Polycystic Ovary Syndrome in Adolescents
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ABSTRACT

- **Objective:** To review the diagnosis and management of polycystic ovary syndrome (PCOS) in adolescent patients.
- **Methods:** Review of the literature.
- **Results:** PCOS is a complex, heterogeneous disorder that frequently manifests during puberty. The symptoms of PCOS (ie, menstrual irregularities, hirsutism, and acne) tend to overlap with normal pubertal changes. Diagnostic criteria for PCOS in the adolescent age-group is still lacking. Current practice is to utilize adult diagnostic criteria, which raises the concern for misdiagnosis. The underlying etiology for the disorder is still unclear, but insulin resistance is present in both obese and non-obese PCOS patients. Although recognizing adolescents with PCOS is challenging, evaluating and managing patients for hyperandrogenemia and metabolic syndrome is imperative to prevent long-term reproductive and metabolic complications.
- **Conclusion:** PCOS is increasingly encountered during adolescence. Recognizing adolescent girls with PCOS is a challenge but important for preventing long-term adverse health outcomes.

Poly cystic ovary syndrome (PCOS) is a complex disorder most commonly characterized by chronic anovulation and clinical and biochemical features of hyperandrogenemia. It affects 4% to 12% of reproductive-aged women [1,2]. In adolescents, the exact prevalence is unknown, but in a recent study the prevalence of a confirmed diagnosis of PCOS in adolescents aged 15 to 19 years was 0.56%, which increased to 1.14% when undiagnosed cases with documented symptoms qualifying for PCOS according to NIH criteria were included [3]. The primary underlying defect in PCOS remains unknown, but key features include insulin resistance, impaired gonadotropin dynamics, and androgen excess.

Profound functional variations in the hypothalamic-pituitary-ovarian axis commonly seen during normal puberty may result in clinical and biochemical changes that mimic some of the features of PCOS. During the early stages of puberty, adolescent girls tend to have anovulatory menstrual cycles, higher androgen levels, and polycystic ovaries [4,5]. Thus, the clinical signs of hyperandrogenemia commonly seen in adults are less reliable in the adolescent age-group. Diagnostic criteria have been developed for adults and are based upon the various combinations of oligomenorrhea, unexplained hyperandrogenemia, and polycystic ovaries on imaging (Table 1) [6–8]. Applying these adult criteria in adolescent patients with suspected PCOS has always raised the concern of misdiagnosis as some of the changes seen in this age-group may likely be due to normal pubertal development. However, due to the paucity of data, the current practice is to utilize the adult diagnostic criteria. Because of the heterogeneous nature of the disorder, recognizing adolescents with PCOS may be challenging. However, early recognition and management is important to prevent some of the long-term reproductive and metabolic complications associated with this syndrome.

CASE STUDY

Initial Presentation

A 16-year-old female patient presents to the PCOS clinic for evaluation of obesity and amenorrhea.

History

The patient, who is otherwise healthy, began gaining weight at age 7. During this period, her weight increased from the 15th to (currently) the 90th percentile; her height remained constant (75th percentile). Menarche was at 12 years of age. Menstrual periods have been irregular since the onset of menarche and she has had no periods for the past 5 months. She noticed excessive hair growth on her face, chin, and neck soon after the onset of menarche. She has been shaving her facial hair once every 2–3 days.

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The patient’s detailed diet history included eating 3 meals daily and snacks in-between meals. The patient was consuming sweet beverages regularly. There was minimal intake fruits and vegetables. The portion sizes for each meal were large. The patient had minimal physical activity and screen time was more than 2 hours daily.

Family history is significant for obesity and type 2 diabetes in her mother and maternal grandmother and is negative for PCOS.

**Physical Examination**

Vital signs were within normal limits. She was 5 ft 6 in tall and weighed 242 lb, with a body mass index (BMI) of 40 (99th percentile; Z-score 2.41). Physical examination showed coarse hair extending from the sideburns to the chin as well as from pubis symphysis to navel with evidence of hair removal. She had acanthosis nigricans on her neck, mild acne, and evidence of central obesity with pink striae marks on the abdomen. She was Tanner stage 5 for breast and pubic hair and there was no evidence of virilization (clitoral hypertrophy, deepening of the voice, severe hirsutism, male pattern baldness, and masculine habitus). Other physical examination findings were within normal limits.

- **What physical findings in this patient are suggestive of clinical hyperandrogenemia?**

Physiologic irregular menstruation is a well known phenomenon in adolescent girls and is generally due to anovulatory cycles [9–12]. Menstrual cycles shorter than 19 days or longer than 90 days at any stage after menarche are considered abnormal. The menstrual irregularity that is commonly seen within the first 2–3 years after the first menarche can last up to 5 years [5]. However, the majority of girls establish 20- to 45-day cycles within the first 2 years [13].

Androgen excess, defined by the presence of clinical and/or biochemical hyperandrogenemia, should be considered in any adolescent girl who is 2 to 3 years’ postmenarche and presenting with irregular menstrual periods, coarse terminal hair in a male distribution pattern (hirsutism), or moderate to severe inflammatory acne. Hirsutism is androgen dependent [14–16] and must be distinguished from hypertrichosis, which is generalized excessive vellus hair growth present all over the body. Clinical hyperandrogenemia, which includes hirsutism, acne vulgaris, as well as androgenetic alopecia, is well correlated with elevated androgen levels; however, the severity of hirsutism does not correlate well with circulating androgen levels [17,18]. Mild hirsutism is often not associated with hyperandrogenemia in otherwise asymptomatic individuals, but it may be a sign of hyperandrogenemia in adolescents when associated with other features of PCOS, ie, menstrual irregularity [14–16, 19–22]. Defining hirsutism in early adolescence may be difficult since the sexual hair may still be developing, and laboratory evaluation should be considered (see below), especially in an overweight/obese adolescent girl presenting with oligomenorrhea. Ethnic variation due to decreased skin sensitivity to androgens can result in minimal hirsutism despite elevated plasma androgen levels and must be considered among certain Asian women. Women with PCOS from China, Japan, Thailand, and East and Southeast Asian countries tend to have low scores on hirsutism rating scales even with elevated plasma androgens levels [16,23].

Although having acne during puberty is not considered as a marker for hyperandrogenemia, patients with moderate to severe inflammatory acne that is poorly

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**Table 1. Diagnostic Criteria for PCOS**

<table>
<thead>
<tr>
<th>National Institutes of Health 1990 (Must meet both criteria)</th>
<th>Rotterdam 2003 (Must include 2 of the following)</th>
<th>Androgen Excess Society 2006 (Requires 2 of the following)</th>
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<tbody>
<tr>
<td>1) Oligo/amenorrhea, anovulation</td>
<td>1) Oligo/amenorrhea, anovulation</td>
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<tr>
<td>2) Clinical and/or biochemical hyperandrogenemia</td>
<td>2) Clinical and/or biochemical hyperandrogenemia</td>
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<td>3) Polycystic ovaries on ultrasound</td>
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Excluding other androgen excess disorders: late-onset congenital adrenal hyperplasia, Cushing’s syndrome, androgen-secreting tumors, hyperprolactinemia, and thyroid diseases.
responsive to topical treatment should be evaluated for underlying hyperandrogenemia [19,24,25].

• What laboratory tests should be obtained to when there is clinical suspicion of hyperandrogenemia?

As with the variability in clinical symptoms, there is a lack of uniformity regarding biochemical testing for this disorder. There is no consensus on which biochemical tests should be done in girls suspected of having PCOS. For the initial evaluation of hyperandrogenemia, measurement of total and/or free testosterone is recommended [13,26–28]. Elevated free testosterone is recognized as the single most sensitive indicator for hyperandrogenemia, as the free fraction is the bioactive portion of serum testosterone. Most circulating testosterone is bound to sex hormone–binding globulin (SHBG), and obesity and androgen excess lower the level of SHBG, thus increasing free testosterone fraction. Clinical evidence of virilization should prompt a workup for disorders mimicking PCOS (Table 2) [27]. Obtain baseline thyroid and prolactin levels in any adolescent with chronic anovulation to exclude hyperprolactinemia and thyroid disorders. Most patients with PCOS have higher luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio; however, the test does not have robust diagnostic utility due to the variability of serum LH levels commonly seen during the different stages of the menstrual cycle. In addition, no difference in LH/FSH ratio was found in a group of obese PCOS patients when compared with a control group [29]. Given the increased association of obesity with PCOS, evaluation for metabolic syndrome is crucial. Laboratory testing requires reliable assays with well-defined normal ranges, especially for free testosterone since the assays are less well standardized, which limits their usefulness [13]. Table 2 provides a comprehensive list of recommended testing that should be tailored to the patient’s presentation.

Table 2. Laboratory Testing Recommendations

<table>
<thead>
<tr>
<th>Recommended laboratory testing for PCOS/oligomenorrhea</th>
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<tr>
<td>Free testosterone (elevated in PCOS)</td>
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<tr>
<td>Total testosterone (elevated in PCOS)</td>
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<tr>
<td>Sex hormone binding globulin (suppressed in PCOS)</td>
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<tr>
<td>LH, FSH (LH/FSH &gt;2.0 little diagnostic sensitivity and not routinely recommended as levels vary with menstrual cycle and is released in pulsatile fashion)</td>
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<tr>
<td>Exclusion of other causes of oligomenorrhea</td>
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<td>Thyroid-stimulating hormone (thyroid disorder)</td>
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<tr>
<td>Prolactin (hyperprolactinemia)</td>
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<tr>
<td>Exclusion of conditions mimicking PCOS if virilization is present</td>
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<tr>
<td>17-hydroxyprogesterone (late onset congenital adrenal hyperplasia)</td>
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<tr>
<td>DHEAS (adrenal tumor)</td>
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<tr>
<td>Salivary cortisol and or 24-hour urine cortisol (to exclude Cushing’s syndrome)</td>
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<tr>
<td>Evaluation for metabolic syndrome</td>
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<td>Chemistry panel, hemoglobin A1c (HbA1c)</td>
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<tr>
<td>Consider 2-hour oral glucose tolerance test if fasting blood glucose 100-125 mg/dL and/or HbA1c in pre-diabetic range (5.7-6.4%)</td>
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<tr>
<td>Fasting lipid panel</td>
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Case Continued

The patient underwent laboratory assessment that included total and free testosterone levels, lipid panel, thyroid studies, prolactin level, comprehensive metabolic panel (CMP) and hemoglobin A1c (HbA1c). Due to lack of virilization, she was not tested for PCOS-like syndromes. Her total and free testosterone were 90 ng/dL (normal, < 41) and 24.7 pg/mL (normal, 0.5–3.9) respectively. Thyroid-stimulating hormone and prolactin levels were normal. She had normal lipid levels and CMP but HbA1c was 5.9% (pre-diabetic range). The results of a 2-hour oral glucose tolerance test revealed a level of 160 mg/dL, indicative of impaired glucose tolerance.

• What is the pathophysiology and diagnostic criteria for PCOS in adolescents?

PCOS has diverse etiology and has been linked to both genetic and environmental factors affecting ovarian steroidogenesis [13,30]. While the familial clustering strongly supports the role of genetic factors, variability in phenotypic features within the same or different families indicates the importance of environmental contribution [31–34].

The exact underlying mechanism leading to disruption of ovulation is still unclear; however, hyperinsulinemia
augmenting ovarian androgen production has been well recognized [35–37]. Insulin resistance is a characteristic finding in PCOS and occurs both in obese and lean patients [38,39]. Obesity further exacerbates the insulin resistance state in PCOS patients. Therefore, obese patients with PCOS have more severe hyperandrogenemia and consequences from it (hirsutism, menstrual abnormalities, and metabolic derangements) than normal-weight PCOS patients [40,41]. Similar to LH, insulin can stimulate ovarian theca cells directly and cause increased production of androgens [42]. Elevated androgen levels cause the irregular menstrual periods as well as clinical signs of hyperandrogenemia, such as hirsutism and acne.

Altered gonadotropin dynamics is another possible etiological factor that is linked with PCOS. Hyperinsulinemia affects the regulation of gonadotropin-releasing hormone (GnRH) pulse generator, causing hypersecretion of LH [43]. Obese peripubertal girls have been identified having altered LH secretion [44,45]. This results in increased LH levels relative to FSH. Normal FSH is required to stimulate ovarian folliculogenesis; insufficient FSH levels cause anovulation and menstrual irregularities. Abnormal LH secretion and fasting insulin levels have been identified as independent predictors for hyperandrogenemia in some peripubertal obese girls [46].

In 2010 Carmina et al. published new criteria to diagnose PCOS in adolescents [27]. They recommended that in diagnosing PCOS in adolescents, all 3 previously mentioned criteria should be present: hyperandrogenemia, chronic anovulation, and polycystic ovaries. With the exception of worsening hirsutism, the new recommendations greatly emphasized biochemical hyperandrogenemia (elevated free testosterone levels using sensitive assays). Chronic anovulation was defined as persistence of menstrual irregularities 2 years post-menarche and pelvic ultrasound (USG) showing increased ovarian size (> 10 cm²). Normal physiological variations unrelated to hyperandrogenemia are common in adolescent ovaries and limits the usefulness of pelvic USG as a diagnostic criterion for PCOS [13,47,48]. Also, the prevalence of increased ovarian size in hyperandrogenemic adolescent patients was reported to be low, and its utility as a criterion for diagnosis needs to be further explored [49]. In our current practice we do not rely on pelvic USG findings to make a PCOS diagnosis.

Due to longstanding controversies and lack of consensus surrounding the accurate diagnostic criteria, a recent guideline was developed by experts in pediatric endocrinology and adolescent medicine invited by the Pediatric Endocrine Society to address these issues [13]. The guideline committee assessed the literature in order to define which criteria have sufficient evidence to be used for diagnosis of PCOS in adolescents. They recommend that PCOS should be considered in an adolescent girl presenting with unexplained menstrual irregularities, moderate to severe hirsutism or acne, and elevated levels of serum androgens (total and free testosterone) using reliable assay with well-defined ranges. Although intrinsic insulin resistance unique to PCOS is well known, none of the current guidelines either for adolescent and adult women include it as part of the diagnostic criteria. Since longitudinal studies focusing on the natural history of PCOS in this age-group are lacking, the current recommendations focus on timely screening and treatment in symptomatic adolescent girls suspected of having PCOS.

When there are PCOS features but menstrual irregularity has not been present for at least 2 years, one can defer the diagnostic label and instead use the term at-risk for PCOS. Such patients should have frequent longitudinal re-evaluations and should be offered treatment for their symptoms [13].

How should adolescents with PCOS be managed?

The treatment of PCOS is symptom-directed and should be tailored according to the complaints of the individual patient. However, it also must focus on the core dysfunctions: anovulation, hyperandrogenemia, obesity, and insulin resistance. It also requires bridging patient expectations of regulating menses, lessening the troublesome clinical signs of hyperandrogenemia (hirsutism, acne), and obesity management with the health care provider’s goals of preventing endometrial hyperplasia and cancer, diabetes mellitus, and cardiovascular disease.

Regulating menstruation and reducing cutaneous manifestations of hyperandrogenemia is the priority for any adolescent with PCOS. Combined oral contraceptive pills (COCs) are the first line of medical treatment for most adolescents. COCs restore endometrial cycling and suppress androgen levels, and are therefore optimal in treating abnormal uterine bleeding, pro-
tecting against endometrial carcinoma, and alleviating cutaneous manifestations of hyperandrogenemia (hirsutism and acne). Progestin monotherapy is considered an alternative therapy in individuals with contraindications to COCs (ie, thromboembolic risk). Although it is not effective in lowering androgen levels thus does not help reduce hair growth and acne, progestin monotherapy protects the endometrium and reduces the risk of endometrial cancer [50].

The majority of patients with PCOS are overweight or obese. Regardless of BMI, patients with PCOS have profound intrinsic insulin resistance that gets worse with overweight or obesity. Weight reduction by restricting caloric intake and increasing physical exercise is vital and has shown to be effective in regulating menstrual cycles, but is difficult to achieve [51–53]. Metformin can regulate menstrual cycles and decrease androgen levels by improving insulin sensitivity [54,55]. The use of metformin in PCOS patients is still controversial and abnormal glucose tolerance is the only approved indication [61]. However, combing metformin with COCs and lifestyle modification in obese PCOS patients has been shown to be used more frequently in pediatric endocrine clinics [56]. COCs are the only agents that can lower testosterone levels and improve ovulation and hirsutism; these effects are seen less frequently with lifestyle modification or metformin, either used alone or in combination.

COC monotherapy is first-line therapy to treat hirsutism. Consider anti-androgen treatment for hirsutism if there is no improvement after 6–9 months of hormonal treatment [57]. Antiandrogens reduce hirsutism by decreasing androgen production and binding the androgen receptors in target tissue. Spironolactone is the most commonly used antiandrogen therapy in adolescent girls with PCOS. Given the risk of teratogenicity with antiandrogens if pregnancy occurs, it is recommended to use it in combination with COCs [57]. Cosmetic measures including direct hair removal and electrolysis should be discussed with patients as other options for treatment of hirsutism.

Obese patients with PCOS are at higher risk for metabolic syndrome, a constellation of features including glucose intolerance, central obesity, hypertension, and dyslipidemia. Hyperandrogenemia and insulin resistance are linked with metabolic syndrome in PCOS. Reducing hyperandrogenemia and insulin resistance could reverse metabolic derangements and further reduce the risk of cardiovascular disease [58].

Worsening insulin resistance with COCs in PCOS has raised the concern of long-term metabolic derangements and cardiovascular adverse effects. COCs tend to increase total cholesterol, triglyceride, and high-sensitivity C-reactive protein levels [59]. However, the long-term implications of these findings are not well understood, attributable to the lack of longitudinal studies, especially in women with PCOS receiving COCs. Newer COCs containing less androgenic progestin may have less deleterious effect on insulin resistance and lipid profile. Due to insufficient use in adolescent patients, a definitive conclusion about their long-term safety cannot be drawn. Thus, there remains a theoretical risk of COCs exacerbating the underlying metabolic derangements in PCOS that can lead to subsequent adverse cardiovascular events.

Adolescent girls with PCOS are also at an increased risk for depression and anxiety disorders. The 2013 Endocrine Society clinical practice guideline suggests that adolescent girls with PCOS should be screened for depression and anxiety by history [51]. If symptoms are present, patients should receive appropriate psychological referral and treatment.

Case Continued

As she had no contraindications to COCs, the patient was started on COC therapy to regulate her menstrual periods and alleviate the symptoms of hirsutism. Due to impaired glucose tolerance test results and increased risk for type 2 diabetes, treatment with metformin was also initiated. The patient met with a dietician, who offered recommendations for adopting a healthy lifestyle and introduced her to the “3,2,1,0, blast off” model: 3 consistent meals, 2 hours or less of screen time, 1 hour or more of physical activity, and 0 sweetened beverages a day. The patient was also advised to increase daily consumption of fruits and vegetables. Results of the 2-item Patient Health Questionnaire (PHQ-2) for depression were negative.

At a follow-up visit 6 months later, the patient reported that her menstrual periods were regular. There was some improvement in hirsutism, requiring less shaving, and there was no increase in weight. Repeat laboratory evaluations showed normal free testosterone level, decreased HbA1c (5.2%), and improved random blood glucose (130 mg/dL). The patient was seen regularly and treatment results monitored. No side effects were seen over a 4.5-year period. As PCOS is a lifelong
condition, at the age of 21 the patient was referred to an adult endocrine clinic for further management.

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Financial disclosures: None.

References
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