Review Article

Polycystic ovary syndrome in adolescence: diagnostic and therapeutic strategies

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Abstract: Controversy continues about the underlying etiopathogenesis, diagnostic criteria, and recommendations for polycystic ovary syndrome (PCOS) in adolescents. Recent literature has recognized these deficiencies and evidence based expert recommendations have become more available. The purpose of this chapter is to offer primary care providers a practical understanding and approach to the diagnosis and treatment of PCOS in adolescents. Although the presence of polycystic ovary morphology (PCOM) is included as a key diagnostic criterion of PCOS in adults, it is currently not recommended for the diagnosis in adolescents. As such, the diagnosis of PCOS in adolescents currently hinges on evidence of ovulatory dysfunction and androgen excess. Recommended evidence of ovulatory dysfunction includes: consecutive menstrual intervals >90 days even in the first year after menstrual onset; menstrual intervals persistently <21 or >45 days 2 or more years after menarche; and lack of menses by 15 years or 2–3 years after breast budding. Recommended evidence of androgen excess include: moderate to severe hirsutism; persistent acne unresponsive to topical therapy; and persistent elevation of serum total and/or free testosterone level. Importantly, a definitive diagnosis of PCOS is not needed to initiate treatment. Treatment may decrease risk of future comorbidity even in the absence of a definitive diagnosis. Deferring diagnosis, while providing symptom treatment and regular/ frequent follow-up of symptomology, is a recommended option. The treatment options for PCOS should be individualized to the presentation, needs, and preferences of each patient. Goals of treatment are to improve quality of life and long-term health outcomes. Lifestyle modifications remain first-line management of overweight and obese adolescents with PCOS. Combined oral contraceptives (COC) are first line pharmacotherapy for management of menstrual irregularity and acne, and metformin is superior to COCs for weight reduction and improved dysglycemia. COCs and metformin have similar effects on hirsutism, but often need to be paired with other treatment modalities to achieve further improvement of cutaneous symptoms. Clinicians should be cognizant that PCOS is associated with significant metabolic and psychological comorbidity and screen for these issues appropriately.

Keywords: Adolescent; diagnosis; polycystic ovary syndrome (PCOS); therapeutics

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women (1). It is associated with significant morbidity including impaired reproductive health, psychosocial dysfunction, metabolic syndrome, cardiovascular disease, and increased cancer risk (2,3). Controversy continues about the underlying etiopathogenesis, diagnostic criteria, and recommendations for PCOS in adolescents. Recent literature has recognized these deficiencies and evidence based expert recommendations have become more available (4-6). The purpose of this chapter is to offer primary care providers a practical understanding and approach to the diagnosis and treatment of PCOS in adolescents.

Case presentation

TS is a 16-year-old female adolescent with a history of normal puberty and menarche at 12 years of age. She states that she has been having irregular periods since onset of menses. Periods initially occurred every 2–3 months, but she has had only 3 over the last year with last menstrual period about 3 months prior. Menses last for about 3–4 days and are described as light blood flow. The patient also has history of coarse dark hair growth on the face and lower abdomen which has progressively increased over the last 2–4 years. She is now shaving every 2–3 days. She has also noticed progressively worsening acne on the face and back.

TS has been overweight since early childhood with more rapid weight gain over the last 5–6 years. Today she has a BMI of 38 kg/m^2. Her blood pressure is 140/90 mmHg. Acne, hirsutism, and acanthosis nigricans are confirmed on physical examination. There are no obvious cushingoid features. Her physical exam is otherwise unrevealing.

Endocrine laboratory testing revealed: 17 hydroxy progesterone =110 ng/dL; DHEAS =225 mcg/dL; total testosterone =70 ng/dL; free testosterone =12 ng/dL; LH =20 mIU/mL; follicle stimulating hormone (FSH) =12 mIU/mL; Hemoglobin A1C 5.9%.

Etiopathogenic considerations

Although the pathogenesis is not well understood, PCOS is likely a complex interaction between genetic and environmental factors. Accepted etiologic theories include disordered neuroendocrine gonadotropin secretion, hyperandrogenism, insulin resistance, and hyperinsulinemia or a combination thereof (7). In many, ovarian hyperandrogenism appears to be the primary dysfunction with additional related findings of hyperinsulinism, insulin resistance, elevated luteinizing hormone (LH) and an association of obesity as well. However, it is recognized that there is heterogeneity in this syndrome (8).

Diagnostic criteria

There are currently three sets of diagnostic criteria for PCOS in adults. The National Institutes of Health (NIH) criteria require menstrual irregularity and evidence of androgen excess (9). The Rotterdam guideline accepts any two out of three criteria consisting of menstrual irregularity, androgen excess, and polycystic ovary morphology (PCOM) on ultrasound (10). The Androgen Excess and PCOS Society (AE-PCOS) recommends diagnosis in the presence of hyperandrogenism with either menstrual irregularity or PCOM (11). In December 2012, the NIH's Evidence-based Methodology Workshop on Polycystic Ovary Syndrome recommended upholding the broad, inclusionary Rotterdam criteria while specifically identifying the distinct PCOS phenotype (*Table 1*) (12).

In routine practice, these same criteria have been extrapolated for use in adolescents. However, the adult diagnostic criteria present a practical challenge in adolescents. Many adolescents exhibit physiologic menstrual irregularity and signs of androgen excess (e.g., acne) in the peripubertal period (13). In addition, normative testosterone levels are ill defined in this age group (14), and normal adolescent ovarian morphology overlaps with that of women with PCOS (15,16).

Experts in the field have long recognized these diagnostic dilemmas for PCOS in adolescents. A recent consensus paper of international pediatric and adolescent specialty societies evaluated which of the adult PCOS criteria have sufficient evidence to be used for PCOS diagnosis in adolescents (4). Important findings of this work are highlighted below.

The authors noted the challenge of differentiating normal 'physiological adolescent anovulation' from true ovulatory dysfunction, but highlighted that most adolescent menstrual cycles still fall within certain parameters. As such, the following were recommended as evidence of ovulatory dysfunction in adolescents: (I) consecutive menstrual intervals >90 days even in the first year after menarche; (II) menstrual intervals persistently <21 or >45 days 2 or more

Table 1 PCOS phenotypes included in specific diagnostic criteria

Diagnostic criteria	PCOS phenotype			
	AE + OD	AE + PCOM	PCOM + OD	AE + PCOM + OD
NIH 1990	+			
Rotterdam 2003/2006	+	+	+	+
AE-PCOS society 2006	+	+		+
NIH 2012	+	+	+	+

All criteria recommend exclusion of other causes. AE, androgen excess; OD, ovulatory dysfunction; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

years after menarche; and (III) lack of menses by 15 or 2–3 years after breast budding.

Persistent elevation of serum total and/or free testosterone level determined in a reliable reference laboratory were put forth as the best evidence of biochemical androgen excess in an adolescent girl with symptoms of PCOS. Although isolated mild hirsutism was considered normal in the early post-menarcheal years, moderate to severe hirsutism was endorsed as clinical evidence of androgen excess as was persistent acne unresponsive to topical therapy. It was recommended that the latter be evaluated for presence of hyperandrogenemia prior to initiation of medical therapies.

With regards to PCOM, the consensus concluded that ovarian imaging can be deferred during the diagnostic evaluation of PCOS in adolescents until high-quality data for PCOM are available. As such, the diagnosis of PCOS in adolescent currently hinges on evidence of ovulatory dysfunction and androgen excess.

Additional important diagnostic considerations highlighted in the consensus publication included:

(I) A definitive diagnosis of PCOS is not needed to initiate treatment. Treatment may decrease risk of future comorbidity even in the absence of a definitive diagnosis;

(II) Deferring the diagnosis of PCOS, while offering symptom treatment and providing regular/frequent follow-up of symptomology, is a recommended option;

(III) Obesity, hyperinsulinemia, and insulin resistance are recognized as common in adolescents with PCOS, but these features should not be used for diagnostic purposes;

(IV) Other causes of hyperandrogenemia and irregular menstrual periods must be ruled out before a diagnosis of PCOS can be established.

Clinical features

Adolescent girls with PCOS may present with abnormal menstrual periods, hirsutism, and/or acne. A stepwise diagnostic approach is recommended in these patients. Historical details should include a review of exogenous medication intake. Androgenic steroids and some anti-seizure medications may cause clinical features similar to those seen in PCOS, and medications commonly used to treat acne may resolve or mask some PCOS features (17).

Various patterns of menstrual irregularity may be seen in adolescents with PCOS including primary amenorrhea (absence of menarche by 15 years of age or 2–3 years after breast budding), secondary amenorrhea (more than 90 days without a period with history of prior menstrual periods), oligomenorrhea, and even excessive uterine bleeding (4). A recent study found that PCOS was the most common underlying etiology in adolescents hospitalized with abnormal uterine bleeding (AUB) and menorrhagia, accounting for 33% of admissions (18).

Hirsutism and acne may be clinical reflections of hyperandrogenemia. The severity and progression of both these features should be carefully followed. The Ferriman-Gallwey score can be used to grade the degree of hirsutism (19,20). Acne severity can be categorized as mild, moderate, or severe based on lesion type and count (21).

It is extremely important that clinicians remain cognizant of other possible underlying pathologies such as thyroid dysfunction, elevated prolactin, hypercortisolemia, and other causes of virilization, which may result in a similar clinical presentation. Clinical and biochemical work up should evaluate for these conditions.

Laboratory evaluation

Measurements of total and/or free testosterone have

been the most recommended hormone determinations to document hyperandrogenemia (11,19,22). In assays using an extraction step, total testosterone concentrations >55 ng/dL are generally considered consistent with hyperandrogenism (23). Dehydroepiandrosterone sulfate (DHEAS) level is also useful to screen for primary adrenal source of hyperandrogenemia.

These hormone levels should preferably be drawn in the morning. A normal afternoon androgen level does not necessarily exclude hyperandrogenemia. If a patient meets clinical criteria for PCOS but the laboratory evaluation fails to demonstrate hyperandrogenemia, repeat morning hormone levels can be drawn (24,25). The clinician should be aware that if treatment has been initiated in the interim, hormone levels may be altered.

Additional laboratory work up may be individualized as needed to rule out other causes of hyperandrogenemia or menstrual irregularity based on clinical features. Generally this work up includes: 17-hydroxyprogesterone (17-OHP), androstenedione, free thyroxine (FT4), thyroid-stimulating hormone (TSH), LH, FSH, and prolactin. Pregnancy should be ruled out in all patients.

A cosyntropin (ACTH) stimulation test should be ideally performed to screen for non-classic congenital adrenal hyperplasia (NC-CAH). However, undertaking the ACTH stimulation testing in all patients may not be practical. Recommendations have been made about the usefulness of a morning 17-OHP level of >200 mg/dL as a screening tool for NC-CAH. It has been reported to detect a majority of women with non-classic CAH (26,27).

Pelvic ultrasonography is generally not recommended for a diagnosis of PCOS in adolescents. The ultrasonographic criteria for diagnosis of PCOS in adolescents are not well defined (4). However, pelvic ultrasonography may be indicated based on clinical features to rule out other underlying pathology (28). Some experts in the field feel it is important to exclude rare causes of androgen producing tumors in all adolescent girls presenting with anovulatory symptoms and hyperandrogenemia (29).

Evaluation for comorbidity

PCOS is associated with significant metabolic and psychological morbidity (30-32). High prevalence of both insulin resistance and hyperinsulinemia has been well documented in PCOS (4). In addition, overweight and obesity are commonly found in adolescents with PCOS and confer their own risk (33). Metabolic syndrome, impaired glucose tolerance, and type 2 diabetes are all more frequent in adolescents with PCOS (30,34-37), and patients should be screened for their presence. The 2-hour plasma glucose level after an oral glucose challenge appears to be the most reliable screening test for abnormalities in glucose tolerance, and some authors have recommended periodic screening for abnormal glucose tolerance using the 2-hour oral glucose tolerance test in adolescents with PCOS (38).

The psychological impact of PCOS should also not be ignored (39). Increased prevalence of depression and anxiety has been documented, and validated tools should be utilized to identify these entities among adolescents with PCOS (31,32). In addition, providers should be cognizant that both clinical and subclinical eating disorders are more prevalent in adolescents with PCOS and be mindful of this as they provide lifestyle counseling (40).

Management considerations

Given that current evidence is of low quality, treatment options for PCOS should be individualized to the presentation, needs, and preferences of each patient while balancing potential side effects (41). Goals of treatment are to improve quality of life and long-term health outcomes.

Lifestyle modifications remain first-line management of overweight and obese adolescents with PCOS. Improved menstrual regularity, decreased cardiometabolic risks, and improved androgen excess can all be achieved with weight loss (42-46).

Combined oral contraceptives (COC) are a first choice pharmacotherapy for PCOS as they can address many of the symptoms of this condition (6). In addition, COC provide contraceptive coverage in patients who are sexually active. The estrogen-progesterone combination suppresses the endogenous hypothalamic-pituitary-ovarian (HPO) axis and thereby interrupts the pathophysiologic mechanism of PCOS resulting in reduced ovarian androgen production. In addition, COC increase sex hormone binding globulin thereby further decreasing androgen excess (47). The progesterone component of the COC also prevents unopposed estrogen action and prevents endometrial hyperplasia. Other combined hormonal contraceptives, such as the patch and ring, likely have similar effects but are less studied.

COC are a first choice for regulation of any pattern of menstrual irregularity including amenorrhea, oligomenorrhea, menorrhagia and AUB (6,19). Improvement in menstrual pattern is generally noted

within the first 2 to 3 months. Hyperandrogenemia is also shown to improve, and testosterone levels may be rechecked after the third month of therapy to document reduction. Duration of treatment with COC is not yet well defined. It has been suggested that a trial off the COC may be considered after one or more years of therapy to allow for recovery of the HPO axis and observe if spontaneous menstrual regularity returns. However, the benefits of this have not been established and must be weighed against potential risk of pregnancy.

COC also serve as a drug of choice for cutaneous manifestations of hyperandrogenemia. Improvements have been noted in both acne and progression of hirsutism with use of COC. Although progestin-only contraceptives may be used for treatment of menstrual regularity, their effect on hyperandrogenism is less, and therefore, decreased improvements in cutaneous manifestations are evident with these methods.

Metformin has been recommended for women with PCOS with type 2 diabetes or impaired glucose tolerance which do not improve with lifestyle changes (6). A recent meta-analysis of randomized controlled trials evaluating the use of metformin versus COC for the treatment of PCOS in adolescents found metformin to be as effective as COC for treatment of hirsutism. Metformin was found to be superior to COC for weight reduction and improved dysglycemia, but COC was preferable for menstrual regulation. The authors stressed however that overall quality of data is poor, and future high quality studies are needed to better address key questions regarding treatment of PCOS in adolescents (41).

To achieve further improvement in cutaneous symptoms additional treatment is often needed as an adjunct to COC or metformin. Spironolactone is a potent anti-androgen that can be used in conjunction with COC or metformin. Spironolactone can improve menstrual irregularities and cutaneous manifestations of hyperandrogenism, but it does not improve metabolic abnormalities (48,49). Ganie and colleagues found that combination metformin and spironolactone was superior to either drug alone in improving menstrual irregularity, hirsutism, serum androgen levels, and insulin resistance (50). As spironolactone is a potential teratogen, it is imperative that it be used in combination with effective contraception in sexually active adolescents. In a pilot study, intermittent low-dose oral finasteride was reported effective for treatment of hirsutism in adolescent girls with PCOS or idiopathic hirsutism (51).

Cosmetic hair removal processes may offer more immediate results than pharmacotherapy, and can be accessed by patients without need for prescription. Electrolysis and laser hair removal therapies have gained popularity as they become more effective and affordable. Prescription methods for topical hair removal include eflornithine cream which offers benefit for hirsutism, but requires indefinite use to maintain efficacy. Eflornithine combined with laser therapy resulted in more rapid reduction in facial hair as compared to laser treatment alone, but data is limited (52,53). In addition, clinicians should be mindful that this therapy is not covered by most insurance plans in the United States.

Summary and conclusions

Based on current diagnostic recommendations, the patient in the case presentation vignette meets the diagnostic criteria for PCOS in an adolescent. She has evidence of ovulatory dysfunction and both clinical and laboratory evidence of hyperandrogenism. In addition, her hemoglobin A1C indicates pre-diabetes. She requires further evaluation for metabolic and psychological comorbidity. Her treatment plan should be individualized to her needs but should address her menstrual irregularity, cutaneous manifestations, and impaired glucose tolerance. Lifestyle counseling with combined initiation of COC and metformin would be an appropriate first step in the ongoing care of this patient.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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