

# Diagnosis and Treatment of Adolescent Polycystic Ovary syndrome: A Review

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**Abstract:** Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder among women of reproductive age. Diagnosing adolescent PCOS is challenging due to the overlap between adult PCOS diagnostic criteria and normal physiological changes in adolescence. This review examines the diagnosis and treatment strategies for adolescent PCOS. The diagnosis of adolescent PCOS should meet two primary criteria—ovulatory dysfunction and biochemical or clinical hyperandrogenism—after excluding other causes. Defining these criteria accurately aids in early diagnosis and management of adolescent PCOS. However, due to limited research, age-specific diagnostic standards remain lacking. Once diagnosed, timely interventions—such as lifestyle, exercise, and dietary changes, along with targeted treatments like metformin and antiandrogens—should be initiated. In addition, the management of adolescent PCOS presents several challenges, including the absence of standardized medication guidelines, adolescent psychological factors that may impede adherence to dietary and exercise recommendations, and parental concerns about the long-term effects of medication on bone health and metabolism. Therefore, additional research is required to establish optimal management protocols to enhance patients' quality of life and prevent complications.

**Keywords:** PCOS, teenagers, diagnosis, treatment, adolescent PCOS

## Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 8–13% of women of reproductive age and 3–11% of adolescents, depending on diagnostic criteria.<sup>1</sup> It is a multifactorial syndrome with unclear etiology, involving genetic, environmental, and hormonal factors.<sup>2</sup> PCOS is characterized by gonadotropin dysregulation, hyperandrogenism, insulin resistance (IR), and polycystic ovarian morphology (PCOM). Genome-wide association studies have identified over 20 genetic loci linked to PCOS,<sup>3</sup> highlighting its strong genetic predisposition.<sup>4</sup> Clinically, PCOS manifests as menstrual irregularities, hyperandrogenism, and PCOM, and it is associated with infertility, miscarriage, type 2 diabetes, metabolic syndrome, cardiovascular diseases, and increased risk of endometrial cancer.<sup>5</sup> Additionally, physical symptoms such as weight gain, acne, and hirsutism heighten the risk of anxiety and depression, particularly in younger women.<sup>6</sup>

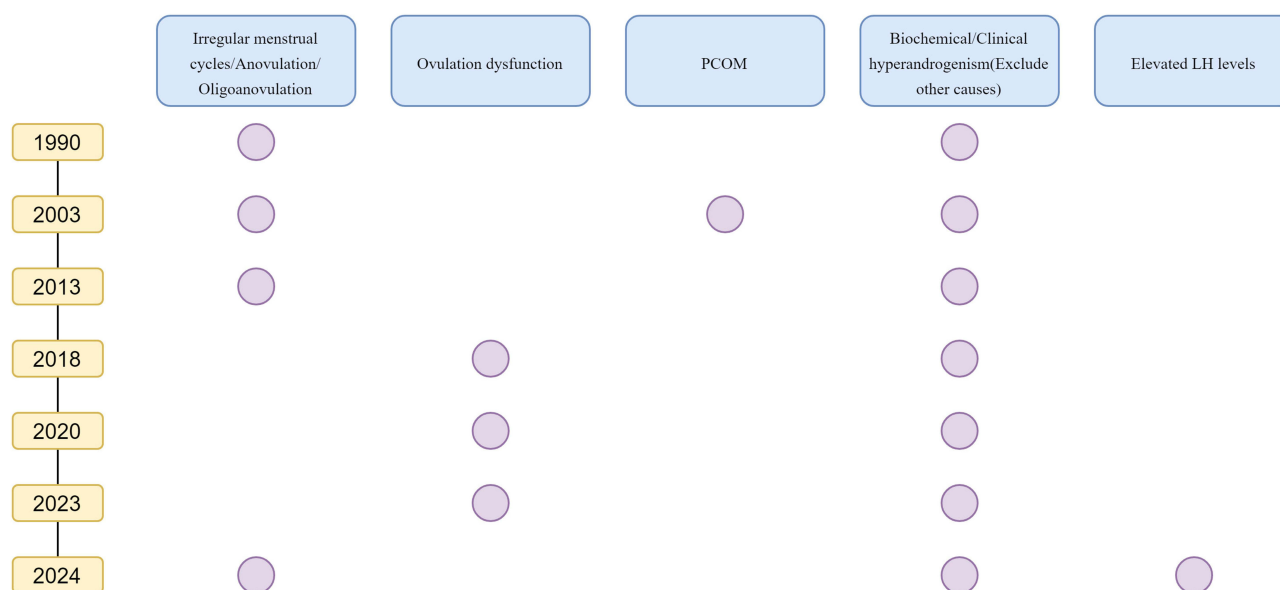
The World Health Organization (WHO) defines adolescence as 10–19 years, during which diagnosing polycystic ovary syndrome (PCOS) is challenging and controversial.<sup>7</sup> Over decades, diagnostic criteria for PCOS have evolved significantly. The initial National Institutes of Health (NIH) criteria required clinical or biochemical hyperandrogenism and chronic anovulation but lacked specificity for adolescents, leading to regional variability.<sup>8</sup> Although various guidelines and consensus documents have since been introduced, discussions specifically addressing adolescent PCOS remain limited, complicating diagnosis during this stage.<sup>9,10</sup> In 2003, the Rotterdam criteria were introduced, requiring two of three conditions: oligo/anovulation, clinical or biochemical hyperandrogenism, and PCOM.<sup>11</sup> However, adolescence involves physiological changes like irregular menstruation, increased androgen secretion, and PCOM, overlapping with

these criteria and rendering them unsuitable. Applying the Rotterdam standards risks overdiagnosis and inflates adolescent PCOS prevalence, contributing to ongoing controversy over appropriate diagnostic criteria.<sup>12–14</sup>

Since 2013, PCOS diagnostic and treatment guidelines have been updated multiple times to reflect new findings and address clinical challenges. In 2013, the American Association of Clinical Endocrinologists (AACE) proposed flexible criteria for adolescents, diagnosing PCOS based on biochemical or clinical hyperandrogenism if oligomenorrhea persists, while accounting for physiological changes like irregular cycles and PCOM.<sup>15,16</sup> In 2018, European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) released the “International Evidence-Based Guideline for the Assessment and Management of PCOS”, excluding PCOM as a diagnostic criterion for adolescents due to its high incidence within 8 years post-menarche and limited transvaginal ultrasound use.<sup>17</sup> The guidelines suggest revising PCOM thresholds, establishing age-specific cut-offs, and including ovulatory dysfunction and biochemical or clinical as diagnostic criteria. Because ovulatory dysfunction may still occur in adolescents even with regular menstrual cycles.<sup>18,19</sup> Adolescents with PCOS features not meeting diagnostic criteria should be classified as “high-risk” and reassessed before reproductive maturity. Androstenedione and dehydroepiandrosterone (DHEA) measurements are recommended for patients with normal testosterone levels. In 2020, guidelines in BMC Medicine reaffirmed excluding PCOM and emphasized identifying “high-risk” patients, recommending symptomatic treatment and reassessment.<sup>13</sup> Menstrual cycle evaluation is advised within 3 years post-menarche and ultrasound within 8 years for irregular cycles or hyperandrogenism. In 2023, ESHRE and ASRM updated their guidelines,<sup>20</sup> introducing Anti-Müllerian hormone (AMH) as an alternative diagnostic tool to ultrasound for PCOS for the first time. However, due to its low specificity and sensitivity in adolescent PCOS patients, AMH is not recommended as a diagnostic tool for adolescent PCOS. In 2024, JSOG introduced the Luteinizing Hormone(LH)/ Follicle-stimulating hormone(FSH) ratio as a diagnostic criterion for adolescents.<sup>21</sup> All guidelines emphasize excluding other causes of biochemical or clinical hyperandrogenism. Figure 1 summarizes the diagnostic criteria.

## Methods

A literature search was conducted using databases such as PubMed, CINAHL, and Web of Science, with search terms including “adolescent PCOS/treatment”, “adolescent PCOS/management”, and “PCOS”, covering the period up to October 31, 2025. Abstracts were limited to those in English. A total of 243 abstracts were screened and assessed by two independent reviewers. Subsequently, one independent reviewer examined the full-text research articles related to the treatment and management of adolescent PCOS and further screened their references to identify additional relevant



**Figure 1** Evolution of Diagnostic Criteria for Adolescent PCOS.

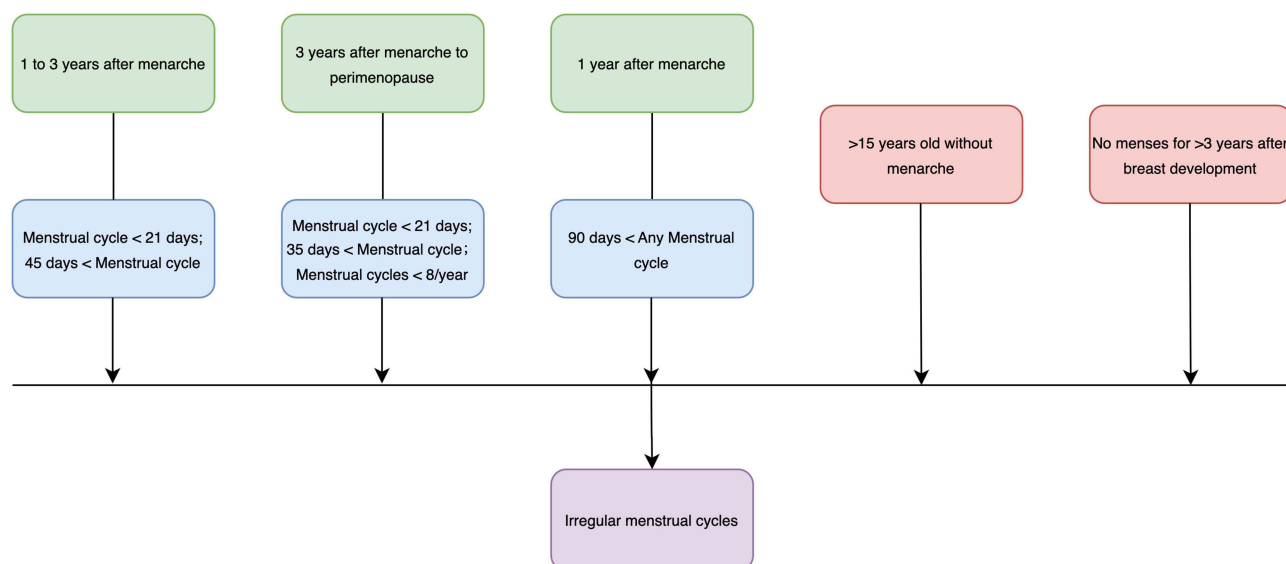
studies. Of the 243 abstracts, 13 were duplicates, 5 lacked an English version, and 13 were untraceable. Fifty-two articles were selected for full-text review. Screening the reference lists identified 132 relevant studies, of which 13 were untraceable. The final basis for this review consists of 103 studies, including 51 cohort studies, 32 reviews, 15 case reports, 10 case-control studies, 7 comparative studies, and 3 qualitative interview studies.

## Main Criteria for the Diagnosis of Adolescent PCOS

### Irregular Menstrual Cycles and Ovulatory Dysfunction

Irregular menstrual cycles are often the earliest clinical sign of adolescent PCOS, typically manifesting as oligomenorrhea or secondary amenorrhea.<sup>22</sup> A 2019 systematic review on diagnostic criteria for adolescent PCOS found that most studies viewed irregular menstrual cycles as a necessary criterion for diagnosis.<sup>12</sup> However, irregular menstrual cycles are also a common physiological occurrence during adolescence. During early adolescence, the gonadal axis gradually activates, and the hypothalamic-pituitary-ovarian axis has not yet established a stable estrogen feedback mechanism, leading to anovulatory cycles and irregular periods.<sup>23</sup> Additionally, immature secretion of FSH and an underdeveloped ovarian response may contribute to irregular menstrual cycles. Therefore, a clear and detailed definition of irregular menstrual cycles is necessary, considering cycle duration and the time since menarche. The latest guidelines define adolescent menstrual irregularities,<sup>20</sup> as summarized in Figure 2.

Significant differences exist in ovulation patterns between adolescent and adult females regarding menstrual cycles. In healthy adult females, approximately 10% of menstrual cycles are anovulatory.<sup>24</sup> A study on ovulation in adolescent females revealed that in the first year after menarche, only 20% of menstrual cycles were ovulatory. This increased to 25%–35% in the second year, 45% in the fourth year, and up to 70% during 5 to 9 years after menarche.<sup>25</sup> Another study indicated that irregular menstrual cycles in adolescent females do not necessarily signify ovulatory dysfunction. A significant proportion of adolescents with irregular cycles still ovulate normally.<sup>19</sup> Thus, irregular menstrual cycles should not serve as a diagnostic criterion for adolescent PCOS. Instead, they should be considered a screening indicator that may suggest the presence of PCOS, warranting further evaluation of ovulatory function.<sup>20</sup> Using a single cycle's serum progesterone level to determine ovulation in adolescent females is inappropriate.<sup>7</sup> If ovulatory dysfunction is suspected, the evaluation should encompass menstrual cycle patterns, basal body temperature, ovulation test kits, and blood hormone levels.<sup>26</sup>



**Figure 2** Definition of Irregular Menstrual Cycles. 1–3 years after menarche: Menstrual cycle < 21 days or > 45 days; 3 years after menarche to perimenopause: Menstrual cycle < 21 days or > 35 days, or < 8 cycles per year; 1 year after menarche: Any menstrual cycle > 90 days; No menarche by age 15; No menstruation 3 years after breast development.

## Hyperandrogenism

Biochemical and clinical hyperandrogenism is a key diagnostic criterion for adolescent PCOS. Most studies recommend assessing biochemical hyperandrogenism in adolescent PCOS patients by measuring free testosterone, the free androgen index, or bioavailable testosterone.<sup>27–29</sup> Current guidelines suggest measuring total and free testosterone to assess biochemical hyperandrogenism, using the free androgen index to evaluate free testosterone levels, which can be calculated.<sup>20</sup> If total and free testosterone levels are not elevated, additional tests for androgens like androstenedione and DHEA may be conducted. However, it is important to note that these hormones have relatively low specificity.<sup>30</sup> Current guidelines recommend using high-precision tandem mass spectrometry (LC-MS/MS) to measure total testosterone levels, as well as for testing androstenedione and DHEA. For measuring free testosterone, methods like calculation, equilibrium dialysis, or ammonium sulfate precipitation are recommended.<sup>10,20</sup> Furthermore, any increase in testosterone levels, even if minimal, should raise suspicion of 21-hydroxylase deficiency.<sup>20</sup> No universal threshold for androgen levels in adolescent PCOS has been established, and most guidelines suggest using the reference ranges provided by local laboratories. Androgen levels in PCOS patients may be normal or only slightly elevated. If significantly elevated, other causes of biochemical hyperandrogenism, including non-classical adrenal hyperplasia and androgen-secreting endocrine tumors, should be considered and ruled out.<sup>13,20</sup> The effects of hormonal contraceptives must also be considered, as they can suppress the production of gonadotropin-dependent androgens. Thus, the evaluation of biochemical hyperandrogenism may be unreliable in patients on hormonal contraceptives. It is recommended that such medications be discontinued for 3 months prior to retesting, with alternative contraception provided during this period.<sup>20,31</sup> Given the limited diagnostic value of imaging techniques in adolescent PCOS, optimizing androgen detection methods and improving measurement accuracy are crucial. Researchers have compared the diagnostic accuracy of commonly used androgen markers, including free testosterone, free androgen index, androstenedione, DHEA, and dihydrotestosterone (DHT).<sup>32</sup> Additionally, researchers have explored new androgen markers, such as the efficacy of 11-oxyandrogens in disease prediction, which were found to be more effective than testosterone and androstenedione.<sup>33</sup>

In adolescent females, the primary clinical manifestations of hyperandrogenism are severe acne and hirsutism. In adult females, hair loss is a common sign of hyperandrogenism. However, it is relatively rare in adolescents, and current studies have not documented it.<sup>34</sup> In healthy adolescent females, non-inflammatory follicular acne, characterized by fewer than 10 facial lesions, typically mild to moderate, tends to increase with age and time after menarche.<sup>35</sup> Mild acne is the most prevalent type, whereas moderate to severe acne may indicate hyperandrogenism.<sup>36</sup> Hyperandrogenism should be considered in adolescent females with more than 10 facial lesions of moderate or severe inflammatory acne around menarche, or if acne persists and does not respond to topical treatments. Current guidelines also indicate that severe acne in adolescent females should be considered a clinical sign of hyperandrogenism.<sup>20</sup> Hirsutism refers to the excessive growth of terminal hair (dark, coarse hair) in androgen-sensitive areas.<sup>36</sup> Hirsutism may be linked to excessive androgen secretion, as androgens bind to androgen receptors (AR), triggering downstream signaling pathways that regulate follicular proliferation, differentiation, and hair growth. Studies have demonstrated a strong interaction between AR signaling and the Wnt/ $\beta$ -catenin pathway, with both collaboratively regulating follicular development and hair growth. Specifically, AR signaling inhibits  $\beta$ -catenin phosphorylation by GSK-3 $\beta$ , preventing its degradation and promoting its accumulation and nuclear translocation, which in turn stimulates follicular cell proliferation and hair production.<sup>37</sup> Additionally, the occurrence and severity of hirsutism are influenced by the sensitivity of hair follicles to androgens. Androgen-metabolizing enzymes in hair follicles play a critical role in regulating local androgen levels. Key enzymes include cytochrome P450 aromatase, type 2 17 $\beta$ -hydroxysteroid dehydrogenase, and 5 $\alpha$ -reductase. Altered expression of these enzymes may modify local androgen activity in hair follicles, explaining why individuals with normal serum androgen levels can still develop hirsutism.<sup>38</sup> The modified Ferriman-Gallwey (mFG) score is the most widely used assessment tool, with scores  $\geq 4$ –6 suggesting hirsutism. The specific cutoff should be adjusted based on ethnic variations.<sup>20</sup> Studies indicate that Hispanic and Middle Eastern females have more hair per unit skin area and a higher likelihood of developing severe hirsutism compared to East Asian females.<sup>39,40</sup> Consequently, some experts recommend a cutoff score of 8 for populations more prone to severe hirsutism (eg, Hispanic and Middle Eastern females), 6 for Caucasian and African females, and 4 for East Asian/Asian females.<sup>41</sup> However, clear guidelines on cutoff scores for

adolescent females across different ethnicities are lacking. In clinical practice, patient self-management of hirsutism must be taken into account, as it can influence assessment results and diagnostic accuracy.

## POCM

Historically, PCOM was a common diagnostic criterion for PCOS in adult females across national and international guidelines. However, advancing research has revealed a weaker correlation between PCOM and adolescent PCOS.<sup>42</sup> As previously mentioned, PCOM may result in overdiagnosis of PCOS in adolescent females.<sup>43</sup> Current guidelines state that due to the absence of a clear definition of PCOM in adolescent ultrasound exams, ultrasound is not recommended for diagnosing PCOS in adolescents.<sup>20</sup> There are two primary reasons to avoid using ultrasound examinations in adolescents. First, most adolescent females can only undergo transabdominal, not transvaginal, ultrasound, limiting the accuracy of the results.<sup>20</sup> Although magnetic resonance imaging (MRI) is considered more accurate, it has not been widely adopted in clinical practice.<sup>44</sup> Secondly, basic research indicates a relatively high incidence of PCOM among adolescent females. From ages 10 to 11, ovarian volume gradually increases due to the growth of antral follicles and ovarian stroma, peaking around 8 years after menarche.<sup>45,46</sup> Studies suggest that PCOM is common in adolescent females, especially those with irregular menstrual cycles, with an incidence as high as 57.9%, significantly overlapping with PCOS diagnostic criteria.<sup>25,47</sup> Consequently, earlier guidelines advised against using pelvic ultrasound to diagnose PCOS in adolescents within 8 years of menarche; however, this recommendation has been omitted in the current guidelines.<sup>20</sup> Nonetheless, current guidelines maintain that ultrasound is unsuitable for diagnosing PCOS in adolescent females but remains an important tool for ruling out other uterine or ovarian abnormalities that may cause primary amenorrhea.

## AMH

AMH is a peptide hormone secreted by the granulosa cells of ovarian follicles. During childhood, AMH levels in healthy females gradually increase, peak in adolescence, and subsequently decline with age.<sup>48,49</sup> AMH levels are closely related to the number of follicles and are often considered a reflection of ovarian reserve function. Generally, higher AMH levels indicate a greater number of available follicles, while lower levels may suggest a decline in ovarian reserve function.<sup>50</sup> Evidence indicates that serum AMH levels in women with PCOS are significantly higher than those in healthy women during both adolescence and adulthood.<sup>51,52</sup> Recent guidelines indicate that seven relevant studies suggest high AMH levels in adult women may reflect PCOM, which can be used as a diagnostic criterion in clinical practice. However, despite significant elevations in serum AMH levels among adolescents with PCOS, studies assessing its diagnostic value in this population have shown low sensitivity and specificity, leading to recommendations against using it for diagnosing adolescent PCOS.<sup>20</sup> Overall, AMH testing is a viable diagnostic tool for PCOM in adult women, but not for adolescent females. Additionally, while AMH testing is valuable for diagnosing PCOS in adult women, unresolved issues like the lack of clear diagnostic thresholds persist. These limitations highlight the need for further research to refine AMH application in PCOS diagnosis.

## Metabolic Factors

Historically, PCOS was viewed primarily as an ovarian disorder; however, growing evidence suggests that neuroendocrine factors significantly contribute to its pathogenesis. The possibility of PCOS should also be considered in patients with obesity, metabolic syndrome (MetS), compensatory hyperinsulinemia, and IR.<sup>53</sup> MetS is a complex condition defined by elevated blood pressure, fasting blood glucose, waist circumference, and triglycerides (TG), alongside decreased low-density lipoprotein (LDL) levels.<sup>54</sup> PCOS and MetS share pathophysiological overlaps, as both are closely associated with insulin resistance. Research indicates that the prevalence of MetS is significantly higher in adolescents with PCOS than in those without.<sup>55,56</sup> A study of adolescent PCOS patients in South China reported a MetS prevalence of 4.7%, with over one-third exhibiting at least one characteristic of MetS, the most common being central obesity and dyslipidemia.<sup>57</sup> Additionally, about half of PCOS patients are obese, which not only increases the risk of developing PCOS but also exacerbates IR and related reproductive and metabolic issues, resulting in hyperinsulinemia. Hyperinsulinemia directly stimulates ovarian granulosa and theca cells, enhancing androgen production and potentially affecting follicular development and ovulation by altering the local ovarian environment.<sup>58,59</sup> A large-scale genome-wide

association study (GWAS) demonstrated a strong genetic correlation between obesity and PCOS, suggesting that individuals genetically predisposed to obesity are also more likely to develop PCOS.<sup>60</sup> In summary, when adolescent females display one or more metabolic abnormalities (such as obesity, dyslipidemia, or impaired glucose tolerance), clinical vigilance should increase to consider the possibility of PCOS, prompting timely screening and assessment. Additionally, with advancements in bioinformatics, the application of metabolomics offers new insights into diagnosing adolescent PCOS, particularly given the current lack of effective diagnostic methods. Researchers have constructed and validated a diagnostic panel model by analyzing the classification of differential lipid metabolites and their association with clinical indices.<sup>61</sup> Metabolic factors clearly hold great potential in diagnosing adolescent PCOS.

Given the widespread risk of IR and abnormal glucose metabolism in PCOS patients, most guidelines recommend early IR assessment following a PCOS diagnosis. Unlike earlier guidelines, the latest recommendations advise assessing glucose metabolism regardless of the Body Mass Index (BMI) of PCOS patients, as even those with a normal BMI can exhibit significant IR.<sup>62</sup> The latest guidelines recommend a 75g Oral Glucose Tolerance Test (OGTT) to assess glucose metabolism. If OGTT is not feasible, fasting blood glucose or glycated hemoglobin (HbA1c) tests can be considered, though their accuracy may be limited.<sup>20</sup> Therefore, routine glucose metabolism assessments should be conducted for all PCOS patients, irrespective of weight, to enable early detection and management of metabolic issues.

## LH/FSH Values

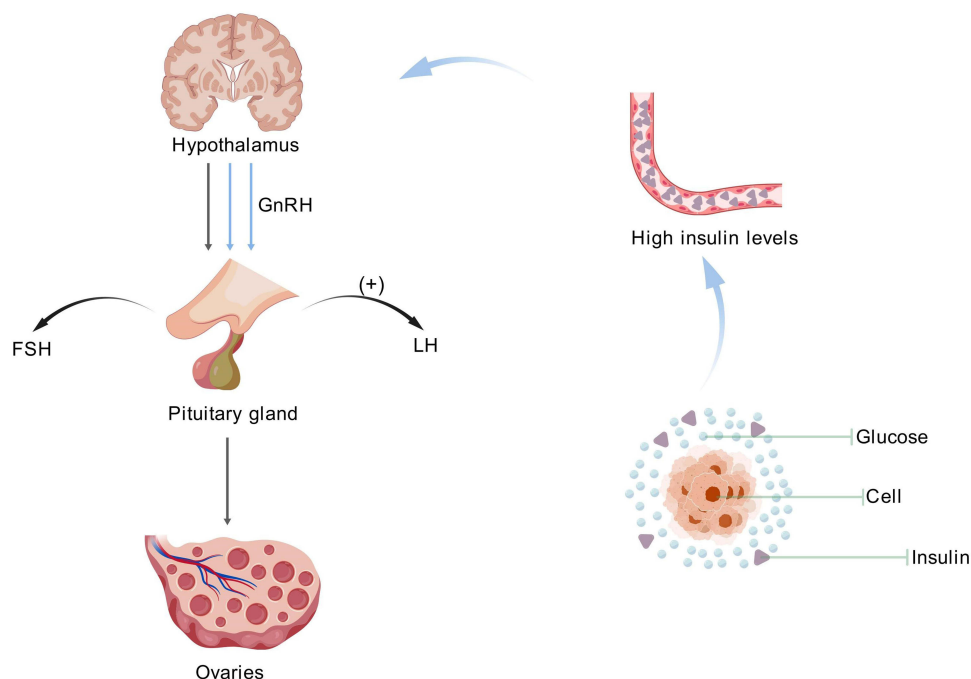
PCOS, a common endocrine disorder, often presents with elevated LH levels and an increased LH/FSH ratio, particularly in adolescents. The LH/FSH ratio in healthy women varies across different stages of the menstrual cycle. During the follicular phase (days 1–14), the LH/FSH ratio is approximately 1:1, with FSH typically exceeding LH. During ovulation (around day 14), LH levels surge, and the LH/FSH ratio may rise to 2:1 or higher. In the luteal phase (days 15–28), the ratio typically returns to approximately 1:1.<sup>63</sup> These hormonal changes are closely linked to the pathophysiological mechanisms of PCOS. On one hand, abnormalities in the hypothalamic-pituitary-ovarian axis in PCOS lead to increased pulse frequency of GnRH from the hypothalamus, resulting in elevated LH secretion. Although GnRH also stimulates FSH secretion, FSH is less sensitive to GnRH pulse frequency than LH. Consequently, higher GnRH pulse frequency preferentially increases LH secretion without significantly elevating FSH levels, and may even suppress FSH secretion.<sup>64–66</sup> Conversely, PCOS often involves insulin resistance (IR), with insulin levels typically elevated even when blood glucose levels are normal. Elevated insulin levels can directly act on the hypothalamus, further promoting GnRH pulse frequency and intensity, thereby exacerbating LH secretion (Figure 3).<sup>67</sup> These two mechanisms work together to cause abnormal hormone secretion in PCOS, particularly in adolescents.

According to the PCOS guidelines published by JSOG this year,<sup>21</sup> diagnosing adolescent PCOS requires the simultaneous fulfillment of two conditions: menstrual cycle abnormalities and hyperandrogenism or elevated LH levels. Previous guidelines and studies often used the LH/FSH ratio as a diagnostic reference criterion, with elevated LH levels determined based on the average LH and LH/FSH ratio in normal females, plus one standard deviation as the cutoff value. Different testing platforms require corresponding cutoff values for accurate assessment. The guidelines specify two criteria based on previous studies: Architect® platform: LH  $\geq$  7.1 mIU/mL, LH/FSH ratio  $\geq$  1.21; Elecsys® platform: LH  $\geq$  9.9 mIU/mL, LH/FSH ratio  $\geq$  1.51.<sup>68</sup> It is important to note that diagnostic criteria vary among patients of different body types: for non-obese patients, both elevated LH baseline levels and high LH/FSH ratios must be met for diagnosis; while for obese patients (BMI  $\geq$  25 kg/m<sup>2</sup>), the high LH/FSH ratio alone suffices for assessment. Furthermore, due to the lack of relevant studies on adolescent PCOS patients, the standards for elevated LH levels used to diagnose adolescent PCOS continue to rely on diagnostic criteria established for adult females.

## Treatment of Adolescent PCOS

### Lifestyle Interventions

Lifestyle interventions are recommended treatment options for both adult and adolescent PCOS patients, including behavioral, dietary, and exercise modifications to reduce weight, central obesity, and IR. This is strongly recommended in the latest guidelines, supported by high-quality evidence according to Grade of Recommendations Assessment (GRADE).<sup>20</sup>



**Figure 3** Mechanism of Elevated LH Levels in PCOS Patients. Elevated insulin levels influence the hypothalamus, enhancing the frequency and intensity of GnRH pulses, thereby increasing LH secretion.

A randomized controlled trial found that lifestyle interventions significantly reduce weight and BMI compared to standard care and improve related clinical and laboratory parameters in PCOS, including the free androgen index, testosterone levels, sex hormone-binding globulin, and hirsutism.<sup>69</sup> Among adolescent PCOS patients, those undergoing lifestyle interventions experienced significantly greater weight loss than those who did not receive these interventions.<sup>70</sup> Additionally, studies indicate that lifestyle interventions significantly reduce total cholesterol (TC), LDL, and insulin levels, consistent with many previous findings.<sup>71–73</sup> Notably, while moderate weight loss (2–5% of body weight) can improve ovulatory function and menstrual irregularities, losing more than 5% can significantly enhance fertility rates, pregnancy outcomes, decrease ovarian volume, and reduce ovarian follicles; however, the relationship between weight loss and improvement in PCOS symptoms is not linear. A cohort study found that even among those achieving target weight loss (over 5%), one-third demonstrated complete recovery from PCOS, while others only partially recovered or did not recover at all.<sup>74</sup> Furthermore, researchers found that PCOS women with greater variations in central obesity and insulin sensitivity experience more significant symptom improvement after weight loss than typical PCOS patients.<sup>75</sup> This suggests that central obesity and insulin sensitivity may predict PCOS patients' responsiveness to weight loss interventions. Thus, as recommended by the latest guidelines, improving central obesity (eg, waist circumference and waist-to-hip ratio) is crucial for lifestyle interventions in PCOS patients with higher BMI.<sup>20</sup> In summary, lifestyle management is central to managing adolescent PCOS patients. For overweight adolescent PCOS patients, BMI management is the focus of lifestyle interventions, whereas for non-overweight patients, the core of lifestyle management is preventing excessive BMI increase.<sup>20</sup>

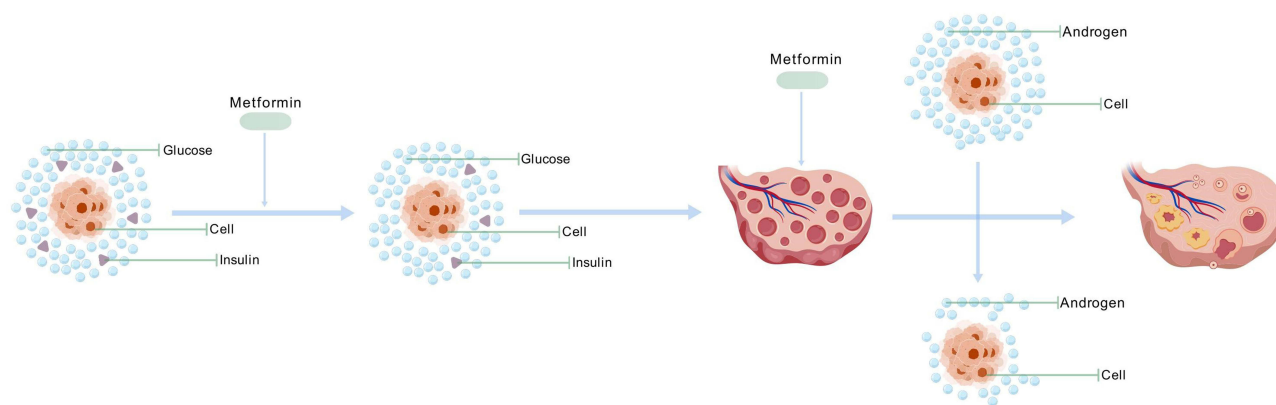
The latest PCOS guidelines indicate that dietary intervention is a first-line treatment for PCOS patients; however, there is currently no evidence that any specific dietary component is superior in managing adolescent PCOS.<sup>20</sup> Consistent with dietary recommendations for the general population, the guidelines advise PCOS patients to adopt sustainable, healthy dietary strategies tailored to their personal preferences and lifestyle needs.<sup>20</sup> The Mediterranean Diet (MedDiet), recognized for its anti-inflammatory, anti-cancer, and anti-obesity properties, is recommended as a dietary pattern in preventive medicine.<sup>76</sup> Due to its numerous health benefits, international guidelines recommend it as a dietary pattern, emphasizing the intake of unsaturated fats, dietary fiber, low carbohydrates, antioxidants, and moderate amounts of animal and plant proteins.<sup>76</sup> Given that the MedDiet reduces inflammation, lowers oxidative stress, and improves insulin sensitivity, and considering that PCOS is closely related to obesity, chronic inflammation, and IR, many scholars

advocate it as a dietary strategy for managing PCOS. The MedDiet primarily consists of plant-based foods, such as vegetables, fruits, nuts, and seeds, which are rich in antioxidants, dietary fiber, and vitamins. Additionally, the high-quality lipids found in olive oil and fish are crucial components of the MedDiet; these unsaturated fatty acids contribute to cardiovascular health and can replace trans fats in daily diets. Research indicates that polyphenols in the MedDiet have therapeutic potential for PCOS, capable of improving inflammatory status, reducing IR, and alleviating compensatory hyperinsulinemia.<sup>77</sup> A three-month randomized controlled trial found that adolescents with PCOS who underwent MedDiet interventions showed significant improvements in total cholesterol (TC), IR status, and anxiety compared to those not receiving the intervention.<sup>78</sup> Furthermore, a 2020 study indicated that 14 overweight PCOS patients experienced significant reductions in weight and BMI, along with improvements in insulin resistance, LH, LH/FSH ratio, and testosterone levels after 12 weeks on a ketogenic diet.<sup>79</sup> Another study conducted in 2022 explored the effects of a ketogenic diet on ovarian reserve and luteal function in PCOS patients, finding significant improvements in metabolic and ovulatory function over a short period.<sup>80</sup> While the ketogenic diet may serve as an alternative to the MedDiet, caution is warranted in its application for managing PCOS due to the lack of long-term studies, potential side effects of high-fat diets, and the chronic nature of PCOS, which requires long-term management. Current dietary intervention studies for PCOS patients primarily involve adult females. Given the unique physiological and psychological characteristics of adolescent females, more research is needed to develop suitable dietary intervention strategies for this population.

In the general population, exercise is widely recognized as a treatment measure for preventing and controlling chronic diseases.<sup>81,82</sup> Several studies have shown that exercise positively impacts the treatment of PCOS.<sup>83</sup> The latest guidelines clarify that exercise intervention is a first-line treatment to improve health, hormone levels, IR, and quality of life in PCOS patients.<sup>20</sup> Currently, there is no evidence that any specific type or intensity of exercise has superior effects on metabolism, reproduction, or hormone treatment in PCOS patients. Therefore, the latest guidelines incorporate relevant management standards from exercise guidelines for the general population. For adolescent females, the guidelines recommend at least 60 minutes of moderate to vigorous intensity exercise daily, along with at least three sessions of strength training per week.<sup>20</sup> In recent years, several studies have explored the optimal exercise intensity, duration, and the relationship between exercise and diet for PCOS patients. However, specific exercise standards for managing PCOS patients are still lacking, and further research is needed to determine the appropriate intensity, duration, and dietary interactions for PCOS patients of all ages. Moreover, another key challenge in lifestyle interventions for adolescents with PCOS is the generally low adherence, primarily due to several factors.<sup>84</sup> First, the unique psychological and behavioral characteristics of adolescence complicate behavior modification. For example, academic pressure and time constraints hinder adherence to health plans, while a high-sugar diet and late-night habits in the social environment disrupt interventions. Additionally, body image anxiety (eg, stemming from obesity or acne-related self-esteem issues) and rebellious tendencies may result in resistance to dietary control and exercise. Second, insufficient family support and financial constraints further hinder adherence. Some parents lack awareness of PCOS or face generational conflicts in health beliefs, making it challenging to provide effective supervision and emotional support. Financial pressures may also limit access to healthy eating options and exercise resources. Moreover, design flaws in intervention programs can reduce their effectiveness. Standardized approaches often neglect individual preferences and cultural backgrounds, while overly strict short-term goals can induce feelings of failure.<sup>85</sup> Psychosocial factors should also be considered. Stigma surrounding the condition may cause patients to conceal their diagnosis and avoid social interactions. The lack of mental health resources leads to unaddressed anxiety and depression, further reducing adherence.<sup>86</sup> To address these challenges, personalized interventions should be designed (eg, integrating exercise forms tailored to personal interests), fostering family-school collaboration, incorporating digital tools, and integrating psychological support. A multi-dimensional support system should be implemented to enhance adherence and improve long-term outcomes.

## Metformin

Metformin is an insulin sensitizer that has been extensively studied, demonstrating its ability to inhibit gluconeogenesis, improve IR, and suppress fat synthesis.<sup>87</sup> Additionally, metformin aids in weight control by regulating appetite-related pathways and is primarily utilized in PCOS patients exhibiting abnormal metabolic indicators.<sup>20</sup> A study conducted by



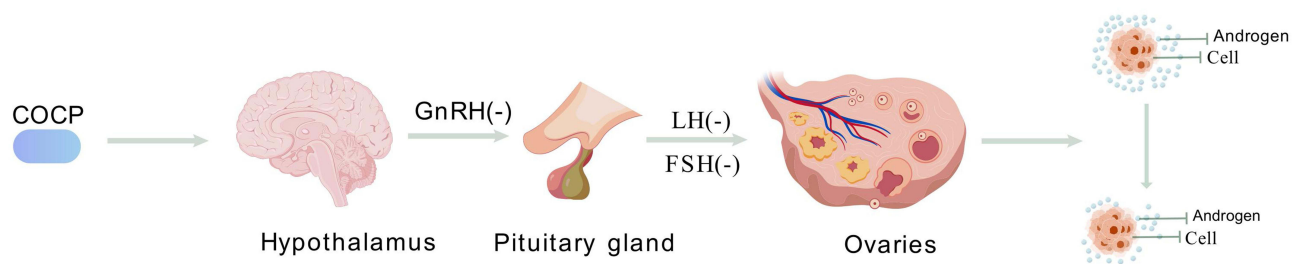
**Figure 4** Mechanism of metformin improving ovarian ovulation. On the one hand, metformin improves insulin sensitivity and reduces insulin levels, thereby decreasing androgen production and enhancing ovarian ovulatory function. On the other hand, metformin directly affects ovarian tissues, decreasing androgen synthesis and promoting follicular development.

Nazari et al (2023) demonstrated that 30 adolescent PCOS patients experienced significant improvements in high-density lipoprotein (HDL), fasting blood glucose (FBG), fasting insulin (FINS), triglycerides (TG), and low-density lipoprotein (LDL) following 6 months of daily treatment with 500 mg of metformin.<sup>88</sup> El-Sharkawy et al (2022) further confirmed through a case-control study that 30 adolescent PCOS patients exhibited significant improvements in weight, body mass index (BMI), fasting blood glucose, postprandial blood glucose, fasting insulin (FINS), and the homeostasis model assessment index (HOMA) after 3 months of metformin treatment.<sup>89</sup> On one hand, PCOS patients frequently exhibit hyperinsulinemia, which promotes the ovaries to synthesize elevated levels of androgens, thereby inhibiting normal ovulation. Metformin improves insulin sensitivity and reduces insulin levels, thereby decreasing androgen production, enhancing ovarian ovulatory function, and helping to restore regular menstrual cycle regularity. Conversely, metformin may act directly on ovarian tissue to decrease androgen synthesis and promote follicular development, thus improving symptoms associated with irregular menstrual cycles.<sup>90</sup> The latest clinical guidelines clearly indicate that for high-risk adolescent patients diagnosed with PCOS, particularly those who are overweight or obese and have contraindications or intolerance to Combined Oral Contraceptive Pills (COCP), metformin may be utilized alone to regulate the menstrual cycle<sup>20</sup> (Figure 4).

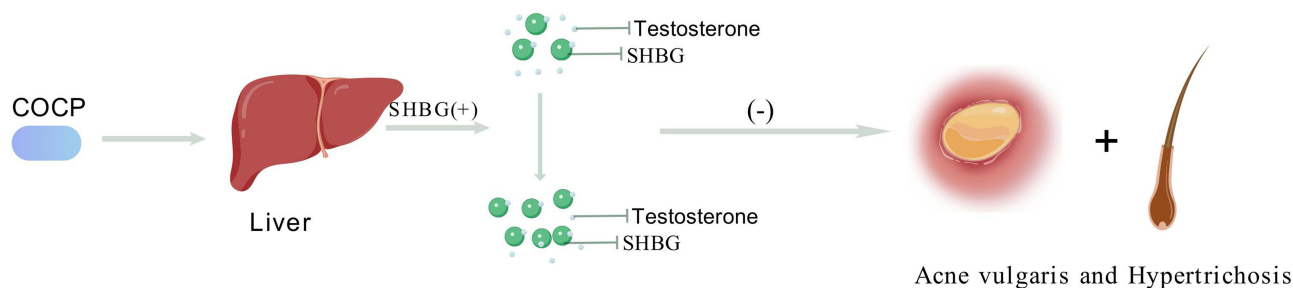
Although metformin has limited effectiveness in treating PCOS, some studies have found that it can significantly lower androgen levels compared to placebo; however, its effect on improving hirsutism in PCOS patients is not significant.<sup>91–93</sup> Research by Melin et al indicated that, regardless of patients' BMI or age, metformin is less effective in treating hirsutism in PCOS patients compared to monotherapy with Combined Oral Contraceptive Pills (COCP) or the combination of COCP and metformin.<sup>94</sup> Therefore, metformin is not recommended as monotherapy for alleviating hirsutism in adolescent PCOS patients. While metformin can lower androgen levels in PCOS patients, it does not appear to have a significant effect on improving hirsutism.<sup>20</sup> The latest guidelines recommend that if metformin monotherapy is considered, adolescent PCOS patients should start with a low dose and increase by 500 mg every 1 to 2 weeks until a maximum daily dose of 2 grams is reached. Additionally, it is recommended to use extended-release metformin to minimize side effects and enhance patient compliance.<sup>20</sup>

## COCP

The primary components of COCP are estrogen and progestin, which are mainly used in the treatment of PCOS to alleviate symptoms such as hirsutism and irregular menstrual cycles.<sup>95</sup> Its mechanism of action primarily involves the following three aspects:<sup>96,97</sup> 1. The estrogen component in COCP inhibits the hypothalamic-pituitary-ovarian axis via a negative feedback mechanism, reducing the secretion of GnRH and subsequently lowering LH and FSH levels. This process prevents follicle maturation and ovulation while reducing the secretion of androgens such as testosterone and androstenedione (Figure 5). 2. Sex hormone-binding globulin (SHBG) is a protein that binds to free testosterone, thereby



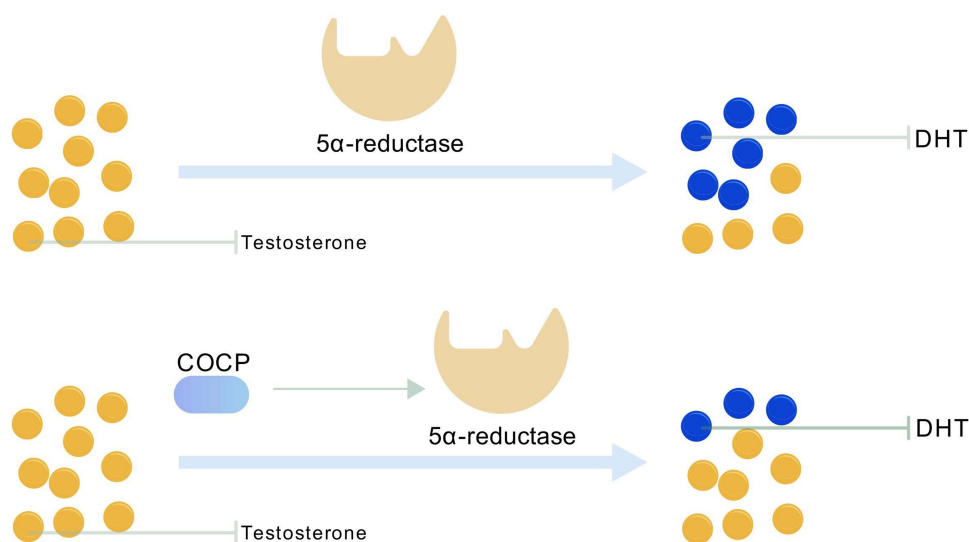
**Figure 5** Gonadal axis pathway. The estrogen component in COCP inhibits the gonadal axis via a negative feedback mechanism, reducing GnRH secretion, which subsequently decreases LH and FSH levels. This prevents follicular maturation and ovulation while decreasing androgen secretion.



**Figure 6** SHBG pathway. The estrogen component in COCP promotes SHBG synthesis in the liver, thereby reducing free testosterone levels and decreasing its effects on target tissues, such as the skin and hair follicles, alleviating symptoms like acne and hirsutism.

lowering the levels of bioactive free androgens in the body. The estrogen component in COCP can promote the synthesis of SHBG in the liver, effectively lowering free testosterone levels and mitigating its effects in target tissues such as the skin and hair follicles, thereby alleviating PCOS symptoms such as acne and hirsutism (Figure 6).<sup>3</sup> In PCOS patients, the activity of  $5\alpha$ -reductase in the ovaries and peripheral tissues may increase, resulting in higher production of DHT, thereby exacerbating hyperandrogenic symptoms. Certain progestin components in COCP can inhibit the activity of  $5\alpha$ -reductase, thereby reducing DHT production and alleviating symptoms caused by excessive androgens. Certain progestin components in COCP can inhibit the activity of  $5\alpha$ -reductase, thereby reducing DHT production and alleviating symptoms caused by excessive androgens (Figure 7).

The latest guidelines suggest that both adolescents at risk of PCOS and those diagnosed with the condition may consider using COCP to treat hirsutism and irregular menstrual cycles.<sup>20</sup> However, it is crucial to note that all types of COCP increase the risk of venous thromboembolism, which is positively correlated with the ethinyl estradiol content.<sup>83</sup> Additionally, the latest guidelines indicate that the effectiveness of COCP in alleviating PCOS symptoms is not dependent on the ethinyl estradiol dose.<sup>20</sup> Therefore, clinical practice should prioritize using low-dose ethinyl estradiol formulations to minimize the risk of venous thromboembolism. Furthermore, although COCP containing cyproterone acetate (CPA) is more effective in treating hirsutism compared to traditional COCP, it also carries a relatively higher risk of venous thromboembolism. Furthermore, although COCP containing cyproterone acetate (CPA) is more effective in treating hirsutism compared to traditional COCP, it also carries a relatively higher risk of venous thromboembolism. The latest guidelines therefore recommend 35  $\mu$ g ethinylestradiol-cyproterone acetate as a second-line treatment option.<sup>98</sup> Currently, there is a lack of standardized guidelines for the use of COCP in PCOS patients. Clinical practice for both adult and adolescent PCOS patients often depends on general guidelines applicable to the broader population, lacking specificity. Although scholars have explored this area, a 2023 meta-analysis comparing the efficacy of different types of COCP found that fourth-generation progestin COCP showed better therapeutic effects than earlier formulations. However, more robust clinical evidence is still needed. Moreover, this study did not conduct an age-specific analysis.<sup>97</sup> Therefore, further research is needed, particularly to identify the optimal types and doses of estrogen, progestin, or combined COCP formulations for different age groups, to develop more precise treatment regimens.



**Figure 7** 5 $\alpha$ -Reductase pathway. Certain progestin components in COCP can inhibit 5 $\alpha$ -reductase activity, thereby reducing DHT production.

## Metformin Combined with COCP

Metformin and COCP exhibit synergistic effects in treating PCOS. Metformin lowers insulin levels, indirectly reducing androgen production, while COCP directly inhibits LH secretion, thereby decreasing ovarian androgen production. Metformin lowers insulin levels, indirectly reducing androgen production, while COCP directly inhibits LH secretion, thereby decreasing ovarian androgen production.<sup>99</sup> This view is supported by several studies. For instance, research by Fraison et al demonstrates that the combined use of COCP and metformin is more effective than either drug alone in improving serum androgen levels, IR, menstrual irregularities, and metabolic characteristics in PCOS patients.<sup>100</sup> Additionally, a study by Johanna Melin et al indicates that combination therapy with metformin and COCP is superior to COCP alone in improving hyperandrogenemia, insulin levels, and IR, although it shows no significant difference in the improvement of hirsutism. However, owing to insufficient clinical evidence, the latest guidelines recommend the combined use of metformin and COCP only in adolescent PCOS patients with high metabolic risk (eg, BMI  $\geq 30$  kg/m<sup>2</sup> or impaired glucose tolerance).<sup>20</sup>

Overall, the combination of metformin and COCP represents a promising research direction for the future of pharmacological therapy for PCOS. To further determine the optimal combined treatment strategy for adolescent PCOS patients, more high-quality, large-scale, age-specific prospective studies are required. Such studies will contribute to the development of more evidence-based clinical guidelines and promote comprehensive management for adolescent PCOS patients. It is noteworthy that there is significant controversy regarding the clinical use COCP and metformin in the treatment of PCOS, primarily due to the uncertainty in the efficacy-risk tradeoff. COCP can rapidly alleviate patient symptoms, however its estrogen component may exacerbate insulin resistance, elevate TG levels, and potentially disrupt the natural accumulation of bone mineral density (BMD) during adolescence. Prolonged use (>3 years) may particularly impair the potential for peak bone mass development.<sup>101</sup> Metformin, an insulin sensitizer, can improve hyperinsulinemia and reduce diabetes risk. However, its gastrointestinal side effects (eg, diarrhea and nausea) lead to poor adherence in adolescents, and there is insufficient high-quality evidence on the long-term impact of metformin on pubertal sexual maturation and growth.<sup>15</sup> In summary, the controversy surrounding both drugs stems from insufficient long-term safety data and limited evidence supporting combination therapy strategies. Clinical decisions should be guided by individualized evaluations and continuous monitoring.

## Antiandrogen Drugs

Anti-androgen drugs include spironolactone, flutamide, finasteride, and cyproterone acetate. Their mechanisms of action can be summarized in three main points: 1. Spironolactone and flutamide reduce androgen levels by inhibiting synthesis

in the ovaries and adrenal glands; 2. Spironolactone, flutamide, and cyproterone acetate competitively bind to androgen receptors, preventing androgen binding and reducing their biological effects; 3. Finasteride-type drugs inhibit 5 $\alpha$ -reductase, preventing the conversion of testosterone to the more active DHT, thereby reducing androgen activity.<sup>102</sup> Through these mechanisms, anti-androgen drugs improve the hyperandrogenic state in adolescent PCOS patients, effectively alleviating related symptoms such as acne and hirsutism. A study of 14 adolescent PCOS patients showed that taking 2.5 mg of finasteride every 3 days for 6 months significantly reduced the FG score for hirsutism compared to the placebo group, with noticeable effects but no significant changes in BMI, testosterone, or SHBG levels.<sup>103</sup> Another analysis noted that while anti-androgen drugs can improve clinical symptoms of PCOS, particularly hirsutism, their effect on irregular menstrual cycles and PCOM is limited. Although many studies show that combining anti-androgen drugs with COCP is more effective for hirsutism than COCP alone, combination therapy is not recommended due to the potential teratogenic and hepatotoxic side effects of anti-androgen drugs. COCP remains the first-line treatment.<sup>104</sup> The latest guidelines recommend considering anti-androgen drugs to improve hirsutism in adolescent PCOS patients who do not respond well to COCP or cosmetic treatments after 6 months. Contraceptive measures should be taken to mitigate potential teratogenic risks. The optimal dosage and type of anti-androgen drugs for treating adolescent PCOS remain to be further explored. Based on general population treatment recommendations, the latest guidelines suggest an oral dose of spironolactone ranging from 25 to 100 mg/day and advise against using anti-androgen drugs like finasteride, flutamide, and cyproterone acetate due to potential hepatotoxic risks.<sup>20</sup>

## Inositol

Inositol is a cyclic polyol involved in various metabolic pathways, primarily found as Myo-Inositol (MI) and D-Chiro-Inositol (DCI). The primary source of inositol in the human body is dietary intake, mainly in the form of MI. Under insulin stimulation, MI can be converted to DCI by an NAD-NADH-dependent epimerase, allowing organs and tissues to regulate the MI/DCI balance in distinct ways. Under physiological conditions, the MI to DCI ratio is approximately 100:1 in follicular fluid and 40:1 in plasma.<sup>105</sup> Numerous studies suggest that a 40:1 MI/DCI ratio is optimal for treating adolescent polycystic ovary syndrome (PCOS).<sup>106</sup> The primary mechanism of inositol in treating adolescent PCOS is its insulin-sensitizing effect.<sup>107</sup> Inositol derivatives, such as inositol hexaphosphate (IP6) and phosphatidylinositol, enhance insulin signaling via the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) pathway. Within this pathway, phosphorylation of the insulin receptor promotes the generation of phosphatidylinositol-3,4,5-triphosphate (PIP3), a second messenger that further activates downstream Akt kinases. When activated, Akt kinases promote the translocation of glucose transporters (eg, GLUT4) to the cell membrane, thus increasing glucose uptake. Inositol metabolites, including inositol triphosphate (IP3) and inositol tetraphosphate (IP4), regulate insulin sensitivity by modulating intracellular calcium ion levels. Additionally, inositol promotes fatty acid oxidation, which reduces liver fat accumulation and further enhances insulin sensitivity.<sup>108</sup> A meta-analysis of 10 randomized controlled trials involving 573 patients demonstrated that inositol treatment significantly improved homeostatic model assessment of insulin resistance (HOMA-IR) in PCOS patients compared to controls and increased serum estradiol (E2) levels, suggesting that inositol may benefit PCOS patients with insulin resistance and help alleviate symptoms linked to low estrogen levels.<sup>109</sup> However, the optimal combination ratio of MI and DCI for adolescent PCOS patients has not yet been established, and its efficacy may vary depending on different metabolic phenotypes.<sup>110</sup>

## Discussion and Conclusion

In summary, the diagnostic criteria for adolescent PCOS are continually evolving and becoming more refined. A confirmed diagnosis of adolescent PCOS requires a comprehensive evaluation of multiple factors, such as irregular menstrual cycles, biochemical or clinical hyperandrogenism, and ultrasound findings. This review summarizes current evidence on adolescent PCOS diagnostic criteria, emphasizing two primary diagnostic requirements: first, ovulatory dysfunction, where adolescent females should be evaluated for ovulatory dysfunction regardless of menstrual regularity; and second, biochemical or clinical hyperandrogenism. Once diagnosed, adolescent PCOS patients should receive an individualized treatment plan that includes lifestyle interventions, medications, physical therapies, and psychological counseling. Additionally, adolescent females exhibiting PCOS characteristics without meeting diagnostic criteria, or

experiencing significant weight gain during adolescence, may be considered “high-risk” individuals. These patients should be reassessed eight years post-menarche and upon reaching sexual maturity.<sup>111,112</sup> Notably, if hormonal contraceptives have been used prior to assessment, they should be discontinued for at least three months before evaluation, and non-hormonal alternatives should be used for management during this period.<sup>111</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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