The diagnosis and treatment of PCOS in adolescents: an update

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Purpose of review
Polycystic ovary syndrome (PCOS) is often difficult to diagnose in adolescents. Recent recommendations and concepts regarding the diagnosis and treatment of PCOS in the adolescent girl are considered.

Recent findings
The diagnosis of PCOS in adolescents should be primarily based on clinical and biochemical signs of hyperandrogenism and presentation with irregular menses. Because of the similarity of normal pubertal development and features of PCOS, the diagnosis should be deferred until at least 2 years following menarche. For girls who do not fulfill the diagnostic criteria, the focus should be on treatment of symptoms.

Summary
PCOS is a complex, multifaceted disorder, and should be diagnosed and treated in adolescents after taking into consideration the patient's full diagnostic picture, metabolic risks, and individual concerns, to both avoid overdiagnosis but yet be able to provide early and meaningful interventions.

Keywords
adolescent, diagnosis, hyperandrogenism, oligomenorrhea, PCOS, polycystic ovary syndrome, treatment

INTRODUCTION: WHAT IS POLYCYSTIC OVARY SYNDROME?

Polycystic ovary syndrome (PCOS) is a common heterogeneous disorder affecting 6–15% of women of reproductive age depending on diagnostic criteria [1–3]. The term 'syndrome' refers to a collection of clinical features or a phenotype. The specific features of the PCOS phenotype include clinical signs of androgen excess, elevated serum androgen concentrations, irregular menses, and infertility.

Defining specific diagnostic features may be problematic for some syndromes such as PCOS. Since the initial descriptions of PCOS by Drs. Stein and Leventhal [4,5], several permutations of expert opinion regarding diagnostic criteria have been utilized. The most recent evidence-based international consensus favors the use of the Rotterdam criteria in adult women. These criteria can be further categorized into four groups (Table 1) [6]. However, the dearth of evidence-based data concerning adolescent PCOS impedes the identification of affected girls [7].

Irregular menses, anovulatory cycles, multifollicular ovary morphology, and mildly elevated serum androgen concentrations occur during normal pubertal development. Given the convergence between normal pubertal milestones and PCOS clinical features, confirming a diagnosis of PCOS in an adolescent girl can be challenging. Insulin resistance, hyperinsulinemia, and obesity commonly accompany PCOS, but are not diagnostic features [8].

In addition to irregular menses, infertility, and hirsutism, the comorbidities associated with PCOS include impaired glucose tolerance, type 2 diabetes mellitus, insulin resistance/hyperinsulinemia, dyslipidemia, hypertension, endometrial cancer, obesity, nonalcoholic fatty liver, and sleep apnea. Depression and impaired quality of life also occur. Early identification of adolescent girls with high risk to develop PCOS encourages targeting of individualized therapeutic interventions. We will review the

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KEY POINTS

- The diagnosis of PCOS in adolescents should be based on the presence of clinical and/or biochemical hyperandrogenism and irregular menses at least 2 years postmenarche; PCOM on ultrasound is not a diagnostic criteria in adolescents.
- Patients who present with irregular menses without clinical/biochemical hyperandrogenism can be labeled 'at-risk' for PCOS. These patients should be followed longitudinally.
- Severe acne, obesity, insulin resistance, and hyperinsulinemia are common in PCOS, but are not a basis of diagnosis.
- During diagnosis, clinicians should be aware that the features of PCOS can overlap with normal puberty, to avoid overdiagnosis and unnecessary treatments.
- Treatment options include cosmetic hair removal techniques, COCPs alone or combined with metformin and/or antiandrogen agents, or metformin alone for patients with metabolic abnormalities.
- No single universal treatment can be identified that is efficacious in all adolescents with PCOS or 'at-risk' for PCOS. Hence, individualized treatment is preferred.

major clinical features and comorbidities associated with PCOS in adolescent girls.

WHAT ARE THE CLINICAL MANIFESTATIONS OF HYPERANDROGENISM?

The clinical manifestations associated with androgen excess include hirsutism, moderate to severe inflammatory acne, and menstrual irregularities. Hirsutism is defined as excessive terminal hair growth for women in male-typical areas of the body. The extent of body hair growth varies according to ethnic/genetic factors [9]. Hirsutism should be distinguished from hypertrichosis which refers to generalized increased body hair growth. Specific drugs, that is dilantin and minoxidil, and genetic disorders can cause hypertrichosis. Androgen secreting tumors need to be excluded when virilizing symptoms rapidly progress.

Table 1. PCOS phenotypes based on expert opinion at the 2012 NIH Evidence Based Methodology PCOS Workshop

Symptoms	Phenotype			
	A	B	C	D
Clinical and/or hormonal hyperandrogenism	Yes	Yes	Yes	–
Oligo-amenorrhea	Yes	Yes	–	Yes
Polycystic ovary morphology	Yes	–	Yes	Yes

Several scoring systems have been proposed to measure the magnitude of hirsutism. All methods are limited by the subjective nature of these assessment tools. Because of the embarrassment and distress associated with hirsutism, patients may seek cosmetic treatment before seeing the healthcare providers which conceals relevant physical examination findings. The most commonly utilized tool is the modified Ferriman–Gallwey (mFG) as adapted by Hatch *et al.* [10,11]. Defining one single cut-point to discriminate hirsutism is challenging because mFG scores vary across populations. Hence, one cut-point does not predict hirsutism in all populations. Although the 5th and 95th percentiles are traditionally used to define normal limits, these cut-points may not accurately reflect physiologic parameters. Another approach using *k*-cluster analysis indicated that a mFG score of 5 was the cut-point among Chinese women [12]. Using cluster analysis, the degree of hair growth among unselected American White and Black women was comparable and suggested a cut-point of 3 [13]. Evidence-based review in the International Guidelines recommended cut-points greater than 4-6 indicate hirsutism [14▪▪].

Importantly, the extent of hirsutism does not reflect the circulating androgen concentrations [15,16]. Androgen receptors exist in hair follicles. In addition, steroidogenic enzymes located within the hair follicle can synthesize androgens. The sensitivity of the androgen receptor and androgen signaling pathway influence the responsiveness and extent of hair growth.

Acne is common in adolescents and usually responds to topical or oral antibiotic treatments [17]. No universally accepted visual assessment tool exists for evaluating acne. Severe acne resistant to topical treatment is uncommon and may indicate hyperandrogenism. Androgenic alopecia can occur in adult women with PCOS, but is extremely rare in adolescents.

WHAT IS HORMONAL HYPERANDROGENISM?

Ovarian steroidogenesis involves theca and granulosa cells. In this two cell steroid biosynthetic pathway in the ovary, theca cells synthesize androstenedione, and granulosa cells (modulated by FSH stimulated aromatase activity) convert androstenedione to estrogens. The zona recticularis in the adrenal cortex secretes DHEAS, DHEA, and

androstenedione. Total testosterone, free testosterone, androstenedione, 17-hydroxyprogesterone, and DHEAS are commonly measured to exclude other causes of adrenal hyperandrogenism such as nonclassic congenital adrenal hyperplasia and androgen-secreting tumors. When confronted with cutaneous features suggestive of androgen excess and/or irregular menses, serum androgen concentrations can be measured.

Elevated serum androgen concentrations define hormonal or biochemical hyperandrogenism. Although this definition seems straightforward, accurate testosterone determinations pose challenges due to the technical details of the assays, interfering substances, poorly defined normal ranges, and the low circulating testosterone concentrations in children and women compared to adult men [18]. Testosterone and other androgen concentrations can be determined using radioimmunoassay, gas chromatography-mass spectroscopy (GC-MS), and liquid chromatography-tandem mass spectroscopy (LC-MS/MS). GC-MS and LC-MS/MS provide improved sensitivity, accuracy, and specificity, but have limited availability and greater cost [19,20]. Direct free testosterone assays are inaccurate and should be avoided.

With the availability of mass spectrometry, 11-oxo steroids determinations have transformed the traditional paradigm regarding adrenal androgen biosynthesis. The 11-oxo steroids are synthesized primarily in the adrenal cortex where the enzyme, 11β-hydroxylase encoded by the 11β-hydroxylase (*CYP11B1*) gene, converts androstenedione and testosterone to their respective 11β-hydroxyl derivatives, 11β-hydroxyandrostenedione (11OHA4) and 11β-hydroxytestosterone (11OHT). Both 11OHA4 and 11OHT can be converted to their 11-keto counterparts [21▪]. All four, 11OHA4, 11OHT, 11KA4, and 11KT, can serve as substrates for steroid 5α-reductase (SRD5A) [22]. Both 11KT and 11KDHT are potent agonists of the androgen receptor [23]. The concentrations of these 11-oxo-steroids were higher in women with PCOS than among healthy premenopausal women. Many circulating androgens in women with PCOS appear to be 11-oxygenated androgens [24]. However, the contribution of the 'backdoor' pathway to adrenal and ovarian steroid biosynthesis in PCOS remains unclear [25].

In most instances, biochemical hyperandrogenism is accompanied by other clinical features typical of androgen excess such as hirsutism or menstrual irregularity. Beginning with adrenarche, adrenal C-19 steroid concentrations rise. Among older adolescent Italian girls, approximately 10% reported isolated irregular menses, 17% reported isolated clinical hyperandrogenism, and 7% reported hyperandrogenemia, but only 4% fulfilled criteria to be diagnosed with PCOS [26]. Measuring other androgens, such as androstenedione and DHEAS, can be useful in evaluating for hyperandrogenism when testosterone is not elevated.

WHAT IS THE DEFINITION OF OLIGO/ANOVULATION?

Menstrual irregularity is common in the first 1–2 years postmenarche. Despite the conventional notion based on limited poor quality data suggesting that early adolescent oligomenorrhea reflects anovulatory cycles, many adolescent girls with irregular menstrual cycles are ovulating [27▪]. For most girls, cycle variability decreases over time culminating in regular monthly cycles by the fifth gynecologic year [28]. Girls who are postmenarchal by 1 year must have fewer than four periods a year to be considered oligomenorrheic, whereas girls who are 3–5 years postmenarche must have fewer than eight cycles. Adult criteria apply (less than nine cycles per year) 5 years postmenarche. The majority of adolescents (75%) establish a menstrual interval between 21 and 45 days in the first year after menarche, and almost all (95%) fall within this 'normal' range 5 by years postmenarche [29]. Importantly, a menstrual interval longer than 90 days even after the first year of menarche is uncommon [30]. Therefore, for girls more than 1 to less than 3 years postmenarche, cycles lasting less than 21 or greater than 45 days or any cycle lasting longer than 90 days should be considered abnormal. Primary amenorrhea at the chronological age of 15 years or more than 3 years post thelarche warrants further investigation for an endocrine disorder.

The clinical issue is whether prolonged menstrual irregularity in adolescents predicts progression to PCOS. A 13-year follow-up study of approximately 100 women showed persistently higher androgen concentrations; higher testosterone concentrations were associated with fewer pregnancies [31]. In another small study involving Swedish young women, persistent menstrual irregularity progressed to a diagnosis of PCOS in 20 of 35 women [32]. In the absence of additional prospective studies, individual assessment and longitudinal re-evaluations will be helpful to avoid risks of overdiagnosis and unnecessary anxiety for some and confirm the diagnosis of PCOS for others.

DOES POLYCYSTIC OVARY MORPHOLOGY CONFIRM DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME IN THE ADOLESCENT GIRL?

The typical life cycle of the ovary involves growth of primordial follicles followed by selection of a

dominant follicle culminating in ovulation. In PCOS, this recurring pattern is disrupted. Numerous follicles grow, but a dominant follicle is not selected. The growing follicles become atretic and can be visualized by ovarian ultrasound studies as polycystic ovary morphology.

With the development of improved tools, the definition of polycystic ovary morphology in adult women has been modified. Using a transducer frequency at least 8 MHz and transvaginal ultrasonography, the Androgen Excess-PCOS Society recommended setting threshold values of at least 25 follicles per ovary and at least 10 cm volume to define PCOM [33]. Although transvaginal ultrasound provides better definition of ovarian morphology, the use of transvaginal ultrasounds in adolescents is limited.

The conundrum is that ovarian volume, follicle number, and size all increase during puberty [34]. Normal girls may have PCOM, which confounds interpretation of ovarian ultrasound studies [35,36]. Expanding on this finding, pelvic ultrasound studies were obtained during the early follicular cycle in adolescent girls; the girls found to have PCOM also had elevated AMH and lower FSH concentrations without biochemical hyperandrogenism [37]. These studies reinforce the concept that PCOM does not indicate PCOS in the adolescent girl. The next step involves longitudinal evaluations of these girls to ascertain the natural history of PCOM. Importantly, ultrasound studies are not necessary for the diagnosis of PCOS in adolescent girls.

Antimullerian hormone (AMH) is a dimeric glycoprotein produced by small ovarian antral follicles. AMH expression declines with selection of the dominant follicle. AMH concentrations provide valuable information regarding ovarian reserve. Data suggest that AMH concentrations provide a surrogate measure of PCOM. However, reliance on AMH concentrations to diagnose PCOS is premature at this time due to technical issues with AMH assays [38,39].

WHAT GENETIC FACTORS ARE ASSOCIATED WITH POLYCYSTIC OVARY SYNDROME?

PCOS clusters within families. Twin studies have demonstrated a higher concordance rate among monozygotic compared to dizygotic twin sisters [40]. Hereditability is estimated to be 79% [40]. Initially case–control studies sought to identify genes associated with PCOS. More recently, unbiased nonhypothesis-driven genome-wide association studies (GWAS) have identified 19 loci associated with PCOS in several population cohorts. These loci are located in close physical proximity to several potential candidate genes including the insulin receptor, thyroid adenoma associated (*THADA*), FSH receptor (*FSHR*), and DENN/MADD domain containing 1A (*DENND1A*). Association with a specific gene does not prove causality. The causal genetic variants may be located outside the coding region of the gene.

The *DENND1A* gene has generated much interest because overexpression of a specific splice variant, DENND1A.V2 has been found in increased concentrations in urinary exosomes of women with PCOS compared to controls. In addition, in-vitro studies demonstrated that overexpression of this variant in theca cells obtained from normal women recapitulated a PCOS phenotype [41]. Although some loci were detected only in specific populations, for example Chinese, many loci have been replicated in Chinese and European cohorts supporting the notion that PCOS is an 'ancient' disease [42]. Future research efforts need to clarify the specific molecular consequences of specific genetic variants [43].

DO NEUROENDOCRINE FACTORS INFLUENCE POLYCYSTIC OVARY SYNDROME?

Despite the conception that PCOS is predominantly an ovarian disease, accumulating data emphasize the contribution of neuroendocrine dysfunction to the pathophysiology of PCOS. Classic features of PCOS include increased luteinizing hormone (LH) pulse frequency, LH pulse amplitude, and increased LH/FSH ratios. The increased LH secretion presumably promotes increased theca cell androstenedione production.

This pattern of gonadotropin secretion with increased LH pulse frequency reflects increased hypothalamic GnRH pulse frequency. GnRH pulse frequency represents the output of the interactions among excitatory and inhibitory hormonal and environmental influences on the kisspeptin and GnRH neurons [44]. Elevated androgen concentrations appear to disrupt the negative feedback actions of estrogen and progesterone. Some adolescent girls manifest reduced sensitivity to progesterone negative feedback [45].

Results of the GWAS studies implicated neuroendocrine dysfunction in the pathophysiology of PCOS [46▪▪]. Specifically, loci in close proximity to the *LHCGR*, *FSHR*, and *FSHB* genes were associated with PCOS.

Preclinical models suggest a link between AMH, LH secretion, androgen receptor signaling, and excessive ovarian androgen secretion. In a mouse model, in-vitro and in-vivo studies demonstrated that AMH increased GnRH-dependent LH pulsatility and

secretion [47]. Treatment of pregnant mice with AMH resulted in delayed puberty, disrupted estrous cycle, and subfertility [48]. These data support a central action of AMH on GnRH neurons. Using targeted deletions (knockouts) of the androgen receptor in specific tissue, neuron-specific AR knockout mice were protected against metabolic and reproductive features in a mouse PCOS model [49,50].

WHAT IS THE ROLE OF INSULIN RESISTANCE IN POLYCYSTIC OVARY SYNDROME?

Insulin resistance specifies decreased responsiveness to insulin actions primarily at liver, muscle, and adipose tissue. The pancreatic beta cells secretes greater amounts of insulin to compensate for the decreased insulin efficacy. Paradoxically, a few tissues such as skin, steroidogenic tissues, and areas of the hypothalamus retain insulin sensitivity [51,52]. In these tissues, insulin can act as a mitogen.

The 'gold standard' to measure insulin sensitivity is the euglycemic hyperinsulinemic clamp study. However, due to financial cost and time burden, this approach is limited to research studies. Other tools to ascertain insulin sensitivity include oral glucose tolerance tests, frequently sampled intravenous glucose tolerance test, and various calculations based on fasting insulin and glucose concentrations.

The molecular basis of insulin resistance is likely multifactorial and has not been fully elucidated. Insulin action is mediated by insulin receptors. Although insulin receptor gene mutations can present with insulin resistance and hyperandrogenism, insulin receptor gene mutations are extremely rare in women with PCOS. It is known that the magnitude of insulin resistance in women with PCOS is greater than would be anticipated based on body weight. A meta-analysis confirmed the presence of insulin resistance when measured by clamp studies in women with PCOS independent of diagnostic criteria, Rotterdam versus NIH, and suggested that low SHBG concentrations provides a good marker of insulin resistance [53]. However, hyperinsulinemia independent of insulin sensitivity may precede the development of insulin resistance [54]. Prolonged primary hyperinsulinemia can lead to downregulation of insulin receptors and postreceptor defects and increasing intracellular fat storage [55].

Lean women with PCOS have insulin resistance [56]. Most data have been accrued in adult women. Evaluation of normal weight girls with PCOS demonstrated decreased peripheral insulin sensitivity, abnormal glucose disposal, relative postprandial hyperinsulinemia, and muscle mitochondrial dysfunction compared to normal weight healthy controls. Thus, metabolic derangements are present in normal weight girls with PCOS [57]. As would be anticipated, obese adolescent girls with PCOS demonstrated reduced peripheral tissue insulin sensitivity, compensatory hyperinsulinemia, and evidence of hepatic insulin resistance [58].

HOW DOES OBESITY INFLUENCE POLYCYSTIC OVARY SYNDROME?

Overweight and obesity occur frequently in adolescent girls and adult women with PCOS. Obesity is associated with adipose dysfunction characterized by macrophage invasion, inflammation, and insulin resistance. In addition, overnutrition leads to ectopic fat storage because adipose storage capacity is exceeded. Nonalcoholic fatty liver represents ectopic fat storage in the liver [59]. Mismatch between low birth weight followed by excessive postnatal weight gain has been reported in a cohort of European girls with PCOS [60]. Early adiposity rebound, a rise in BMI around 6 years of age, was associated with PCOS diagnosis in a longitudinal analysis involving the longitudinal Northern Finland Birth Cohort 1966 Study [61].

WHAT PRENATAL FACTORS ARE RELEVANT FOR POLYCYSTIC OVARY SYNDROME?

The Barker hypothesis and ensuing data showed that low birth weight is associated with an increased risk for impaired glucose tolerance, type II diabetes mellitus, and cardiovascular disease [62]. A meta-analysis demonstrated that the odds ratio to develop PCOS was 1.76 for women with birthweight less than 2.5 kg when the Rotterdam criteria were utilized, but birthweight did not influence outcome when the NIH criteria were used [63]. Observational studies revealed that prenatal growth restriction and low birth weight followed by postnatal weight gain are associated with development of premature pubarche and PCOS [59].

Studies performed in rodents, sheep, and nonhuman primates support the prenatal developmental origins theory for PCOS [64]. In these studies, prenatal administration of testosterone or dihydrotestosterone induced a PCOS-like phenotype characterized by altered neuroendocrine steroid feedback, functional hyperandrogenism, and altered insulin sensitivity. Data exist suggesting that a hyperandrogenic prenatal environment influences genes implicated in the pathogenesis of PCOS [65]. In humans, one phenotypic marker associated with prenatal androgen exposure is anogenital distance. Among 300 mother–daughter pairs, anogenital distance was greater in

among daughters born to women diagnosed with PCOS compared to non-PCOS mothers [66].

WHAT ARE THE DIAGNOSTIC CRITERIA FOR POLYCYSTIC OVARY SYNDROME IN THE ADOLESCENT GIRL?

Guidelines for diagnosis in adult women include the 1990 National Institute of Health (NIH) criteria, the 2003 Rotterdam criteria, and the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) criteria [67–69]. Because of the similarity of normal pubertal development and features of PCOS, the adult diagnostic criteria are not applicable for adolescent girls [14▪▪]. PCOS is a diagnosis of exclusion, meaning that other disorders associated with androgen excess need to be excluded from consideration.

For girls who are at least 2 years postmenarche, hyperandrogenism (clinical and/or biochemical), and irregular menses are the required diagnostic criteria for PCOS in adolescents [14▪▪]. If the patient does not fulfill these criteria, rather than prematurely labeling with a diagnosis, she can be considered 'at risk' for PCOS [14▪▪]. All adolescents with PCOS should be longitudinally followed. Acne and PCOM may be observed, but are not diagnostic criteria. Obesity, insulin resistance, and hyperinsulinemia are common comorbidities.

TREATMENT

For the adolescent girl diagnosed with PCOS or considered to be 'at risk' for PCOS, treatment needs to be individualized and chosen to optimize symptom relief. The first therapeutic recommendation involves discussion and encouragement of appropriate dietary and exercise interventions especially for overweight or obese PCOS patients.

Oral contraceptives, metformin, and antiandrogens are commonly used. Cosmetic treatments, such as hirsutism, waxing, bleaching, and topical 13.9% eflornithine cream, can be used almost immediately. Permanent cosmetic methods such as electrolysis and laser hair removal should be deferred until androgen concentrations are decreased. Laser hair removal in particular has demonstrated improvement of quality of life in a select cohort of hirsute women [70].

Combined oral contraceptives (COCPs) decrease androgen concentrations, increase SHBG concentrations, normalize menses, prevent pregnancy, and protect the endometrium. Among adult women, COCPs increase total cholesterol, high-density lipoprotein-cholesterol, and triglyceride concentrations; available data suggest no significant changes in glucose tolerance or body weight [71]. COCPs consist of an estrogen and a progestogen. The estrogen component is typically a synthetic estrogen such as ethinyl estradiol with concentrations ranging between 20 and 35 mcg per tablet. Ethinyl estradiol does not bind to SHBG and is resistant to liver metabolism.

Synthetic progestogens are used in COCPs and vary in their androgenic activity. Newer progestogens such as desogestrel, gestodene, and norgestimate have low androgenic activity. Dienogest, cyproterone acetate, and drospirenome have antiandrogenic activity. Both estrogens and progestogens are associated with a greater risk for venous thromboembolism (VTE). The VTE risk ascribed to estrogen rises with increasing estrogen dosage. The newer progestogens are associated with a slightly higher risk for VTE [72]. Family history of VTE or thrombophilia needs to be ascertained.

Insulin-sensitizing drugs, such as metformin, improve insulin sensitivity leading to decreased insulin concentrations, improved glycemic control, and decreased androgen concentrations. By lowering androgen concentrations, metformin can improve ovulatory function. However, metformin does not improve hirsutism and should be used primarily for those girls with abnormal glycemic control, insulin resistance, and hyperinsulinemia [73].

Antiandrogens, such as spironolactone, flutamide, or finasteride, reduce the growth of new terminal hairs. Highly effective birth control must be used simultaneously because antiandrogens impair external genital development in male fetuses. Hyperkalemia is an extremely rare side-effect of spironolactone. Flutamide has rarely been associated with hepatotoxicity [74]; among Catalan girls low-dose flutamide has been shown to be effective and well tolerated by several studies [75,76]. In a randomized placebo-controlled study involving only a few adolescent girls, an intermittent finasteride regimen decreased terminal hair growth without major side effects [77].

No single comprehensive treatment for PCOS exists. Treatment approaches are, therefore, symptom-oriented. Shared decision making with the patient and her family facilitates thoughtful discussion regarding her concerns and specific needs. This process will enable individualized interventions for the patient.

CONCLUSION

Given the recommendations of the International Evidence Based Guidelines, healthcare professionals have the opportunity and novel tools to provide early, meaningful interventions for adolescents with PCOS (https://www.monash.edu/medicine/

sphpm/mchri/pcos) [14▪▪]. The ultimate goal will be to identify 'at risk' adolescents to enable intervention and avoid progression to PCOS and associated comorbidities. Balancing between overdiagnosis and overlooking affected girls is essential. Clinicians who are knowledgeable regarding the multiple complexities regarding pathophysiology, diagnosis, treatment, and comorbidities associated with PCOS can only benefit adolescents and emerging young adult women with PCOS.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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