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International evidence-based recommendations for polycystic ovary syndrome in adolescents

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Abstract

Background During adolescence, accurate diagnostic criteria and/or identification of adolescents "at risk" of polycystic ovary syndrome (PCOS) are critical to establish appropriate screening, treatment, and lifelong health plans. The 2023 International Evidence-Based Guideline for PCOS aimed to provide the most up-to-date evidence-based recommendations to improve health outcomes for individuals with PCOS, emphasizing accurate and timely diagnosis of PCOS from adolescence.

Methods The best practice methods following the Appraisal of Guidelines for Research and Evaluation (AGREE-II) criteria were applied. Healthcare professionals and patients/consumers reviewed extensive evidence synthesis/meta-analysis for 55 prioritized clinical questions. Databases (OVID MEDLINE, All EBM, PsycInfo, EMBASE, CINAHL) were searched until August 2022 as part of the 2023 update of the Guideline. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework guided experts on evidence quality, feasibility, acceptability, cost, implementation, and ultimately recommendation strength.

Results This manuscript focuses on the adolescent-specific recommendations of the 2023 Guideline. The diagnosis is based on the presence of both irregular menstrual cycles (defined according to the time postmenarche) and clinical/biochemical hyperandrogenism following the exclusion of other disorders that mimic PCOS. Adolescents with only one of these features can be considered "at risk" of PCOS requiring the management of symptoms and ongoing follow-up. Polycystic ovarian morphology on pelvic ultrasonography or anti-Müllerian hormone levels should not be used for diagnosis during adolescence. Lifelong health planning is recommended to include healthy lifestyles, screening for depression and metabolic features and the transition to adult care, all underpinned by shared decision-making. Healthcare professionals should explain weight-related health risks to adolescents, while minimizing weight stigma. In adolescents with PCOS or "at risk" of PCOS, combined oral contraceptive pills are indicated for menstrual irregularity and clinical hyperandrogenism, focusing on low dose preparations, and metformin could be considered for metabolic features and cycle regulation. Overall, the evidence is limited in adolescents with PCOS, and recommendations are based on low to moderate certainty evidence.

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Conclusions Extensive international engagement and rigorous processes generated International Guideline diagnostic criteria for adolescents that differ from adult criteria and clarified appropriate screening and management strategies for PCOS during adolescence.

Keywords Adolescents, Girls, Polycystic ovary syndrome, Evidence-based, Diagnosis, Management

Background

Polycystic ovary syndrome (PCOS) is a common endocrine condition affecting ~ 8% of adolescents [1]. The adolescent PCOS diagnostic criteria have been controversial due to the overlap of the pubertal changes with adult PCOS diagnostic criteria. These pubertal changes including menstrual irregularities, acne, and polycystic ovarian morphology (PCOM) are well recognized [2, 3]. Given the prevalence of menstrual irregularities during the early postmenarcheal years, mild acne or PCOM, these PCOS diagnostic criteria during adolescence can result in overdiagnosis. Conversely, disregarding diagnostic features can result in delayed or underdiagnosis with adverse long-term consequences [2, 4–6]. Delayed diagnosis has been reported by individuals who described symptoms starting in adolescence [7]. Hence, nuanced diagnostic criteria are key to accurate and timely diagnosis.

The original consensus-based Rotterdam criteria for PCOS diagnosis were upgraded to evidence-based criteria in the 2018 and 2023 International Evidence-based PCOS Guideline. The 2023 Guideline recommends adult diagnosis on the basis of the identification of at least two of these recognized features: (1) menstrual irregularities/ovulatory dysfunction, (2) clinical/biochemical hyperandrogenism, and (3) PCOM on ultrasound or elevated anti-Müllerian hormone (AMH) levels [4, 8, 9]; however, neither PCOM nor AMH levels are suitable for diagnosing PCOS during adolescence [2, 4, 9].

In the 2023 update of the PCOS International Evidence-based Guideline ("The Guideline"), we aimed to develop and provide comprehensive evidence-based recommendations for diagnosis, assessment, and treatment to improve the lives of those with PCOS worldwide from adolescence to adulthood [8, 9]. This manuscript highlights the adolescent-specific recommendations from the 2023 Guideline with supporting evidence. The term "adolescent" refers to individuals between 10 and 19 years of age according to the World Health Organization definition and women within 8 years postmenarche (gynecological age of 8 years or less) have also been identified for specific recommendations.

Methods

Methods used to develop, update, and expand this Guideline align with international best practices and comply with the Appraisal of Guidelines for Research and Evaluation (AGREE II) process. Databases (OVID MEDLINE, All EBM, PsycInfo, EMBASE, CINAHL) were searched until August 2022. Evidence synthesis procedures included integrity assessments using the Research Integrity in Guideline Development framework, which incorporates tools such as the Research Integrity Assessment and the Trustworthiness in Randomized Controlled Trials checklist [1, 10, 11]. Full details of the methodology are included in the publicly available Guideline and Technical report (https://www.monash.edu/medicine/mchri/pcos/guideline) [1, 8].

An international advisory board, project board and five guideline development groups (GDGs) with 80 members representing 39 organizations across six continents (71 countries) were engaged over 12 months. The GDGs included individuals with PCOS and multidisciplinary experts in PCOS including pediatricians, endocrinologists, gynecologists, reproductive endocrinologists, psychologists, allied health professionals, researchers, and others, who were involved at all stages of guideline development. The guideline addressed 55 questions via 52 systematic reviews and three narrative reviews conducted and/or overseen by an evidence team. The quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Judging each outcome for risk of bias, inconsistency, indirectness, imprecision, and other considerations, evidence quality was ranked from very low to high, reflecting certainty in the effect estimate from evidence synthesis (Tables 1 and 2) [12].

The Guideline recommendation categories were then formulated by applying the GRADE evidence-to-decision framework (Table 3) [13]. GDGs members drafted recommendations that were international peer reviewed by partnering societies and the general public. Evidence was required to support recommendation modifications. Peer review results are available online: https://www.monash.edu/medicine/mchri/pcos/guideline, and the final Guideline was approved by the Australian National Health and Medical Research Council and endorsed by participating societies.

Results

The full 2023 Guideline update provides recommendations in five areas: screening, diagnosis, and risk assessment; psychological features; lifestyle; management of

Table 1 Quality (certainty) of evidence (adapted from GRADE)

High ⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect
Moderate ⊕⊕⊕□	Moderate confidence in the effect estimate – the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low ⊕⊕□□	Limited confidence in the effect estimate – the true effect may be substantially different from the estimate of the effect
Very low ⊕□□□	Very little confidence in the effect estimate – the true effect is likely to be substantially different from the estimate of effect

Table 2 The Grading of Recommendations, Assessment Development, and Evaluation (GRADE) framework recommendation strength

❖❖❖❖	Strong recommendation for the option
❖❖❖	Conditional recommendation for the option
❖❖	Conditional recommendation for either the option or the comparison
❖	Conditional recommendation against the option

Table 3 Categories of the PCOS Guideline recommendations

Evidence-based recommendations (EBR)	Evidence-based recommendations are made where evidence is sufficient to inform a recommendation made by the guideline development group
Consensus recommendations (CR)	Consensus recommendations have been made by the guideline development group in the absence of adequate evidence on PCOS and informed by evidence from the general population
Practice points (PP)	Practice points have been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations and where evidence was not sought

nonfertility features; and infertility [8, 9]. This paper summarizes 63 adolescent recommendations (Table 4) and does not cover infertility.

Screening, diagnostic, and risk assessment

The criteria required to diagnose adolescent PCOS include menstrual irregularities and hyperandrogenism, following the exclusion of conditions that mimic PCOS.

1) Diagnostic criteria required

1a) Menstrual irregularities

The updated search using the clinical question "In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?" revealed no studies that met the selection criteria [1]. Based on the natural history of menstrual cycles/ovulation in healthy adolescents, there was no change in the previous definition of irregular menstrual cycles according to years postmenarche [1, 2, 4, 9]. Menstrual irregularities can occur during the physiological maturation of the hypothalamic-pituitary-ovarian axis over several

Table 4 Adolescent recommendations for the assessment and management of polycystic ovary syndrome. Modified from 2023 Guideline [8]

Topics	Category of recommendation	Recommendations	Grade/quality
Screening, diagnosis, and risk assessment	1) Criteria required		
	1a) Menstrual irregularities and ovulatory dysfunction		
	CR	Irregular menstrual cycles are defined as: - Normal in the first-year post menarche as part of the pubertal transition - 1 to < 3 years post menarche: < 21 or > 45 days - 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year - 1 year post menarche > 90 days for any one cycle - Primary amenorrhea by age 15 or > 3 years post thelarche (breast development) When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to these PCOS Guideline	❖❖❖❖
	PP	The mean age of menarche may differ across populations	
	PP	In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors	
	PP	Ovarian dysfunction can still occur with regular cycles and, if anovulation needs to be conformed serum progesterone can be measured	
	1b) Biochemical and/or clinical hyperandrogenism		
	EBR	Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index	❖❖❖❖/⊕□□□
	EBR	If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate, noting their poorer specificity and greater age associated decrease in dehydroepiandrosterone sulfate (the later only applied to adult women)	❖❖❖⊕ □□□
	EBR	Laboratories should use validated, highly accurate tandem mass spectrometry assays for measuring total testosterone and, if needed, for androstenedione and dehydroepiandrosterone sulfate. Free testosterone should be assessed by calculation, equilibrium dialysis, or ammonium sulfate precipitation	❖❖❖❖/ ⊕⊕□□
	EBR	Laboratories should use tandem mass spectrometry assays over direct immunoassays (e.g., radiometric, enzyme-linked, etc.) for assessing total or free testosterone, which have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS	❖❖❖❖/ ⊕⊕□□
	PP	In most adolescents, androgen levels reach adult ranges at 12–15 years of age	
	PP	It is very difficult to reliably assess for biochemical hyperandrogenism in women on the COCP as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP and assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception should be managed otherwise during this time	
	PP	If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumor	
	CR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents	❖❖❖❖
	CR	Health care professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and should consider the reporting of unwanted excess hair growth and/or female pattern hair loss as being important, regardless of apparent clinical severity	❖❖❖
	CR	A modified Ferriman Gallwey (mFG) score of ≥ 4–6 indicates hirsutism, acknowledging that self-treatment is common and can limit clinical assessment	❖❖❖❖

Table 4 (continued)

Topics	Category of recommendation	Recommendations	Grade/quality
	CR	Healthcare professionals should consider that severity of hirsutism may vary by ethnicity, but the prevalence of hirsutism appears similar across ethnicities	❖❖❖
	PP	Healthcare professionals should • Be aware that standardized visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas • Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss (rare in adolescents) • Note that there are no universally accepted visual instruments for assessing the presence of acne • Recognize that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity • Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination • Note that only terminal hairs need to be considered in defining hirsutism, and these can reach > 5 mm if untreated, vary in shape and texture, and are generally pigmented • Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumors and ovarian hyperthecosis • Monitor clinical signs of hyperandrogenism, including hirsutism, acne, and female pattern hair loss, for improvement or treatment adjustment during therapy	
	2) Investigations not recommended for diagnosis of PCOS during adolescence		
	2a) Ultrasound and polycystic ovary morphology		
	PP	There are no definitive criteria to define polycystic ovary morphology on ultrasound in adolescents; hence, it is not recommended in adolescents	
	2b) Anti-Mullerian hormone (AMH)		
	EBR	AMH should not yet be used in adolescents	❖❖❖❖/⊕⊕⊕▯
	3) Adolescents "at risk" of PCOS		
	PP	For adolescents who have features of PCOS, but do not meet diagnostic criteria, an "increased risk" could be considered, and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before COCP commencement, those with persisting features and those with significant weight gain in adolescence	
	4) Other risks associated with PCOS		
	EBR	Healthcare professionals and women with PCOS should be aware that, regardless of age and body mass index, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes	❖❖❖❖/⊕⊕▯▯
	EBR	Glycemic status should be assessed at diagnosis in all adults and adolescents with PCOS	❖❖❖❖/⊕⊕▯▯
	PP	Healthcare professionals, adults, and adolescents with PCOS and their first-degree relatives should be aware of the increased risk of diabetes and the need of regular glycemic assessment	
Psychological features	EBR	Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adults and adolescents with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools	❖❖❖❖/⊕⊕⊕⊕
	EBR	Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools	❖❖❖❖/⊕⊕⊕⊕
	EBR	Healthcare professionals should be aware that features of PCOS can have a negative impact on body image	❖❖❖❖/⊕⊕▯▯
	EBR	Eating disorders and disordered eating should be considered in PCOS, regardless of weight, especially in the context of weight management and lifestyle interventions	❖❖❖/⊕⊕▯▯

Table 4 (continued)

Topics	Category of recommendation	Recommendations	Grade/quality
Lifestyle management	EBR	Lifestyle interventions (exercise alone or multicomponent diet combined with exercise and behavioral strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile	❖❖❖❖/⊕▯▯
	PP	In those who are not overweight, in the adolescent and key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain	
	EBR	Health care professionals and women should consider there is no evidence to support any type of diet composition over another for anthropometric, metabolic, hormonal, reproductive, or psychological outcomes	❖❖❖/⊕▯▯
	EBR	Health care professionals and women should consider that there is lack of evidence to support any type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive, or psychological outcomes	❖❖❖/⊕▯▯
	CR	Adolescents should aim for at least 60 min of moderate to vigorous intensity physical activity per day including activities that strengthen muscle and bone at least three times a week	❖❖❖❖
	PP	Increasing awareness of weight stigma among family members of women and adolescents with PCOS should be considered	
Management of nonfertility features	1) General principles		
	PP	Shared decision making between the patient and parent/s or guardian/s and the healthcare professional is required	
	PP	An individual's characteristics, preferences, and values must be elicited and considered when recommending any intervention alone or in combination	
	PP	Understanding how individual adult and adolescents value treatment outcomes is essential when prescribing medications	
	PP	Medical therapy is generally not approved for use specifically in PCOS and recommended use is therefore evidence-based, but off-label. Healthcare professionals need to inform adults, adolescents, and their parents/s or guardian/s and discuss the evidence, possible concerns, and side effects. Regulatory agencies should consider approval of evidence-based medications for use in PCOS	
	2) COCP		
	EBR	The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles	❖❖❖/⊕▯▯▯
	EBR	General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestins, estrogens, or combinations of COCP cannot currently be recommended	❖❖❖/⊕▯▯▯
	EBR	The 35 μg ethinyl estradiol plus cyproterone acetate preparations should be considered as second-line therapy, versus other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks	❖❖❖/⊕▯▯▯
	EBR	Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited	❖❖❖/⊕▯▯▯
	EBR	COCP could be used over metformin for management of hirsutism and irregular menstrual cycles in PCOS	❖❖❖/⊕▯▯▯
	PP	When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS: • It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies • Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence • Natural estrogen preparations and the lowest effective estrogen doses (such as 20–30 μg of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side effects, cost, and availability • The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines • The relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualized discussion • PCOS specific features, such as higher weight and cardiovascular risk factors, need to be considered	

Table 4 (continued)

Topics	Category of recommendation	Recommendations	Grade/quality
	3) Metformin		
	EBR	Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence	❖❖❖/⊕▯▯▯
	PP	Where metformin is prescribed the following need to be considered: • Shared decision making needs to consider feasibility and effectiveness of active lifestyle intervention. Women should be informed that metformin and active lifestyle intervention have similar efficacy • Mild adverse effects, including gastrointestinal side-effects are generally dose dependent and self-limiting • Starting at a low dose, with 500 mg increments 1–2 weekly and extended-release preparations may minimize side effects and improve adherence • Suggested maximum daily dose is 2.5 g in adults and 2 g in adolescents • Use appears safe long-term, based on use in other populations; however, indications for ongoing requirement needs to be considered • Use may be associated with low vitamin B_{12} levels, especially in those with risk factors for low vitamin B_{12} (e.g., diabetes, post bariatric/metabolic surgery, pernicious anemia, vegan diet etc.), where monitoring should be considered	
	EBR	Metformin could be used over COCP for metabolic indications in PCOS	❖❖❖/⊕▯▯▯
	4) Antiandrogen medications		
	EBR	In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of 6 months of COCP and/or cosmetic therapy	❖❖❖/⊕▯▯▯
	PP	Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/s, or guardian/s, regarding the risks of incomplete development of external genital structures of male fetuses (under virilization) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counseled to use effective contraception (e.g., intrauterine device or COCPs)	
	PP	When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that: • Spironolactone at 25–100 mg/day appears to have lower risks of adverse effects • Cyproterone acetate at doses ≥ 10 mg is not advised due to an increased risk including for meningioma • Finasteride has an increased risk of liver toxicity • Flutamide and bicalutamide have an increased risk of severe liver toxicity • The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants	
	5) Other medications: anti-obesity medications and inositol		
	CR	Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines	❖❖❖
	PP	Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence	
	6) Cosmetic therapies		
	EBR	Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety, and quality of life in women with PCOS	❖❖❖/⊕▯▯▯
	EBR	A greater number of laser treatment sessions may be required in women with PCOS, compared to women with idiopathic hirsutism, to achieve hair reduction	❖❖❖/⊕▯▯▯
	CR	Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers	❖❖❖❖

Table 4 (continued)

Topics	Category of recommendation	Recommendations	Grade/quality
	PP	Where laser hair removal is prescribed, the following need to be considered: • Wavelength and delivery of laser treatment varies by skin and hair color • Laser is relatively ineffective in women with blond, grey or white hair • The addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone • Low and high fluence laser appear to have similar efficacy in reducing facial hair, while low fluence laser has reduced associated pain	
	PP	Mechanical hair removal with intense pulse light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence to support the efficacy of home-based IPL kits	
Models of care and transition	EBR	Tailored information, education, and resources that are high-quality, culturally appropriate, and inclusive should be provided to all with PCOS	❖❖❖❖/⊕⊕⊕▯
	EBR	Information, education, and resources are a high priority for patients with PCOS and should be provided in a respectful and empathic manner	❖❖❖❖/⊕⊕⊕▯
	CR	Models of care should prioritize equitable access to evidence-based primary care with pathways for escalation to integrated specialist and multidisciplinary services as required	❖❖❖❖
	EBR	Healthcare professionals should employ shared decision-making and support patient agency or ability to take independent actions to manage their health and care	❖❖❖❖/⊕⊕⊕▯
	EBR	The importance of being knowledgeable about PCOS, of applying evidence-based practices when sharing news on diagnosis, treatment, and health implications, and of ascertaining and focusing on patient priorities, should be recognized	❖❖❖❖/⊕⊕⊕▯
	PP	A reproductive life plan and age-appropriate education on optimizing reproductive health is recommended in adolescents and women with PCOS, including healthy lifestyle, prevention of excess weight gain, and optimizing preconception risk factors	

Abbreviations: *CR* consensus recommendation, *PCOS* polycystic ovary syndrome, *PP* practice point, *EBR* evidence-based recommendation, *mFG* modified Ferriman Gallwey, *COCP* combined oral contraceptive pill, *AMH* anti-Mullerian hormone, *IPL* intense pulse light

years [14, 15]. The timing at which menstrual irregularities may indicate PCOS remains unclear as the cycle's length can vary considerably in the first postmenarcheal years. However, by the third postmenarcheal year, 95% of cycles had an average adult length of 28 days (range 24–35 days) [14, 16]. Therefore, well defined menstrual irregularities are one of the two criteria required for adolescent PCOS diagnosis (Table 4).

1b) Hyperandrogenism: biochemical and/or clinical

The updated search using the clinical question "In women with suspected PCOS, what is the most effective measure to diagnose PCOS-related hyperandrogenism (biochemical)?" revealed 17 studies (two studies including 249 adolescents) [1, 17, 18]. Most studies ($n=11$) have evaluated total testosterone and calculated the free androgen index (FAI). Four evidence-based recommendations (EBRs) (Table 4) were generated and supported by a meta-analysis showing that compared with other androgens, the calculated free testosterone level and FAI had the best sensitivity (80.3% and 80.2%) and specificity (93.3% and 86.4%) for the diagnosis of hyperandrogenism. Total testosterone, androstenedione, and dehydroepiandrosterone had sensitivity of approximately 70% and specificity of approximately 75–85% and are not routinely recommended for diagnosis [1]. The updated search using the clinical question "In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS-related hyperandrogenism?" identified seven studies (none in adolescents) with significant heterogeneity [1]. Only consensus recommendations (CRs) were made for adolescents (Table 4). These findings were based on the fact that mild acne is common in adolescents, but severe acne during perimenarcheal years is uncommon and is more likely to indicate hyperandrogenism [1, 2]. Modified Ferriman-Gallwey score cut-offs were based on adult studies [1, 2].

2) Investigations not recommended for adolescent PCOS diagnosis.

Pelvic ultrasound for PCOM evaluation and AMH levels are not recommended for the PCOS diagnosis until 8 years postmenarche, when the hypothalamic-pituitary-ovarian axis is deemed mature and evidence-based criteria for the diagnosis of PCOM are available (Table 4). Normative data on ultrasonographic and serum markers

of ovarian morphology show a rapid increase in ovarian size and follicle populations during adolescence, peaking in early adulthood (20 years) [19, 20]. The elevated and dynamic nature of ovarian morphology during adolescence renders adult definitions for PCOM inappropriate for use during this developmental stage [1, 17, 18, 21, 22]. While pooled evidence suggests that ovarian volume and AMH have some diagnostic value in adolescents, these data are limited by small sample sizes, a focus on older adolescents, the use of multiple imaging modalities or assays, and variable criteria to define adolescent PCOS cases [1, 8, 17, 18, 21, 23–25].

3) Adolescents "at risk" of PCOS

Adolescents who have only one of the two features required for adolescent PCOS diagnosis (menstrual irregularities/ovulatory dysfunction or hyperandrogenism) should be considered "at risk" for PCOS and require longitudinal evaluation (Table 4).

4) Other risks associated with PCOS

While PCOS in adults is associated with increased cardiovascular disease, impaired glucose tolerance/type 2 diabetes, obstructive sleep apnea, endometrial hyperplasia, and cancer, PCOS in adolescents is associated with increased risk for impaired glucose tolerance/type 2 diabetes (Table 4). While there were studies evaluating the performance of tests for dysglycemia in adult women with PCOS, there were none in adolescents with PCOS. These studies showed that the 75 oral glucose tolerance test was the most accurate test to assess dysglycemia in women with PCOS regardless of body mass index (BMI). Recommendation in adult women also highlighted that if an oral glucose tolerance test cannot be performed, fasting plasma glucose and/or glycated hemoglobin could be considered noting reduced accuracy. In the absence of evidence, the Guidelines did not recommend any specific test to assess dysglycemia in adolescents.[1] An increased risk of diabetes also occurs in first degree relatives of those with PCOS [1, 8].

Psychological features

Four EBRs were formulated for psychological features (Table 4). The first recommends screening for depression on the basis of a meta-analysis of 47 studies (six studies including1098 adolescents) showing up to a four-fold higher prevalence of depression in adolescents with PCOS than those without PCOS [1, 26–31]. Generic online screening resources are available [1, 32] and should be used for screening and rescreening according to clinical judgment, life changes, and risk factors. A qualitative evidence synthesis reported challenges for adolescents in interactions with healthcare professionals. These challenges were attributed to their impression that their symptoms were normalized, dismissed, or not taken seriously, that doctors failed to discuss all available options with them, that follow-up plans were inappropriate because they focused primarily on future fertility, and that the immediate concerns of young people were overlooked [1, 7]. Healthcare professionals should become more knowledgeable of shared decision-making and methods for sharing medical news and supporting patient activation in adolescents.

Other EBRs underscore awareness regarding other psychological comorbidities in adults with PCOS (Table 4). EBRs were based on a meta-analysis of 27 studies (3 studies including 455 adolescents) showing that adults with PCOS had a greater prevalence of anxiety that did those without PCOS; however, this was not reflected in the small number of adolescents. [1, 27, 29, 30] Similarly, few studies on negative body image and eating disorders have not shown a higher prevalence in adolescents with PCOS compared to controls [1, 27, 33]. However, healthcare providers should note the limited studies to date, the associations in adulthood and the fact that negative body image and eating disorders are commonly observed in adolescents without PCOS.

Lifestyle

Excess weight and weight gain risks are prevalent in the general population and are exacerbated in adolescents and adults with PCOS, due to our obesogenic environment [34]. Obesity and excessive weight gain adversely affect reproductive, metabolic, and psychological health and are particularly challenging in adolescents when their self-image is developing [35]. The risk associated with excess weight should be discussed with sensitivity to avoid weight bias and stigma. Similarly, health care professionals should consider asking permission prior to obtaining weight [36].

Lifestyle interventions have been shown to have beneficial effects on adolescents, but randomized intervention trials to inform best practice are limited [1, 37, 38]. On the basis of population data, it is recommended that all adolescents, including those who are not currently overweight, pursue healthy lifestyles, and prevent excess weight gain. If the adolescent's goal is to achieve weight loss, a tailored energy deficit could be prescribed, considering individual energy requirements, weight, and physical activity levels.

EBRs highlight that no specific diet or exercise over another is recommended. Rather evidence-based general population strategies should focus on healthy individual preferences that are sustainable, recognizing the role of broader family engagement. The CR in relation to the

duration of exercise was also based on population guidelines (Table 4) [1, 39].

Management of nonfertility features

Regardless of whether an adolescent is diagnosed with PCOS or is "at risk" for PCOS, specific individual concerns should guide interventions. The first management step involves a decision-making discussion with the adolescent and parents/guardians to identify specific treatment goals. The topics that merit discussion include the following: (1) lifestyle changes, (2) the use of combined oral contraceptive pills (COCP) and metformin for PCOS is evidence-based, (3) both COCP and metformin are generally "off-label" for PCOS, and (4) considerations of other interventions.

COCP could be considered for the management of hirsutism and/or menstrual irregularities in adolescents with or "at risk" of PCOS according to 10 studies (420 adolescents) [1, 40, 41]. Metformin alone could be considered in adolescents with or "at risk" of PCOS for cycle regulation, acknowledging limited evidence (six studies [185 adolescents]) [1, 42]. Metformin could be used over COCP for metabolic features and COCP could be used over metformin for hirsutism and/or menstrual irregularities based on four studies (142 adolescents) [1, 43]. The combination of COCPs and metformin in those with a body mass index < 30 kg/m^2 has minimal additional benefit in women with no data in adolescents. The role of antiandrogens is limited according to 26 studies (two studies in adolescents that used antiandrogens combined with two insulin sensitizers) (Table 4) [1, 44].

No specific adolescent recommendations were made for anti-obesity medications and cosmetic therapies due to lack of data in this population. However, anti-obesity medications have beneficial effects in individuals with obesity and there is some evidence in PCOS. Additionally, laser and light therapy are effective treatments for hirsutism and related psychological features according to eight studies in adults with PCOS. Inositol preparations cannot currently be recommended in adolescents as no data exist in this population and only biochemical efficacy has been demonstrated in adults with PCOS (Table 4) [1, 45].

Models of care and transition

Limited data are available regarding models of care in women and adolescents with PCOS [1, 35, 46, 47]. General considerations are included in Table 4.

Only one qualitative study evaluated the transition to adult care [48]. Adolescents with PCOS and those "at risk" of PCOS should have longitudinal follow-up; hence, appropriate transition to adult care is important [2]. Some adolescents have failed to connect with healthcare professionals for several years. During these years, obesity, dysglycemia, dyslipidemia, depression, and subfertility often progress. Consequently, reliable accurate information sources, including the free AskPCOS app, are important. Prior to transition, healthcare professionals and adolescents should discuss comorbidities and develop lifelong plans [48]. Shared decision-making discussions to educate adolescents regarding their health care needs are designed to improve their ability to assume responsibility for self-care during and beyond transition. Transition should be a planned process with the ultimate goals of continued, high-quality health care and increased patient responsibility for self-care.

Discussion

This manuscript summarizes specific adolescent recommendations from the 2023 International Evidence-based PCOS Guideline [8, 9]. The Guideline was a result of extensive international engagement and robust methodological evidence-based processes and was independently reviewed. This manuscript provides healthcare professionals, adolescents, and their families with the most recent evidence-based recommendations to improve health outcomes. There are fewer recommendations for adolescents than for adult women highlighting the limited number of adolescent PCOS studies and emphasizing the need for further research.

Adolescent PCOS diagnosis has always been challenging as normal physiological changes overlap with adult PCOS diagnostic criteria resulting in delayed and underdiagnosis as well as potential overdiagnosis [2, 3]. While evidence supports the use of PCOM and AMH levels for the diagnosis of PCOS in adults [1, 8, 9], PCOM or AMH should not be used for diagnosis in adolescents to minimize the risk of overdiagnosis [2, 4–6, 9]. PCOM or AMH can be used at approximately 8 years postmenarche when the hypothalamic-pituitary-ovarian axis is mature and evidence-based criteria for PCOM are available [8, 9].

For adolescent PCOS diagnosis, the Guideline recommends the combination of menstrual irregularities defined according to the time postmenarche and clinical/biochemical hyperandrogenism following the exclusion of other disorders [8, 9]. The use of these well-defined criteria for PCOS diagnosis during adolescence will promote accurate and timely diagnosis during this life stage. This approach will allow the detection of adolescents at considerable risk of weight gain and diabetes by establishing early screening with the management of long-term metabolic risks and enabling the optimization of long-term fertility outcomes [1, 6, 34]. As delayed diagnosis has been reported in adolescents [7], adolescents with either menstrual irregularities or clinical/biochemical hyperandrogenism can be considered "at risk"

for PCOS. This tactic addresses concerns of inappropriately labeling an adolescent with a PCOS diagnosis while avoiding delayed diagnosis when appropriate follow-up is in place.

Adolescents "at risk" of PCOS require ongoing follow-up and management according to symptoms [2, 8, 9]. Timing of follow-up and re-evaluation of the diagnosis should be discussed and emphasized with adolescents and their families to avoid disruption in care which frequently occurs during transition. Adolescents "at risk" of PCOS can be diagnosed with PCOS during follow-up if they present with a combination of both menstrual irregularities and hyperandrogenism, even before 8 years postmenarche. Thus, re-evaluations before and following transition are essential to ascertain outcomes. Additionally, recent data suggest that adolescents "at risk" for PCOS have abnormal metabolic profiles [49]. Prospective longitudinal studies evaluating adolescents "at risk" of PCOS and healthy adolescents are needed to provide evidence-based data to better advise on the timing of follow-up and the future risk of developing PCOS.

The Guideline provides increasing evidence of psychological features and highlights the need for routine screening and management of depression in adolescents with PCOS due to the high prevalence of this condition [1, 8, 26–31]. Adolescents with PCOS reported suboptimal emotional wellbeing management and dissatisfaction in relation to the education and emotional support offered [7]. More research is required on other psychological features and on strategies to optimize emotional wellbeing management and evaluate anxiety, quality of life, body image, and eating disorders in adolescents with PCOS.

A lifelong health plan, including age-appropriate education, healthy lifestyles, timely screening for long-term metabolic risks, reproductive life plans, and the transition to adult care, is recommended. Management should be guided by shared decision-making addressing adolescent-specific concerns [8, 9, 48]. The Guideline recommends that adolescents with PCOS or "at risk" of PCOS be treated with COCP for menstrual irregularity and hyperandrogenism. COCP with lowest effective estrogen dose are recommended but specific types or doses of progestins, estrogens, or combinations of COCP cannot currently be recommended. Although relatively safe, COCP have absolute and relative contraindications that need consideration, and this should be guided by general recommendations from the World Health Organization Medical Eligibility Criteria. When prescribing COCP to adolescents "at risk" of PCOS, adolescents and parents should be counseled about the potential need of at least 3-month withdrawal of COCP for re-evaluation of diagnosis especially if there is lack of hyperandrogenism and there is a possibility of hypogonadism. Metformin is recommended for metabolic features and cycle regulation in adolescents with PCOS or "at risk" of PCOS. Of note, assessment of insulin resistance can be challenging and while most common in those with a higher BMI adolescents with normal BMI can have insulin resistance and metformin therapy have been beneficial in this population. More studies are needed to evaluate other treatments in adolescents with PCOS, including patient preferences for contraception, hair reduction therapies, antiandrogens, and antiobesity medications. The latter addresses one of the most important adolescent concerns: weight management [7, 48].

The strengths of the Guideline include the following: extensive international engagement including consumers and a range of multidisciplinary healthcare professionals, rigorous methods aligned with international best practices and complying with AGREE-II, and detailed evidence synthesis processes including integrity assessments [1, 10–12]. Additionally, the Guideline was independently evaluated as being of high quality and has a comprehensive and multifaceted translation program aiming for consistent worldwide implementation of evidence-based care [47, 50]. Limitations include that priorities were determined mostly from women with PCOS, not adolescents. However, data are accumulating in adolescents highlighting similar priorities except for infertility [7, 48]. Despite an increased number of studies involving adolescents with PCOS, studies including "only adolescents" or those defining the postmenarcheal period or applying current Guideline diagnostic criteria are limited in number and quality [1, 2]. This highlights that research, using well defined cohorts of adolescents with PCOS, on the natural history of PCOS, emotional wellbeing, optimal treatments, strategies to improve weight, models of care, and transition, is a priority. Additionally, where there are no adolescent studies, some adult recommendations are likely to have applicability, but they need to be considered in the context of adolescence.

Conclusions

Adolescent-specific recommendations from the 2023 International Evidence-based PCOS Guideline enable accurate and timely diagnosis with well-defined Guideline criteria for PCOS diagnosis during adolescence that differ from adult diagnostic criteria. Additionally, recommendations highlight the importance of identifying and managing adolescents "at risk" of PCOS, screening for depression and glucose abnormalities in adolescents with PCOS and establishing management strategies guided by adolescents' concerns including a lifelong health plan. The overall evidence is limited and of low to moderate quality, highlighting the critical need for further research on PCOS during adolescence and in the longer term.

Abbreviations

AGREE-II	Appraisal of Guidelines for Research and Evaluation
AMH	Anti-Müllerian hormone
BMI	Body mass index
COCP	Combined oral contraceptive pills
CR	Consensus recommendation
EBR	Evidence-based recommendation
GDGs	Guideline development groups
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
IPL	Intense pulse light
mFG	Modified Ferriman Gallwey
PCOM	Polycystic ovarian morphology
PCOS	Polycystic ovary syndrome
PP	Practice point

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Authors' contributions
AP and HT conceptualized this manuscript. AP wrote the first draft of the manuscript. HT led the guidelines from funding, engaging partners, coordinating processes, prioritizing clinical questions, co-chairing guidelines meetings, coordinating peer review responses and leading writing, approval, and publication responses. AM and CTT led the evidence synthesis network. SW, TB, JB, CE, KH, ML, AM, SO, CTT wrote specific sections of the manuscript. All authors reviewed and critically revised the manuscript. All authors read and approved the final manuscript. All authors have full access to all the evidence included in the manuscript and accept responsibility to submit for publication.

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