Diagnosis and Management of Polycystic Ovary Syndrome in Adolescent Girls

Erin Lanzo, BA, MA, MS I,
University of Maryland School of Medicine

Maria Monge, MD, MAT, and
Dell Medical School, University of Texas at Austin, Austin, Texas

Maria Trent, MD, MPH
Johns Hopkins School of Medicine, Baltimore, Maryland

Abstract

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder in adolescent girls having both reproductive and metabolic implications. Patients with PCOS typically present to their pediatrician for evaluation of menstrual irregularity and/or signs of hyperandrogenism, such as hirsutism and acne. The diagnosis of PCOS is made by clinical symptoms and laboratory evaluation. Because of the long-term health consequences that can accompany the disorder, pediatricians should consider PCOS in their initial evaluation of menstrual irregularity. Lifestyle modification is the cornerstone of treatment for girls with PCOS, however hormonal medication such as oral contraceptive pills and insulin sensitizing agents are useful and effective adjuncts to therapy. The goals of treatment for girls with PCOS are to improve clinical manifestations of the disorder, health-related quality of life, and long-term health outcomes.

Keywords
Polycystic Ovary Syndrome (PCOS); Adolescent; Menstrual disorders; hirsutism; diagnosis; treatment

Case Presentation

Christina is a 17-year-old female who presents for evaluation of 9 months of amenorrhea. She has had irregular menses since menarche at age 12 and was prescribed birth control pills last year for menstrual regulation, but discontinued them 10 months ago. A recent home pregnancy test was negative and she admits being concerned about fertility as she has been having unprotected intercourse with her boyfriend.

On review of systems, she reports weekly professional hair removal, but denies problems with facial acne, weight changes, nipple discharge, headaches, abdominal pain, or other symptoms.
symptoms. Her past medical history is significant for elevated cholesterol, but she denies other health problems and takes no medications.

Her family history is remarkable for obesity, diabetes, hypertension and subfertility in an older sister. She lives with both parents and recently finished 11th grade with plans to attend college. She has a part-time job at a fast food restaurant and admits that her eating habits could be better. She does not use alcohol, tobacco or other drugs of abuse and does not exercise regularly.

On exam, she is a well-developed female with normal blood pressure, BMI of 35, with acanthosis nigricans (AN) in her neck and axillae, acne pustules on her chest and back, and Ferriman-Gallwey score of 20. She has Tanner V breast development. External genital examination reveals Tanner V pubic hair with heavy extension of hair along the linea alba. Pelvic examination shows a normal cervix without discharge, no uterine or ovarian enlargement and no cervical motion or adnexal tenderness. Her exam is otherwise unremarkable and urine HCG testing is negative.

Clinical Problem

Christina meets the current criteria for Polycystic Ovary Syndrome (PCOS), which is a common reproductive endocrine disorder among females, affecting 5–10% of women of reproductive age.1 The disorder is the most common cause of chronic anovulation and female infertility. PCOS is characterized by menstrual dysfunction and clinical or biochemical evidence of androgen excess. Many patients are overweight or obese and show evidence of insulin resistance. There is evidence for a genetic basis of disease, with 24% of mothers and 32% of sisters of PCOS patients also affected.2 The etiology of PCOS is unknown and as a heterogeneous disease, clinical presentation varies.3,4

Patients with PCOS usually present with disorders of menstrual function.5 Metabolic syndrome and hyperinsulinemia are associated with PCOS, thus women with PCOS are at higher risk for Type 2 diabetes and cardiovascular morbidity.6 There is also increased risk of endometrial hyperplasia and endometrial cancer.7

Adolescents with PCOS have been shown to have lower health-related quality of life (HRQL) compared to healthy adolescents girls.8 These reductions in HRQL are largely associated with obesity,9 but the effects of hirsutism, acne, and infertility are also well established in the literature.10 Further, in a study of 283 healthy and PCOS-affected adolescents aged 13 to 22 years, 68% of girls with PCOS were “worried about their ability to become pregnant in the future” and 3.4 times more likely to be concerned about their fertility than their healthy peers.8

History and Pathogenesis

Stein and Leventhal first described the disorder in 1935 after conducting clinical correlations with overweight women who had amenorrhea and difficulty conceiving a child.11 However, research in the field stalled until the 1980s when the oral contraceptive pill (OCP) became
widely available and hormonal treatment was demonstrated to improve menstrual regulation and the clinical effects of hyperandrogenism.\textsuperscript{12}

PCOS may surface early in the peri-menarchal period as evidenced by an abnormal physiological transition through puberty. Biochemical abnormalities that contribute to this process include LH hypersecretion resulting from increased frequency of gonadotrophic-releasing hormone (GnRH) release, excess ovarian and/or adrenal androgen production, and abnormalities in insulin secretion and sensitivity. While the cause for PCOS remains unknown, recent research has focused on LH stimulation of the ovary, GnRH secretion and gene expression, and insulin involvement in androgen production.\textsuperscript{13,14}

**Clinical Features and Diagnostic Criteria**

In 1990, an expert panel met at the National Institutes of Health and proposed diagnostic criteria for the “classic” diagnosis of PCOS, which include oligo- or anovulation, and biochemical or clinical signs of hyperandrogenism after exclusion of other causes of these symptoms.\textsuperscript{15} Menstrual dysfunction may manifest as amenorrhea, oligomenorrhea, sub- or infertility, and abnormal uterine bleeding. Because ovulation is difficult to measure, menstrual irregularity is typically used as a surrogate marker for ovulation abnormalities. Hyperandrogenism is marked by hirsutism,\textsuperscript{16,17} acne, male pattern baldness or alopecia, and one or more elevated androgens (e.g. total testosterone, free testosterone, dehydroepiandrosterone-sulfate (DHEA-S) and/or androstenedione).\textsuperscript{22}

The diagnostic criteria were updated and expanded at the Rotterdam meeting in 2003, broadening the spectrum of clinical findings to accommodate patients demonstrating symptoms of PCOS but not meeting NIH criteria.\textsuperscript{18} According to the Rotterdam criteria, any two of the three of hyperandrogenism, oligo- or anovulation and polycystic ovaries on ultrasound are sufficient for diagnosis. Clinical findings to support the diagnosis include: obesity, insulin resistance, and elevated luteinizing hormone (LH) levels. This reassessment of symptoms and findings highlights the heterogeneous and variable phenotypes for PCOS across patients and increases the number of diagnoses.\textsuperscript{18}

The Androgen Excess Society task force produced diagnostic guidelines in 2006 and concluded that PCOS is primarily a disorder of hyperandrogenism and its presence is requisite for diagnosis.\textsuperscript{19} (Figure 1). Patients with PCOS who have the highest levels of circulating androgens are at a greater cardiometabolic risk as compared to patients who have lower or normal androgen levels, thus understanding the criteria used for diagnosis is important for screening and counseling.\textsuperscript{20,21}

Clinicians must also consider other diagnoses that may underlie the patient’s presentation, particularly when the patient presents with a non-classic symptoms. Other potential diagnoses to consider include idiopathic hirsutism, late-onset congenital adrenal hyperplasia, ovarian or adrenal tumors, and Cushing syndrome.
Clinical Assessment

Clinical assessment begins with a detailed adolescent-centered interview that includes assessment of pubertal history (e.g. premature adrenarche), menstrual history (menarche, menstrual patterns), reproductive health history (contraceptive use and pregnancies,) past medical history, review of systems with attention to symptoms that are consistent with a diagnosis of PCOS (e.g. hair or skin changes, weight gain) and to rule out other disorders that may result in amenorrhea or abnormal bleeding (e.g. headaches, galactorrhea, weight changes, skin/nail changes) and family history with some focus on reproductive health and endocrine disorders in first degree relatives. The provider should also query the patient about use of over the counter or prescription medications and cosmetic procedures such as waxing, shaving or hair removal that may have altered appearance of acne or hirsutism.

Adolescents should also have a comprehensive physical examination that includes: 1) vital signs (assess for hypertension), 2) anthropometric assessment (assess for elevated BMI) 3) general appearance (evaluate upper body muscle mass) 4) skin assessment (assess for hair loss, acne, hirsutism/Ferriman-Gallwey score) for evidence of androgen excess, and acanthosis nigricans as evidence of insulin resistance, (Table 1, Figures 2 a & b)) 5) Tanner staging 6) examination of external genitalia (assess for evidence of virilization such as clitoromegaly (clitoral size >5mm diameter)) and 7) bimanual examination (if tolerated, to assess for ovarian mass).

Signs of hyperandrogenism, such as presentation in middle childhood with premature pubarche, may be observed in perimenarchal girls. Symptoms of ovarian dysfunction, such as irregular menses, may not be present until years after menarche. Girls with PCOS have higher LH levels and more cases of insulin resistance than their healthy peers. Many of the symptoms of PCOS (e.g. acne, irregular menses, and increased androgens) may be present with normal pubertal changes, but ultimately improve with time. Some caution, therefore, should be used when diagnosing PCOS in the 1–2 years following menarche.

Insulin resistance is an important component underlying the pathogenesis of PCOS as insulin augments the ovarian androgen response to LH and insulin may enhance LH secretion and contribute to dysregulation of LH at the pituitary level. Approximately 50% of adolescents with PCOS have evidence of insulin resistance. Overall, studies show that girls with PCOS have higher LH levels and more insulin resistance than non-hyperandrogenic girls during the pubertal process.

Laboratory and radiographic evaluation

Laboratory evaluation includes testing to support a diagnosis of PCOS and to rule out other causes of irregular menses and hyperandrogenism. Free and total testosterone and dehydroepiandrosterone-sulfate (DHEA-S) should be measured as markedly elevated levels raise the possibility of an adrenal or ovarian tumor. If late onset congenital adrenal hyperplasia is suspected, a 17-hydroxyprogesterone should be obtained. Due to enhanced LH secretion, the ratio of LH to follicle stimulating hormone (FSH) may be elevated, however, it should not be used in isolation for diagnosis as many women with PCOS will not have an elevated LH/FSH ratio. Elevated anti-müllerian hormone (AMH) has also been
implicated in the anovulation and infertility associated with PCOS due to its impact on FSH. AMH is also a potential prognostic biochemical marker for follow-up after initiation of treatment with an insulin-sensitizing agent; however, guidelines for use in clinical practice have not yet been established.29

Pelvic ultrasounds are commonly ordered in patients with PCOS to determine if the classic ovarian morphology (thickened, white capsule, enlarged ovary (>10 cc volume) with multiple small cysts, or at least 10 follicles, 2–8mm in diameter) is present. While studies confirm increased ovarian volume and classic morphology in PCOS affected adolescents compared with controls using ultrasound,30 it is important to remember that while supportive, the ultrasound findings are not specific to PCOS. Polycystic ovaries are present in 92% of women with idiopathic hirsutism, 87% of women with oligomenorrhea, 30–40% of women with amenorrhea, and 23% of women with regular cycles.31 Ultrasound should be reserved for adolescents with suspected ovarian pathology (significant enlargement and/or tenderness) on bimanual examination, for those in whom reproductive structures cannot be assessed using clinical exam, and/or young women who are formally seeking fertility evaluation services.

Metabolic screening using a fasting cholesterol and glucose is recommended in all adolescents diagnosed with PCOS and if abnormal or there are significant concerns about glucose intolerance or diabetes, a detailed lipid profile, and 2-hour oral glucose tolerance test (OGTT) should be obtained. Fasting glucose and OGTT are often difficult to facilitate for adolescent patients, therefore a random glucose and hemoglobin A1C can be measured with other laboratory testing, as a second fasting visit is not required. Patients should continue to be screened every 1–2 years as a subset of patients with normal baseline results develop impaired glucose tolerance or diabetes within six years.32 Adolescents with normal weight should also be screened for metabolic abnormalities, as they often show evidence of glucose intolerance and hyperlipidemia.33 If initial screening is normal and no risk factors develop, repeat testing is unnecessary.

Finally, urine pregnancy testing, serum prolactin, and thyroid stimulating hormone are important screening tests to evaluate for pregnancy, hyperprolactinemia, and thyroid dysfunction as common causes of menstrual dysfunction in affected girls.

### Treatment Options

The ultimate goals of PCOS treatment are to improve the clinical manifestations, HRQL, and long-term health outcomes for affected patients. The short-term priority for adolescent girls is to lower ovarian androgen levels via hormonal suppression. Ideally, controlling these androgen levels will improve menstrual regularity and in turn prevent endometrial hyperplasia. In some patients, treatment should target insulin sensitivity to help decrease long-term complications with metabolic syndrome and diabetes. The patient may also wish to address the aesthetic issues associated with PCOS, (e.g. hirsutism and acne) as these problems have been associated with reduced health-related quality of life in adolescents.34
Non-pharmacologic and Lifestyle Changes

Non-pharmacologic treatments, such as weight loss and lifestyle modification to include exercise, can contribute to improved menstrual regularity. In a 2011 study of adolescent girls with PCOS, during which the patients were given nutritional counseling and who complied with a modified diet, results showed that girls who recorded changes in weight and BMI were more likely to resume menstrual function than those who had not lost weight.\(^{35}\) An additional 2011 study shows that lifestyle intervention that includes dietary and exercise modifications improved body composition, hyperandrogenism, and insulin resistance in women with PCOS.\(^{36}\) One should recognize that while lifestyle modifications have been shown to result in significant improvements in clinical status, they are behavioral changes that may be difficult to maintain over time. There is a high degree of relapse and, studies of adolescents engaged in intensive lifestyle modification programs show a 30% drop out rate.\(^{37}\)

Pharmacologic Interventions

**Menstrual Management**—Pharmacologic therapies are important strategies for managing the endocrine features of PCOS\(^{38}\) and combined estrogen-progesterone OCPs have been the mainstay of pharmacologic treatment for most patients who are not actively seeking pregnancy. OCPs decrease LH levels and decrease androgen synthesis, while also increasing sex hormone binding globulin (SHBG) levels and testosterone binding, thereby decreasing free testosterone. Additionally, OCPs inhibit 5 alpha-reductase, which reduces the conversion of testosterone to dihydrotestosterone (its more active form). Early initiation of treatment is essential to prevent the development of changes in physical appearance. While there has been limited research on the use of alternative combined estrogen and progesterone delivery methods in treatment of PCOS signs and symptoms, use of the vaginal ring and contraceptive patch may be preferred by patients due to the less cumbersome nature of self-management.\(^{39}\) Girls who choose combined OCPs, however, may opt for extended cycling for menstrual management.

When prescribing OCPs, providers should reference the Centers for Disease Control and Prevention Medical Eligibility for Contraceptives guidelines to contextualize any medical issues the patient may have.\(^{40}\) Patients for whom estrogen is contraindicated may benefit from using progestin only pills (POPs). For example, medroxyprogesterone at 10mg daily for 12–14 days every 1–3 months can help regulate menses and lessen the risk of endometrial cancer by producing an organized withdrawal bleed. However, because POPs do not impact androgen levels, they may not achieve optimal menstrual regulation or symptom relief as with combined OCPs. While long-acting reversible contraceptives (LARCs) have emerged as an important option in adolescent pregnancy prevention,\(^{41,42}\) these methods do not contain estrogen and thus adolescents with PCOS who have many of the clinical features of the disorder would not receive the clinical benefits (e.g. androgen suppression) of combined hormonal methods. Careful counseling regarding optimal methods to self-manage PCOS in the context of pregnancy risk is warranted, particularly in patients for whom adherence is problematic or patients whose menstrual status has improved with lifestyle modification and/or treatment (e.g. weight loss, return to menstrual function with insulin sensitizing agents). All sexually active adolescents should be encouraged to use condoms.
regularly as a back-up method of contraception and for prevention of sexually transmitted infections (STIs).

Treatment of Hirsutism and Acne

Prior to their initial medical evaluation, many patients with PCOS have started to self-manage hirsutism and acne using over-the-counter products as well as community cosmetology and dermatology resources. Health providers should be cognizant of this when assessing baseline Ferriman-Gallwey scores as patients may have modified the distribution of hair growth for cosmetic reasons. A score less than 8 is considered normal, whereas 8–15 indicates mild hirsutism and >15 indicates moderate to severe hirsutism. Adding additional questions about thickness of body hair in these areas without intervention, the frequency of intervention, and the pain associated with removal (coarse hair is often more painful to remove) may provide additional insight into the patient’s needs. Finally, use of photography at baseline and subsequent visits may assist the patient in better self-assessment of improvement. Since many hair removal treatments are considered cosmetic, most patients pay out of pocket to self-manage hirsutism.

Through their effects on androgen levels, hormonal medications (OCPs) play a key role in the management of hirsutism, in addition to menstrual regulation. Unfortunately, hair removal methods are often a required adjunct to minimize the appearance of hirsutism. Temporary methods for hair removal include bleaching, shaving, chemical depilatories, tweezing, and waxing. Potential side effects of mechanical methods may include skin irritation, allergic response, scarring, and folliculitis. There are also topical creams, such as eflornithine 13.9%, which acts at the level of the hair follicle and is most effective if used in conjunction with mechanical hair removal methods. Side effects may include burning and folliculitis. It is important to counsel patients that hair growth will resume once ongoing application is discontinued.

Permanent hair removal methods include electrolysis, thermolysis, and laser treatment. Laser treatment is effective for treating large areas with fewer side effects than electrolysis or thermolysis. Overall, laser treatment is most effective in patients with light skin and dark hair. Significant side effects (e.g. hyperpigmentation, hypopigmentation, and scarring) have been observed in patients with darker skin, but newer laser techniques have been shown to improve outcomes across skin types. Adolescents need to be counseled that multiple dermatology visits are required, to inquire about the types of available laser treatments, and that cost of treatment may not be covered by insurance. The latter limits laser as a viable option for many patients.

Anti-androgens such as spironolactone can substantially reduce hair diameter over 12 months of use. The initial dose of spironolactone [50–100 mg] is best used in conjunction with OCPs as it is a pregnancy category C drug and outcomes are improved if the two agents are used in conjunction. Recent data also suggest that the combination of OCPs, metformin, and spironolactone significantly reduces clinical hyperandrogenism. Spironolactone is clinically indicated for patients with moderate/severe hirsutism (baseline Ferriman-Gallwey score), those requiring frequent cosmetic hair removal methods, and hirsute patients in whom OCPs and/or other combined methods are contraindicated.
Potential, but uncommon, side effects hypotension, lethargy, urinary frequency, hyperkalemia, and nausea.\(^{47}\)

Regarding acne treatment, combined hormonal contraceptives have been demonstrated to reduce acne, however standard daily skin regimens should also be prescribed.\(^{48}\) Standard treatment for mild acne includes use of gentle cleansers, topical benzoyl peroxide or salicylic acid and hypoallergenic moisturizers. Patients with moderate to severe acne also benefit from routine cleansing, but topical antibiotics, retinoic acid, and azelaic acid are useful adjuncts. Patients with body involvement (e.g. chest, back) may benefit from systemic antibiotics and isotretinoin may be indicated for severe acne.

**Treatment of Insulin Resistance, Glucose Intolerance, and Obesity**

Patients with PCOS are at risk for metabolic syndrome and type 2 diabetes, and weight loss is an essential component of their treatment plan\(^7\) as it reduces peripheral estrogen production, cardiovascular risks and insulin resistance, and suppresses ovarian androgen production.\(^{49}\) Patients should be encouraged to engage in regular exercise and reduce caloric intake with the goal of normoglycemia.

Insulin sensitizing agents are an effective adjunct to lifestyle modification and weight loss. Metformin is the preferred and safest medication for use in adolescents.\(^{50}\) Adolescent patients with PCOS who are candidates for metformin treatment include those who also have diabetes, glucose intolerance, obesity or evidence of insulin resistance, as well as those who have a strong family history of diabetes in the context of PCOS.\(^{38}\) The recommended dosing is 500 mg TID, 850 mg BID, or extended release (multiple formulations of 500mg, then increase to 1–2g per day for most formulations). Side effects are primarily gastrointestinal and include flatulence, cramping, and diarrhea. Because metformin can result in return of ovulation, use of this medication in sexually active adolescents should prompt a discussion about contraception given the potential for increased fertility. Similarly, successful weight loss is often accompanied by return of menstrual regularity and increased fertility.\(^{35}\)

**Sexual Health and Fertility Concerns**

Adolescents with PCOS tend to be less sexually active than their non-PCOS peers (36% of PCOS patients, compared with 55% of non-PCOS patients), though there is no apparent difference in age of sexual debut. However, 68% of these adolescents express fertility concerns and some PCOS patients report that the disease does “nothing to their life” other than make them “afraid [they] will never be able to have children.”\(^{13}\) Pediatricians should be prepared for questions and concerns about fertility in these adolescents as it is a common concern.\(^{51}\) There are many reproductive technologies now available and pregnancy outcomes are similar in women with PCOS and non-affected women of similar clinical status.\(^{52}\)

Because the rates of sexually transmitted infections (STI) such as Chlamydia trachomatis are highest in youth,\(^{33}\) sexually active PCOS patients still face risks for STI acquisition.
Development of recurrent or complicated STIs and/or pelvic inflammatory disease [PID] may further impair future fertility.\(^{54}\)

Some adolescents with PCOS will periodically ovulate and/or return to ovulation with treatment\(^ {59}\) and subsequently are at risk for pregnancy. Sexuality education and contraceptive counseling with routine STI screening remain important components of clinical care for young women with PCOS.

Referral to an adolescent medicine specialist and/or pediatric endocrinologist can facilitate patient management if there are underlying complexities. Young adult patients interested in childbearing should be referred to a reproductive endocrinologist for a fertility evaluation in the context of family planning. The pediatric provider should also work with the patient and family to ensure other developmental milestones are met. Future access to advanced reproductive technologies typically requires private health insurance through an employer and/or access to personal financial resources as currently, only 20\% of private insurers cover these services and they are not covered under the Affordable Care Act.\(^ {55}\) As such, vocational attainment developmental outcomes emerging through adolescence into young adulthood are critical for securing future fertility resources if needed.

**Summary**

PCOS is a common reproductive health disorder that affects young women as they move through puberty and into adulthood. Young women may experience a range of menstrual abnormalities and infertility, as well as other clinical complications associated with androgen excess, obesity, and insulin resistance. As such, health-related quality of life can be significantly impacted. Fortunately, there are effective medications to treat PCOS and its associated clinical symptoms. Use of adolescent-friendly clinical, mental health, and cosmetology consultative services may facilitate building an interdisciplinary team to support patients and families affected by the disorder.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**References**

6. Coviello AD, Legro RS, Dunai A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. 2006; 91(2):492–497.


Figure 1.
Venn diagram depicting the overlapping relationship between the consensus recommendations for diagnosis of PCOS.
Figure 2.
Hirsutism and acne (a) and acanthosis nigricans (b) in female patients. [DermAtlas: Online Dermatology Image Library, With Permission [Cohen, B (ed)], All rights reserved.]
Table 1
Common clinical findings associated with PCOS

<table>
<thead>
<tr>
<th>Signs of Androgen Excess</th>
<th>Evidence of Menstrual/Reproductive Dysfunction</th>
<th>Evidence of Metabolic Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hirsutism</td>
<td>1 Amenorrhea</td>
<td>1 Obesity</td>
</tr>
<tr>
<td>2 Acne</td>
<td>2 Oligomenorrhea</td>
<td>2 Acanthosis nigricans</td>
</tr>
<tr>
<td>3 Male pattern hair loss</td>
<td>3 Dysfunctional Uterine Bleeding</td>
<td>3 Elevated blood glucose (Glucose intolerance, Type 2 diabetes mellitus)</td>
</tr>
<tr>
<td>4 Upper body muscle mass</td>
<td>4 Anovulation or oligoovulation</td>
<td>4 Elevated Insulin levels</td>
</tr>
<tr>
<td>5 Clitoromegaly</td>
<td>5 Ovarian Enlargement</td>
<td>5 Hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td>6 Endometrial hyperplasia Infertility</td>
<td></td>
</tr>
</tbody>
</table>