

Polycystic Ovary Syndrome: Special Diagnostic and Therapeutic Considerations for Children

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Abstract: Polycystic ovary syndrome (PCOS) is an endocrine syndrome with variable phenotypic expression and important systemic associations and sequelae, including obesity, insulin resistance, infertility, risk of endometrial cancer, and possible risk of cardiovascular events. PCOS is recognized as a condition influenced by genetic and environmental factors and distinct manifestations in all stages of life, including the prenatal period, childhood, adolescence, and adulthood. Identification of this disorder in childhood and adolescence has received growing attention, in part because of emerging evidence of the benefit of early intervention, but the diagnosis and management of PCOS in children and adolescents can be challenging. Diagnostic and therapeutic considerations of PCOS in children are reviewed to enhance identification and evaluation of patients suspected of having this disorder. When a diagnosis of PCOS is suspected in a child but cannot be confirmed, a provisional diagnosis is strongly recommended so as to prompt ongoing monitoring with an emphasis on important early interventions such as obesity reduction.

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder characterized by oligomenorrhea, hyperandrogenism, and characteristic polycystic ovaries on ultrasound. Classic dermatologic manifestations in PCOS are acne (53% of

patients) (1), hirsutism (65%–70%) (2), androgenic alopecia (33%), acanthosis nigricans (5%), and seborrheic dermatitis (35%) (3). It is the most common cause of hyperandrogenism, with a prevalence of 5% to 10% in adults (4–6). The Rotterdam

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TABLE 1. Revised 2003 Consensus on Rotterdam Diagnostic Criteria of Polycystic Ovary Syndrome (7,37)

1. Oligo- or anovulation (<8 menstrual cycles per year)
 2. Clinical or biochemical signs of hyperandrogenism (hirsutism, acne, androgenic alopecia, or high dehydroepiandrosterone sulfate, total testosterone, free testosterone levels)
 3. Polycystic ovaries (AFC >12 or follicular volume >10 cc per ovary; newer guidelines suggest an AFC >25 or follicle count in a single cross section >9)
- Two of three criteria and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome) are required for diagnosis

AFC, antral follicle count.

consensus diagnostic criteria (7,8) for PCOS require two of three clinical features to render a diagnosis: oligomenorrhea, biochemical or clinical hyperandrogenism, and polycystic ovaries on ultrasound (Table 1). These criteria also require the exclusion of other diagnostic possibilities, including underlying endocrine disorders, many of which present in childhood.

The diagnosis of PCOS has significant implications for an individual's health because it is a systemic disorder associated with high morbidity. Women and girls with PCOS are at higher risk of impaired glucose tolerance, obesity, and the development of diabetes and may experience a greater degree of fertility problems and complications with pregnancy (1). Women with PCOS are also at risk of certain malignancies, such as endometrial cancer, and possible cardiovascular complications (1,9). Active monitoring and interventions including hormonal therapy, weight reduction, exercise, and dietary modifications

may lower the risk of the development of these complications (1,10).

Although it was once thought to be a disorder in adult women, there is evidence that PCOS is a lifelong syndrome, with manifestations beginning prenatally and evolving throughout childhood, adolescence, and adulthood (Fig. 1). Just as the clinical features of adult PCOS shift with advancing age (11), the presentation of PCOS in childhood is variable. Furthermore, the overlap of the Rotterdam criteria and normal puberty, such as irregular cycles and high follicle counts, makes the diagnosis elusive or challenging to confirm, even when strongly suspected. The presentation of PCOS in childhood may include features such as menstrual irregularities or amenorrhea, signs of hyperandrogenism, and metabolic derangements, especially obesity and insulin resistance (Table 2).

The prevalence of PCOS in children is largely unknown. Based on the Rotterdam diagnostic criteria,

TABLE 2. Comparison of the Phenotype of Polycystic Ovary Syndrome in Children and Adults (1,12,30,34)

Symptom	Children (%)	Adults (%)
	%	
Menstrual irregularity	64	84
Obesity	70	30–60
Insulin resistance	63	50–70
Elevated androgens	52	60–80
Metabolic syndrome	37	30–40
Hirsutism	60	65–73
Acne	70	53

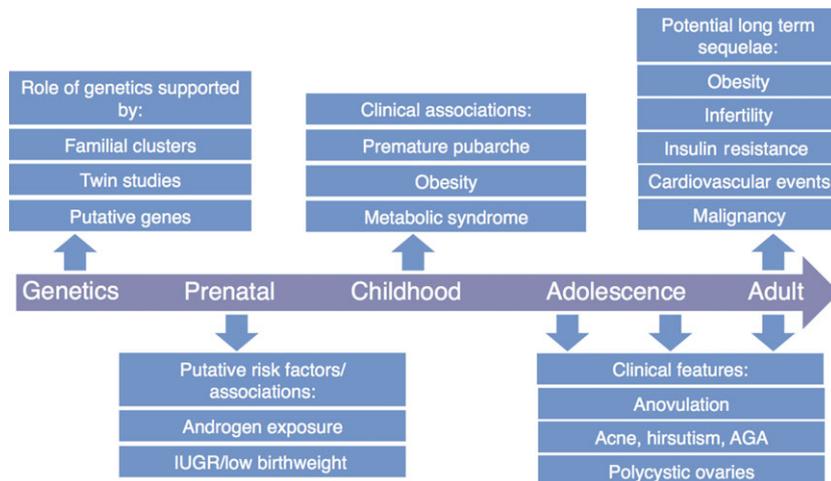


Figure 1. Clinical associations with polycystic ovary syndrome (PCOS) throughout the years. PCOS evolves across an individual's lifetime, beginning in the prenatal period, with manifestations in childhood, adolescence, and adulthood. A combination of genetic and environmental factors contribute to a patient's phenotype (15,16,31,50).

the prevalence in adolescents has been reported to be as low as 3% (12) and as high as 11% to 26% (13). A review (14) of 28 studies in a 3-year time span (2006–2008) that included PCOS patients younger than 18 years reported that 6.4% were younger than 13 years. Four of these studies were primarily in children and reported that 9.4% of patients with PCOS were younger than 13 years. Furthermore, data characterizing the clinical features in children with PCOS are limited. In a study of 58 girls (26% preadolescents ages 9–12 years, 74% adolescents ages 13–18 years), preadolescents with PCOS had significantly earlier onset of pubarche (1.9 yrs earlier) and thelarche (1.5 yrs earlier) than adolescents with PCOS, and PCOS developed 2.1 years sooner after thelarche in preadolescents (13).

PRENATAL ERA: THE ROLE OF GENETICS AND ENVIRONMENT

It is likely that there is a genetic predisposition to PCOS, as suggested by familial clustering of cases (15,16) and concordance in data from identical twin studies (17). In a study of 78 mothers and 50 sisters of individuals with PCOS, 19 (24%) and 16 (32%) were affected with PCOS, respectively. Considering only premenopausal women who were not taking hormones, the rates increased further to 35% of mothers and 40% of sisters. The rates of PCOS in family members in this study were significantly higher than the rates of PCOS in the general population, strongly suggesting that there is a genetic component in the disorder (18). Although the precise mode of inheritance is unclear (15,19), it is likely that it is polygenic in nature (15,20,21).

It has been proposed that environmental influences are risk factors for the development of PCOS later in life. A study of Rhesus monkeys exposed to high concentrations of testosterone in utero showed the development of female offspring with features of PCOS, including ovarian dysfunction, abnormal luteinizing hormone secretion, and insulin resistance (15,22), although similar results have not been replicated in human studies (23). In human pregnancy, placental aromatases and sex hormone-binding globulin largely preclude maternal androgens from crossing the placenta at significant levels (24). Fetal androgen exposure is still believed to play a role in the development of PCOS, and one likely source of this excess androgen is from the fetal ovary itself, and possibly also fetal adrenal-derived androgens (15).

Other prenatal factors may increase the risk of developing PCOS later in life. Intrauterine growth

restriction leading to low birthweight may initiate developmental pathways that culminate in PCOS (6,25) and has been associated with premature adrenarche and lean PCOS (PCOS in nonobese individuals) in adolescence (25). Rosenfield et al (26) postulate that low birthweight and small prenatal size for gestational age may induce postnatal insulin resistance, in turn predisposing to premature pubarche and PCOS (26).

Additional risk factors for childhood onset of PCOS include insulin-resistant obesity in early childhood with acanthosis nigricans, metabolic syndrome, and atypical sexual precocity (27).

CHILDHOOD AND ADOLESCENCE

Diagnosing PCOS in children is challenging because disease presentation is highly variable. In childhood, early signs of hormonal and metabolic dysfunction may be present, including premature pubarche, obesity, and metabolic syndrome (Table 2). Classic findings of PCOS (anovulation, acne, hirsutism, biochemical hyperandrogenism, polycystic ovaries) typically become more evident in adolescence and early adulthood.

Childhood obesity is a well-documented risk factor for PCOS. Obese girls have greater severity of insulin resistance and greater risk of metabolic syndrome and of developing PCOS later in life (23). This evidence suggests that obesity is a modifiable risk factor for PCOS; the use of metformin during puberty has been shown to reduce abdominal adiposity (28). Weight reduction is not necessarily protective; because lean individuals with PCOS also demonstrate insulin resistance, all patients suspected of having PCOS should be screened for insulin resistance. It has not been confirmed whether obesity, along with a predisposed genetic risk, leads to PCOS or whether it is the underlying PCOS that leads to obesity.

IMPORTANT DIAGNOSTIC CONSIDERATIONS IN THE PEDIATRIC POPULATION

The diagnostic approach to PCOS in children remains controversial. The Rotterdam diagnostic criteria can be used, with two important caveats. First, there is phenotypic variability in PCOS patients at all ages, with well-established subtypes (Table 3). Some subtypes may lack important clinical features, such as an irregular menstrual history, hyperandrogenism, or ultrasonographic evidence of polycystic ovaries, and may be challenging to diagnose (29). Second, there are

TABLE 3. Phenotypes for Polycystic Ovary Syndrome (PCOS) Subtypes Based on 2003 Rotterdam Criteria (1,29)

Criterion	Type I classic PCOS	Type II classic PCOS	Ovulatory PCOS	Normoandrogenic PCOS
Anovulation	+	+	–	+
Hyperandrogenism (clinical or biochemical)	+	+	+	–
Polycystic ovaries	+	–	+	+

limitations in the Rotterdam criteria, described below, that may lead to misdiagnosis of PCOS in children and teens.

ROTTERDAM CRITERION: MENSTRUAL IRREGULARITIES

Oligomenorrhea, defined as fewer than eight menstrual cycles per year, is common in the first 18 months after menarche (30), making it an unreliable diagnostic sign in adolescents. Primary amenorrhea and ovarian failure must also be excluded as a cause. Other important diagnostic considerations of amenorrhea in children include thyroid abnormalities and a suppressed hypothalamic-pituitary-ovarian axis.

ROTTERDAM CRITERION: BIOCHEMICAL HYPERANDROGENISM

Biochemical testing for hyperandrogenism may be falsely negative since androgen measurement is calibrated primarily to adult male levels; women and girls—even those with high androgens—may have falsely normal levels depending on which laboratory is used and what are considered normal reference values. Furthermore, puberty is a time of physiologic hyperandrogenism (31). Other factors that may contribute to difficulty interpreting laboratory testing include wide variability of androgen levels in the normal population and that normative ranges for androgen levels have not been established with control populations, especially with respect to age and body mass index (BMI). There are almost no normative data regarding androgen levels in adolescents. Finally, high serum androgen levels are not required to make a diagnosis of PCOS, and not all patients with PCOS have serum abnormalities (7,32,33). Although studies regarding the prevalence of biochemical hyperandrogenism have not been conducted specifically in adolescents, in adults, the prevalence of excess dehydroepiandrosterone sulfate (DHEA-S) is approximately 20% in Caucasian women and 30% in African American women (34). Sixty percent of individuals with PCOS (diagnosed according to 1990

National Institutes of Health criteria) demonstrate high free testosterone levels (35). The presence of other signs of hyperandrogenism raises an important differential diagnosis, including clinical entities that may present in childhood: androgen-secreting neoplasm (adrenal gland or ovary); classic or nonclassic congenital adrenal hyperplasia; Cushing syndrome; prolactinoma; the syndrome of hyperandrogenism, insulin resistance, and acanthosis nigricans; and exogenous androgens (testosterone, dehydroepiandrosterone [DHEA]) (36,37). The most common cause of hyperandrogenism is PCOS, accounting for 70% of cases in adult studies.

Variants within younger individuals may also exist, as suggested by a cohort of young adult women (mean age 25 yrs) diagnosed with PCOS with high adrenal androgens (DHEA-S) only (38). Higher DHEA-S levels correlated with a greater prevalence of acne (odds ratio 2.5) (38) and were inversely correlated with abdominal obesity (38). The correlation between DHEA-S and the acne phenotype in PCOS emphasizes the importance of adrenal-derived androgens. This group of women with low to normal BMI still had higher rates of metabolic syndrome, which was independently linked to hyperandrogenism (39).

ROTTERDAM CRITERION: CLINICAL HYPERANDROGENISM

Acne, a clinical feature associated with hyperandrogenism, is almost universal in adolescence. Several clinical features regarding acne may suggest underlying hyperandrogenism in an adolescent: therapy-resistant acne, prepubertal acne, a history of premenstrual flare, stress-exacerbated acne, and other accompanying signs such as hirsutism, androgenic alopecia, and seborrhea. Acne that is distributed along the jaw line and chin may be associated with hormone-related acne. Hyperandrogenism should also be considered in patients with a severe, sudden onset of acne that may be associated with irregular menstrual periods. Clinical signs of hyperandrogenism suggesting virilism, including clitoromegaly, deepening of the voice, and increased libido, may also be present (40). While

patients with hyperandrogenism benefit from an examination for underlying PCOS, virilism in PCOS is rare; patients presenting with virilism should be evaluated for endocrine malignancy and endocrine tumors (if viri 41). Furthermore, there is a paucity of information regarding the prevalence of signs of clinical hyperandrogenism across the age spectrum in patients in PCOS. A study by Lucky et al (42) found significant differences in the prevalence of upper lip hair in African American and Caucasian girls during puberty, as measured using Ferriman–Gallwey scoring. Specifically, this study revealed that up to 2 years after menarche, 90% of girls had no upper lip hair, although more than 2 years after menarche, 48.8% of African American girls and 9.0% of Caucasian girls had small amounts of upper lip hair (42). There was no association between upper lip hair and serum androgen levels. Numerous additional studies have indicated a lack of association between cutaneous signs of hyperandrogenism and high androgen levels. Because hyperandrogenism is one of the important diagnostic features of PCOS, the lower Ferriman–Gallwey score in girls before and up to 2 years after menarche may further contribute to the challenges of diagnosing PCOS in adolescents.

ROTTERDAM CRITERION: ULTRASOUND FEATURES

Current Rotterdam criteria regarding ovarian morphology in PCOS require ultrasonographic documentation of an antral follicle count (AFC) greater than 12 or a follicular volume greater than 10 cc per ovary, and recent updated ultrasound criteria for PCOS have suggested using an AFC greater than 25, a follicle count in a single cross section greater than 9, or a follicular volume greater than 10 cc per ovary (43). The current Rotterdam or updated ultrasound criteria

may not be relevant during puberty since there is normal variation in AFC and volume during development. It may also not always be possible to perform a transvaginal or transrectal ultrasound in younger patients, leading to a delayed or deferred diagnosis; transabdominal ultrasound often does not offer adequate resolution to assess ovarian morphology (44,45). Although the pathophysiology remains poorly defined, there is a strong correlation between the presence of ovaries with a polycystic morphology and androgens (caused by excessive stimulation by insulin), luteinizing hormone, or both (1,9,37).

In a younger population, the three key diagnostic features for PCOS may be in evolution or may only be transient findings. Some authors have suggested avoiding a formal diagnosis of PCOS until the age of 18 years (46), whereas others have proposed specific, strict criteria for the diagnosis that differ from the Rotterdam criteria based on the inclusion of clinical and biologic hyperandrogenism, chronic anovulation, or polycystic ovaries on ultrasound (Table 4) (46,47). Carmina et al (46) suggest it may be best to assign a diagnosis only to girls with a high probability of having the disease, questioning the potential harm of early labeling and unclear benefit of lowering cardiovascular and metabolic risk profiles. In contrast, Sultan et al (47) favor an approach of earlier screening and assignment of a provisional diagnosis for high-risk individuals to implement interventions intended to prevent the long-term sequelae of PCOS. Given the possibility of early intervention, there is an emerging voice in the literature that clinicians should attempt to perform a comprehensive evaluation of a patient suspected of having PCOS as early as possible; if a diagnosis cannot be established, a provisional diagnosis with a plan for ongoing clinical evaluation should be strongly considered since this may offer opportunities for active monitoring and early intervention (48).

TABLE 4. Comparison of Two Proposed Diagnostic Criteria of Polycystic Ovary Syndrome (PCOS) in Adolescents (46,47)

Carmina et al (46) proposed criteria	Sultan et al (47) proposed criteria
Diagnosis of PCOS: + Hyperandrogenism*, chronic anovulation†, and polycystic ovaries‡	At least four of the five criteria must be met for a diagnosis of PCOS:
Diagnosis of PCOS probable but not confirmed: + Hyperandrogenism, + chronic anovulation, – polycystic ovaries	Oligomenorrhea or amenorrhea, 2 yrs after menarche
Diagnosis of PCOS not possible during adolescence: + Hyperandrogenism, – chronic anovulation, + polycystic ovaries	Clinical hyperandrogenism: persistent acne, severe hirsutism
OR	Biologic hyperandrogenism: plasma testosterone >50 ng/dL, high luteinizing hormone/follicle-stimulating hormone ratio >2
– Hyperandrogenism, + chronic anovulation, + polycystic ovaries	Insulin resistance or hyperinsulinemia: acanthosis nigricans, abdominal obesity, glucose intolerance
	Polycystic ovaries on ultrasound scan: enlarged ovaries, peripheral microcysts, increased stroma

*Hirsutism is considered a sign of hyperandrogenism only when progressive.

†Oligomenorrhea, or anovulation, must be present for at least 2 yrs.

‡Polycystic ovaries according to abdominal ultrasound must include ovarian size >10 cm³.

RECOMMENDATIONS FOR DIAGNOSTIC EVALUATION

The diagnostic examination for PCOS in all patients suspected of having hyperandrogenism should include an assessment of endocrine and metabolic parameters relevant to PCOS and other diseases on the differential diagnosis, including rare causes of hyperandrogenism. For accurate testing, a patient should discontinue oral contraceptive pills and spironolactone for 4 to 6 weeks and testing should occur as close to the luteal phase of the menstrual cycle as possible (Table 5). Metabolic evaluation should not be postponed, because obese and lean patients may be at significant risk of insulin resistance. Assessment of the metabolic status of a patient is recommended, including BMI, fasting lipids, fasting and 2-hour glucose, and insulin levels after glucose challenge. Thyroid assessment should also always be performed in patients with irregular menses, because thyroid abnormalities are a common cause of menstrual irregularities and sometimes cutaneous symptoms. A transvaginal ultrasound should be performed, if possible.

IMPORTANT TREATMENT CONSIDERATIONS IN CHILDREN

The goals of PCOS treatment in children are similar to those indicated in adults. Uterine protection, or prevention of endometrial cancer, can be established with a combination of oral contraceptive pills, a hormone-eluting intrauterine device, or a cervical hormone ring, and spironolactone can be added if cutaneous or other signs of hyperandrogenism exist, such as acne, hirsutism, or androgenic alopecia. Emerging evidence strongly supports the effect of lifestyle modification; optimizing cardiovascular fitness, healthy nutrition, and weight loss have been demonstrated to have a significant effect on the

phenotypic expression of PCOS (1,15). In a study of 59 obese girls ages 12 to 18 years with PCOS, Lass et al (49) demonstrated that the 26 who reduced their BMI during the course of the study (by a mean of 3.9 kg/m²) improved their cardiovascular risk factors, decreased testosterone concentrations, and reduced the prevalence of oligomenorrhea. Additional studies indicate that adolescent girls diagnosed with PCOS benefit from comprehensive care through an interdisciplinary approach that would reduce the medical, social, and economic burdens associated with this syndrome (43).

As such, lifestyle modification may be a critical intervention in children and adolescents with a confirmed or provisional diagnosis of PCOS, as there is compelling early evidence that weight loss may reduce the risk of insulin resistance and PCOS expression later in life (23). Nutrition and exercise counseling of patients and their families may be essential to establish lifelong habits in children that may mitigate the expression of PCOS. Because PCOS is well documented to have a significant effect on quality of life and self-esteem, ongoing psychological counseling may be necessary to promote the psychological health of patients with a provisional or confirmed diagnosis (1,15). Patients should be evaluated annually to monitor metabolic profiles and, when possible, a transvaginal ultrasound should be performed to help confirm the diagnosis.

CONCLUSION

The diagnosis of PCOS in childhood or adolescence may be critical to initiate early intervention and possible prevention of later sequelae of this lifelong disease, but phenotypic differences of this syndrome and a lack of accepted diagnostic criteria in children make diagnosis difficult. In addition, various features

TABLE 5. *Diagnostic Evaluation for Polycystic Ovary Syndrome (PCOS)*

I. Endocrine evaluation	II. Metabolic examination
Hyperandrogenism Examination for PCOS: Total testosterone* Free testosterone* Dehydroepiandrosterone sulfate* Androstenedione* Luteinizing hormone:follicle-stimulating hormone ratio (>3:1 is suggestive)	Laboratory tests to exclude other diagnoses that may mimic those of PCOS: 17-hydroxyprogesterone (screen for congenital adrenal hyperplasia) Prolactin (screen for pituitary neoplasm) Thyroid-stimulating hormone (screen for thyroid disorder, most common cause of menstrual irregularity) Cortisol measurement (screen for Cushing disease)
Body mass index Fasting lipid panel 2-hour glucose challenge (check fasting and 2-hour glucose and insulin levels during the glucose challenge)	

Laboratory testing should occur 4 to 6 weeks after stopping oral contraceptives and spironolactone and as close to the luteal phase of the menstrual cycle as possible.

*PCOS is associated with increased androgens, but not all lab abnormalities are seen in all patients.

of normal puberty (irregular menses, high follicle numbers, acne) overlap with those of PCOS. Further research is needed to characterize the clinical features of PCOS throughout different stages of life and to validate the role of early intervention in modifying the evolution of the syndrome and its outcomes. When a PCOS diagnosis cannot be established, a provisional diagnosis should be strongly considered to avoid delays in metabolic evaluation and to form a therapeutic alliance with the patient for ongoing clinical monitoring.

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