondary to hyperandrogenemia, insulin resistance and obesity in an independent manner (67,68). The cardiovascular risk observed in adult women with PCOS, can be assessed by the measurement of intima-media thickness (IMT), a good predictor of cardiovascular events in adulthood (69,70). In 160 obese adolescents girls, the subgroup with the metabolic syndrome (48 girls) demonstrated significantly higher testosterone and DHEA-S concen-
trations compared with the 112 girls without MS. Levels of testosterone correlated significantly with systolic and diastolic blood pressure, 2 h glucose in oGTT, triglycerides, uric acid, waist circumference and IMT (71).

In conclusion, the use of the three different sets of diagnostic criteria for PCOS in adults has resulted in the description of widely variable phenotypes in the presumably affected patients. These patients appear to have different long-term metabolic risks, as shown in Table 2, but several publications have shown that hyperandrogenism is the most important risk factor in these patients. During adolescence, there is no consensus as whether to use either the NIH or AES criteria to diagnose PCOS. We suggest that the diagnosis of PCOS should be based on the presence of hirsutism and biochemical hyperandrogenism, associated with menstrual cycles persistently longer than 45 days during adolescence. Intermediate phenotypes suspicious for PCOS should be followed closely during adolescence and stimulated to keep a healthy lifestyle and evaluated further during early adulthood, searching for signs of hyperandrogenism and ovulatory dysfunction. The diagnosis of PCOS carries a long-term stigma, so the temptation to make this diagnosis and consider medical therapy during adolescence should be tempered against the real benefits of such therapy, and the possible risks of the drugs employed to treat this condition.

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