THE PCOS SOCIETY INDIA

PCOS TUTORIALS

A Post Graduate Certificate Course in PCOS Management

Module 2

Adolescent PCOS: The Global Epidemic

Brought to you by The PCOS Society (India)

THE PCOS SOCIETY INDIA

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Module II

Adolescent PCOS:
The Global Epidemic

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Module Overview

Polycystic ovarian syndrome (PCOS) affects on average about 10% women of reproductive age group and is the cause of hyperandrogenism in more than 70% adult women. [1]

The cause is not clearly known, however multiple factors such as hereditary and non-hereditary; intrauterine and extra uterine; environmental factors; disparity in insulin resistance; modification in steroidogenesis may influence this disease/ syndrome.

The menstrual irregularity and/or elevated androgen levels have been noted in adolescence in women with PCOS and infertility is encountered in later life, this strengthens the importance of early diagnosis of PCOS in adolescence.

Diagnosis of PCOS in adolescence could give an opportunity to create awareness of this lifelong condition and provide prospective interventions such as healthy lifestyle counselling, testing for co-morbidities, or medications to treat the clinical manifestations. However the diagnosis of PCOS in adolescents can be challenging due to overlap of normal pubertal physiological changes that occur at the same time.

Further the diagnosis and management of PCOS in adolescence has been evolving continuously. [1]

This module intends to provide the latest consensus and recent updates on PCOS in adolescence.

References:

1. Fauser BC, Tarlatzis RW, Rebar RS, *et al*. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil. Steril*. 2012;97:28–38.e25.
2. West S, Lashen H and Bloigu A. Irregular menstruation and hyperandrogenemia in adolescence are associated with polycystic ovary syndrome and infertility in later life: Northern Finland Birth Cohort 1986 study. *Hum. Reprod*. 2014; 29(10):2339–2351.

Learning Objectives

At the conclusion of this module, the participant will be able to understand:

- The burden of PCOS in adolescent population
- Causative factors of PCOS
- Normal puberty vs. PCOS: Clinical and metabolic manifestations
- PCOS diagnosis and phenotypes in adolescence and how it varies from the adult diagnostic criteria
- Early features of PCOS: Hyperandrogenemia and insulin resistance
- Consequences of PCOS
- Management of PCOS in adolescence and how it is different from adult management

Adolescent PCOS: The Global Epidemic

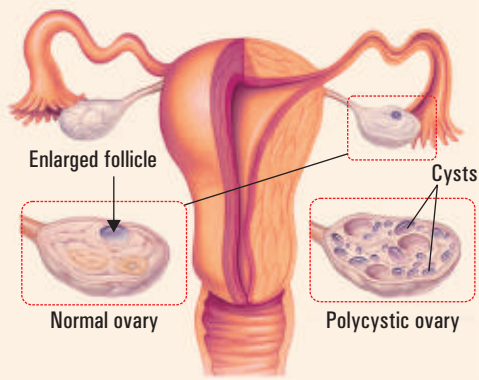
PRE-TEST

Are the following statements True or False?

1. **PCOS is rarely seen in adolescence**
   True
   False
2. **Presence of polycystic morphology on ultrasound in adolescence is a pathognomic diagnostic feature for PCOS**
   True
   False
3. **All adolescents with PCOS are obese**
   True
   False
4. **PCOS is more of a disease of western countries and seen in only affluent societies**
   True
   False
5. **There are different phenotypic manifestations of PCOS in adolescence**
   True
   False
6. **Oral contraceptive pills cannot be used for treatment in adolescence**
   True
   False
7. **Inflammatory markers have no role in PCOS**
   True
   False
8. **The only metabolic issue associated with PCOS is diabetes**
   True
   False
9. **First line of treatment is diet and lifestyle modification for weight reduction**
   True
   False
10. **Anti-Mullerian hormone (AMH) is a useful biomarker for diagnosis of PCOS in adolescence**
    True
    False

Answers: 1. False; 2. False; 3. False; 4. False; 5. True; 6. False; 7. False; 8. False; 9. True; 10. False

PCOS – Module 2
Adolescent PCOS: The Global Epidemic



Welcome to the learning module of the PCOS Tutorials: A post-graduate certificate course, brought to you by the PCOS Society, India. In this module we discuss the background, pathophysiology and diagnosis of adolescent PCOS.

PCOS Background

- Adolescence begins with the onset of puberty and ends with an adult identity
- For medical practitioners: Age is arbitrarily set chronological threshold between adolescence and adulthood
- This period of development corresponds roughly to the period between the ages of 10–19 years[1]
- The diagnosis of PCOS in adolescence is difficult, as features of PCOS overlap normal pubertal development
- Obesity, insulin resistance, hyperinsulinemia and androgen excess are frequently seen among adolescents[2]

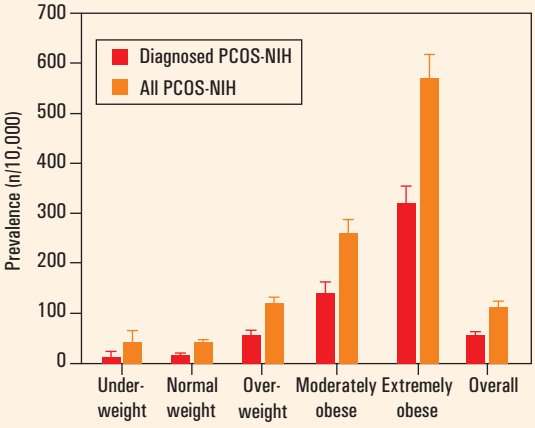
- Adolescence begins with the onset of puberty and ends with an adult identity. Medical practitioners involved in the care of adolescents must often deal with an arbitrarily set, chronological threshold between adolescence and adulthood, which varies from place to place. This period of development corresponds roughly to the period between the ages of 10 to19 years.[1]
- The diagnosis of PCOS in adolescence is difficult, as features of PCOS overlap normal pubertal development. Hence, caution should be taken before diagnosing PCOS without longitudinal evaluation. However, treatment may be indicated even in the absence of a definitive diagnosis. Features like

obesity, insulin resistance, and hyperinsulinemia are common in adolescents with hyperandrogenism, these features should not be used alone to diagnose PCOS among adolescent girls.[2]

References:

1. Adolescent Health committee. Age limits and adolescents. *Paediatr. Child. Health*. 2003;8(9): 577.
2. Witchel SF, Oberfield S, Rosenfield RL *et al*. The diagnosis of polycystic ovary syndrome during adolescence. *Horm. Res. Paediatr*. 2015;83:376–389.

Prevalence of PCOS in Adolescence



Odds ratio (OR) compared to normal or underweight girls[1]	%
Overweight adolescents	3.85
Moderately obese adolescents	10.25
Extremely obese adolescents	23.10

- In the study conducted by Christensen *et al.* the prevalence of diagnosed (black) and undiagnosed PCOS according to NIH criteria (gray) in adolescents aged 15–19 years has been demonstrated graphically.
- It is found that compared to normal/underweight girls, the odds ratios (OR [95% CI]) for confirmed PCOS diagnosis were 3.85 (3.04–4.88), 10.25 (8.16–12.84), and 23.10 (18.66–28.61) for overweight, moderately obese, and extremely obese adolescents, respectively, after adjusting for potential confounders.
- The analysis shows that overweight and obese individuals were at higher odds of developing PCOS in adolescence. Studies based solely on diagnosis codes may underestimate the prevalence of PCOS and overestimate the magnitude of the association between obesity and PCOS.[1]

Reference:

1. Christensen SB, Black MH, Smith N, *et al*. Prevalence of polycystic ovary syndrome in adolescents. *Fertil. Steril*. 2013;100(2):470–477.

Prevalence of PCOS in India

- An urban community based study conducted in Mumbai found:
  - Prevalence by Rotterdam criteria: 22.5%
  - Prevalence by Androgen Excess Society criteria (AESC): 10.7% [1]
- Study among the rural patients with PCOS:
  - Diagnosed by Rotterdam criteria found 71.8% were non-obese
  - The most common phenotype was mild PCOS (oligomenorrhea and polycystic ovaries on USG) consisting of 52.6% of the studied population [2]
- In a study conducted among adolescents, 12–19 year aged females:
  - 18% of participants were diagnosed with PCOS
  - Urban population had higher proportion of PCOS when compared with rural counterparts [3]

- In India, higher incidence of PCOS risk factors such as high body mass index and insulin resistance is seen. These suggest that the real extent of the problem may be currently underestimated.
- The reported overall prevalence rates of PCOS according to Rotterdam criteria were twice as high as those according to NIH criteria.
- In India prevalence of PCOS was higher among urban population as compared to rural.
- Urban patients with PCOS were more inclined to be obese, while rural patients with PCOS were more likely to be non-obese.
- In a study comparing the clinical phenotypes in PCOS in rural vs. urban India, the authors found the following prevalence of various characteristics.

Table 1: Rural vs. Urban PCOS in India. Note higher proportion of oligomenorrhea, recent weight gain and obesity among urban population with PCOS as compared to the rural population [2]

Characteristic	Rural (%)	Urban (%)
Oligomenorrhea	16	64
Recent weight gain	12	52
Obese	50	88
Non-obese	50	12
Physically active	40	

References:

1. Joshi B, Mukherjee S, Patil S, *et al*. A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. *Indian. J. Endocrinol. Metab*. 2014;18(3):317–24.
2. Balaji S, Amadi C, Prasad S, *et al*. Urban rural comparisons of polycystic ovary syndrome burden among adolescent girls in a hospital setting in India. *BioMed Research International*. 2015;158951.
3. Mallik S, Shah D, Sheth R, *et al*. PCOS guideline: Management of polycystic ovary syndrome in India. *Fertility Science and Research*. 2014; 1(1).
4. Radha P, Devi RS, and Madhavi J. Comparative study of prevalence of polycystic ovarian syndrome in rural and urban population. *Journal of Advanced Medical and Dental Sciences Research*. 2016;4(2):90.

Prevalence of PCOS in Different Countries

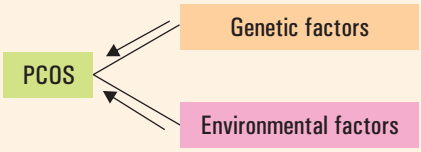
Country	PCOS criteria used			First author, year (reference)
	NIH 1990	ESHRE/ASRM 2003	AE-PCOS 2006	
Australia	8.7–15.3	11.9–21.3	10.2	March, 2010; Boyle, 2012
Brazil	–	8.5	–	Gabrielli, 2012
China	2.2–7.1	5.6–16.6	7.4–13.9	Chen, 2008; Ma, 2010; Li, 2013; Zhuang, 2014
Denmark	–	16.6	13.9	Lauritsen, 2014
Greece	6.8	–	–	Diamanti-Kandarakis, 1999
Iran	4.8–7.1	14.1–15.2	7.92–12	Tehrani, 2011; Mehrabian, 2011; Rashidi, 2014
Italy and Spain	5.4	–	–	Sanchon, 2012
Mexico	6.0	–	–	Moran, 2010
Palestine	7.3	–	–	Musmar, 2013
Sri Lanka	–	6.3	–	Kumarapeli, 2008
Turkey	6.1	19.9	15.3	Yildiz, 2012
UK	8.0	–	–	Michelmore, 1999
USA	4.0–13.0	–	–	Knochenhauer, 1998; Azziz, 2004; Goodarzi, 2005

- In an article recently published in the journal "Fertility and Sterility" the prevalence of PCOS based on different diagnostic criteria appears to vary. The table representing the variability in prevalence in different countries using different criteria is shown here. [1]

Reference:

1. Lizneva D, Suturina L, Walker W, *et al*. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil. Steril*. 2016; 106(1):6–15.

Etiology



- Multifactorial disease with full clinical expression is the result of synergistic pathological interaction between genetic and environmental factors.

Genetic Susceptibility of PCOS

- Familial clustering is evident with PCOS
- Increased prevalence of the following components is seen among PCOS patients:
  - Hyperandrogenemia
  - Type 2 diabetes mellitus (T2DM) in first-degree relatives of women with PCOS
  - High heritability
- The mode of heritance of PCOS remains unclear. It may be:
  - Dominant and/or
  - Multigenic modes of transmission

- Evidence for genetic contribution includes a well-documented familial clustering of PCOS, as well as increased prevalence of its components, including hyperandrogenemia, and T2DM in first-degree relatives of women with PCOS; and a high heritability ($h^2 = 0.70$) in a Dutch twin study.
- Nonetheless, the mode of inheritance of PCOS remains unclear, and both dominant and multigenic modes of transmission have been proposed.

The table below discusses the candidate gene studies involved with PCOS.

Table 2: Gene studies involved with PCOS[1]				
Gene	**Chromosome locus**	**Polymorphism**	**Phenotypes**	**Remarks**
Fibrillin-3 (FBN3)	19p13.2 D19S884 allele 8 (A8)	Polymorphism in *FBN3* on TGF-β signalling molecules	Significantly lower circulating total TGF-β1, and higher Inhibin B and aldosterone levels	FBN3 may exert its effect during fetal development, and influence a person's predisposition to PCOS later in life, supporting previously proposed hypotheses on fetal origins for PCOS
Insulin (INS)	5' regulatory element of the insulin gene	Variable number tandem repeat (VNTR) polymorphism	Hyperinsulinemia, fasting insulin levels, susceptibility to T2DM, birth weight, and childhood obesity and juvenile obesity	Contribution of INS to the aetiology of PCOS is still in question and needs larger studies for evaluation
Insulin receptor (INSR)	Tyrosine kinase domain of *INSR* (exons 17–21) His1085 in dbSNP rs2252673		Mutations in *INSR* result in hyperandrogenemia	rs2252673 was found associated with PCOS
Insulin receptor substrate 1 (IRS1)	Arg972 allele	*IRS1*, Gly972Arg		Risk factor for PCOS, it is mediated through increased levels of fasting insulin
Transcription factor 7-like 2 (TCF7L2)		rs7903146 and rs12255372 (in introns 3 and 4)	*wnt* signaling pathway T2DM	Modest association between rs7903146 and PCOS different variation in the same gene might result in susceptibility to different phenotypes
Calpain 10 (CAPN10)		UCSNP –43, –19 and –63)	T2DM Association between UCSNP-44 and PCOS-related phenotypes	

Table 2: Gene studies involved with PCOS[1] (contd...)

Gene	Chromosome locus	Polymorphism	Phenotypes	Remarks
			CAPN10 haplotypes and other phenotypic characteristics of PCOS (including hypercholesterolemia and hirsutism) Metabolic syndrome	Small sample sizes. Need larger studies/ meta analysis to validate associations
Fat and obesity associated gene (FTO)		SNP rs9939609	Childhood obesity Adult obesity PCOS	It seems likely that possible effects of FTO in PCOS are limited to the metabolic phenotypes
Sex hormone-binding globulin (SHBG)		*SHBG* (TAAAA)n	Decreases androgens in target tissue	Influence PCOS phenotype indirectly

Reference:

1. Kosova G and Urbanek M. Genetics of the polycystic ovary syndrome. *Mol. Cell. Endocrinol.* 2013; 373(0): 29–38.

Genome-wide Association (GWA) Studies[1]

Three distinct regions showed strong evidence of association with PCOS in the combined meta-analysis and these were designated with PCOS susceptibility loci

Region 1

- Located on 2p16. 3 chromosome

Genes:

- *GTF2A1L* (TFII1-alpha and beta like factor)
- LHCGR (luteinizing hormone/choriogonadotropin receptor)
- FSHR (follicle stimulating hormone receptor) gene

Region 2

- Located on chromosome 2p21
- *THADA* (thyroid adenoma associated) gene- also associated with T2DM susceptibility

Region 3

- Located on chromosome 9q33.3
- Encodes protein involved in endosomal membrane trafficking
- Influences ERAP1

Overall, after the three primary genetic regions were identified in the GWA studies, insulin receptor gene was one of the most promising candidate gene for PCOS susceptibility in the Asian population

Three distinct regions were designated PCOS susceptibility loci and showed strong evidence of association with PCOS in the combined meta-analysis.

Region 1

- The first locus is located on chromosome 2p16.3, and contains two genes, *GTF2A1L* (TFII1-alpha and beta like factor) and *LHCGR* (luteinizing hormone/choriogonadotropin receptor).
- LHCGR has a crucial function in ovarian physiology and reproductive processes. Interestingly, this locus is also ~200 kb downstream of *FSHR* (follicle stimulating hormone receptor) gene, which is another plausible PCOS candidate due to its role in the development of the ovarian follicles.

Region 2

- The second locus is located on chromosome 2p21, and two independently associated SNPs at this locus are located in the *THADA* (thyroid adenoma associated) gene. This region has previously been implicated in T2DM susceptibility region in the Europeans.

Region 3

- The third locus is located on chromosome 9q33.3, in the *DENND1A* (DENN domain-containing protein 1A) gene, which encodes a protein involved in endosomal membrane trafficking and also has a function in guanine exchange for the small GTPase Rab35. It affects a wide range of physiological processes, and is expressed ubiquitously. It is expected that it might also influence some of the many organ systems PCOS affects, perhaps through altered activity of endoplasmic reticulum aminopeptidase 1 (*ERAP1*).
- Overall, after the three primary genetic regions identified in the GWAS, insulin receptor gene is one of the most promising candidate gene for PCOS susceptibility in Asian population.

Reference:

1. Kosovo G and Urbanek M. Genetics of the polycystic ovary syndrome. *Mol. Cell. Endocrinol.* 2013; 373(0): 29–38.

Familial Association of Diseases and PCOS

- Significantly higher positive family history of diabetes is seen among PCOS group
- Risk of breast cancer varied in studies and further studies are necessary to substantiate the association
- Endometrial cancer and diabetes was observed in mother or among maternal family
- Heart attack and thrombosis was observed in father or paternal family predominantly

- Study finds significantly increased number of women with the positive family history of diabetes among PCOS group (28.21% vs. 19.20%, $p=0.01$).
- Risk of breast cancer varied in studies and further studies are necessary to substantiate the association.
- Endometrial cancer and diabetes were observed in mother or mother's side of the family.
- Heart attack and thrombosis manifested in father or father's side of the family more.

Reference:

1. Moin A and Eslami B. Familial associations between polycystic ovarian syndrome and common diseases. *J. Assist. Reprod. Genet*. 2009 ; 26(2–3): 123–127.

Prevalence of Personal or Family History

Family history of the disease	PCOS n=273 (n)(%)	Control n=276 (n)(%)	*P* value
Breast cancer	3 (1.30)	12 (4.35)	0.02
Ovarian cancer	1 (0.43)	0 (0)	NS
Endometrial cancer	3 (1.30)	3 (1.09)	NS
Heart attack	29 (10.62)	24 (8.70)	NS
Thrombosis	13 (5.65)	8 (2.90)	NS
Diabetes (%)	77 (28.21)	53 (19.20)	0.01
Cardiovascular disease (%)	19 (8.26)	22 (7.97)	NS

- In this analysis, there were significantly higher incidences of positive family history of diabetes among PCOS group (28.21% vs. 19.20%, $p=0.01$).
- A statistically significant positive family history of breast cancer was noted in control group (4.35% vs. 1.30%, $p=0.02$).

- Higher prevalence of family history of diabetes, endometrial cancer, heart attack and thrombosis were seen among individuals with PCOS as compared to the controls.

Reference:

1. Moin A and Eslami B. Familial associations between polycystic ovarian syndrome and common diseases. *J. Assist. Reprod. Genet*. 2009;26(2-3):123–127.

Male Equivalent of PCOS

- The autosomal genetic transfer of the disease predisposition is the basis for hypothesis that there can exist a male equivalent of PCOS
- Androgenetic alopecia has been suggested as the symptom of the male phenotype of PCOS
- Higher insulin resistance was seen in these patients
- Hormonal derangements matched those of women with PCOS

- PCOS is a multifactorial disease.
- The autosomal genetic transfer of the disease predisposition is the basis for hypothesis that there can exist a male equivalent of PCOS.
- Androgenetic alopecia has been suggested as the symptom of the male phenotype of PCOS.
- Similar hormonal changes as women with PCOS, namely lower sex hormone-binding globulin (SHBG), lower follicle-stimulating hormone (FSH) and elevated free androgen index are seen.
- Patients with hormonal changes resembling those of PCOS, showed a significantly higher insulin resistance than the group without these changes.

Reference:

1. Dusková M1, Hill M and Stráka L. The polycystic ovary syndrome and its male equivalent. *Cas. Lek. Cesk*. 2007;146(3):251–5.

Environmental Determinants of PCOS

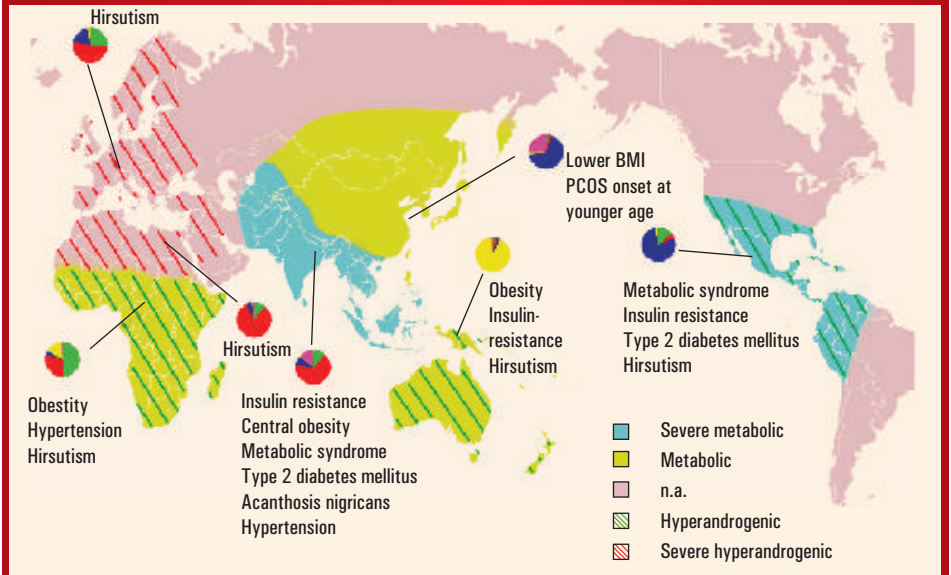
- Environment is likely to play an important role in the expression of the genetic traits
  - Environmental toxins: Endocrine-disrupting chemicals (EDCs)
  - High carbohydrate intake also exacerbates PCOS
  - Generalized obesity and body fat distribution[1]

- Recent reviews of PCOS research have found that genetic susceptibility is associated with PCOS, and that the environment is likely to play an important role in the expression of these genetic traits. They are:
  - Environmental toxins which include endocrine-disrupting chemicals (EDCs)
  - High carbohydrate intake can be an exacerbating factor for PCOS
  - Generalized obesity and body fat distribution are unlikely causes of PCOS, although they may exacerbate the phenotype and weight loss has been found to improve PCOS-related symptoms

Reference:

1. Merkin SS, Jennifer L, Cynthia K, *et al*. Environmental determinants of polycystic ovary syndrome. *Fertil. Steril*. 2016;106 (1):16–24.

Effect of Geographic Variation on PCOS

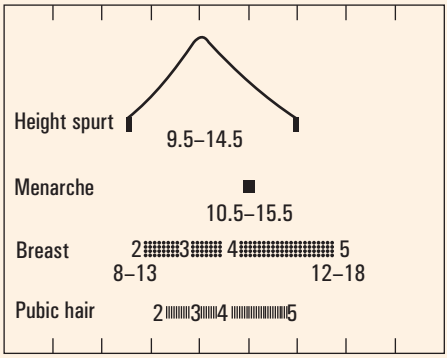


- World distribution of the affinity to the genetic clusters and PCOS phenotypes prevalence is displayed in the figure given here.[1]

Reference:

1. Casarini L and Brigante G. The polycystic ovary syndrome evolutionary paradox: A genome-wide association studies–based, in silico, Evolutionary Explanation. *Journal of Clinical Endocrinology & Metabolism.* 2014; 99(11): jc20142703.

Development During Normal Puberty



Normal puberty is associated with:

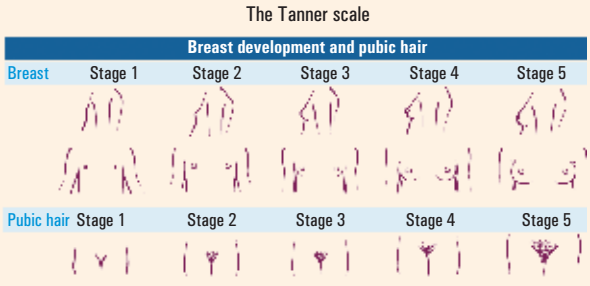
Height spurt, menarche, thelarche (breast growth) and appearance of pubic hair. The respective age for development of these features is demonstrated in the graph above.

Other features commonly seen during normal puberty include:

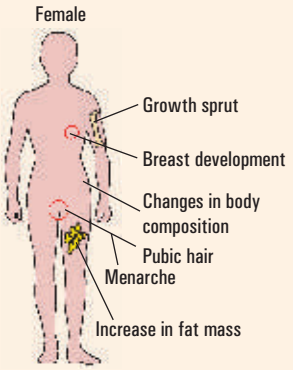
- Oligomenorrhoea
- Amenorrhea
- Acne
- "Multicystic" ovaries

These latter features may overlap with the symptoms and signs of PCOS.

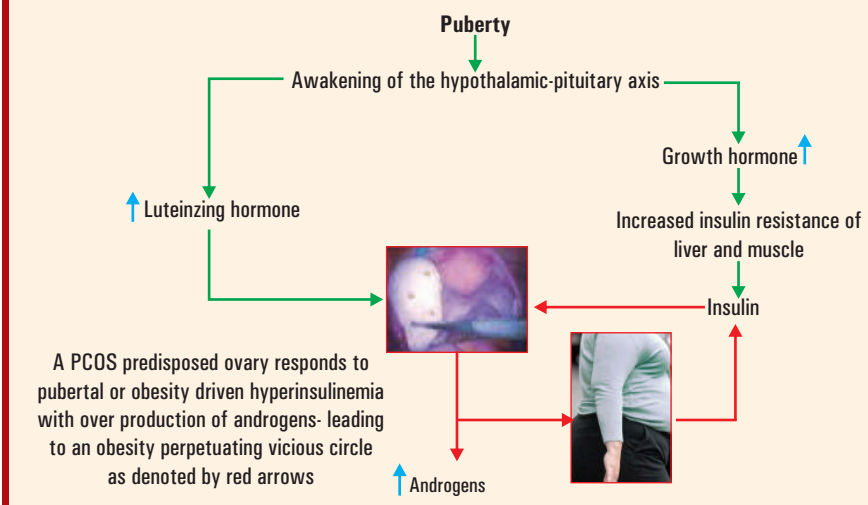
Physical Changes During Normal Puberty



Normal changes at puberty in girls

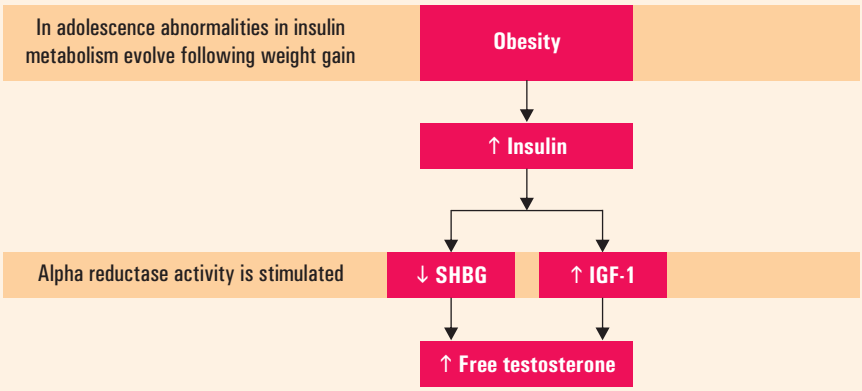


Normal Puberty vs. PCOS Pathophysiology



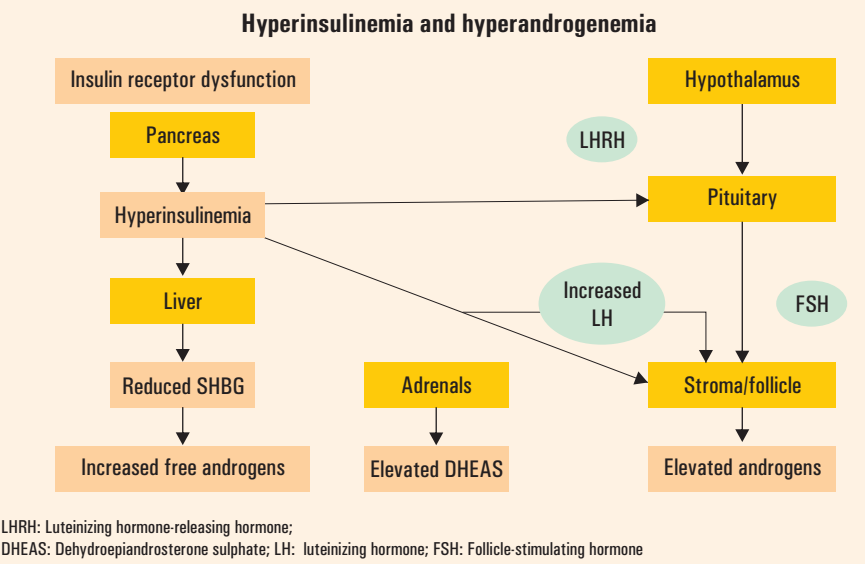
- Puberty is initiated with the maturation of the hypothalamic-pituitary ovarian axis and secretion of gonadotrophin-releasing hormone (GnRH). The activity of GnRH is suppressed during childhood.
- Varying GnRH pulse frequencies trigger the pituitary to release luteinizing hormone (LH) and FSH, which in turn stimulate ovarian theca and granulosa cells, respectively.
- Theca cells produce androstenedione, which nearby granulosa cells aromatize into estradiol (E2). The resulting estrogenic changes during puberty include breast development, bone growth, and fat deposition.
- During this period the adrenal glands also releases increasing amounts of androgens, such as dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS), which are responsible for the development of pubic and axillary hair, as well as acne. The subsequent increase in ovarian androgens further facilitates the development of sexual hair growth.
- During puberty hyperinsulinemia is common in healthy adolescents; insulin sensitivity decreases by about 50% and there is a compensatory rise in insulin secretion, which later returns to prepubertal levels in adulthood.

Obesity, Insulin Resistance and Androgens



- However, both insulin resistance and hyperinsulinemia are more severe in adolescents with PCOS compared with the general adolescent population.
- Insulin stimulates ovarian theca cell synthesis of androgens and inhibits hepatic production of SHBG.

Early Features of PCOS



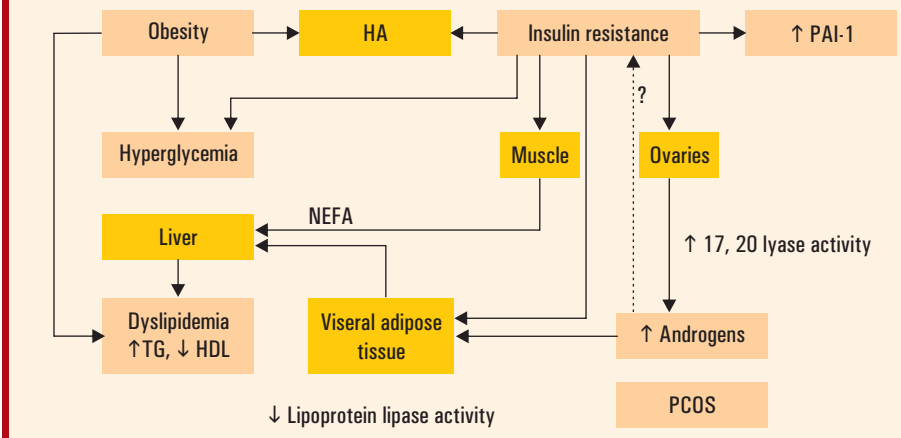
LHRH: Luteinizing hormone-releasing hormone;
DHEAS: Dehydroepiandrosterone sulphate; LH: luteinizing hormone; FSH: Follicle-stimulating hormone

- Together, these effects result in increased circulating free androgen levels, thus perpetuating the underlying pathophysiology of PCOS.

References:

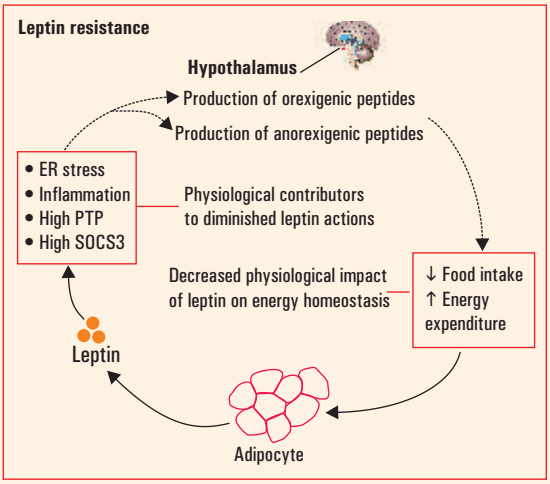
1. Rue AH and Dokras A. The diagnosis of polycystic ovary syndrome in adolescents. *Rev. Obstet. Gynecol.* 2011; 4(2): 45–51.
2. Tania S. Burgert. The Case of the Adolescent Who Can't Lose Weight - Medscape - Jul 05, 2011.

Pathophysiology of Metabolic Risks in PCOS



- Insulin resistance promotes hyperandrogenism and dyslipidemia
- When accompanied with obesity hyperglycemia and hypertension are further accentuated
- Metabolic dysfunction constitutes an important risk associated with PCOS, and it can manifest at an early age[1]
- Higher leptin levels are associated with women with PCOS
- Hyperleptinemia in PCOS appears to be the masking effect of hyperinsulinemia. Elevated leptin in hyperinsulinemic PCOS women is a secondary consequence of insulin-stimulated synthesis of leptin[2]
- While leptin inhibits insulin-mediated promotion of gonadotropin-stimulated steroidogenesis, decreases glucose-mediated insulin secretion through its receptors in the hypothalamus
- The cellular signalling interactions among gonadotropins, insulin, and leptin is quite complex and has been demonstrated in the figure given below.

Leptin Resistance and PCOS



Increase in the number of cells

↓

Increased leptin and insulin levels and preferential increase in LH, but not FSH

↓

Stimulate partial development of follicles that secrete supra-normal levels of T, which rarely ovulate hence low P4

Leptin resistance in PCOS[1,2]

ER: Endoplasmic reticulum; PTP: Protein tyrosine phosphate; SOCS3: Suppressor of cytokine signaling 3; T:Testosterone; P4: Progesterone

References:

1. Rue AH and Dokras A. The Diagnosis of Polycystic Ovary Syndrome in Adolescents. *Rev. Obstet. Gynecol.* 2011 Summer; 4(2): 45–51
2. Chakrabati J. Serum leptin level in women with polycystic ovary syndrome: Correlation with adiposity, insulin, and circulating testosterone. *Ann. Med. Health. Sci. Res.* 2013 Apr-Jun; 3(2): 191–196.
3. St-Pierr J and Tremblay ML. Modulation of leptin resistance by protein tyrosine phosphatases. *Cell Metabolism*. 2012; 15(3):292–297.
4. Patil M. Pathophysiology of PCOS. The PCOS Society of India Newsletter. *Pandora*. 2016; 1:6–8.

Diagnostic Criteria for PCOS in Adults

Parameter	ESHRE/ASRM 2012	Endocrine Society 2013
Criteria	• Clinical or biochemical hyperandrogenism • Oligo-/anovulation • Polycystic ovarian morphology	• Clinical or biochemical hyperandrogenism • Persistent oligo-/anovulation
Limitation	Three of three criteria required with exclusion of other aetiologies	Two of three criteria required with exclusion of other aetiologies

ASRM: American Society for Reproductive Medicine; ESHRE: European Society for Human Reproduction and Embryology

- Given here are both the recent diagnostic criteria; one proposed by the ESHRE/ASRM and one by the Endocrine Society that are widely used.

- However, neither of the proposed criteria has been validated for diagnosis of PCOS in adolescence.

Reference:

1. Lizneva D, Suturina L, Walker W, *et al*. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil. Steril*. 2016; 106(1):6–15.

ESHRE/ASRM Diagnostic Criteria for PCOS in Adolescence

- All three elements of the Rotterdam criteria should be present in teenagers to make the diagnosis of PCOS
- Oligomenorrhea or amenorrhea:
  - Present for at least 2 years after menarche or
  - Primary amenorrhea at age 16 years
- Polycystic ovarian morphology (PCOM) on ultrasound should include increased ovarian size >10 cm^3
- Hyperandrogenemia rather than just signs of androgen excess

All three elements of the Rotterdam Criteria should be present in teenagers to make the diagnosis of PCOS:

- Oligomenorrhea or amenorrhea: Present for at least 2 years after menarche or primary amenorrhea at the age of 16 years

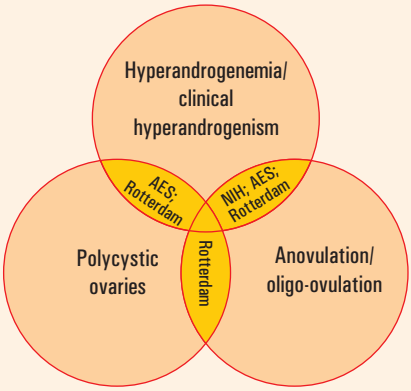
In all young women, irregular menses are common immediately post menarche. Eighty five percent of menstrual cycles are anovulatory during the first year after menarche, and up to 59% are still anovulatory during the third year after menarche. Increased body mass index, however, was the major risk factor for persistent anovulation.

- Polycystic ovarian morphology (PCOM) on ultrasound should include increased ovarian size >10 cm^3. Only approximately 40% of adolescent women with menstrual irregularity have PCOM on ultrasound
- Hyperandrogenemia rather than just signs of androgen excess, since acne is common among adolescents irrespective of PCOS, hirsutism associated with PCOS typically develops later and not in adolescence, hence, hyperandrogenemia may be a more consistent marker for PCOS during the teenage years[1]

Reference:

1. Lizneva D, Suturina L, Walker W, *et al*. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil. Steril*. 2016; 106(1):6–15.

Diagnostic Criteria for PCOS in Adolescence



Reference:

1. Fauser BCJM, Tarlatzis BC, Rebar RW, *et al*. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil. Steril.* 2012;97(1):28–38.e25.

Criteria for Hyperandrogenism

Clinical	Biochemical
• Isolated mild hirsutism is not a clinical evidence of hyperandrogenism in the early postmenarcheal years • Moderate-to-severe hirsutism constitutes clinical evidence of hyperandrogenism • FG score above the 95th percentile for the given population is necessary for the diagnosis • Acne that is persistent and poorly responsive to topical dermatologic therapy may be the sign of hyperandrogenemia	• Persistent elevation of serum total and/or free testosterone levels • DHEAS levels to rule out virilising adrenal disorder • FAI • Early morning 17OH-progesterone during preovulatory or luteal phase of the cycle • SHBG (16–119 nmol/L) as surrogate marker for insulin resistance

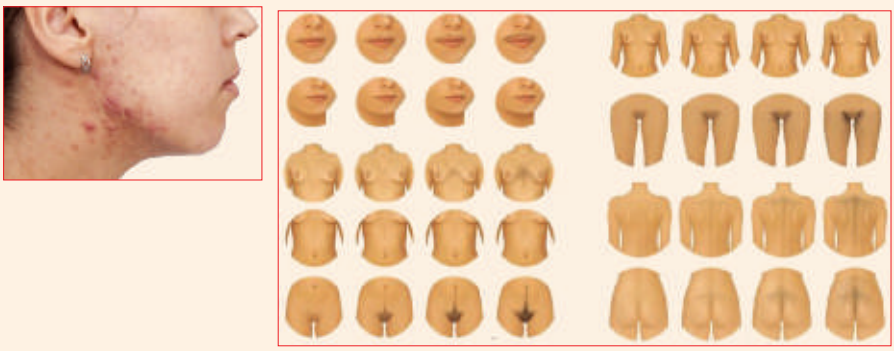
FG: Ferriman-Gallwey; FAI: Free androgen index; SHBG: Sex hormone binding globulin; DHEAS: Dehydroepiandrosterone sulfate

Clinical hyperandrogenism

- Isolated mild hirsutism should not be considered clinical evidence of hyperandrogenism in the early postmenarcheal years when it may be in a developmental phase (level C).
- Moderate-to-severe hirsutism constitutes clinical evidence of hyperandrogenism (level B).

- Hair growth varies from population of one ethnicity to the other. One approach to defining hirsutism is using a modified Ferriman-Gallwey (FG) score above the 95th percentile for the given population.
- Alopecia-frontal balding and anterior hairline recession may be seen, generally in more severe cases of androgen excess.
- Girls with acne that is persistent and poorly responsive to topical dermatologic therapy should be evaluated for the presence of hyperandrogenemia before initiation of any medical therapies (level C).

Hyperandrogenism



Biochemical hyperandrogenism

Hyperandrogenemia needs to be defined based on the detailed characteristics of the testosterone assay used (level A).

- Biochemical evidence of hyperandrogenism, is indicated by persistent elevation of serum total and/or free testosterone levels and determined in a reliable reference laboratory, provides the clearest support for the presence of hyperandrogenism in an adolescent girl with symptoms of PCOS (level B).
    - o A single androgen level >2 SD above the mean for the specific assay should not be considered to be evidence of hyperandrogenism in an otherwise asymptomatic adolescent girl (level C).
    - o Most patients with PCOS have serum testosterone concentrations 29 to 150 ng/dL (1.0 to 5.2 nmol/L). A total testosterone >200 ng/dL (6.9 nmol/L) increases the likelihood of a virilizing neoplasm.
- DHEAS elevation is the functional adrenal hyperandrogenism of PCOS, the main purpose of measuring DHEAS levels is to rapidly identify an unusual virilizing adrenal disorder.
- Early morning 17 OH progesterone – is also important to obtain the sample when the patient is amenorrheic, or within the first 10 days after the start of a

menstrual cycle in regularly cycling patients because 17-OHP rises during the preovulatory and luteal phases of the cycle.

- SHBG is a surrogate marker for insulin resistance.

References:

1. Witchel SF, Oberfield S, Rosenfield RL, *et al*. The diagnosis of polycystic ovary syndrome during adolescence. *Horm. Res. Paediatr.* 2015;83:376–389.
2. Rosenfiled RL. Diagnostic evaluation of polycystic ovary syndrome in adolescents. Available at www.uptodate.com

PCOS and Menstrual Irregularities in Adolescence

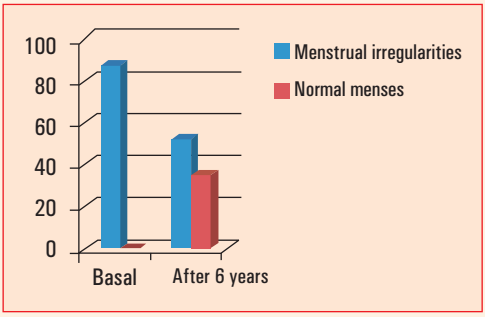
Regular cycle (58)	Irregular (50)	Oligomenorrhea (29)
PCO 9%	PCO 28%	PCO 45%

Reference:

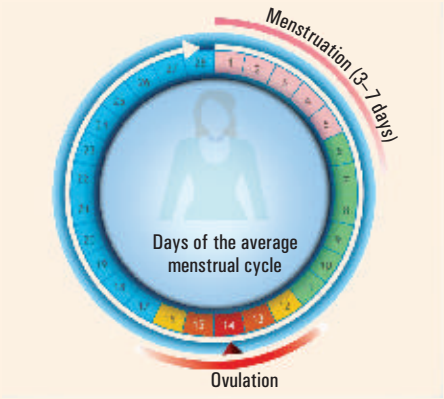
1. van Hooff MHA, Voorhorst FJ , Kaptein MBH, *et al*. Polycystic ovaries in adolescents and the relationship with menstrual cycle patterns, luteinizing hormone, androgens, and insulin. *Fertil and Steril.* 2000; 74(1)49–58.

Menstrual Irregularities Vs. Normal Menses

- Usually the girls with PCOS tend to have late onset of menarche
- Later the onset of menarche, the longer it will take to have regular menses
  - o < 11 years: 14% took > 5 years
  - o 17 years: 33% took > 5 years



Regular Normal Menstrual Cycle



Criteria for menstrual irregularity among adolescents

- The majority of adolescents establish a menstrual interval of 20–45 days within the first 2 years after menarche. Menstrual intervals persistently shorter than 20 days or greater than 45 days in individuals 2 or more years after menarche are evidence of oligo-anovulation (level B).
- A menstrual interval greater than 90 days is unusual even in the first year after menarche. As such, consecutive menstrual intervals greater than 90 days are rare and require further investigation regardless of years after menarche (level B).
- Lack of onset of menses by age 15 years or by more than 2–3 years after thelarche regardless of chronological age is statistically uncommon and warrants evaluation and consideration of diagnosis such as PCOS (level B).

Reference:

1. Witchel SF, Oberfield S, Rosenfield RL, *et al*. The diagnosis of polycystic ovary syndrome during adolescence. *Horm. Res. Paediatr*. 2015; 83:376–389.

PCOS: Young vs. Adult

Adult PCOS criteria cannot be used for young patients because:

- Adolescents have functional ovarian cysts as normal sonographic findings
- Maximum ovarian volume occurs in adolescence
- Transabdominal sonography is inaccurate
- Anovulatory and/or irregular periods occur in ~40% of girls until about 2–3 years following menarche
- Clinical evidence of androgen excess (acne) is common during puberty and resolves over time[1]

Important points when dealing with adolescents:

- Although obesity, insulin resistance and hyperinsulinemia are common findings in adolescents with hyperandrogenism, these features should not be used to diagnose PCOS among adolescent girls[2]
- Other disorders associated with irregular menses or hyperandrogenism need to be excluded from diagnostic consideration[2]

- The overlap between normal pubertal development and characteristic features of PCOS may complicate an accurate diagnosis of PCOS among adolescent girls.
- Some points that may suggest PCOS in young patients are:
  - Persistence of ovulatory dysfunction 2–3 years after menarche
  - Rapid progression and exacerbation of hyperandrogenism at menarche
- Great caution should be taken before diagnosing PCOS in adolescent girls with clinical features of androgen excess such as hirsutism and biochemical hyperandrogenism if oligomenorrhea has not persisted for more than 2 years. These patients can be considered at risk of PCOS.[2]

Challenges with the Use of Different Criteria in PCOS in Adolescents

Challenges with use of broad criteria-	• Several features may be in evolution, or only be transitory during the transition to adulthood • All Rotterdam criteria may be transient during adolescence • AES PCOS criteria more adapt but need to be modified to be specific
Prematurely assigning an adolscent with diagnosis of PCOS	• May be incorrect • May result in unnecessary treatments • May worsen psychological distress as PCOS is associated with the disorders and therapies involving body image

- The challenges with use of broad criteria are ongoing evolution of these features during adolescence/transient presence of these symptoms and signs during adolescence.
- On the other hand, prematurely assigning an adolescent with PCOS may not only be incorrect, but it would also add to the psychological burden and lead to unnecessary treatments.

References:

1. Speise PW. PCOS in the Adolescent and Young Adult: Diagnosis, Treatment & Implications. Cohen Children's Medical Ctr of NY. Available at: http://am2015.aace.com/presentations/Friday/F11/PCOSInTheAdolescentAndYoungAdultDiagnosisTreatmentAndImplictaions.pdf. Last accessed on: 26th April 2017.
2. Witchel SF, Oberfield S, Rosenfield RL, *et al*. The diagnosis of polycystic ovary syndrome during adolescence. *Horm. Res. Paediatr*. 2015.

Precautions During Diagnosis of PCOS in Adolescence

- Aim is to facilitate timely diagnosis while preventing over diagnosis and unnecessary treatment in otherwise healthy normal pubertal girls (level C)
- It should be kept in mind that the overlap between normal pubertal development and characteristic features of PCOS confound an accurate diagnosis of PCOS in adolescence (level A)
- Other disorders associated with irregular menses or hyperandrogenism must be excluded (level A)
- Presence of clinical features of androgen excess such as hirsutism and biochemical hyperandrogenism in absence of oligomenorrhea of more than 2 years is not diagnosed PCOS but considered to be at risk for PCOS

Diagnostic Recommendations for PCOS in Adolescence

- To avoid misdiagnosing physiological pubertal changes as PCOS, deferred diagnostic labelling accompanied by frequent longitudinal re-evaluations of these girls who are considered to be "at risk for PCOS" is beneficial and prudent during adolescence (level C)
- Despite no definitive diagnosis or approved therapy for PCOS in adolescence, treat the symptoms to decrease the risk for subsequent associated co-morbidities (level B)
- Although obesity, insulin resistance, and hyperinsulinemia are common findings in adolescents with hyperandrogenism they are not considered for diagnosis in this group (level A)

- Even in the absence of a definitive diagnosis and the lack of an approved therapy for PCOS in adolescence, treatment options that both alleviate the current symptoms and decrease the risk for subsequent associated co-morbidities are recommended (level B).
- Although obesity, insulin resistance, and hyperinsulinemia are common findings in adolescents with hyperandrogenism, these features should not be used due to diagnose PCOS among adolescent girls (level A).
- Prospective longitudinal research studies will be helpful to understand the natural history for girls considered to be at risk for PCOS. Research evaluating long-term interventions using high-quality RCTs and follow-up of girls with PCOS diagnosed during adolescence would be ideal.
- Through such research studies, it is hoped that validated diagnostic criteria supported by robust clinical and hormonal findings can be established to facilitate timely diagnosis while preventing over diagnosis and unnecessary treatment in otherwise healthy normal pubertal girls (level C).

Reference:

1. Witchel SF, Oberfield S, Rosenfield RL, *et al*. The diagnosis of polycystic ovary syndrome during adolescence. *Horm. Res. Paediatr*. 2015;83:376–389 .

Anti-Mullerian Hormone (AMH)

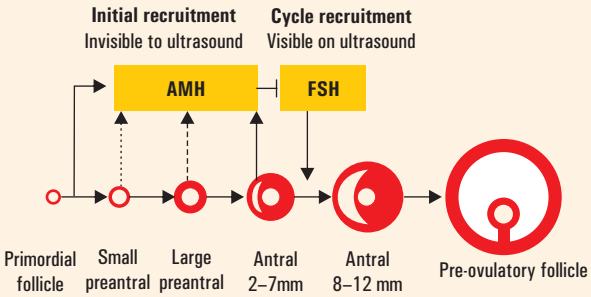
Not a biomarker for diagnosis of PCOS in adolescence

- AMH is related to oligo- or amenorrhoea in adolescence
- AMH is not a good marker for metabolic factors
- AMH measurement lacks international standardization
- High cut-off value of AMH predicts adolescents that are likely to develop PCOS in adulthood. Has good sensitivity but low specificity
- AMH is not an ideal diagnostic marker
- Its routine use in clinical practice currently is not recommended

- AMH is related to oligo- or amenorrhoea in adolescence but it is not a good marker for metabolic factors.
- AMH measurement lacks international standardization and therefore the concentrations and cut-off points are method dependent.
- Using a high enough cut-off value of AMH to predict which adolescents are likely to develop PCOS in adulthood could help to manage the condition from an early age due to a good sensitivity.
- However, because of its low specificity, it is not an ideal diagnostic marker, its routine use in clinical practice cannot, at present, be recommended.[1]

Anti-Mullerian Hormone (AMH) (contd...)

AMH is secreted by early growing follicles



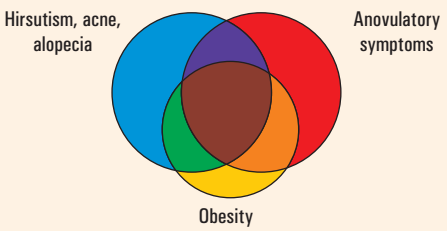
AMH: Anti-mullerian hormone; FSH: Follicle stimulating hormone

Reference:

1. Pinola P, Morin- Papunen LC, Bloigu A, *et al*. Anti-Müllerian hormone: correlation with testosterone and oligo- or amenorrhoea in female adolescence in a population-based cohort study. *Hum. Reprod*. 2014;29(10):2317–2325.

Clinical Presentation of PCOS in Adolescence

Clinical feature	%
Menstrual irregularities	30 %
Androgen excess	60 %
Overweight	84 %
IGT or T2DM	9%
Infertility	Rarely an issue



IGT: Impaired glucose tolerance; T2DM: Type 2 diabetes mellitus

- The primary clinical features of PCOS in adolescence are overweight/ obesity, followed by hirsutism, acne, alopecia – signs of hirsutism and menstrual irregularity. [1]
- Insulin and leptin levels are higher among overweight and obese children, which reflect insulin and leptin-resistance. [2]
- As discussed in module 1 abnormalities of leptin secretion predisposes to weight gain in adolescents with PCOS.
- Obese adolescents with PCOS have higher leptin and insulin resistance than thin adolescents with PCOS.
- Nine percent of PCOS population are diagnosed with impaired glucose tolerance (IGT) or T2DM[3]

References:

1. Bekx T, Connor EC and Allen DB. Characteristics of adolescents presenting to a multidisciplinary clinic for polycystic ovarian syndrome. *Journal of pediatric and adolescent gynecology*. 2010;23(1)7–10.
2. Bahrami E, Mirmoghtadaee P, Ardalan G, *et al*. Insulin and leptin levels in overweight and normal-weight Iranian adolescents: The CASPIAN-III study. *J. Res. Med. Sci*. 2014;19(5): 387–390.
3. Rosenfield RL, Ghai K, Ehrmann DA, *et al*. Diagnosis of the polycystic ovary syndrome in adolescence: Comparison of adolescent and adult hyperandrogenism. *Journal of Paediatrics' Endocrinology and Metabolism*. 2000;13(5):1285–1289.

Metabolic Risks of Adolescent PCOS

	PCOS (n = 114)	Controls (n = 41)	NHANES adolescents, 1999–2002
BMI $\geq 90^{th}$ percentile	38.6%	12.2%	15.7%
Blood pressure $\geq 90^{th}$ percentile	29.8%	12.2%	7.5%
LDL $\geq$ 130mg/dL	14.9%	0%	6.8%
Triglycerides $\geq$ 150 mg/dL	15.8%	7.3%	21%
HDL $\leq$ mg/dL	12.3%	9.8%	18%
Metabolic syndrome (Cook's criteria)	8.8%	2.4%	5.3%

BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; NHANES: National Health and Nutrition Examination Survey

- Metabolic syndrome is a cluster of adverse cardiovascular features including central obesity, atherogenic dyslipidemia, insulin resistance, a prothrombotic state, elevated blood pressure, and increased circulating proinflammatory markers.

- Metabolic abnormalities in the PCOS group were compared to adolescent controls and to National Health and Nutrition Examination Survey (NHANES) adolescent data.
- Using AE-PCOS criteria, 65% of a referral group of adolescents had PCOS.
- The risk of metabolic abnormalities was significantly different between adolescents with and without PCOS, emphasizing the importance of accurate diagnosis.
- Screening all PCOS adolescents for metabolic risk is essential to decrease associated long-term co-morbidities. [1]

Reference:

1. Roe AH, Prochaska EC and Dokras A. Early and accurate diagnosis of polycystic ovary syndrome (PCOS) in adolescents is essential to detecting metabolic abnormalities in this high-risk population. *Fertil. Steril*. 2011;96(3):S92.

Testing in Adolescents Presenting with PCOS-Like Symptoms

- Thyroid stimulating hormone (TSH)
- Prolactin
- Total and free testosterone DHEAS 17OH progesterone
- Ultrasound of ovaries (not essential if other two criteria are met)
- FSH, LH, E2 (in amenorrheic adolescents)

Once PCOS has been confirmed

- Fasting and 2-hour GTT
- Lipid panel
- Fasting insulin

DHEAS: Dehydroepiandrosterone sulfate; GTT: Glucose tolerance test

The work-up includes both laboratory and ultrasound testing as described below.

Investigations in PCOS[1]

Investigation		Remarks
Ultrasonography	Antral follicle count Ovarian volume	• Not recommended in adolescents • Primary purpose of ultrasonography in the hyperandrogenemic adolescent is to exclude causes other than PCOS
Androgens • DHEAS • Total testosterone • Free testosterone • FAI	Elevated	Elevated serum free testosterone is the single most sensitive test to establish the presence of hyperandrogenaemia
17OH progesterone	Decreased	This is a good screening test for non-classical congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency
SHBG	Decreased	The combination of an upper-normal total testosterone and a lower-normal SHBG yields a high free testosterone concentration
Serum prolactin	Elevated	• Hyperprolactinemia • Prolactin elevation is unusual in PCOS
Serum cortisol	Elevated	If Cushing associated
Serum FSH	Normal or decreased	May be normal or lower
LH	Elevated	Both pulse and amplitude
LH/FSH ratio	Elevated	
AMH	Elevated	Hyperandrogenism
OGTT, IR and lipid profile	Deranged	Hyperinsulinism, T2DM, dyslipidemia
TSH	Elevated	Hypothyroidism associated with PCOS

DHEAS: Dehydroepiandrosterone sulfate; FAI: Free androgen excess; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; AMH: Anti-mullerian hormone; OGTT: Oral glucose tolerance test; IR: Insulin resistance; TSH: Thyroid stimulating hormone; T2DM: Type 2 diabetes mellitus

Reference:

1. Rosenfield RL. Diagnostic evaluation of polycystic ovary syndrome in adolescents. Available at : www.uptodate.com.

Diagnostic Criteria for Metabolic Syndrome in Adolescents ≤ 16 years

IDF consensus group criteria for diagnosis of metabolic syndrome among girls > 10 years ≤ 16 years of age		
Blood glucose	> 100 mg/dL	≥ 5.6 mmol/L
High density lipoprotein-cholesterol	< 40 mg/dL	< 1.03 mmol/L
Triglycerides	≥ 150 mg/dL	≥ 1.7 mmol/L
Obesity	≥ 90th percentile or adult cut-off if lower	
Blood pressure 90th percentile for age and sex	Systolic ≥ 130/diastolic ≥ 85 mmHg	

Diagnostic Criteria for Metabolic Syndrome in Adolescents >16 years

IDF consensus group criteria for diagnosis of metabolic syndrome among women > 16 years of age is same as criteria for adults		
Blood glucose	> 100 mg/dL	≥ 5.6 mmol/L
High density lipoprotein-cholesterol	< 50 mg/dL	< 1.29 mmol/L
Triglycerides	≥ 150 mg/dL	≥ 1.7 mmol/L
Obesity	≥ 80 cm for European women, ethnicity specific values for others	
Blood pressure 90th percentile for age and sex	Systolic ≥ 130/diastolic ≥ 85 mmHg	

The IDF consensus definition of metabolic syndrome in adolescents is given here. Once the diagnosis of PCOS has been established in an adolescent girl, she should be screened for metabolic abnormalities[1]

Reference:

1. International Diabetes Federation Consensus group. The IDF consensus definition of metabolic syndrome in children and adolescents, Pediatric Diabetes, 2007.

Management of PCOS in Adolescence

Providing psychological support

Treating symptoms

Treating insulin resistance

Integrated, individualized, comprehensive, scientifically designed, multifaceted approach to address all aspects of adolescent PCOS

Cognitive behavioral therapy → Exercise plan → Nutrition plan and diet → Addiction awareness plan

Addiction awareness plan → Nutraceutical complementary and pharmaceutical agents

Nutraceutical complementary and pharmaceutical agents → Bariatric surgery → Weekly support and reinforce

Table 3: Management plan for PCOS in adolescents

Assessment history	Cognitive behavioural assessment	Dietary counselling	Exercise	Pharmacotherapy and surgery	Regular review
• BMI and WHR to determine degree and distribution of fat • Hormone LH and androgen, glucose and lipid profile • USG • If obese assess and treat obesity and related co-morbidities	• Screen for depression, mood and eating disorders • Assess mental barriers and readiness to change • Devise lifestyle modification strategies with patient and family • Tackle addiction smoking, alcohol, caffeine, food	• Low GI and calorie restricted food • Aim is to achieve weight loss of 5–10% of body weight over 6 months 	• Daily moderate exercise for 30 minutes or more to high intensity for 60 minutes	• Antiandrogens • Metformin • Orlistat • Bariatric surgery 	• Reinforce goals for weight loss • Maintenance of discipline • Prevent weight regain

BMI: Body mass index; WHR: Waist hip ratio; LH: Luteininzing hormone; GI: Glycemic index

Psychological Intervention

- Psychological counseling both individually and in group should be provided
- Psychological intervention is necessary for the following problems:
  - Behavioral problems
  - Abnormal eating patterns (21% vs. 2.5%)
  - Damaged self confidence due to acne, hirsutism and obesity
  - Increased level of anxiety and depression

Psychological intervention forms the main stay of the treatment and is the first step in the management of PCOS in adolescence.

Lifestyle Intervention: Diet and Exercise

- Diet and exercise are important and must be recommended early in management of PCOS
- Weight loss of only 5% of total body weight is associated with:
  - Decreased insulin and LH levels
  - Increased SHBG and decreased free E2
  - Improved menstrual function
  - Reduced hirsutism and acne
  - Lower testosterone levels
  - Improved cardiovascular risk factors including blood pressure

Weight loss due to lifestyle intervention is effective to treat menstrual irregularities, normalize androgens, and improve cardiovascular risk factors and intima media thickness which is associated with changes in blood pressure in obese adolescent girls with PCOS.

Reference:

1. Lass N, Kleber M, Winkel K, *et al*. Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. *J. Clin. Endocrinol. Metab*. 2011;96 (11): 3533–3540.

Treating Symptoms

- Treatment for PCOS in adolescents is primarily directed at the major clinical manifestations, which are:
  - Abnormal uterine bleeding
  - Cutaneous hyperandrogenism
  - Obesity and insulin resistance

The objective of treatment for PCOS in adolescence is management of clinical manifestations, which are:

- Abnormal uterine bleeding that is associated with menstrual irregularity or excessive bleeding
- Cutaneous hyperandrogenism which may manifest as primarily hirsutism and persistent acne
- Obesity and insulin resistance are frequent association among PCOS patients[1]

Reference:

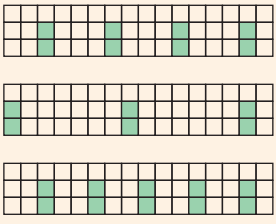
1. Rosenfield RL. The diagnosis of polycystic ovary syndrome in adolescents. *Paediatrics*. 2015; 136:1154.

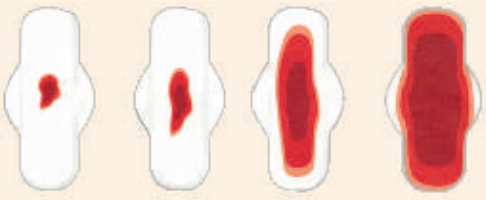
Abnormal Uterine Bleeding (AUB) – Menstrual Irregularity or Excessive Bleeding

Type of AUB	Definition
Primary amenorrhea	Lack of menarche by 15 years of age or by three years after the onset of breast development.
Secondary amenorrhea	More than 90 days without a menstrual period, after previously menstruating.
Oligomenorrhea (infrequent AUB)	• Post-menarcheal year one: Average cycle length > 90 days (fewer than four periods per year). • Post-menarcheal year two: Average cycle length > 60 days (fewer than six periods per year). • Post-menarcheal years three to five: Average cycle length > 45 days (fewer than eight periods per year). • Post-menarcheal year six and after: Average cycle length > 38 to 40 days (fewer than nine periods per year).
Excessive uterine bleeding	Bleeding more frequently than every 21 days or is heavy or prolonged (lasts more than seven days or soaks more than one pad or tampon every one to two hours).

Amount of Uterine Bleeding

Kaltenbach chart





Scant amount
Blood only on time when wiped or less than one-inch stain on maxi-pad

Light amount
Less than four-inch on maxi-pad within one hour

Moderate amount
Less than six-inch stain on maxi-pad within one-hour

Heavy amount
Saturated maxi-pad within one hour

Reference:

1. Rosenfield RL. The diagnosis of polycystic ovary syndrome in adolescents. *Paediatrics*. 2015; 136:1154.

Treatment of Abnormal Uterine Bleeding

Menstrual irregularity

- Treatment necessary for:
  - Reducing chronic anovulatory cycles which increase the risk of developing endometrial hyperplasia
  - Endometrial hyperplasia is associated with endometrial carcinoma
  - Treatment also necessary for psychosocial reasons
- Treated with combined oral contraceptives (COCs)
- Progestin is the critical ingredient in COCs that inhibits endometrial proliferation; it prevents the hyperplasia that results from unopposed estrogen action
- Progesterone, either synthetic progesterone or dydrogesterone are administered in the second half of the cycle

Excessive menstrual bleeding

- Anemia due to heavy uterine bleeding needs immediate attention
- COCs or progestin-only regimens are usually effective

- Several treatment options are available however the choice of therapy depends on the individual symptoms, goal for treatment, and preferences.
- Combination oral contraceptives (COCs) are the first-line treatment for adolescents who suffer the menstrual and cutaneous symptoms of PCOS, rather than other therapies (grade 2B). The progestin component inhibits endometrial proliferation, prevents hyperplasia and the associated risk of carcinoma.
- The estrogen component reduces excess androgen, which corrects menstrual abnormalities promptly and improves hirsutism and acne.
- For patients not keen to use COC, progestin only therapies may be considered.
- Treatment of anemia associated with heavy bleeding is necessary with appropriate supplements.

Reference:

1. Rosenfield Rl. Treatment of polycystic ovary syndrome in adolescents. Available at: www.uptodate.com

Cutaneous Hyperandrogenism

- More than 50% PCOS adolescents have hirsutism or acne vulgaris
- Cosmetic and dermatologic care is first step
- Medical endocrine therapy is indicated if the above fails
- The goal of hormonal therapy is to decrease the effect of excess androgens by:
  - o Reducing androgen production
  - o Reducing serum free androgen levels by increasing androgen binding to plasma-binding proteins
  - o Blocking androgen action at the level of target organs (e.g., hair follicle)

Classification of Drugs Used to Reduce Androgen Excess Based on Their Mode of Action

Androgen suppression	Antiandrogens	5 alpha reductase inhibitors	Insulin –lowering agent
• Oral contraceptive pills	• Cyproteroneacetate 100 mg/day	• Finasteride	• Metformin
• GnRH agonists	• Spironolactone		• Thiazolidinediones
• Ketoconazole	• Flutamide		• D chiro Inositol
• Glucocorticoids/ Dexa			

The use of insulin lowering agents for reducing androgen excess is not quite clear yet.

Medications Used to Treat Different Symptoms of Hyperandrogenism

Hirsutism	• Cosmetic measures (waxing, shaving, laser) • Oral contraceptives • Metformin • Antiandrogens • 5 alpha reductase inhibitors
Acne	• Antibiotic and topical therapies • Tetracycline, erythromycin and minocycline • Antiandrogen therapy • Topical non steroidal antiandrogen, oncoterone acetate, benzoyl peroxide, 13- cis retinoic acid (tretinoin)
Alopecia	• 2% Minoxidil with antiandrogen therapy

Cutaneous Hyperandrogenism: Treatment

COCs

- Lower serum free testosterone levels mainly by:
  - o Decreasing ovarian production via suppression of serum gonadotropin levels, and
  - o The estrogenic component increases SHBG levels
- Modestly lower DHEA-sulfate levels
- Treatment with COCs can be expected to arrest progression of hirsutism, reduce the need for shaving by half, and improves acne within 3 months

Antiandrogenic therapy

- Inhibits binding of androgen to its receptor
- Is indicated for patients with hirsutism that does not respond sufficiently to COC treatment and physical measures

- Oral contraceptive pills (OCPs) must be prescribed after taking necessary safety precautions to ensure no contraindications exist.
- In patients with severe hyperandrogenism OCPs containing Cyproterone acetate, that is one with antiandrogenic effect, may be considered.
- An effect of COCs on hirsutism can be seen after three to six months of therapy.

- For patients with substantial hirsutism who have an unsatisfactory response to initial treatment by cosmetic measures (such as shaving, bleaching, and depilatory agents) in combination with COCs, we suggest either physical hair reduction and/or antiandrogen therapy. The decision among these options involves patient preference, including cost of the measure, tolerance of discomfort/pain, risk of complications, and outcome.
- For patients who choose physical hair reduction, the choice of technique is dependent on the extensiveness of the area affected by hirsutism and patient preference, and includes electrolysis, and/or laser therapy.

Reference:

1. Rosenfield Rl. Treatment of polycystic ovary syndrome in adolescents. Available at: www.uptodate.com

Management of PCOS in Adolescents: Treating Insulin Resistance

- Reduction of insulin resistance improves ovulation moderately and hyperandrogenemia slightly
- First-line treatment: Diet and exercise
- For patients with impaired glucose tolerance: Metformin[1]
- For metabolic disorders: Myoinositol is safe and effective method
- Combination of Myoinositol and OCPs:
  - Antiandrogenic effects are enhanced
  - Negative impact of OCPs on weight gain is balanced
  - Metabolic profile is improved[2]

Insulin Resistance

- Treatments that reduce insulin resistance improve ovulation moderately and hyperandrogenemia slightly
- Diet and exercise are first-line treatment to address obesity and insulin resistance in adolescents with PCOS
- Metformin is appropriate for patients with impaired glucose tolerance[1]
- Administration of Myoinositol is a safe and effective method to prevent and correct metabolic disorders in teenagers affected by PCOS. With combination of Myoinositol and OCPs anti androgenic effects are enhanced, negative impact of OCPs on weight gain is balanced, and metabolic profile is improved[2]

References:

1. Tang T, Glanville J, Hayden CJ, *et al*. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. *Hum. Reprod*. 2006; 21:80.
2. Pkhaladze L, Barbakadze L and Kvashilava N. Myo-Inositol in the Treatment of Teenagers Affected by PCOS. *International Journal of Endocrinology*. Volume 2016, Article ID 1473612, 6 pages.

Guideline Recommendations for Metformin Use in PCOS

- Metformin is not the first line of treatment for;
  - Cutaneous manifestations
  - Prevention of pregnancy complications
  - Treatment of obesity
- It is recommended only for patients with T2DM or umpired glucose tolerance who fail lifestyle modification
- For women with PCOS with menstrual irregularity who cannot take or do not tolerate hormonal contraceptives Metformin may be used as second-line therapy

- The Endocrine Society task force advises against the use of Metformin as a first-line PCOS treatment.
- Metformin is recommended for women with PCOS and T2DM or IGT who do not succeed with weight loss and exercise.
- Metformin is also recommended for women who cannot take hormonal contraceptives.

Reference:

1. Legro RS, Arslanian SA, Ehrmann DA, *et al*. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol. Metab*. 2013;98 (12):4565-4592.

Myoinositol in PCOS

- Use of Myoinositol in PCOS was associated with controlling of metabolic parameters, glucose, C-peptide,insulin, HOMA-IR, slight decrease in androgens and weight reduction.
- Myoinositol can prevent developing of serious metabolic disturbances in adolescents with PCOS in future.

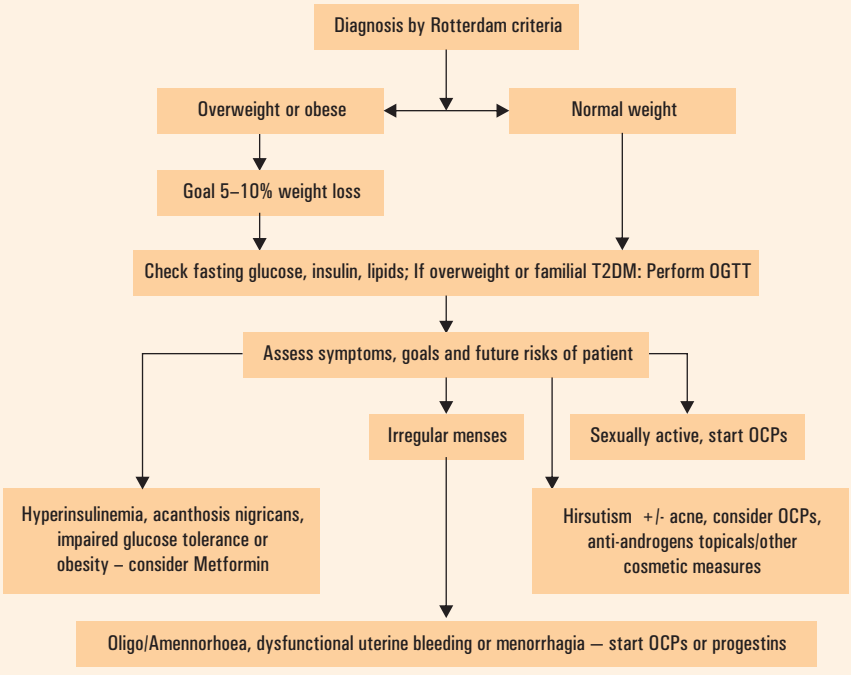
HOMA-IR: Homeostatic model assessment-insulin resistance

- The guideline recommendations for use of inositol vary.
- Myoinositol may have a role in metabolic syndrome associated with PCOS.
- However, further longitudinal studies among Indian population are necessary to understand its use and indications in adolescent PCOS.

Reference:

1. Pkhaladze L, Barbakadze L, and Kvashilava N. Myo-Inositol in the Treatment of Teenagers Affected by PCOS. *International Journal of Endocrinology*. 2016, Article ID 1473612, 6 pages.

Summary of Management of PCOS in Adolescence



T2DM: Type 2 diabetes mellitus; OGTT: Oral glucose tolerance test; OCP: Oral contraceptive pills

Reference:

1. Hassan A and Gordon CM. Polycystic ovary syndrome update in adolescence. *Current Opinion in Pediatrics*. 2007. 19;389-397

Conclusion

- PCOS is highly prevalent among adolescents
- It may present as late menarche/primary amenorrhea or in some cases as early menarche/oligomenorrhea and irregular bleeding
- Obesity in adolescent PCOS is associated with increased:
  - Insulin resistance leading to functional hyperandrogenism
  - Increase in ovarian and uterine volume and PCOM
  - Clinical manifestation in those with genetic or developmental predisposition
- Diagnosis of PCOS in adolescence is difficult due to overlap of clinical features with those of normal puberty
- The diagnostic criteria applicable in adults are not the same for adolescent girls
- Hyperandrogenemia and hyperinsulinemia may be the key features in PCOS with adolescence

Reference:

1. Hassan A and Gordon CM. Polycystic ovary syndrome update in adolescence. *Current Opinion in Pediatrics.* 200719, 389–397.

Key Points

- Adolescence corresponds roughly to the period between the ages of 10 and 19 years
- Obesity, insulin resistance, hyperinsulinemia and androgen excess are frequently seen among adolescents
- Prevalence of PCOS increases with increase in severity of obesity
- Weight loss is associated with improvement in symptoms of PCOS
- Enhanced insulin resistance and hyperinsulinemia during puberty may trigger PCOS manifestations in adolescents
- Insulin resistance accentuates hyperandrogenemia and metabolic dysfunction in these patients

Key Points (Contd...)

- The Pediatric Endocrine Society and the AE-PCOS laid down diagnostic criteria are the updated and most frequently utilized diagnostic criteria
- AMH is not considered as a biomarker for diagnosis of PCOS in adolescence
- Metabolically healthy and metabolically unhealthy obese are the two important phenotypes of PCOS in adolescence
- Work up of these patients must include tests for diagnosis, tests to evaluate the metabolic derangement and tests to rule out other causes of hyperandrogenemia and other clinical features associated with PCOS
- Treatment of PCOS includes treating the symptoms and treatment of insulin resistance
- COCs, antiandrogens, Metformin and Myoinositol are part of the pharmacological armamentarium of PCOS in adolescence

Suggested readings

1. Witchel SF, Oberfield S, Rosenfield RL, *et al*. The diagnosis of polycystic ovary syndrome during adolescence. *Horm. Res. Paediatr.* 2015;83:376–389.
2. Rosenfiled RL. Diagnostic evaluation of polycystic ovary syndrome in adolescents. Available at: www.uptodate.com
3. Bekx T, Connor EC and Allen DB. Characteristics of adolescents presenting to a multidisciplinary clinic for polycystic ovarian syndrome. *Journal of pediatric and adolescent gynecology*. 2010;23(1)7–10.
4. Roe AH, Prochaska EC and Dokras A. Early and accurate diagnosis of polycystic ovary syndrome (PCOS) in adolescents is essential to detecting metabolic abnormalities in this high-risk population. *Fertil. Steril*. 2011;96(3):S92.
5. Lass N, Kleber M, Winkel K, *et al*. Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. *J. Clin. Endocrinol. Metab*. 2011;96 (11): 3533–3540.

Adolescent PCOS: The Global Epidemic

POST-TEST

1. **Which of the statement is incorrect**
   a. Obesity is highly prevalent among adolescence
   b. Obesity is the cause of PCOS
   c. Loss of weight improves symptoms in PCOS
2. **How many of the Rotterdam criteria are necessary to make the diagnosis of PCOs in adolescent patient:**
   a. Any one is sufficient
   b. At least two out of three
   c. All three criteria must be present
3. **Unless the criteria are met for PCOS diagnosis, treatment is not necessary. Individual clinical manifestations do not need to be treated.**
   a. True
   b. False
4. **PCOS occurs due to:**
   a. Excessive carbohydrate intake
   b. Genetic predisposition
   c. Endocrine disrupting chemicals- toxins
   d. All the above
   e. None of the above
5. **Which is correct?**
   a. Isolated mild hirsutism is clinical evidence of hyperandrogenism in the early post menarche years
   b. Moderate-to-severe hirsutism constitutes clinical evidence of hyperandrogenism
   c. Treatment of acne is not necessary in adolescence
   d. All are incorrect
6. **PCOS should be considered when menstrual irregularity persists for:**
   a. ≥ 2 cycles
   b. ≥ 6 months
   c. ≥ 1 year
   d. ≥ 2 years

7. **Which of the following does not qualify as criteria for evidence of oligo-anovulation in adolescents:**

   a. Menarche in 2012, 60 days 6 cycles since Feb 2014–August 2017

   b. Menarche in 2013, 40 days cycle, since March 2014–June 2016

   c. No menarche at 16 years age

   d. Menarche in 2013, regular cycles: 30 days, 90 days 2–3 consecutive episodes every year since 2014

8. **Which of the following is true about polycystic ovarian morphology (PCOM):**

   a. Is a common finding among adolescent girls: 30–40% prevalence

   b. The ovarian volume starts to increase with the onset of puberty, and is maximum volume soon after menarche

   c. AE-PCOS taskforce suggested that PCOM should be defined as follicle number per ovary >24 using transvaginal ultrasound imaging

   d. All of the above

   e. None of the above

9. **15 year old girl, weighing 90 kg is 5 feet 2 inches tall, has blood glucose of 104 mg/dL and 45 days cycles since about 2 years. Her menarche was at the age of 11 years. On examination she has prominent facial hair and pigmented neck and underarms. You would advise her:**

   a. To start Metformin 250 mg/ day before meals

   b. Myoinositol daily

   c. Diet and exercise program

   d. All of the above

   e. None of the above

10. **Treatment with Myoinositol for PCOS in adolescence is expected to lead to:**

    a. Decrease in hyperinsulinemia

    b. Decrease in glucose levels

    c. Decrease in androgens

    d. Reduction in weight

    e. All the above

Answers: 1. c; 2. b; 3. b; 4. d; 5. b; 6. c; 7. b; 8. d; 9. d; 10. e

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