



POLYCYSTIC OVARY SYNDROME IN ADOLESCENCE

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Definition

- Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by hyperandrogenism and chronic anovulation
- The term ‘syndrome’ refers to a collection of clinical features or a phenotype.
- PCOS is a diagnosis of exclusion hence its definition would evolve with time and updated research findings

Etiology / Pathophysiology

- The exact aetiology of PCOS is still not well defined.
- There is a complex interplay between genetic, metabolic, endocrine, environmental, and lifestyle factors.
- PCOS has been shown to have a strong hereditary component as evidence by familial clustering and twin studies.
- Although the pathogenesis of PCOS is yet to be elucidated, four mechanisms have been identified to effect the clinical presentation in varying degrees. These are
 1. increased ovarian androgen secretion
 2. partial folliculogenesis arrest
 3. insulin resistance
 4. neuroendocrine axis dysfunction
- These mechanisms contribute to the four PCOS phenotypes in various degrees. In the classical phenotype (A+B) alterations occurs in all four aspects, with mainly hyperandrogenism and insulin resistance. Whereas in the ovulatory phenotype (C), it is predominately hyperandrogenism and neuroendocrine axis dysfunction without folliculogenesis arrest. In normoandrogenic phenotype (D), partial folliculogenesis arrest plays the most important role with absent of hyperandrogenism.

The Phenotypic System of PCOS Diagnosis		
<i>The Rotterdam and AE-PCOS Society criteria</i>	<i>NIH 2012 extension of ESHRE/ASRM 2003</i>	<i>Lizneva 2016</i>
Frank PCOS (oligomenorrhea, hyperandrogenism, and PCO)	Phenotype A: HA + OD + PCOM Phenotype B: HA + OD	“Classic” PCOS
Ovulatory PCOS (hyperandrogenism, PCO, and regular menstrual cycles)	Phenotype C: HA + PCOM	“Ovulatory” PCOS
Non-PCO PCOS (oligomenorrhea, hyperandrogenism, and normal ovaries)	Phenotype D: OD +PCOM	“Nonhyperandrogenic” PCOS

<p>The Rotterdam criteria also recognize a fourth phenotype, mild or normoandrogenic PCOS, which is defined by oligomenorrhea, PCO, and normal androgens.</p>		
<p>HA: clinical and/or biochemical hyperandrogenism OD: ovulatory dysfunction PCOM: polycystic ovarian morphology</p>		

Note: Phenotype B is probably the only 'classic' PCOS in adolescents as PCOM is not a diagnostic criteria in adolescents

Prevalence

- The prevalence is about 6-20% depending on the diagnostic criteria being used
- About 3-33% of these young women have mothers with PCOS
- 20-40% have family members with PCOS
- There is an increased risk for obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) in first-degree male and female relatives

Presentation

Symptoms

- Irregular cycles
- Amenorrhoea (Primary or secondary)
- Heavy menstrual bleeding
- Oligomenorrhoea
- Excessive weight gain
- Moderate to severe acne
- Excessive facial or body hair
- Alopecia (hair loss)

Signs

- High body mass index
- Moderate or severe comedonal acne (i.e. 10 or more facial lesions)
[Moderate inflammatory acne is uncommon -< 5% prevalence]
- Hirsutism
- Acanthosis nigricans
- Hypertension (in some cases)

Diagnosis

Diagnostic criteria:

- *Ovulatory dysfunction* is the key diagnostic features of PCOS with irregular menstrual cycles . It is important to note that during the first year post-menarche, it is consider as normal to have irregular cycles due to immaturity of the HPO axis.

Irregular menstrual cycles are defined as:

- Between 1-3 years post menarche if the cycles are < 21 or > 45 days
- Post menarche > 3 years till perimenopause if the cycles are < 21 or > 35 days or < 8 cycles per year
- After 1 year post menarche if any cycle is > 90 days

Note: Girls suspected of having PCOS due to irregular cycles within the first 1-2 years post menarche, should be followed up with a provisional diagnosis of “at risk for PCOS”

Note: Recent commentary by Rosenfield(2020) suggests the need to assess the adolescent’s general health status, exclude pregnancy and look for signs of PCOS in those who has been amenorrhoeic for two months. If her assessment are normal, she should be followed to see if the menstrual disturbance has revert back to normal. However, if she remains to be amenorrhoeic for more than 90 days or missed her cycle for more than 2 months, laboratory screening would be reasonable.

Hyperandrogenism is a key diagnostic feature of PCOS with the prevalence of 60% - 100%. It can be divided into two: clinical or biochemical

Clinical hyperandrogenism:

- The most recognisable clinical sign of hyperandrogenism is **terminal hairs in a male-like pattern** in women or “hirsutism”
- Depending on ethnicity, a modified **Ferriman-Gallwey (FG) score of at least 4 to 6** indicates hirsutism. It is important to note that self-treatment for hirsutism is common thus may reduce the FG scores
- Moderate or severe comedonal acne (i.e. ≥ 10 facial lesions) is likely to be associated with hyperandrogenism.
- Adolescent girls with acne that is persistent and not responsive to topical therapy should be investigated for causes of hyperandrogenaemia before starting of any medical treatment
- There is lack of study on the use of alopecia as a sign of clinical hyperandrogenism in adolescents

Biochemical hyperandrogenism:

- It is the most useful method to establish the diagnosis of PCOS
- However, the interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used as there are wide variation depending on the methods and laboratories used
- The best parameters would be the calculated free testosterone, free androgen index or calculated bioavailable testosterone
- For the most accurate assessment of total or free testosterone, a high quality assays such as liquid chromatography-mass spectrometry (LCMS)/ mass spectrometry should be used
- Androstenedione and dehydroepiandrosterone sulfate (DHEAS) should be considered if total or free testosterone are not elevated. However, there is scarce information of its usefulness in assisting in the diagnosis of PCOS.

Diagnostic Challenge

- Diagnosis may pose a challenge as clinical presentation may mimic normal pubertal changes in adolescents

Menstrual irregularity	<ul style="list-style-type: none"> ▪ During 1st year after menarche, 85% of menstrual cycles are anovulatory ▪ Even at 3 years post-menarche, 59% of the menstrual cycles are still anovulatory ▪ It is unclear as when irregular cycles reflect reproductive immaturity or clinical presentation of PCOS, thus making the diagnosis more challenging. There are concerns about over-diagnosis as it would cause unnecessary labelling and intervention hence create anxiety to these young women and their families.
Acne and mild hirsutism	<ul style="list-style-type: none"> ▪ These are common pubertal findings due to increase ovarian and adrenal production of androgens
Obesity	<ul style="list-style-type: none"> ▪ Obesity is common in adolescent, affecting 1 in 5
Assessing ovarian morphology	<ul style="list-style-type: none"> ▪ Transabdominal ultrasound is usually being performed rather than transvaginally, thus assessment maybe suboptimal especially in obese adolescents ▪ Multiple follicles are normal findings in adolescents ▪ Normal ovarian volumes in adolescents is less or equal to 10 cm³

Investigations not recommended

Pelvic ultrasound

- Ultrasound is now no longer recommended to be used for the diagnosis in those with gynaecological age of <8 years as multiple follicles are common in these age groups.
- Presence of PCOM alone can lead to over diagnosis in these adolescents.

Serum AMH levels

- Till date, serum AMH levels is not recommended to be use as a single test for diagnosis nor as an alternative to PCOM
- There is emerging evidence that with improved standardisation of assays and established cut off levels or thresholds based on large scale validation in populations of different ages and ethnicities, AMH assays will be more accurate in the detection of PCOM.

Differential diagnosis

PCOS is a diagnosis of exclusion hence there is a need to rule out other causes of menstrual irregularities and hyperandrogenism. It is important to rule out pregnancy especially in those sexually active presented with amenorrhoea.

The differential diagnosis that need to be considered in those with menstrual irregularities/amenorrhoea ± hyperandrogenism include

- Functional hypothalamic amenorrhoea
- Thyroid dysfunction
- Hyperprolactinemia
- Cushing's disease
- Androgen-secreting tumour
- Adrenal tumour
- Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Investigations that are needed to assist in the diagnosis and exclude the differential diagnosis:

- pregnancy test, PRL, TSH, FSH, LH, estradiol, calculated free testosterone, free androgen index or calculated bioavailable testosterone, DHEAS, androstendione, 17-OH-progesterone, glucose, insulin
- Pelvic ultrasound can be used to exclude other uterine or ovarian lesions

Management of PCOS

No approved treatment of PCOS exists for adolescents.

Management is based on alleviating symptoms (e.g. irregular menses, acne, obesity) with pharmacological agents and lifestyle interventions.

Information and education

- Information and education resources for healthcare professionals should promote the recommended diagnostic criteria, appropriate screening for comorbidities and effective lifestyle and pharmacological management.

- In an adolescent with menstrual irregularities, optimal timing of assessment and diagnosis of PCOS should be discussed. It is important to acknowledge the diagnostic challenges at this life stage. Psychosocial and cultural factors should also be taken into consideration.
- For those who have features of PCOS but do not meet diagnostic criteria, an “increased risk” could be considered. They should be followed up and reassessed at a later stage (at or after 8 years post-menarche).

Lifestyle intervention for weight reduction

- Metabolic disorders in adolescent PCOS are worsened by concomitant obesity.
- It is important to prevent obesity during management of PCOS.
- A 5% reduction in body weight can reduce metabolic and cardiovascular risks.
- Lifestyle interventions should be recommended as first-line therapy for weight reduction in adolescents with PCOS and these would include diet, exercise and behavioural strategies
- The principles of healthy eating is similar to general population.
- When optimising the lifestyle and weight, the BMI and waist circumference should be tailored according to different ethnic background
- Behavioural strategies that are useful to be implemented include goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training and eating slowly. It is also useful to reinforce changes and take measures to prevent relapse.

Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:

- in adolescents, at least 60 minutes of moderate to vigorous intensity physical activity/day, including those that strengthen muscle and bone at least 3 times weekly
- activity be performed in at least 10-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days

Addressing psychological issues

- Some of the adolescents with PCOS may have concerns over their body image while others may have eating disorders. At the same time, they should be screened for anxiety and depressive symptoms.
- ‘Screening for depression in children and adolescents’ is a useful screening tool.
- Those found to have psychological issues should be referred to a qualified health professional to address and manage their problems.

- It is crucial to engage with the adolescents and seek their co-operation to lifestyle interventions.

Pharmacological treatments

Combine oral contraceptive pills (COCP)

- Other than contraceptive benefits, COCP has an advantage of reducing testosterone levels, regulates menstrual cycles, improves acne and prevents endometrial hyperplasia
- Hence COCP alone should be considered in adolescents with PCOS who presents clinical hyperandrogenism and/or menstrual irregularities
- The COCP should also be considered in adolescents “at risk” of PCOS with clinical hyperandrogenism and menstrual irregularities.
- There is no advantage of certain type of progestins or estrogen or COCP in treatment of PCOS..
- However, special cautious in prescribing COCP in adolescents with high BMI, hyperlipidemia and hypertension.
- No single COCP is superior than others in treating hirsutism.

Metformin

- In addition to lifestyle interventions, metformin could be considered in adolescents with PCOS and those at risk of PCOS’.
- There is a role of adding metformin in those with BMI $\geq 25\text{kg/m}^2$ where COCP and lifestyle were not able to achieve the ideal weight.
- Metformin has been reported to reduce the BMI, waist-to-hip ratio and triglycerides level
- The recommended dose is 1500-1700 mg per day. It is found to be associated with mild to moderate gastrointestinal side effects that were self-limiting. The common side effects were nausea, vomiting, diarrhoea, abdominal pain and non-specified gastrointestinal discomfort.

Anti-androgen

- The Endocrine Society guidelines recommends the use of cosmetic and COCP therapy as the first-line treatment for hirsutism in women with PCOS. Antiandrogens can be considered for treatment of hirsutism in those who have failed cosmetic therapy and have consumed COCP for more than 6 months.
- In cases where COCPs are contraindicated or poorly tolerated, antiandrogens could be considered for treatment of hirsutism or androgen-related alopecia. For those taking antiandrogen, it is best to avoid pregnancy as these drugs are teratogenic and can affect external genital development of male fetuses. Hence it is important to use a reliable contraceptive method.

- Till now, there was insufficient evidence to suggest a specific type of antiandrogens

Anti-obesity

- Anti-obesity medications are not recommended for adolescents

Inositol

- Inositol found in nutritional supplement has been shown to play a role in insulin signalling transduction through its action as a second messenger.
- There is emerging evidence on its use in treating PCOS however it is still at experimental level.

Prevention

- Referral to other specialty (e.g. paediatric endocrinologist) is advisable in cases where the diagnosis is uncertainty.
- Adolescents should be re-evaluate for persistence of PCOS by the time they finish high school or after withdrawing treatment for 3 or more months.
- Sexually active adolescents should be advised to take non-hormonal contraception to prevent pregnancy if they decided to stop their COCP as infertility in PCOS is not absolute.
- In cases where there is persistence of ovulatory dysfunction and hyperandrogenism, treatment for PCOS should be reinstated. These young women would require follow up in anticipation for infertility problem.

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