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Management of adolescent polycystic ovary syndrome

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Abstract
Polycystic ovary syndrome (PCOS) is a common adolescent problem and its prevalence is rapidly increasing worldwide. Diagnosis of PCOS during this period is difficult due to the overlapping of the diagnostic criteria with normal pubertal development. Currently, the International evidence-based guideline (2018) has recommended using the Rotterdam criteria excluding the polycystic ovarian morphology component. However, the definition of each component depends on the age of the menarche. Similarly, the treatment options are not adequately evidence-based, rather adopted mostly from adult guidelines. Due to several concerns, a combined oral contraceptive pill-sparing combination therapy (spironolactone+pioglitazone+ metformin= SPIOMET) might be a promising therapeutic option. Duration of treatment is another uncertain issue. Prospective studies as well as well-designed randomized controlled trials are required for adequate management of adolescent PCOS. *[J Assoc Clin Endocrinol Diabetol Bangladesh, July 2022; 1 (2): 55-64]*

Keywords: Adolescent polycystic ovary syndrome, Combined oral contraceptive, Metformin, Spironolactone

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Introduction

Polycystic ovary syndrome (PCOS) is a chronic condition with mild hyperandrogenism that may affect around 6% - 15% of females in their reproductive years. The pathophysiology is still enigmatic. Recently it is thought that PCOS starts in intrauterine life and features develop as a result of post-natal adaptations in response to environmental factors to escape from the harmful effects.[1] Along with reproductive features, patients may present with extra-reproductive features (cardiometabolic, psychiatric, etc.), especially after the reproductive years.[2]

'Adolescence' is an intermediate period between childhood and adulthood with rapid changes in physical as well as mental features. Among physical features, reproductive maturation is the most characteristic feature. During this transition period, it may require around 5 years for the hypothalamic-pituitary-ovarian axis to become mature.[3] According to World Health Organization (WHO), the age between 10 and 19 years is defined as 'adolescence'.[4] However, considering the average age of menarche at 12 years and the complete maturation of ovarian volume at 20 years, up to 8 years post-menarche (gynecological age) is considered the 'adolescence period'.[5,6]

Adolescence PCOS

Diagnosis of adolescent PCOS is crucial for early management to prevent future issues since around 70% of PCOS patients remain undiagnosed.[7] Many patients may present in the adult period with delayed diagnosis and dissatisfaction.[8] On the other hand, the wrong diagnosis may lead to unnecessary treatment, psychological stress, and social stigmata.[9] The prevalence of adolescent PCOS among the Bangladeshi population is still lacking. A meta-analysis conducted among Indian adolescent girls found around 18% prevalence depending on Rotterdam criteria.[10]

Clinical features

PCOS is a heterogeneous condition and the clinical features may depend on race. PCOS patients from South-Asian backgrounds usually present with severe hirsutism and higher free androgen index (FAI) with lower sex hormone binding globulin (SHBG), lower body mass index (BMI) with higher central obesity, acanthosis nigricans as well as insulin resistance.[11] A study conducted in an Endocrine out-patient

department of a medical college hospital showed that among 175 adolescent girls (10 – 19 years) around 88% presented with oligomenorrhea, having a median modified Ferriman-Gallwey (mFG) score of 12, with only 34% having hyperandrogenemia. However, metabolic features were very common (generalized obesity: 39%, central obesity: 66%, hypertension: 3%, acanthosis nigricans: 78%, abnormal glycemic status: 24%, dyslipidemia: 91%, and metabolic syndrome: 42%).[12] Besides, metabolic-associated (e.g., metabolic-associated fatty liver disease, obstructive sleep apnea, increased cardiovascular disease, etc.) and psychiatric morbidities (e.g., anxiety, depression, disordered eating, negative body imaging, etc.), as well as poor quality of life, are also very common at this age group. Similarly, a nationwide study among 409 Bangladeshi females with PCOS (60% between 15 to 25 years) showed a high prevalence of different psychiatric disorders.[13]

Diagnostic pitfalls

Adult diagnostic criteria cannot be applied to diagnose adolescent PCOS, because several features of PCOS overlap with normal pubertal development, such as-

- Most of the menstrual cycles are anovulatory.[14]
- 50% of mild hirsutism are not due to hyperandrogenemia
- Acne may develop in 90% of the adolescent girls
- No reference levels for androgens in the adolescent
- Ultrasonography detects more polycystic ovarian morphology (PCOM) in adolescents than in adults without progression to PCOS
- Puberty is associated with a 25%–50% increase in insulin resistance due to growth hormone surge with compensatory hyperinsulinemia causing hyperandrogenemia.[15,16]

At the end of the adolescent period, all these features may be reversible. In this scenario, the diagnosis of PCOS depends on two features: persistence and co-existence of diagnostic criteria.[16] If an irregular cycle persists for one year then it will persist in around 60% of cases after 6 years and 50% of cases after 8 years. Similarly, if an irregular cycle co-exists with hyperandrogenism, then around 80% will persist after

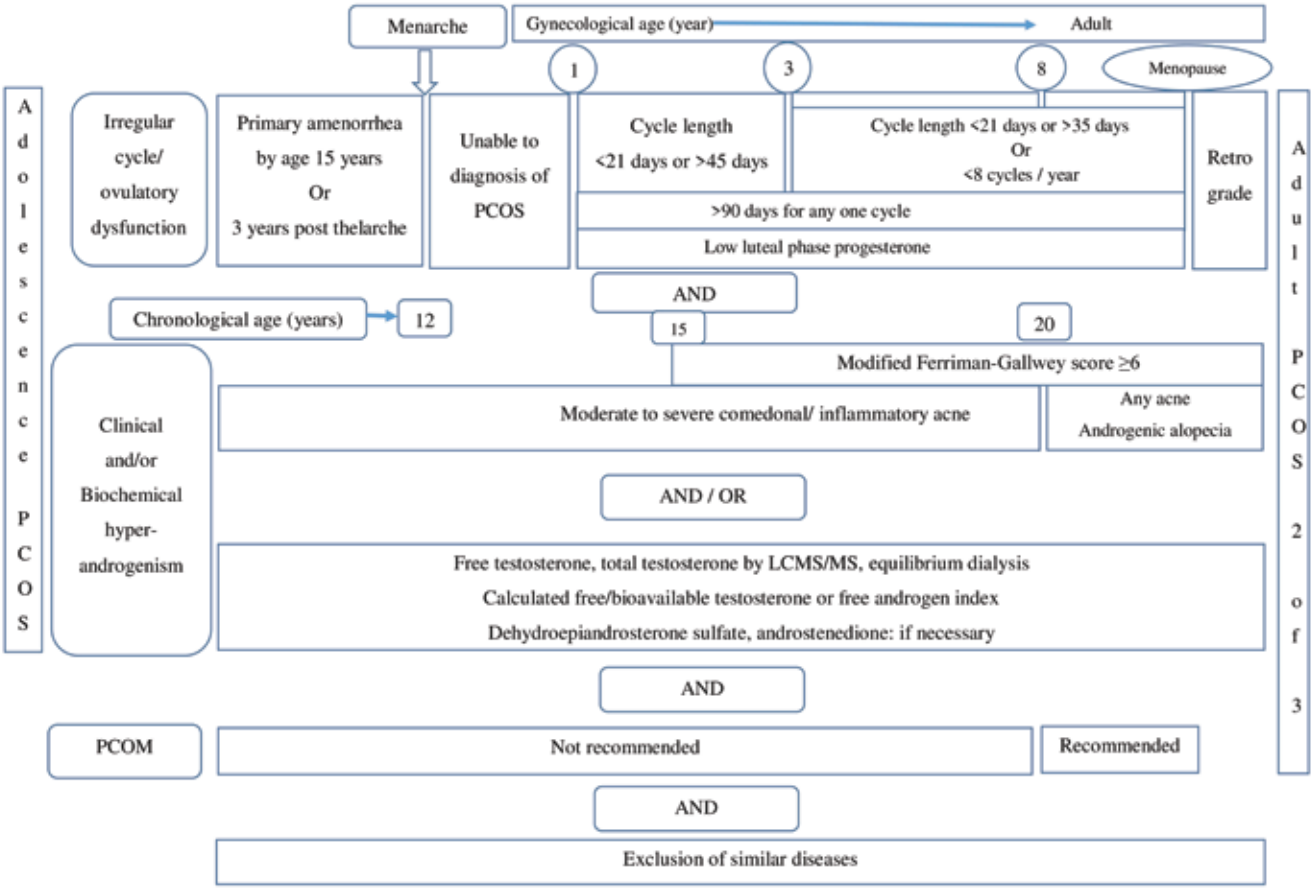

Figure-1: Diagnostic features of adolescent PCOS and comparison with adult criteria

3 years, and the rest of the cases are due to physiological anovulation.[15,16] Metabolic features including insulin resistance are very common and exacerbate the manifestations of PCOS. However, they are too nonspecific to consider for the diagnosis of PCOS despite their significant role in the pathogenesis of the condition.[17]

Individual component of the diagnostic criteria

Menstrual irregularity:

Any degree of menstrual irregularity is generally considered normal during the early years of menarche. In fact, regular menstrual cycles may establish in 6 -12 months of menarche. The 95th percentile of menstrual cycle length even at 1st year is 83 days. So, any cycle length of more than 90 days at any time is abnormal.[18] Around 75% of menstrual cycles' length is between 21-45 days even in the first gynecological year, however, around 85% of them are anovulatory.[19] However, these cycles are not completely anovulatory, but rather indicate luteal insufficiency.[16] Considering the relationship between menstrual cycle lengths with age, the International evidence-based guideline set criteria for irregular menstrual cycles (Figure-1). In the case of a regular menstrual cycle, serum progesterone can be measured 7 days before the expected menstruation date to diagnose anovulation.[20]

Clinical hyperandrogenism

Only hirsutism and acne are considered features of hyperandrogenism during the adolescence period. Androgenic alopecia (female pattern hair loss) is uncommon (<2%), and evidence is lacking to consider it as a feature of hyperandrogenism.[21]

Hirsutism

Despite several limitations, mFG score is the standard of practice for quantifying hirsutism (terminal hair, >5 mm in length if untreated).[21] In the case of local treatment, reassessment can be done at least 3 months after laser or electrolysis, 4 weeks after waxing, and 5 days after shaving.[22] Isolated mild hirsutism should not be considered a feature of hyperandrogenism until the patient is concerned. Being South Asian, the cut-off should be used 6 (out of 36). The cut-off was reduced from 8 (95th percentile) to 6 (90th percentile), because of its association with hyperandrogenemia in 90% of cases.[21] The mFG score is applicable from the age of 15 years or 2 years after the menarche.[16]

Acne

Although mild acne is common, moderate-severe comedonal acne during early puberty and inflammatory acne throughout the perimenarcheal years are rare (<5%) and should be considered a sign of hyperandrogenism, especially for persistent and treatment-resistant acne.[23] There is no universally accepted visual tool for the assessment of acne.[21]

Biochemical hyperandrogenism:

Androgen levels in adolescents reach adult levels around the time of puberty. So, the reference levels of adults can be used for adolescents.[24,25] Until the availability of a population-specific reference range, the reference range provided by the laboratory should be used. Due to the unavailability of an extraction method, free testosterone is generally not suitable for our setting.[26] Calculated free testosterone, bioavailable testosterone (http://www.issam.ch/freetesto.htm), or FAI may be used as a standard of practice.[21] If these androgen levels are normal, then dehydroepiandrosterone sulfate and androstenedione can be measured (10% of isolated elevation for each).[21,27] A 3-month washout period is required in the cases of girls taking hormonal contraceptives (after ensuring another contraceptive method) before measuring androgen. If the androgen levels are twice above the upper limit of the reference range, imaging is also required to assess the ovary and/or adrenals for a tumor.[21]

Polycystic ovarian morphology (PCOM):

PCOM is common during puberty (≥6 cysts, 4 - 10 mm in diameter, increased volume) and is not associated with reproductive dysfunction. These multi-follicular appearances disappear after the end of puberty.[15,28] Adult criteria for PCOM are not validated in adolescents, and USG use may be limited by puberty and acceptance of transvaginal route USG. So, these criteria cannot be used for adolescents. Development of age and the race-specific anti-mullerian hormone may replace this PCOM in the future.[21]

Diagnostic criteria

Initial guidelines did not address adolescent PCOS. In 2015, two papers specifically address the issue.[15,17] Then, the guideline proposed by International PCOS Network (2018) endorsed the Rotterdam, 2003 criteria except PCOM to diagnose adolescent PCOS and a separate paper from the same group was published to address adolescent PCOS (Figure-1 and Figure-2).[20,21]

So, both menstrual irregularity and hyperandrogenism are required to diagnose adolescent PCOS and the phenotype of adolescent PCOS is always classic (type A or B).

The guideline gave more importance to clinical features over biochemical findings. If patients present with one feature, then they are labeled as 'at risk' for PCOS. Treatment can be started and patients should be reassessed in the future to reach a final diagnosis (Figure-2).

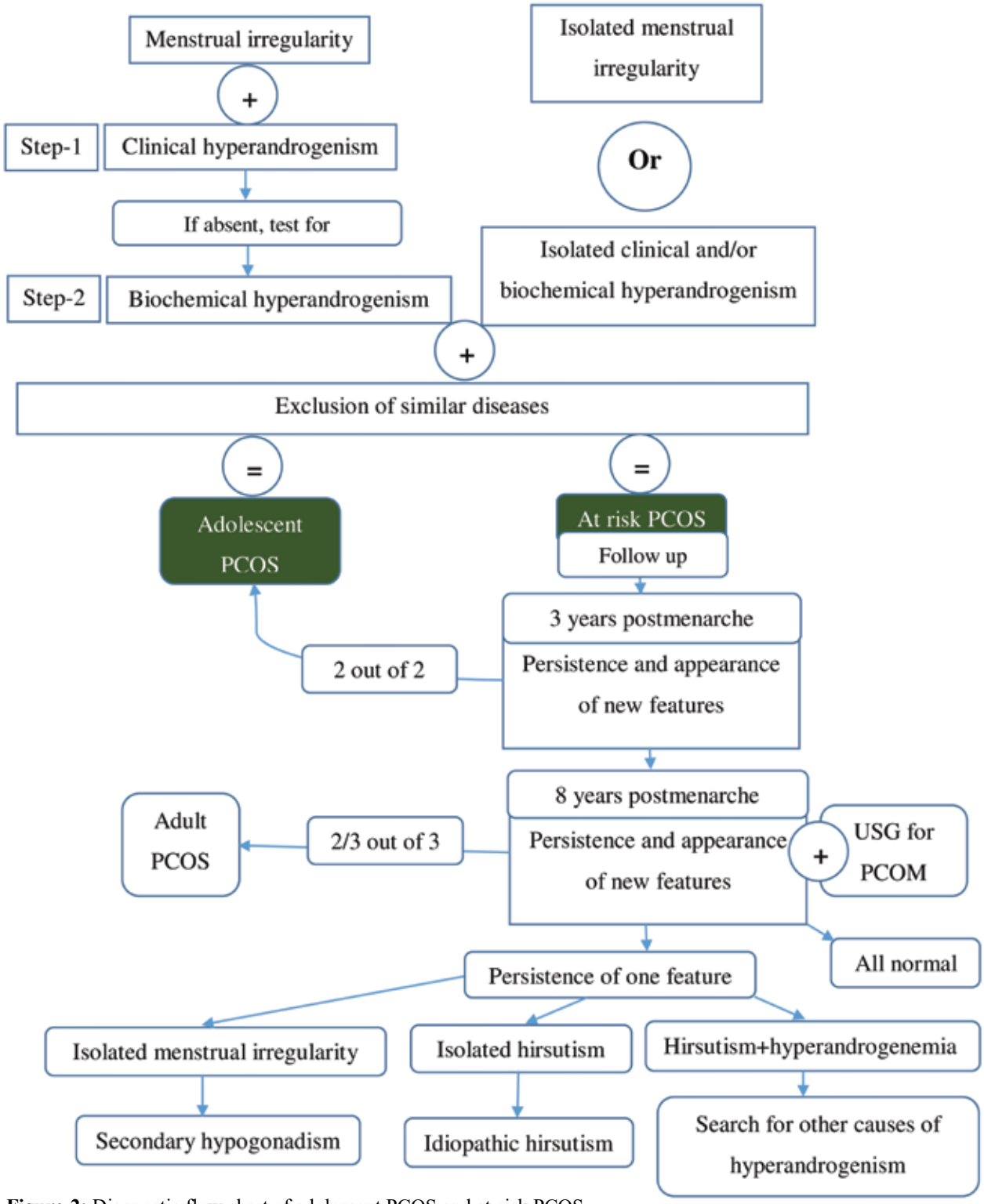

Figure-2: Diagnostic flow chart of adolescent PCOS and at-risk PCOS

Exclusion of similar diseases (Secondary PCOS):
The exact cause of PCOS is unknown and there is no single diagnostic test for PCOS. So, diagnosis of PCOS is considered in an otherwise unexplained case of persistent hyperandrogenic oligo/anovulation with reproductive status-specific criteria. Several disorders may mimic features of PCOS especially, hypothyroid, hyperprolactinemia, nonclassic congenital adrenal hyperplasia, androgen-secreting ovarian/adrenal tumor, etc.[29] Recently, obesity is considered an important cause of secondary PCOS, as, the complete remission of all features after bariatric surgery and lifestyle management. These patients are characterized by lower waist circumference and androstenedione. [30,31] Similarly, diabetes mellitus (DM) even type 1 DM may also present with menstrual irregularity due to hypothalamic inhibition.[32] Severe insulin-resistance syndromes and epilepsy±valproic acid are other important differentials.[33] Evaluation should be done according to suspicion. A table is added for the evaluation of an adolescent girl with suspected PCOS (Table-I).

Search for comorbidities
Psychiatric morbidities: All adolescent girls at the time of diagnosis should be screened for anxiety and depression by a validated tool. Screen-positive patients should be referred to a Psychiatrist for further management. Drugs should be chosen considering the effect on body weight.[20] Cognitive behavioral therapy may be a better option that can address both issues effectively. Disordered eating, psychosexual disorder, and negative body image are other psychiatric issues.[21]

Metabolic dysfunctions
Obesity, central obesity, and hypertension should be diagnosed by using pediatric diagnostic tools and cut-off values every 6-12 months. Lipid profile, oral glucose tolerance test, and liver enzymes should be measured every 1-3 years.[21] Every component should be addressed as per the pediatric guideline.[34] Obstructive sleep apnea should be screened by appropriate tools and referred to a specific specialty if required.[20]

Management
1st line treatment: Management is symptomatic with addressing each component considering the patient's preference (Figure-3). Data is lacking in the adolescent group and is mostly derived from adult guidelines. One randomized controlled trial (RCT) with a small number of patients with 24 months showed beneficial effects of combined therapy with lifestyle (LS) and combined oral contraceptives (COCs) (ethinyl estradiol 30 µgm + drospirenone 3 mg) over each feature of PCOS. Metformin is not beneficial without lifestyle management and added minor benefits with LS+COCs.[35] A meta-analysis of 4 RCTs with low-quality evidence including 170 adolescents showed more beneficial effects of metformin over COCs in metabolic aspects, while COCs had modest beneficial effects over metformin with respect to menstrual irregularity and acne.[36] However, the use of these drugs in PCOS is off-label but evidence-based.

Table-I: Diagnostic evaluation of a suspected case of adolescent PCOS

History	Examinations	Investigations
• Menarche • 1st day of last menstrual period • Duration of each cycle • Number of cycles/year • Family history of PCOS • Hirsutism: Onset, progression, treatment • Acne: Onset, treatment • Weight gain • Lifestyle: Diet, physical activity, sleep • Drugs- Valproate • Features of hypothyroidism, galactorrhea, and others	• Height, weight, waist circumference (CDC BMI chart) • Blood pressure (percentile for age, sex, and height; if age <13 years) • Hirsutism by mFG • Acne • Acanthosis nigricans • Thyromegaly • Features of virilization • Specific features for exclusion of similar diseases • Psychiatric screening	• Total testosterone and SHBG to calculate FAI • TSH, prolactin, 17OH progesterone (Fasting state, in follicular phase of menstrual cycle) • Metabolic profile (OGTT, lipid profile, ALT, AST) (Fasting state) • USG liver (fatty liver) • USG lower abdomen in case of amenorrhea • Others depending on suspicion

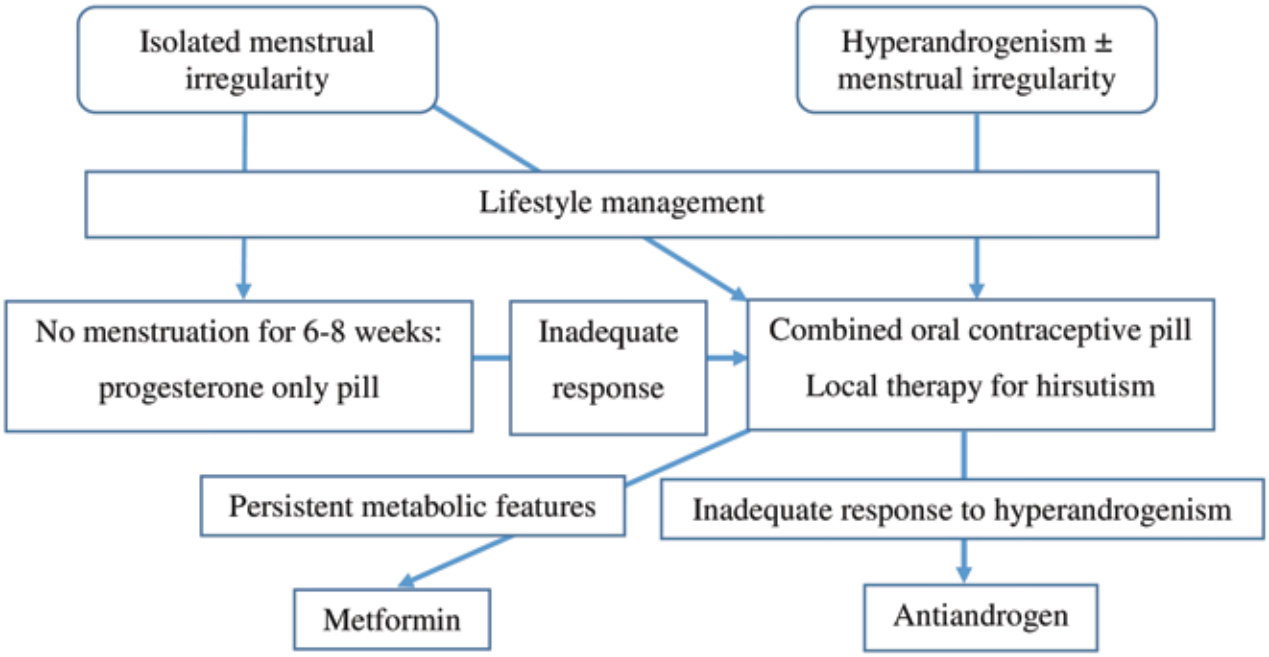

Figure-3: Treatment approach in adolescent PCOS and at-risk PCOS

Lifestyle management

Lifestyle includes a healthy balanced diet, regular physical activity, age-specific adequate sleep, and behavioral modification. Total energy requirement depends on individual energy requirement, current BMI, and physical activity levels. For girls with overweight/obesity, a 30% energy-deficient diet (500-750 Kcal/day) may be prescribed.[20] For lean girls, a weight-maintaining balanced diet including a sufficient amount of fruits and vegetables is advised. In adolescents, at least 60 minutes of moderate to vigorous intensity physical activity per day, including those that strengthen muscle and bone at least 3 times weekly is recommended for all.[21] Higher levels of physical activity may help in modest weight loss, prevent weight regain, and provide greater health benefits. Behavioral modifications include minimization of the sedentary, screen, and sitting time, slower eating, etc.[20,21] A multidisciplinary healthcare professionals comprising dietitians, psychologists, and endocrinologists may be effective for weight management.[37]

Pharmacotherapy:

The use, mechanism of action, dose, side effects, and contraindications of the commonly prescribed drugs in adolescent PCOS are shown in Table-II.

COCs pill

This is the most effective treatment that addresses both menstrual irregularity and hyperandrogenism. It usually takes 2-3 months for the improvement of menstrual irregularity, acne, and hyperandrogenemia, and 6 months for hirsutism. Testosterone levels may be rechecked after the third month of therapy to document improvement.[38] The use of COCs should be directed by WHO's guidelines.[39] Due to significant side effects, COCs containing cyproterone acetate should not be used as 1st line choice.[20]

Concerns about the COCs during adolescence:

- Venous thromboembolism (VT): The risk of VT is generally low in comparison to pregnancy (5–20 per 10,000 women per year) and postpartum (40–65 per 10,000 women per year) period. In general, the higher the dose of estrogen and progestin generation, the higher the risk of VT. A Cochrane review showed a higher risk with 35 µg than 30 µgm EE and a higher risk with gestodene, desogestrel, cyproterone acetate, and drospirenone than levonorgestrel, norethisterone, and norgestimate.[40] The risk of VT becomes increased after 4 months of use, then reduces over time up to the age of 30 years in 1st-time users, and disappears after 3 months of stoppage. VT developed

Table-II: Drugs used in the treatment of adolescent PCOS.[17]

Drugs	M/A	Dosage	Problems	Contraindications
Micronized progesterone	Withdrawal bleeding	0.1-0.2 mg/day for 7-10 days in every 6 weeks	No effect on androgen, no contraception	Thrombo-embolic event, Ca breast/genitalia, liver disease
COCs (30 µg EE)	↓ovarian androgen ↑SHBG	21 out of 28 days per month	Breast tenderness, headache, thromboembolism	Pregnancy, uncontrolled HTN, liver dysfunction, migraine with aura
Metformin	Insulin sensitizer ↓ androgen production	850 mg – 1 gm/day	GI discomfort, lactic acidosis	Renal and liver dysfunction, acidosis
Pioglitazone	Insulin sensitizer Adipocyte differentiation	7.5 – 30 mg/day	Weight gain at higher doses, unavailable	Pregnancy, liver dysfunction, bladder cancer
Spironolactone	Aldosterone antagonism,	50 – 200 mg/day, dose reduction after improvement	Irregular bleeding, headache, nausea, ↓ libido, fatigue	Pregnancy, renal failure, hyperkalemia
Flutamide	AR blocker	62.5 – 250 mg/day	Hepatotoxicity (>1 mg/kg /day), meningioma, cost	Pregnancy, renal, and liver dysfunction
Finasteride	5α reductase inhibitor	1 – 5 mg/day, 2.5 mg every 3rd day	Less effective	Pregnancy
Eflornithine hydrochloride	irreversible inhibitor of ornithine decarboxylase	Cream, twice daily	Required continuous use, stinging, burning	Pregnancy, hypersensitivity

M/A (mechanism of action), COCs (combined oral contraceptives), EE (ethinyl estradiol), SHBG (sex hormone binding globulin), HTN (hypertension), GI (gastro-intestinal), AR (androgen receptor)

within 1 year of start usually indicates an inherited clotting defect.[41,42]

- Peak bone mass: Both COC use and discontinuation were associated with low bone mineral density relative to nonusers (differences < 2% after 12–24 months for all skeletal sites) in adolescents.[43] Low dose (<30 µgm of EE) COCs may lead to low endogenous estradiol levels insufficient for the acquisition of peak bone mass during the adolescence period with unstable cycles.[44] Among progestins, norethisterone is partially converted to EE and may have a positive effect on bone mass.[45]
- Height: COCs have little impact on final height, as height gain after menarche is minimal.[46]
- Weight: A Cochrane systematic review found different combination contraceptives as weight neutral.[47]

Choice of estrogen and progestin

Considering the risk of VT and low bone mass, 30 µg of EE is suitable until the availability of safer estradiol (estradiol valerate, esotetrol, etc.). All progestins are similar in efficacy including their effect on hirsutism; so, considering side effects, natural progesterone (micronized progesterone, dydrogesterone) and 2nd generation progestins (levonorgestrel, norethisterone) are preferred. Although drospirenone has a higher risk of VT, the absolute risk is still low and it may be a choice due to several benefits.

Treatment duration

The duration of treatment is not yet established. The longer the duration of treatment, the less chance of relapse within a given time. OCP treatment should be continued until the patient is gynecologically mature (5 years postmenarchal) or has lost a substantial amount of excess weight.[48] Longitudinal reevaluation requires withdrawing COC for 3 months to determine the persistence of hyperandrogenic anovulation. One study showed, 0%, 28%, and 56% deterioration of hirsutism after 6, 12, and 24 months of stopping COCs.[49]

Adjunctive treatment

- Metformin: Metformin is only effective with lifestyle and/or COCs and is indicated in girls with metabolic features (BMI ≥25 kg/m^2, features of insulin resistance, prediabetes, etc.) including high-risk ethnicity (e.g., south Asian).[20] At least

850-1500 mg/day is effective and a higher dose may not be more effective. Short-term gastrointestinal side effects are generally tolerable.[21]

- **Oral antiandrogens:** These include spironolactone, flutamide, and finasteride. They are indicated after 6 months of inadequate control of hyperandrogenism by LS+COCs+cosmetic therapy. It may be used alone in presence of contraindication to COCs but with another contraception to avoid teratogenicity on male fetuses.[21] They usually take around 9-12 months for significant effects on hirsutism.[48]
- **Local therapy for hirsutism:** Eflornithine hydrochloride 13.9% cream can reduce facial hirsutism in 70% of cases within 4-8 weeks of twice-daily use and improve further with laser photoepilation. But hair growth reverts back within 8 weeks of discontinuation.[38]

COCs sparing therapy

Due to several concerns, a COCs sparing combination therapy of spironolactone (50 mg/day), pioglitazone (7.5 mg/day), and metformin (850 mg/day) (SPIOMET) have recently emerged as a better option in controlling ovulation, hyperandrogenism, and visceral fat than COCs even after discontinuation after 1 year.[50]

Conclusions

PCOS diagnosis during adolescence is challenging. Periodic follow-up is the best way to confirm the diagnosis. Treatment is similar to adults and a newer combination (SPIOMET) might have a promising result.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

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