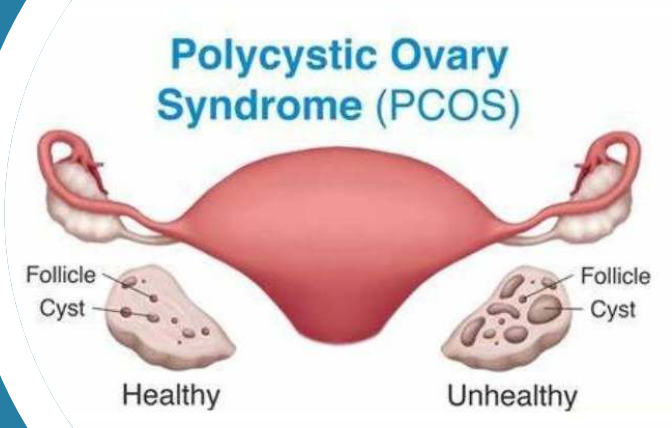
INDIAN FERTILITY SOCIETY

SIG Newsletter

September 2024



PCOS

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IS SHE OR SHE NOT? : DILEMMA IN DIAGNOSIS OF ADOLESCENT PCOS

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Introduction

- Polycystic ovary syndrome (PCOS) is the most common endocrine condition affecting between 8 -13% of women of reproductive age and 6 –18% of adolescent girls.[1]
- Adolescence, as defined by the World Health Organisation, is the period between 10 and 19 years of age that includes significant and critical changes in growth, development and puberty.
- Diagnosis of PCOS during adolescence is both controversial and challenging due to the overlap of normal pubertal physiological changes with adult PCOS diagnostic criteria (irregular menstrual cycles, acne and polycystic ovarian morphology on pelvic ultrasound)
- Challenges include the risk of under diagnosis, delayed diagnosis and over diagnosis

International PCOS guidelines

- Aim of the first International Evidence-based Guideline for the Assessment and Management of PCOS (2018) was accurate diagnosis of PCOS, optimal care, prevention of complications and improved health outcomes from adolescence to adulthood.[2]
- Key changes within the Guideline recommendations (2023) include the elimination of specific unnecessary tests and the importance of identifying adolescents **'at risk'** of PCOS.[3]

Diagnostic criteria

a. Irregular menstrual cycles and ovulatory dysfunction
b. Hyperandrogenism: Biochemical or clinical

- PCOS cannot be diagnosed during adolescence unless both irregular menstrual cycles and hyperandrogenism are present.
- Pelvic ultrasound not included in the diagnostic criteria

Irregular menstrual cycles and ovulatory dysfunction

- Physiological maturation of the hypothalamic–pituitary ovarian axis occurs over the years.[4]
- Ovulation and menstrual cycles in adolescents may not match those of women in reproductive age
- Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.

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)

Clinical hyperandrogenism

- A comprehensive history and physical examination for symptoms and signs of clinical hyperandrogenism
- In adolescents it includes severe acne and hirsutism
- Recommendation based on the fact that mild comedonal acne is common in adolescent girls
- Severe comedonal or severe inflammatory acne (10 or more facial lesions) is uncommon in these girls

Modified Ferriman Gallwey Score

- Score of 0- 4 is given for 9 areas of the body – upper lip, chin, upper chest, upper abdomen, lower abdomen, upper arms, thighs, upper back, lower back.[5]
- Only terminal hairs need to be considered, which are long (>5 mm), coarse and dark.
- Level ≥ 4–6 indicates hirsutism, depending on ethnicity
- However, cut-offs based mainly on studies in adults, not adolescents.
- Adolescents may have lower scores due to reduced exposure time
- Important to acknowledge that self-treatment is common and can limit clinical assessment.

Biochemical hyperandrogenism

- Assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism
- In most adolescents, androgen levels reach adult ranges at 12-15 years of age.
- Total and free testosterone to assess biochemical hyperandrogenism for diagnosing of PCOS
- Free testosterone can be calculated using total testosterone, SHBG and albumin using a mathematical formula.
- Meta-analyses results showed that calculated free testosterone and calculated free androgen index (FAI) (Total testosterone x 100/SHBG) had the best sensitivity and specificity to diagnose biochemical hyperandrogenism compared with all other tests.
- Laboratories should use Liquid chromatography – mass spectrometry (LC-MS/MS) assays over direct immunoassays(radiometric, enzyme-linked) for assessing total or free testosterone, which have limited accuracy.[6]
- If total or free testosterone is not elevated, androstenedione and dehydroepiandrosterone sulphate (DHEAS) can be measured to provide limited information for diagnosing PCOS (noting poorer specificity)
- Androstenedione is elevated in non- classical adrenal hyperplasia . DHEAS is a predominantly adrenal androgen with significant elevations in androgen-secreting adrenal tumours.
- If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenemia other than PCOS, including ovarian and adrenal tumors, congenital adrenal hyperplasia, Cushing's syndrome should be ruled out.
- Avoid assessment of biochemical hyperandrogenism in girls on combined OCPs (drug withdrawal of 3 months is recommended)

Role of pelvic ultrasound

- Pelvic ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years post menarche) due to the high incidence of multi-follicular ovaries in this life stage.[7]
- Risk of overdiagnosis in adolescents if ultrasound criteria included in this age group.
- Limitations in performing transvaginal ultrasounds in those not yet sexually active

Role of AMH

- Although serum AMH levels in adolescents and adult women with PCOS are significantly higher than in those without PCOS, there are overlaps between the two groups, especially in adolescents.[8]
- AMH assays have improved over time and hence a new recommendation on the role of AMH assays in diagnosing PCOS was made in adults only.
- Serum AMH could be used for defining PCOM in adults.
- In adolescents, specificity and accuracy are limited, therefore AMH is not recommended.

Adolescent 'at risk' of PCOS

- 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.
- Reassessment is particularly important for adolescent girls with persisting PCOS features and those with significant weight gain in adolescence
- This recommendation is based on the need to address isolated symptoms, such as irregular menstrual cycles or clinical hyperandrogenism, where diagnosis of PCOS remains unclear as pelvic ultrasound is not recommended
- This will avoid delayed diagnosis yet avoid over-diagnosis or premature labelling

Exclusion of other causes

- All etiologies that can cause menstrual irregularities and/or hyperandrogenism in adolescents must be excluded
- Hypothyroidism, hyperprolactinemia, Non classical Congenital adrenal hyperplasia (NC CAH), Cushing's disease, androgen-secreting ovarian or adrenal tumours can cause menstrual irregularity and/or hyperandrogenism.[9]
- History and physical examination to look for signs of hypothyroidism, galactorrhoea, glucocorticoid excess or virilisation are imporant in the evaluation of an adolescent girl with suspected PCOS.
- Measurement of thyroid profile, prolactin, 17 OHP (NC CAH), salivary cortisol (Cushings) may be considered to exclude other causes
- 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.

Key points

- Normal pubertal development to be kept in mind while diagnosing adolescent PCOS
- Diagnosis of PCOS in adolescents hinges only on ovulatory dysfunction and androgen excess
- No role of pelvic ultrasound in diagnosis
- Avoid unnecessary investigations and 'under' as well as 'over diagnosis'.
- Adolescents 'at risk' of PCOS should be identified and followed up

NEWER DEVELOPMENTS IN MANAGEMENT OF PCOS IN ADOLESCENTS

Lifestyle management

- Lifestyle management is the core focus in PCOS management.[10]
- There are benefits to healthy lifestyle even in the absence of weight loss.
- Exercise alone or diet along with exercise and behavioural strategies should be recommended for all girls with PCOS, to improve metabolic health (central adiposity & lipid profile) and for maintaining and preventing weight gain and/or modest weight loss.
- For girls not overweight, in the adolescent, the focus should be on healthy lifestyle & prevention of weight gain.

Management of Menstrual symptoms

Symptoms include delayed menses, prolonged bleeding, noncyclical early or late bleeding

Combined oral contraceptives (COCP)

- COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of irregular menstrual cycles and/or hirsutism.[3]
- No advantage of using high dose ethinylestradiol (EE)(≥ 30 µg) versus low dose EE(< 30 µg) when treating hirsutism.
- 35 µg EE plus cyproterone acetate preparations should be considered as **second-line therapy** over other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks, metabolic risk profile, side-effects, cost and availability.
- PCOS specific features such as obesity and CV risk factors, need to be considered when prescribing COCP.

Metformin

- Metformin vs active lifestyle intervention have similar efficacy.
- Mild adverse GI side-effects are generally dose dependent and self-limiting.
- Start low dose, with 500 mg increments weekly. Extended-release preparations may minimize side-effects and improve adherence.[11]
- Maximum daily dose 2 g in adolescents. Safe for long-term use, however, indications for ongoing requirement needs to be considered.
- Long term use may be associated with low vitamin B12 levels, with risk factors such as vegan diet, where monitoring should be considered.

Metformin and combined oral contraceptive pills (COCP)

- COCP better than metformin for management of hirsutism with irregular menstrual cycles.
- Metformin could be used over COCP for metabolic indications in PCOS.[12]
- Combination of metformin with the COCP, may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m^2, impaired glucose tolerance or high-risk ethnic groups, hirsutism and irregular cycles.[13]
- Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles and for hirsutism.

Progestogens or micronized natural progesterone (MNP) or progesterone only pills

- Irregular long cycles with normal menstrual bleeding:
  Progestogen for withdrawal bleeding given every 20 to 30 days or later if desired) MPA or norethisterone (total dose 100 mg) 10 mg BD X 5 days– bleeding in 5-10 days after last tablet
  If no withdrawal bleeding: rule out pregnancy and thin endometrium

- Irregular long cycles with prolonged or heavy menstrual bleeding:
  Progestogen or MNP or progesterone only Pill continuous and cyclically till bleeding amount and duration becomes normal.
  If no relief in heavy menses - USG for endometrial thickness and vaginal examination to rule out submucous fibroid/polyp in the uterine cavity or cervix.
  USG for endometrial thickness during menses:
  If >5 mm: progestogen or MNP to revert or prevent endometrial hyperplasia
  If <5 mm: regularize cycles with MPA withdrawal any day between day 21-35: -10mg BD X 5 days or low dose oral contraceptive pills for 21 days. [14]
  Note: Endometrial hyperplasia occurs by prolonged, unopposed estrogenic stimulation of endometrium. Untreated estrogen excess in PCOS, without progesterone exposure, is associated with an increased risk of endometrial cancer.

Inositols

Inositol given on individual preferences, as has limited harm with potential for improvement in metabolic measures, yet with very limited clinical benefits on ovulation, hirsutism or weight.[15]
Metformin to be considered over inositol for hirsutism and central adiposity, though metformin has more GI side-effects than inositol.
Women taking inositol and other complementary or nutritional therapies must inform their health professional.
Specific types, doses or combinations of inositol cannot currently be recommended in adolescents and adults with PCOS, due to lack of quality evidence.

Management of hirsutism

Pharmacological interventions

Combined oral contraceptive pills (COCP)

Treatment of acne and hirsutism should not be withheld during ongoing longitudinal evaluation for 'at risk' PCOS.
Hormonal therapy should not be started before menarche.
If response is suboptimal after 6 months additional hair removal therapies or antiandrogens can be added.
For moderate-to-severe hirsutism, hormonal therapy and antiandrogens can be started concomitantly. Any estrogen-containing therapy (COCPs) should be more effective at reducing acne, particularly for adolescents with premenstrual acne flare-ups.

Anti-androgens

Anti-androgens used to treat hirsutism, in presence of another effective form of contraception.

If suboptimal response after 6 months of COCP with cosmetic therapy or there is contraindications for COCP or COCPs are poorly tolerated anti androgens to be used.[3]

- Anti-androgens usage based on recommendations:

  a) Spironolactone- Aldosterone antagonist. Dose 25-100 mg/day has lower risks of adverse effects compared to other antiandrogens.

  b) Side effects include hyperkalemia, irregular menses, polyuria, postural hypotension and liver anomalies with higher doses.

  c) Cyproterone acetate (CPA)- Competes with Dihydrotestosterone (DHT) for binding to androgen receptor and also reduces serum LH and ovarian androgen production.

  d) Side effects include fatigue, mood change, mastalgia and low libido. Used in higher dose (12.5 to 100mg) as monotherapy

- *Topical Eflornithine*

  - Eflornithine hydrochloride(13.9% cream),FDA approved. Irreversible Inhibitor of ornithine decarboxylase (enzyme essential for hair growth).
  - Monotherapy for mild cases of facial hirsutism or as adjunct to other therapies.
  - Effect seen in 4 to 8 weeks
  - Reversal of hair growth within 8 week of discontinuation
  - Dose: BD application at least 8 hours apart.
  - Eflora ,Hinder, Elyn, Vaniqa

Cosmetic measures: Waxing, Shaving, Plucking

Mechanical laser and light therapy

Mechanical laser and light therapies not only reduces facial hirsutism but also therapeutic for related depression, anxiety and quality of life.

More treatment sessions required in PCOS, compared to idiopathic hirsutism.

Consider following when laser prescribed:

Wavelength and delivery of laser treatment varies by skin and hair colour.

Laser is relatively ineffective in women with blond, grey or white hair.

Addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone.

Mechanical hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. No evidence to support efficacy of home-based IPL kits.

Patients should be assessed at routine intervals (every 3–6 months) for adverse effects and response to treatment until their condition is stable; they then should be monitored annually.

Monitoring serum androgens is not recommended.

Psychological therapy, antidepressant and anxiolytic treatment

- Adolescents with PCOS diagnosed with depression, anxiety, disordered eating, body image distress, low self-esteem, or psychosexual dysfunction should be offered cognitive behaviour therapy where appropriate.[16]
- Psychological therapy could be considered first-line management, and antidepressant medication second line preferably mostly in adults.
- Lifestyle intervention and other therapies (COCP, metformin, laser hair removal) targeting PCOS features are important, as they have potential to improve psychological symptoms.
- Not managing anxiety and depression may impact adherence to PCOS treatment/management.

Follow up of adolescent PCOS

- Weight once a week
- Ensure menses at least every 40 to 45 days
- OGTT yearly
- BP yearly
- Lipid profile yearly

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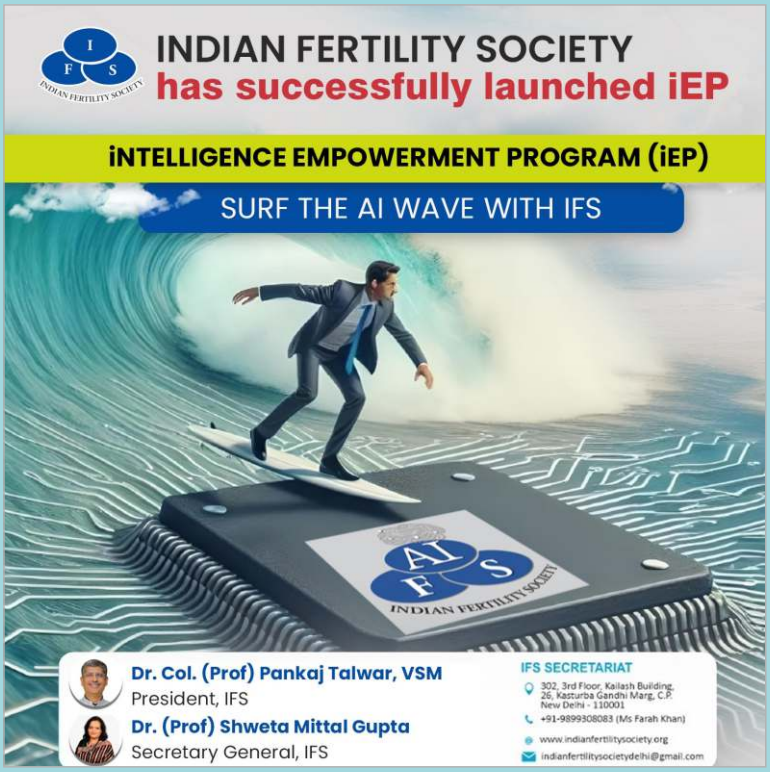
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