THE PCOS SOCIETY

PCOS TUTORIALS

A Post Graduate Certificate Course in PCOS Management

Module 1

PCOS: Background, Pathophysiology and Diagnosis

Brought to you by The PCOS Society (India)

THE PCOS SOCIETY INDIA

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Module I

PCOS: Background, Pathophysiology and Diagnosis

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Module Overview

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrinological disorder affecting women–the exact aetiology of PCOS is unknown. However, it is known to be a heterogeneous disorder resulting in androgen overproduction, primarily from the ovary, and is associated with insulin resistance (IR). PCOS has a complex pathogenesis and may be familial.

PCOS is a collection of signs and symptoms with no one single diagnostic test. The affected patients suffer from both reproductive and metabolic adverse effects. PCOS is seen to affect families and both female and male relatives may show stigmata of the syndrome, including metabolic abnormalities. The most common pathological characteristics include:

- Abnormal gonadotropin secretion
- Hyperandrogenemia
- IR with hyperinsulinism

The common symptoms of PCOS can range from menstrual disorders, infertility and hyperandrogenaemia to metabolic syndrome. PCOS diagnosis may imply an increased risk for infertility, abnormal uterine bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus (T2DM), dyslipidaemia, hypertension and other cardiovascular diseases (CVD).[1,2]

References:

1. Malik S, Jain K, Talwar P, *et al*. Management of Polycystic Ovary Syndrome in India. F*ertil. Sci. Res.* 2014;1:23–43.
2. Patil M. Pathophysiology of PCOS. The PCOS Society of India Newsletter. *PANDORA*. 2016;1:6–8.

Learning Objectives

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

- Epidemiology of PCOS
- Pathophysiology of PCOS
- Diagnosis of PCOS
- PCOS phenotypes
- Differential diagnosis of PCOS
- Investigations or laboratory work-up for PCOS

PCOS: Background, Pathophysiology and Diagnosis

PRE- TEST

Are the following statements True or False?

1. **Every patient with PCOS is overweight/ obese.**

   True

   False

2. **Mothers with PCOS has a high chance of passing it to their daughter**

   True

   False

3. **Whenever you see polycystic ovarian morphology on ultrasound it is PCOS.**

   True

   False

4. **Hyperandrogenism is seen in every case of PCOS**

   True

   False

5. **PCOS only affects the adolescent population.**

   True

   False

6. **Ultrasound is the only way to diagnose PCOS**

   True

   False

7. **Management of PCOS does not comprise of menstrual regulation alone**

   True

   False

8. **Framingham criteria are used for diagnosis of PCOS**

   True

   False

9. **Diagnostic criteria for PCOS are same for all age groups**

   True

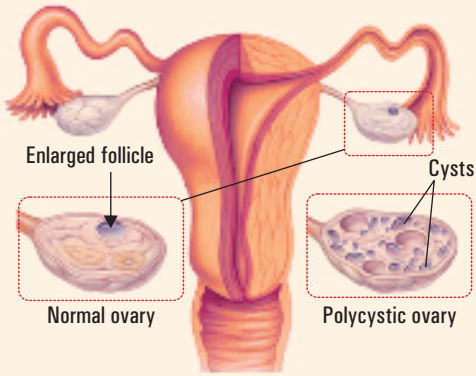
   False

10. **Hyperinsulinism is associated with PCOS**

    True

    False

PCOS - Module 1
Background, Pathophysiology and Diagnosis



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 PCOS.

PCOS Background

- PCOS is an endocrinological disorder with metabolic consequences that may be seen at puberty, during reproductive age or even after menopause
- The spectrum of this disorder may extend from menstrual irregularity, hirsutism and acne in adolescence
- This may continue in reproductive age wherein the main concern is anovulation which needs to be treated
- These patients need to be monitored for the effects of unopposed estrogen on endometrium which can cause endometrial hyperplasia- simple or complex and can even extend to endometrial cancer

PCOS - Prevalence

- Global prevalence estimates of PCOS- 2.2–26%; highly variable
- Limited studies in India
- Indian studies report a prevalence of 9.13–36%[1]
- The risk of developing T2DM is 10 times greater in PCOS patients[2]
- Associated environmental factors related to PCOS are:
  - Physical inactivity
  - Obesity
  - IR[2]

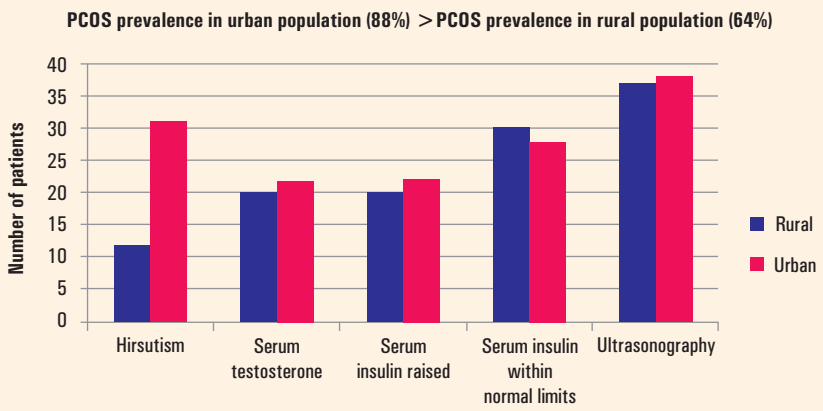
Indian study (2014) results: PCOS prevalence among 600 girls (15–24 years) was 22.5% by Rotterdam criteria and 10.7% by the AES criteria[1]

- PCOS shows a highly variable global prevalence ranging from 2.2–26%. Asian countries like China and Sri Lanka have reported a prevalence of from 2–7.5% and 6.3%, respectively
- There is a paucity of epidemiological studies around PCOS in India. However, the reported prevalence is estimated to be 9.13–36%, which is quite high
- The risk of developing type 2 diabetes mellitus (T2DM) is 10 times greater in PCOS patients. Physical inactivity, obesity and insulin resistance (IR) are the associated environmental factors associated with PCOS
- According to results of an Indian study (2014) prevalence of PCOS among 600 adolescent and young girls (15–24 years) was 22.5% by Rotterdam criteria and 10.7% by the AES criteria[1,2]

References:

1. Joshi B, Mukherjee S, Patil A, *et al*. A cross-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. *Indian Journal of Endocrinology and Metabolism*.2014;18(3):317–324.
2. Radha P, Devi RS, 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.

PCOS - Prevalence (India)



Rural-urban differences in PCOS[1]

- An Indian study was undertaken (2016) with the hypothesis that the burden of PCOS would be considerably lower among rural Indian adolescents compared to their urban counterparts
- Oligomenorrhoea, hirsutism and obesity was higher among the urban population as compared to their rural counterparts
- In this study, the rural participants diagnosed with PCOS had raised serum insulin levels in 40% of the cases compared to 44% in urban participants
- The study also concluded that the serum testosterone levels were raised in about 21% of total participants. The crude prevalence rate for PCOS as determined from the study was 20%[1]

References:

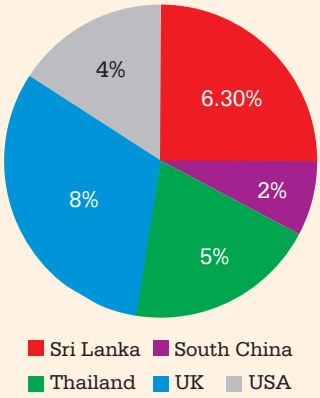
1. Radha P, Devi RS, Madhavi J. Comparative study of prevalence of polycystic ovarian syndrome in rural and urban population. *Journal of Advanced Medical and Dental Sciences Research*. 2016;4(2):90.

PCOS Pathophysiology

- PCOS is a multi-gene disorder with several environmental factors that interact to cause menstrual irregularity, insulin resistance and hyperandrogenism.
  - Menstrual irregularity is due to anovulatory cycles
  - Hyperinsulinism predisposes to higher incidence of metabolic syndrome, T2DM, hypertension and cardiovascular disorder
  - Hyperandrogenism manifests as hirsutism, acne and female balding

Genetic and Ethnic Variation of PCOS

- Japanese women are less hirsute with lower body mass index (BMI) but have comparable biochemical hyperandrogenism and IR than white Europeans
- Caribbean Hispanic women have greater IR than non-Hispanic Caucasians[1]
- Young South Asians with PCOS have higher chance of being centrally obese, and one third have metabolic syndrome not related to androgenic phenotype[2]
- South Asians and Mexican–Americans have a greater prevalence of PCOS[1]



Ethnic variation in the community prevalence of PCOS[1]

- There is a considerable ethnic variation in the PCOS phenotype
- It is important to understand the implications of ethnic variation on screening and diagnosis of PCOS
- The data pertaining to the genetic and ethnic variation of PCOS is mentioned above
- The pie chart shows the ethnic variation in the community prevalence of PCOS in different countries

References:

1. Wijeyaratne CN, Udayangani SAD, Balen AH. Ethnic-specific polycystic ovary syndrome epidemiology, significance and implications. *Expert. Rev. Endocrinol. Metab.* 2013;8(1):71–79.
2. Wijeyaratne CN, Seneviratne Rde A, Dahanayake S, *et al*. Phenotype and metabolic profile of South Asian women with polycystic ovary syndrome (PCOS): Results of a large database from a specialist Endocrine Clinic. *Hum. Reprod.* 2011 Jan;26(1):202–13.

Evidence of Genes Involved in PCOS

- Evidence for genetic contribution includes –
  - Well-documented familial clustering of PCOS
  - Increased prevalence of its components: hyperandrogenemia and T2DM in first-degree relatives of women with PCOS
  - High heritability seen in Dutch twin study[1]

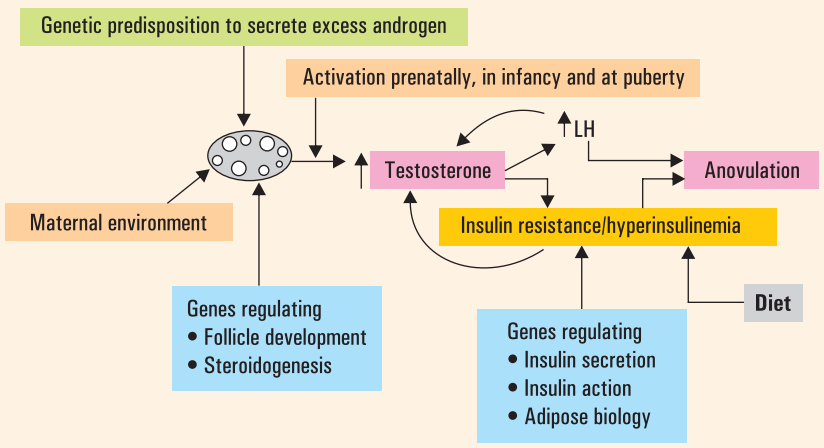
- However, the mode of heritance of PCOS is unclear, and both dominant and multi-genic modes of transmission have been proposed

- Genes with functions in TGF-β pathway, insulin signalling, and associated with T2DM and/or obesity have been investigated for association with PCOS
- The recent genetic approaches that are gaining popularity among PCOS researchers are –
  - o Genome-wide association studies (GWAS) and
  - o Next-generation sequencing (NGS)[2]
- Genetic polymorphism,associated phenotypes and GWAS are discussed in details in module 2.

References:

1. Vink JM, Sadrzadeh S, Lambalk CB, *et al*. Heritability of polycystic ovary syndrome in a Dutch twin-family study. *J. Clin. Endocrino .Metab*. 2006;91:2100–4.
2. Kosovo G and Urbanek M. Genetics of the polycystic ovary syndrome. *Mol. Cell. Endocrinol*. 2013 Jul 5; 373(0): 29–38.

Developmental Origin of PCOS



Proposed developmental origin of PCOS[1]

- It has been proposed that foetal ovary in PCOS is genetically predisposed to secrete higher than normal levels of androgen
- The androgen excess could manifest, and exert its effects, at one or more susceptible stages during development including foetal life, early infancy, or at the onset of puberty
- During fetal/intra uterine stage the alterations in the maternal-fetal environment likely program adult PCOS. These include-

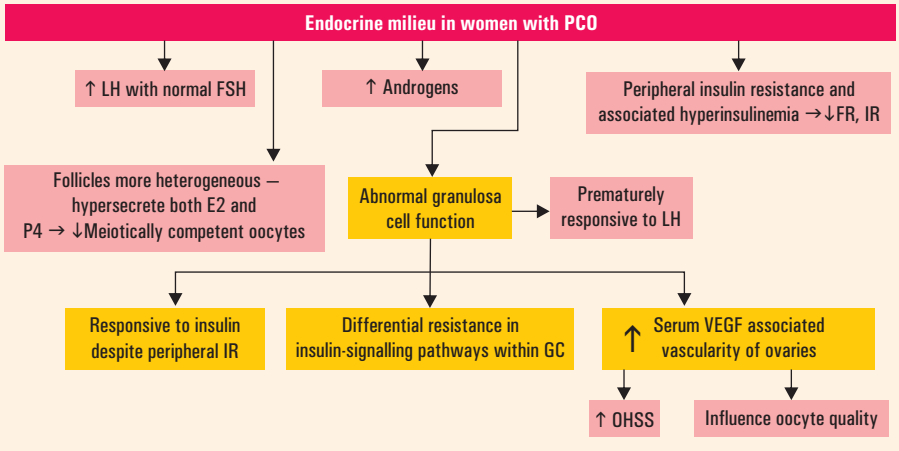
- Gestational diabetes in mother
- Human fetal androgen excess from congenital adrenal hyperplasia or virilising tumours[2]

- Once the process begins, the consequent hypersecretion of luteinising hormone (LH) and hyperinsulinemia may further amplify androgen production by ovarian theca cells, thus creating a vicious circle of events
- During childhood the exposure to excessive androgens can lead to precocious puberty, and polycystic ovarian morphology (PCOM), hyperandrogenism, insulin resistance and obesity
- As ageing continues these patients are predisposed to metabolic and endocrinological defects
- In addition, environmental factors, particularly dietary factors, would influence the clinical and biochemical abnormalities of PCOS

References:

1. Franks S and Berga SL. A debate: Does PCOS have developmental origins? *Fertil. Steril.* 2012;97(1): 2–6.
2. Dumesic DA, Goodarzi MO, Chazenbalk GD, *et al*. Intrauterine Environment and PCOS. *Semin Reprod Med*. 2014 May; 32(3): 159–165.

Metabolic and Endocrinological Defects in PCOS[1]



Pathophysiological events in PCOS[1]

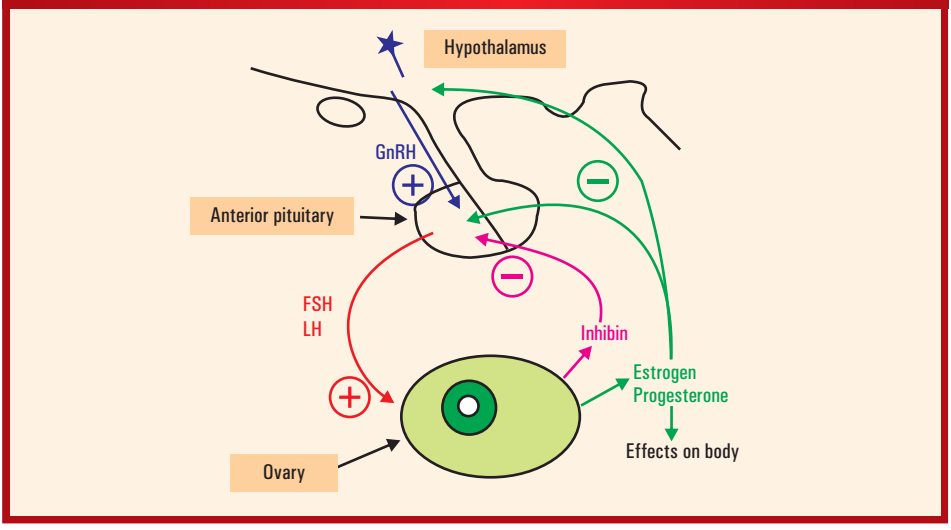
LH: Luteinising hormone; FSH: Follicle stimulating hormone; IR: Insulin resistance; E2: Estradiol; GC: Granulosa cells; OHSS: Ovarian hyperstimulation syndrome; VEGF: Vascular endothelial growth factor; P4: Progesterone

- LH levels increase while follicle stimulating hormone (FSH) is normal
- Ovaries hypersecrete E2
- Androgen levels increase
- Granulosa cell function is affected
- Peripheral insulin resistance and hyperinsulinemia occurs

References:

1. Patil M. Pathophysiology of PCOS. The PCOS Society of India Newsletter. *Pandora*. 2016;1:6–8.

Effect of Gonadotrophin Regulating Hormone (GnRH)



- Elevated LH levels was seen in 75 %
- Elevated LH : FSH ratio was seen in 94 %[1]
- Relatively low plasma FSH levels[2-4]
- Rapid GnRH pulse frequency was seen which signifies a failure of systems necessary to suppress GnRH pulsatility. This may be the result of primary hypothalamic defects, abnormal hormonal milieu or combination of the two
- Increased LH pulse amplitude[5]
- Exaggerated LH responses were seen with exogenous GnRH

Luteinising Hormone (LH) Dysregulation

LH dysregulation

Secondary to the peripheral events within the ovary

Abnormal secretion of ovarian androstenedione (ASD) an intrinsic property of PCOS Theca cells

↓

Uncoupling of hypothalamic E2 inhibition and E2 related sensitisation of pituitary LH release

↓

Increase in LH secretion

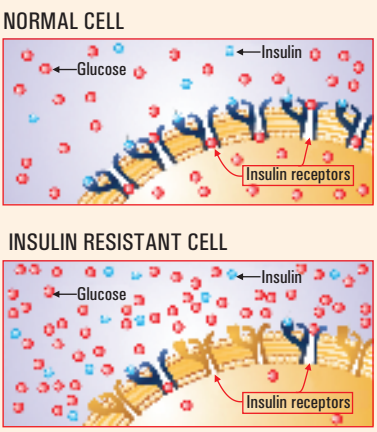
Obesity → Decreased ASD synthesis or Development of insulin resistance

Both of which decrease LH secretion independently of each other

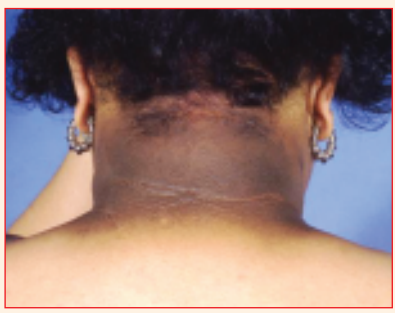
References:

1. Taylor AE, McCourt B, Martin KA, *et al*. Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 1997 Jul;82(7):2248–56.
2. Rebar R, Judd HL, Yen SS, *et al*. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. *J. Clin. Invest.* 1976 May;57(5):1320–9.
3. Hall JE, Taylor AE, Hayes FJ, *et al*. Insights into hypothalamic-pituitary dysfunction in polycystic ovary syndrome. *J. Endocrinol. Invest.* (1998) 21:602.
4. Marshall JC1, Eagleson CA. Neuroendocrine aspects of polycystic ovary syndrome. *Endocrinol. Metab. Clin. North. Am.* 1999 Jun;28(2):295–324.
5. Waldstreicher J, Santoro NF, Hall JE, *et al*. Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian disease: Indirect evidence for partial gonadotroph desensitization. *J. Clin. Endocrinol. Metab*. 1988; 66:165–172.

Pathophysiology of Insulin Resistance (IR)



Mechanism of IR



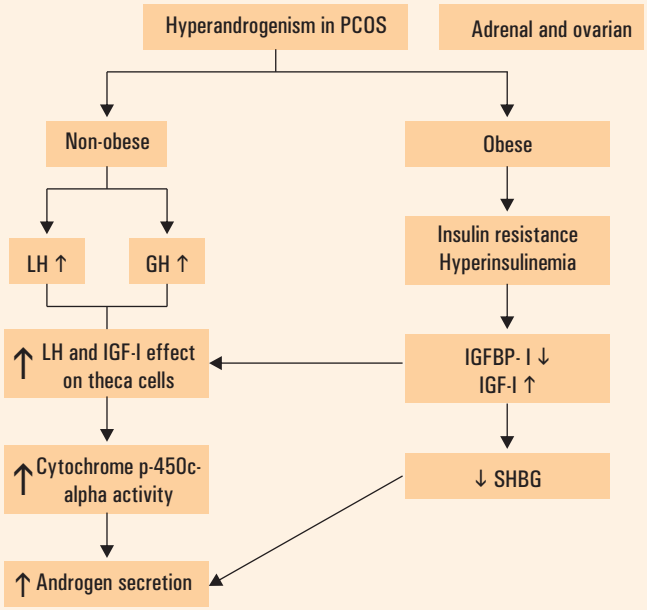
Acanthosis nigricans

- Insulin resistance probably plays a pathogenetic role in PCOS
- IR has higher incidence in people who are obese, irrespective of their ethnicity
- Functional IR is considered a consequence of defects in insulin-mediated glucose transport and signalling in adipocytes and myocytes which leads to dysregulation in adipokine production and signalling from adipose tissues
- The resulting hyperinsulinemia leads to insulin spill-over into other tissues, most commonly the skin
- Insulin acts via insulin-like growth factor receptors to cause excess keratinocyte growth, producing velvety skin patches known as acanthosis nigricans[1,2]

References:

1. Patil M. Pathophysiology of PCOS. The PCOS Society of India Newsletter. *Pandora*. 2016;1:6–8.
2. Basskind NE and Balen AH. Hypothalamic–pituitary, ovarian and adrenal contributions to polycystic ovary syndrome. *Clinical Obstetrics and Gynecology*. 2016;37:80–97.

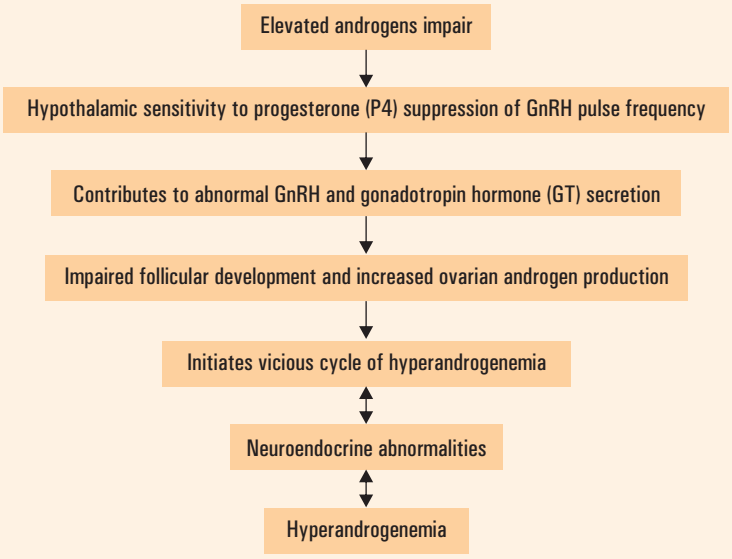
Hyperandrogenism in PCOS



GH: Gonadotropin hormone; IGF–I: Insulin-like growth factor 1; IGFBP: Insulin-like growth factor-binding protein; SHBG: Sex hormone-binding globulin

- Different mechanisms of hyperandrogenism occur in obese and non-obese. Hyperinsulinemia led reduction in SHBG affects the obese individuals while rise in LH affects theca cells and causes increased androgen secretion

Effect of Androgens on Follicle Development

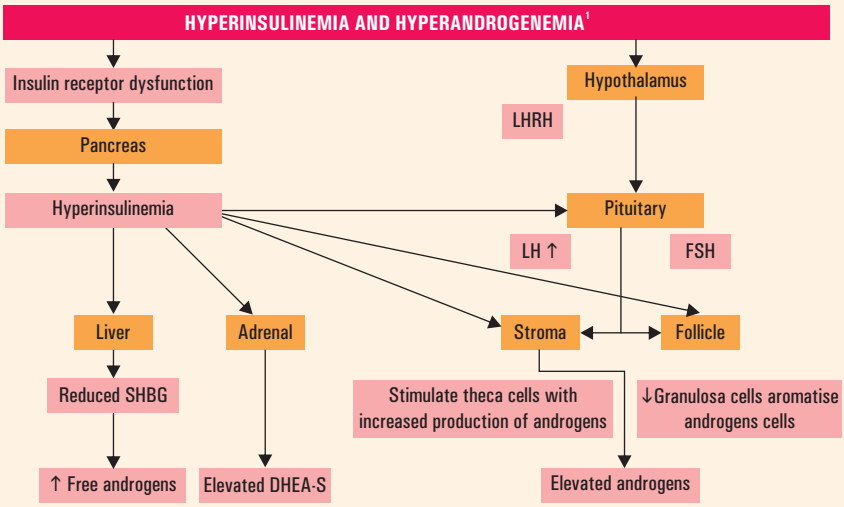


- Increase in androgens affect the follicular development and sets up the vicious cycle of hyperandrogenemia

References:

1. Insler V1, Shoham Z, Barash A, *et al*. Polycystic ovaries in non-obese and obese patients: possible pathophysiological mechanism based on new interpretation of facts and findings. *Hum. Reprod*. 1993 Mar;8(3):379–84.
2. Robert L. Rosenfield. Hyperandrogenism in Peripubertal Girls. *Pediatric Clinics of North America*. 1990;37(6): 1333–1358.
3. Carmina E1, Koyama T, Chang L, *et al*. Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? *Am. J. Obstet. Gynecol*. 1992 Dec; 167(6):1807–12.
4. Patil M. Pathophysiology of PCOS. The PCOS Society of India Newsletter. *Pandora*. 2016;1:6–8.

Hyperinsulinemia and Hyperandrogenemia



LHRH: Luteinising hormone-releasing hormone; DHEA-S: Dehydroepiandrosterone sulfate; LH: Luteinising hormone; FSH: Follicle stimulating hormone; SHBG: Sex hormone-binding globulin

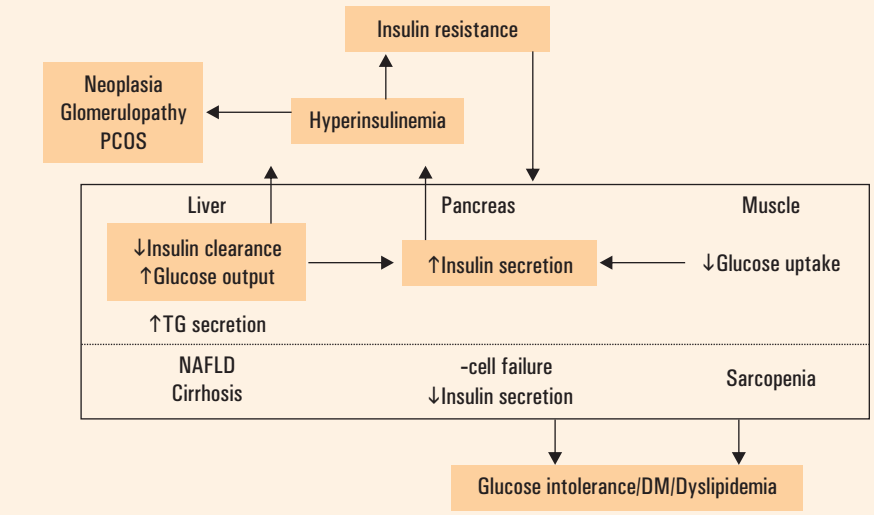
- Hyperandrogenemia inhibits production of hepatic sex hormone/steroid binding globulin (SHBG). Due to decreased SHBG in circulation, more androgens are left unbound and therefore produce a greater clinical response in terms of hirsutism, acne, and other manifestations of androgen excess. Hyperandrogenism can result in glucose intolerance and elevated levels of insulin
- It is a well known fact that hyperinsulinemia begets hyperandrogenism
- Insulin may increase androgen synthesis by various mechanisms:
  - Increasing ovarian androgen synthesis by interacting with its own receptor or with the receptor for insulin-like growth factor-1, thereby increasing P450c17-alpha enzyme activity
  - Insulin amplifies the luteinising hormone (LH) response of granulosa cells, thereby causing an abnormal differentiation of these cells with premature arrest of follicular growth thus causing anovulation. It may also change the ovarian response to LH
  - It also suppresses hepatic production of SHBG, which increases free testosterone levels
  - Insulin alters normal folliculogenesis by increasing intra-ovarian androgens

- Obesity is known to increase androgen, insulin and leptin levels, IR and risk of early pregnancy loss. Adipose tissue dysfunction may be a central factor in the pathogenesis of PCOS. There is a complex interaction between the pituitary gland, pancreas and ovary that results in a changed hormone secretion pattern[1]

References:

1. Patil M. Pathophysiology of PCOS. The PCOS Society of India Newsletter. *Pandora*. 2016;1:6–8.

Effects of Insulin Resistance



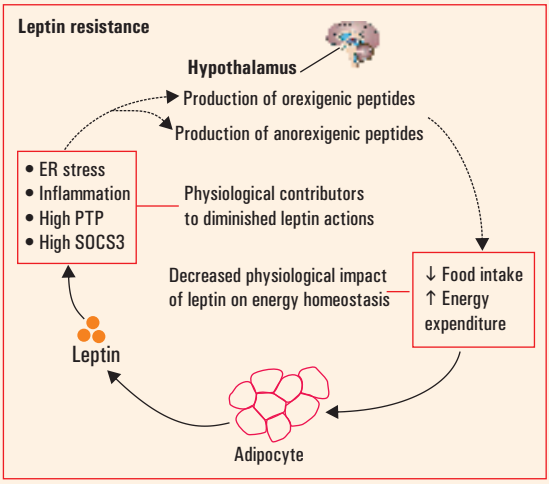
TG: Triglycerides; NAFLD: Non-alcoholic fatty liver disease; DM: Diabetes mellitus

- Insulin resistance and hyperinsulinemia affect the ovaries causing exaggerated response that leads to PCOS
- In liver, it decrease insulin clearance and increases glucose uptake
- In pancreas, insulin resistance leads to increased insulin secretion
- In muscles it causes decrease in glucose uptake resulting in sarcopenia
- IR is at the core of development of glucose intolerance, diabetes mellitus and dyslipidemia

References:

1. Castro AVB, Kolka CM, Kim SP, *et al*. Obesity, insulin resistance and comorbidities – Mechanisms of association. *Arq. Bras. Endocrinol. Metabol*. 2014 Aug; 58(6): 600–609.

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]

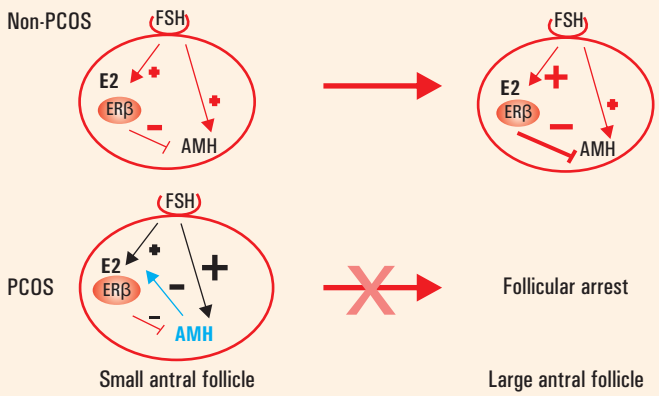
ER: Endoplasmic reticulum; PTP: Protein tyrosine phosphate; SOCS3: Suppressor of cytokine signaling 3; T:Testosterone; P4: Progesterone

- Leptin acts on specific neurons to increase the expression of anorexigenic peptides and reduces the expression of the orexigenic peptides
- This produces reduced appetite and increased energy expenditure, contributing to the maintenance of metabolic balance
- Under pathological conditions the actions of leptin are impaired leading to increased adipocyte mass and a positive trigger for even more leptin secretion by the fat tissues
- Abnormalities of leptin secretion predispose to weight gain in women with PCOS
- Leptin resistance is more common in insulin resistant states and overweight women rather than thin PCOS
- Obesity in women with PCOS results in anovulation as shown in the figure[1,2]

References:

1. St-Pierr J and Tremblay ML. Modulation of leptin resistance by protein tyrosine phosphatases. *Cell Metabolism*. 2012;15(3):292–297.
2. Patil M. Pathophysiology of PCOS. The PCOS Society of India Newsletter. *Pandora*. 2016;1:6–8.

Role of Anti-Müllerian Hormone (AMH) in PCOS



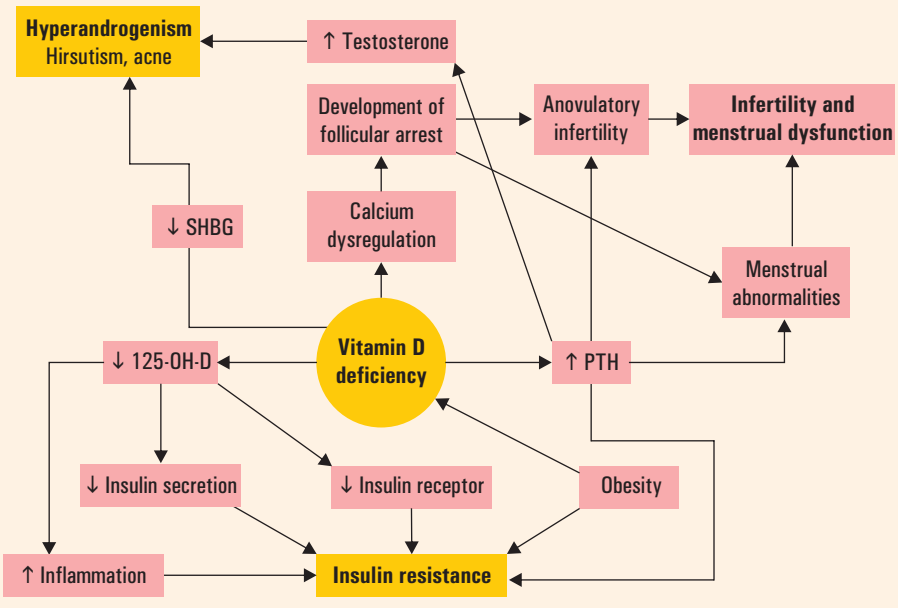
AMH regulation by FSH and E2 in granulosa cells of small and large antral follicles[1]

- Excessive ovarian production of AMH, secreted by growing follicles, is an important feature of PCOS
- Serum AMH concentration is strongly correlated with the number of growing follicles
- Up to the small antral stage, AMH secretion is stimulated by different factors like FSH
- Estradiol (E2) production under the influence of FSH is impaired by the inhibiting effect of AMH on aromatase
- When estradiol concentration reaches a certain threshold in large antral follicles, it is capable of completely inhibiting AMH expression through ERβ, thus overcoming the stimulation by FSH
- In PCOS, the lack of FSH-induced E2 production and the high level of AMH impair the shift from the AMH to the E2 tone, causing follicular arrest[1]

References:

1. Dumont A, Robin G, Catteau-Jonard S, *et al*. Role of Anti-Müllerian Hormone in pathophysiology, diagnosis and treatment of polycystic ovary syndrome: a review. *Reproductive Biology and Endocrinology*. 2015;13:137.

Role of Vitamin D in PCOS



Role of vitamin D in the pathogenesis of PCOS[1]

SHBG: Sex hormone-binding globulin; 125-OH-D: Dihydroxy vitamin D; PTH: Parathyroid hormone

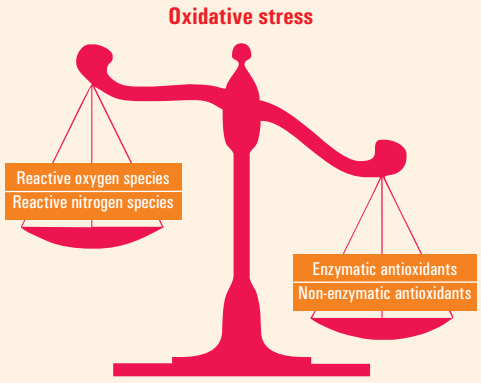
- The effects of Vitamin D in the pathogenesis of PCOS are mediated via both genetic and cellular pathways
- Vitamin D regulates gene transcription through nuclear vitamin D receptors (VDR) that are present in various body tissues
- The pathogenesis of PCOS has been linked to the effects of VDRs on LH and SHBG levels, testosterone levels, insulin resistance and serum insulin levels
- The combination of vitamin D deficiency and dietary calcium insufficiency (because serum calcium regulates parathyroid hormone [PTH] release) may be largely responsible for the menstrual abnormalities associated with PCOS
- Vitamin D regulates oestrogen biosynthesis through direct regulation of the expression of the aromatase gene and by maintaining extracellular calcium homoeostasis
- Vitamin D enhances insulin action by its synthesis and release, increasing insulin receptor expression or suppression of pro-inflammatory cytokines that are believed to mediate insulin resistance
- In addition, Vitamin D may also mediate insulin sensitivity by improving calcium status, increasing local production of 25-OH-D, which leads to

transcriptional regulation of specific genes or suppressing serum levels of PTH. It is important to note that Vitamin D levels are associated with IR[1]

References:

1. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. *Clinical Endocrinology*. 2012;77:343–350.

Role of Oxidative Stress in PCOS



Oxidative stress seems to be involved in altered steroidogenesis in the ovaries leading to:

- Increased androgen production
- Disturbed follicular development
- Infertility[1,2]

- Oxidative stress refers to an imbalance caused by excessive formation of oxidants in the presence of limited antioxidant defenses
- In addition to hormonal derangements, insulin signalling defects and adipose tissue dysfunction; oxidative stress, has been actively implicated in causation of PCOS
- Oxidative stress, along with other aetiological factors and environmental factors, leads to an adverse redox status[1]
- Antioxidants scavenge excess reactive oxygen species (ROS) to counteract potential for significant cell damage caused by excess ROS

References:

1. Papalou O, Victor VM, Diamanti-Kandarakis E. Oxidative stress in polycystic ovary syndrome. *Curr. Pharm. Des.* 2016;22(18):2709–22.
2. Lee JY, Baw C-K, Gupta S, *et al*. Role of oxidative stress in polycystic ovary syndrome. *Current Women's Health Reviews*. 2010;6:96–107.

Circulating Markers of Oxidative Stress

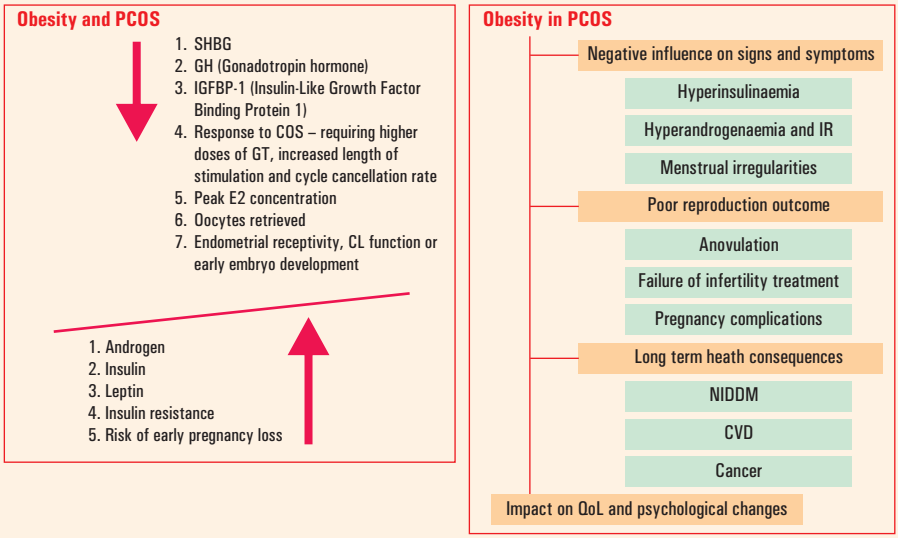
Promoters and by-products of oxidative stress		
Homocysteine	Promotes reactive species	↑
Asymmetric dimethylarginine	Promotes reactive species	↑
Malondialdehyde	End product of lipid peroxidation	↑
Nitric oxide	Promotes reactive nitrogen ↔ species	
Antioxidants		
Glutathione	Detoxifies hydrogen peroxide and lipid peroxides, prevents proteins from oxidation	↓
Paraoxonase-1	Prevents oxidation of lipoproteins by reactive species	↓
Superoxide dismutase activity (SOD)	Converts superoxide anions to hydrogen peroxide and molecular oxygen	↑
Glutathione peroxidase	Detoxifies hydrogen peroxide, peroxynitrites and lipid peroxide	↔
Total antioxidant capacity	Prevents oxidation and ↔ detoxifies	↔

- Circulating markers in women with PCOS are abnormal
- They are independent of weight excess
- They may contribute in the pathophysiology of PCOS
- Routine measurement of markers of oxidative stress nor the use of anti-oxidant therapies is recommended in PCOS

References:

1. Murri M, Luque Ramirez M, *et al*. Circulating markers of oxidative stress and PCOS: A systemic review and meta analysis. *Human Reproduction Update*. 2013;Vol.19, No.3:268–288.

Role of Obesity in PCOS (Relationship between obesity and PCOS[1])



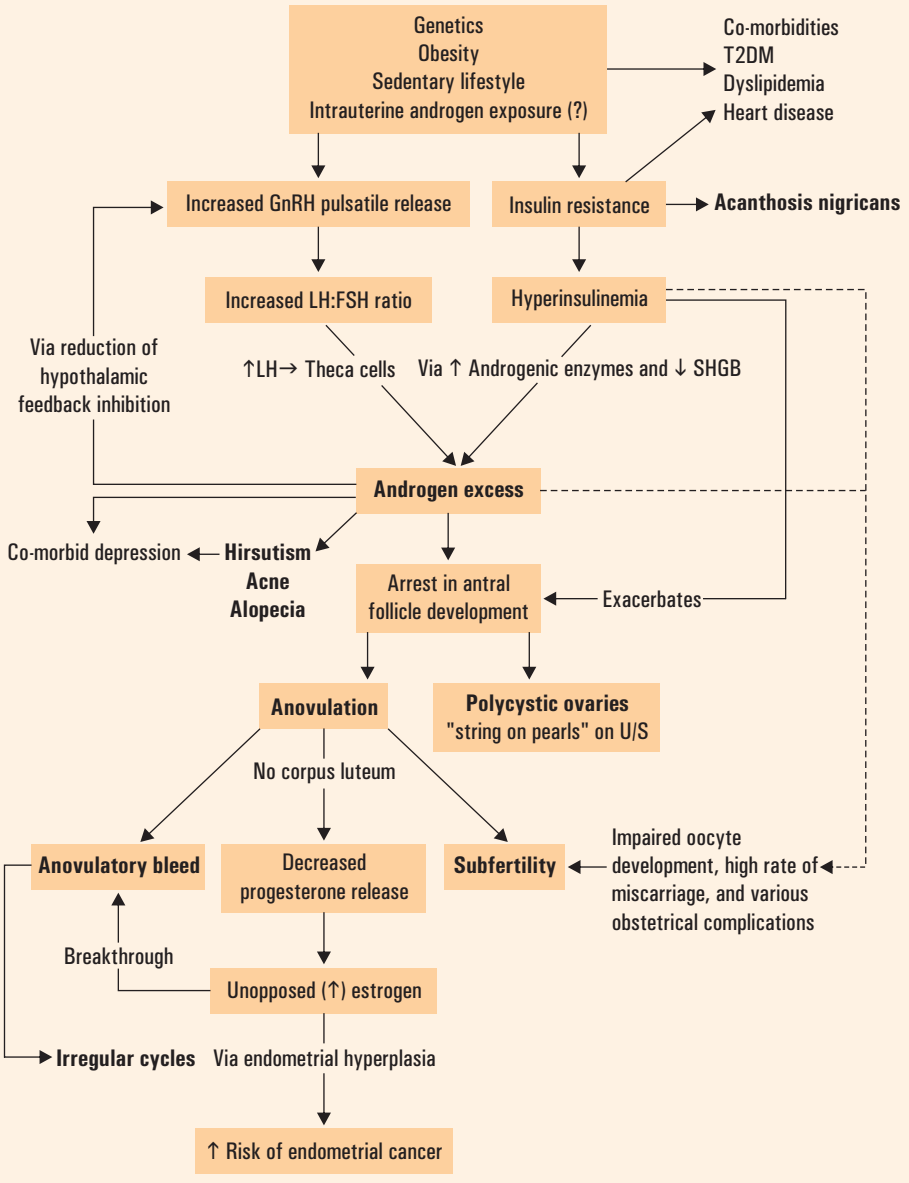
COS: Controlled ovarian stimulation; GT: Gonadotropins; E2: Estradiol : CL: Corpus luteum;
NIDDM: Non-insulin dependent diabetes mellitus; CVD: Cardiovascular disease; QoL: Quality of life

- Obesity is present in 30–75% of women with PCOS
- Adipose dysfunction is associated with glucose intolerance and hyperinsulinemia, which in turn can exaggerate the manifestations of hyperandrogenism
- Obese women with PCOS are at increased risk of anovulation and consequent subfertility[1,2]

References:

1. The PCOS Society. Education. Available at: http://www.pcosindia.org/algorithms.php. Last accessed on: 26th April 2017.
2. Basskind NE and Balen AH. Hypothalamic–pituitary, ovarian and adrenal contributions to polycystic ovary syndrome. *Clinical Obstetrics and Gynecology*. 2016;37:80–97.

Summary of Pathophysiology of PCOS



T2DM: Type 2 diabetes mellitus; SHGB: Sex hormone-binding globulin; LH: Luteinising hormone; FSH: Follicle stimulating hormone; U/S: Ultrasound; GnRH: Gonadotropin-releasing hormone

This algorithm summarises the multi-etiological pathophysiology of PCOS.

References:

1. Rotstein A, Srinivasan R, Wong E. Pathophysiology of PCOS. Available at: http://www.pathophys.org/pcos/

2. Goodarzi MO1, Dumesic DA, Chazenbalk G, *et al*. Polycystic ovary syndrome: Etiology, pathogenesis and diagnosis. *Nat. Rev. Endocrinol*. 2011 Apr;7(4):219–31.

Diagnostic Criteria for PCOS

NIH 1990	Rotterdam 2003	AE-PCOS Society
• Chronic anovulation • Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies e.g., congenital adrenal hyperplasia) (Both criteria needed)	• Oligo-and /or anovulation • Clinical and/or biochemical signs of hyperandrogenism • Polycystic ovarian morphology (Two of three criteria)	• Clinical and/or biochemical signs of hyperandrogenism • Ovary dysfunction (Oligo- anovulation and/or polycystic ovarian morphology [PCOM]) (Both criteria needed)

Exclude other etiologies of androgen excess – Late onset congenital adrenal hyperplasia, Androgen secreting tumours, Cushing's syndrome

The NIH (1990), Rotterdam (2003) and Androgen excess and PCOS Society criteria (2006) for Diagnosis of PCOS are comapred in the table

- PCOS diagnosis has been a topic of debate and many consensus/definitions have evolved over time
- The National Institute for Health (NIH) Criteria 1990 was revised in 2003 and the Rotterdam criteria were adopted worldwide
- According to the Rotterdam criteria (2003) PCOS was defined as incidence of any two of the three key criteria, namely, oligoovulation and/or anovulation, excess androgen activity and polycystic ovarian morphology (PCOM)
- This definition was later revised by the AES by defining PCOS as a hyperandrogenic state, and it emphasises the presence of either clinical and/or biochemical features of hyperandrogenism along with other features[1,2] of PCOS for diagnosis

References:

1. National Institutes Of Health. Evidence-based Methodology Workshop on Polycystic Ovary Syndrome. 2012. Available at: https://prevention.nih.gov/docs/programs/pcos/FinalReport.pdf. Last accessed on: 26th April 2017.
2. Malik S, Jain K, Talwar P, *et al*. Management of Polycystic Ovary Syndrome in India. *Fertil. Sci. Res*. 2014;1:23–43.

Other Aetiologies for Androgen Excess[1]

Physiologic adolescent anovulation
Functional gonadal hyperandrogenism
PCOS: Primary functional ovarian hyperandrogenism (common form of PCOS)
Secondary functional ovarian hyperandrogenism
Virilising congenital adrenal hyperplasia
Adrenal rests of the ovary
Syndromes of severe insulin resistance
Acromegaly
Epilepsy ± valproic acid therapy
Ovarian steroidogenic blocks
Disorders of sex development
Pregnancy-related hyperandrogenism

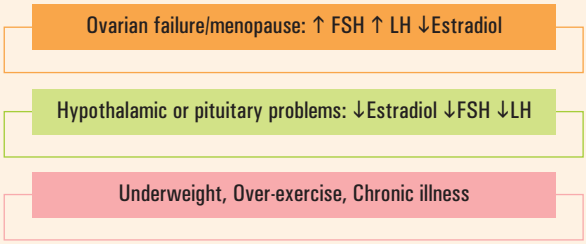
Functional adrenal hyperandrogenism
PCOS: Primary functional adrenal hyperandrogenism (uncommon form of PCOS); Virilising congenital adrenal hyperplasia
Other glucocorticoid-suppressible functional adrenal hyperandrogenism
Prolactin excess
Cortisone reductase deficiency (and apparent cortisone reductase deficiency); Dehydroepiandrosterone sulphotransferase deficiency, apparent
Glucocorticoid-non-suppressible functional adrenal hyperandrogenism
Cushing's syndrome
Glucocorticoid resistance
Peripheral androgen overproduction
Obesity
Idiopathic hyperandrogenism; Portohepatic shunting
Virilising tumours (adrenal or ovarian)
Androgenic drugs (e.g., exogenous androgenic steroids or valproic acid)

The table enumerates the other causes of hyperandrogenism.

References:

1. Rosenfield RL. Diagnostic evaluation of polycystic ovary syndrome in adolescents. UpToDate. 2016. Available at: https://www.uptodate.com/

Other Causes for Menstrual Irregularity



LH: Luteinising hormone; FSH: Follicle stimulating hormone

Differential Diagnosis of PCOS[1]

Condition	Differentiating signs/symptoms	Differentiating investigations
21-hydroxylase deficiency	• Clinical presentation may be indistinguishable from that of PCOS	A morning, follicular-phase 17-hydroxyprogesterone level
Thyroid dysfunction	• Menstrual irregularities • Hyperandrogenism • Clinical features of hypothyroidism/hyperthyrodism	Thyroid stimulating hormone (TSH) level
Hyperprolactinaemia	• Infrequent or absent menses • Mild hyper androgenic features • Galactorrhoea • Headache or visual field deficit	Prolactin level
Cushing's syndrome	• Moon facies, central fat deposition, hypertension, muscle wasting, abdominal striae and osteoporosis • Obesity, hirsutism, acne and menstrual irregularity • Circulating cortisol and androgen levels are elevated • Severe hirsutism and virilisation	24-hour urinary free cortisol
Androgen-secreting neoplasms	• Steroid-producing tumours of the adrenal or ovary • Progressive virilisation (frontal balding, severe hirsutism, increased muscle bulk, deepened voice, clitoromegaly)	• Total testosterone or free testosterone • Ultrasound of the ovaries • Dehydroepiandrosterone sulpate (DHEA-S) • Computed tomography (CT) scan of the adrenals
Syndromes of severe IR	• Degrees of insulin resistance, hyperinsulinaemia, and hyperandrogenism tend to be more severe than in PCOS; HAIR-AN syndrome • Lipodystrophy may be present	• Fasting insulin • Peak insulin during a 3-hour 75-g oral glucose tolerance test
Androgenic/ anabolic drugs	• History of use or abuse of testosterone, anabolic steroids, danazol, DHEA, androstenedione, 19-norprogestins, norgestrel, levonorgestrel or norethisterone • Severity of hyper-androgenism varies depending on dose and duration of drug use	• Depend on agent used
Hypogonadotrophic hypogonadism	• Oligo-anovulation • Hyper-androgenism is absent	• Serum follicle stimulating hormone (FSH) and estradiol
Premature ovarian failure	• Anovulation • Hyper-androgenism is absent	• High serum FSH and low serum estradiol
Apparent cortisone reductase deficiency	• Clinically may be indistinguishable from PCOS	• Ratio of tetrahydrocortisols to tetrahydrocortisone • Both adrenals often enlarged • Urinary free cortisol may appear elevated

References:

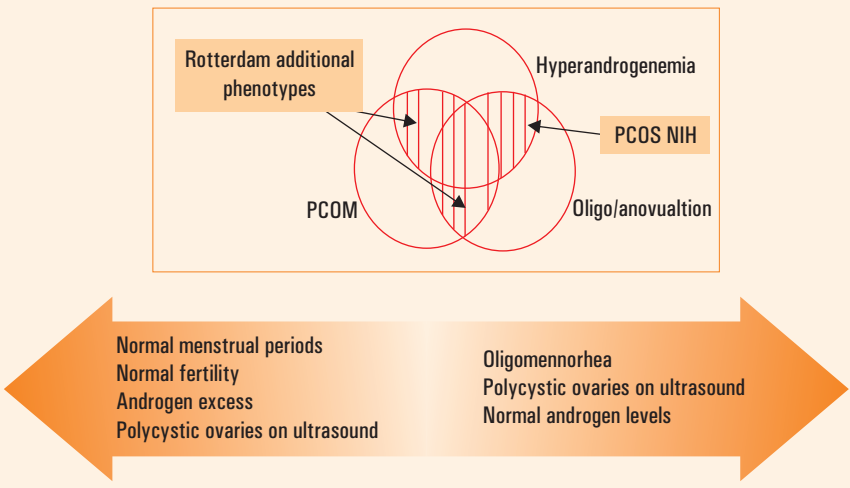
1. BMJ Best Practice. Available at: http://bestpractice.bmj.com/best-practice/monograph/141/diagnosis/differential.html; Last updated on: 19th June 2016; Cited on: 21st February 2016.

PCOS Phenotypes

	Androgen levels	LH/FSH	Insulin resistance	CV risk
Type 1 classic PCOS	Increased	Increased	Increased	Increased
Type 2 classic PCOS	Increased	Mild increase	Increased	Increased
Ovulatory PCOS	Increased	Normal	Mild increase	Mild increase
Normoandrogenic PCOS	Normal	Increased	Normal	Normal?

Rotterdam criteria added two new phenotypes to the NIH criteria as shown in figure below.

Rotterdam Criteria and Phenotypes

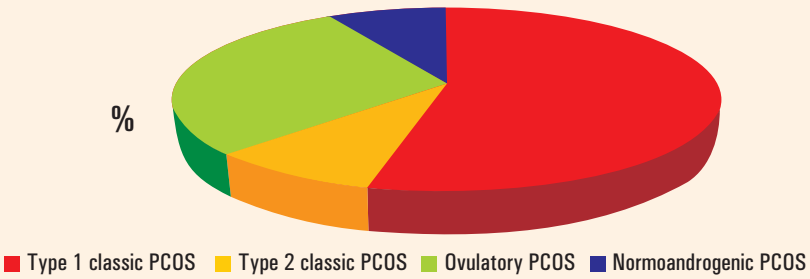


NIH workshop 2012 recommended maintaining the broad inclusionary diagnostic criteria of Rotterdam (which includes the classic NIH and AE PCOS criteria) while specifically identifying phenotypes.

NIH workshop 2012

1. Androgen excess + Ovulatory dysfunction
2. Androgen excess + Polycystic ovarian morphology
3. Ovulatory dysfunction + Polycystic ovarian morphology
4. Androgen excess + Ovulatory dysfunction + Polycystic ovarian morphology

% Prevalence of Different Types of PCOS Phenotypes



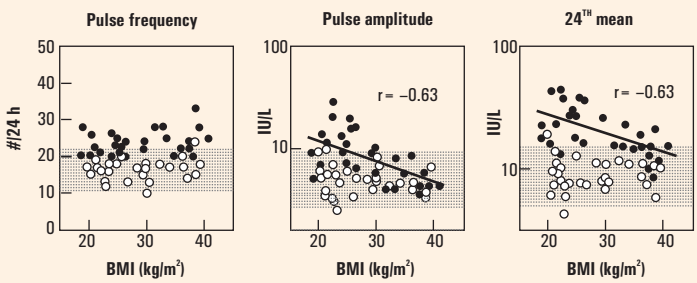
Why LH/FSH Ratio was Excluded from NIH 2012 Criteria?

Difficulties with using serum LH/FSH levels of diagnosis PCOS

Many women with functional hypothalamic amenorrhea have elevated LH and FSH levels

Levels are variable due to pulsatile nature, therefore multiple measurements are needed

Levels in women with PCOS are blunted with increasing obesity



BMI: Body mass index; LH: Luteinising hormone; FSH: Follicle stimulating hormone

LH/FSH ratio was excluded from the NIH 2012 criteria due to difficulties with using serum LH/FSH levels for diagnosing PCOS.

PCOS Criteria in Adolescents

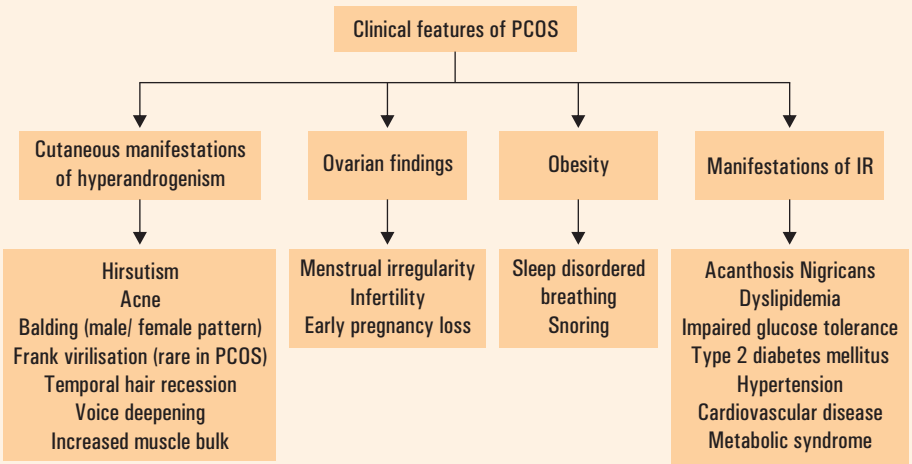
Diagnostic criteria for PCOS in adolescents[1]		
Parameter	**ESHRE/ASRM 2012**	**Endocrine Society 2013**
Criteria	1. Clinical or biochemical hyperandrogenism[a] 2. Oligo-/anovulation[b] 3. Polycystic ovarian morphology[c]	1. Clinical or biochemical hyperandrogenism[a] 2. Persistent oligo-/anovulation[b]
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.
[a] Increased serum androgens and/or progressive hirsutism
[b] Oligo-/amenorrhea for at least 2 years, or primary amenorrhea by age 16 years
[c] Ovarian volume $> 10\ cm^3$

References:

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

PCOS Manifestation



The flowchart depicts the various clinical features of PCOS.

Cutaneous manifestations of hyperandrogenism:

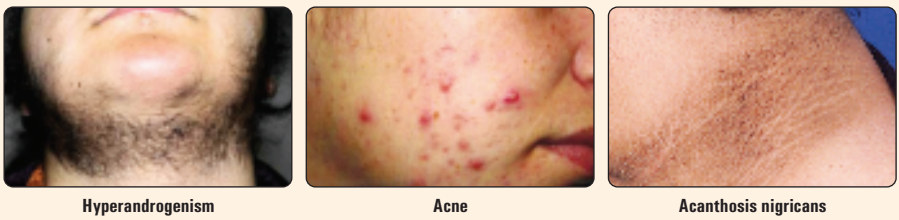
A) Hirsutism: This refers to an abnormal amount of sexual hair that appears in a male pattern. The adolescent PCOS guidelines consider only moderate to severe hirsutism to constitute clinical evidence of hyperandrogenism. This is a less reliable evidence of hyperandrogenism than persistent testosterone elevation determined by laboratory investigation.

B) Acne vulgaris: Excessive acne vulgaris is an important cutaneous manifestation of hyperandrogenemia in adolescents. The presence of moderate (>10 facial lesions) or severe inflammatory acne through the perimenarcheal years suggests hyperandrogenemia. It has been agreed that "moderate-to-severe inflammatory acne vulgaris that is persistent and poorly responsive to topical treatment is an indication to test for hyperandrogenemia."

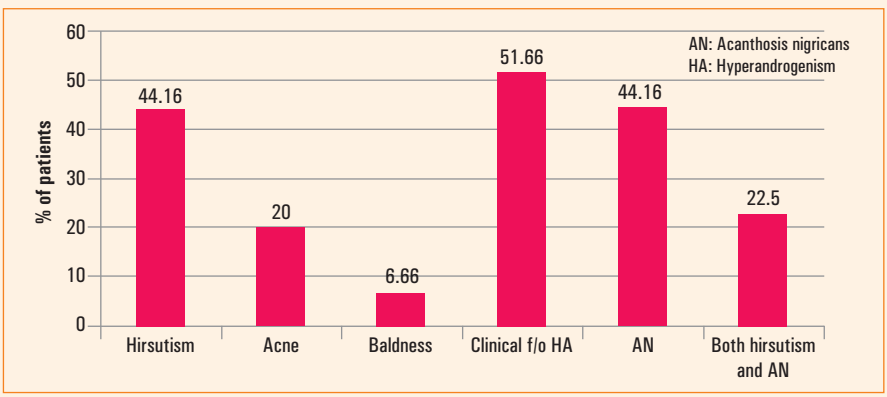
C) Baldness: It can represent as male-pattern (affecting the fronto–temporo–occipital scalp) or female-pattern (affecting the crown, typically manifesting early as a midline part widened in a "Christmas tree" pattern).

D) Virilisation: The features of frank virilisation include: rapid onset or progression of hirsutism, temporal hair recession, increased muscle bulk, voice deepening and onset of clitoromegaly. This is rare in PCOS, and should alert for other causes of hyperandrogenemia.

PCOS - Clinical Manifestations



Hyperandrogenism | Acne | Acanthosis nigricans



Clinical findings in women with PCOS[1]

The results of the study conducted by Ramanad *et al*. (2013) have been depicted in the slide. PCOS can present as a combination of various clinical features like multiple follicles on USG, oligomenorrhoea, obesity, acanthosis nigricans (AN)

and hirsutism. These findings may be present alone or in various combinations with one another. More than half of the patients showed clinical features of hyperandrogenism. The study showed that the prevalence of AN and hirsutism in PCOS is comparable. It highlights an important point that there is a need to increase awareness regarding obesity and AN.

References:

1. Ramanand SJ, Ghongane BB, Ramanand JB, *et al*. Clinical characteristics of polycystic ovary syndrome in Indian women. *Indian Journal of Endocrinology and Metabolism*. 2013;17 (1):138–145.

PCOS - Biochemical Manifestations

IGT	• Seen in 45% of women with PCOS[2] • Tests recommended for screening IGT o OGTT o A1C of 5.7–6.4% (39–47 mmol/mol)[1]
Androgens	• DHEA may be normal or slightly above the normal range • Elevated testosterone • Androstenedione levels are also elevated
SHBG	• Low
Lipid profile	• Low HDL cholesterol • Increased LDL • High triglyceride concentrations
FSH/ LH	• FSH levels are within the reference range or low • LH levels are elevated • LH-to-FSH ratio is usually greater than 3

DHEA: Dehydroepiandrosterone; OGTT: Oral glucose tolerance test; A1C: Glycosylated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; IGT: Impaired glucose tolerance; SHBG: Sex hormone–binding globulin; FSH: Follicle stimulating hormone; LH: Luteinising hormone

References:

1. American Diabetes association. Standards of Medical Care in Diabetes–2016. Diabetes Care 2016;39(Suppl. 1):S13–S22.
2. Richard Scott Lucidi. Polycystic Ovarian Syndrome Workup. 2016.
3. Barbieri RL and Ehrmann DA. Clinical manifestations of polycystic ovary syndrome in adults. Uptodate. 2017. Available at: https://www.uptodate.com/

Investigations in PCOS[1]

Investigation	Findings	Remarks
Transvaginal ultrasonography	Antral follicle count (AFC) Ovarian volume	• Primary purpose of ultrasonography in the hyperandrogenemic adolescent is to exclude causes other than PCOS • Polycystic ovary contains 12 or more follicles measuring 2–9 mm in diameter on day 2 or 3 of menstrual cycle (MC) and/or • Increased ovarian volume (>10 cm^3) • No dominant follicle >10 mm or corpus luteum (CL) • Does not apply to women taking oral contraceptive pills (OCP), as ovarian size is reduced, even though the polycystic appearance may persist
Androgens • DHEA-S (secreted by the adrenal gland) • Androstenodione (secreted by the ovaries) • Total testosterone • Free testosterone • Free androgen Index	Elevated	• Elevated serum free testosterone is the single most sensitive test to establish the presence of hyperandrogenemia • Androgens are not strong markers of PCOS, but may be done to exclude other etiologies • Hyperandrogenism (HA) is a diagnostic feature that allows for discrimination from other causes of the combination of oligomenorrhea and polycystic ovaries
17-hydroxyprogesterone	Decreased	• Done to rule out adrenal conditions • Non-classical congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency detection
SHBG (Sex hormone-binding globulin)	Decreased	The combination of an upper-normal total testosterone and a lower-normal SHBG yields a high free testosterone concentration
Serum prolactin		• Not always elevated • Done to rule our other causes of menstrual irregularity such as hyperprolactinemia and thyroid disorders
Serum cortisol		Elevated if Cushing's syndrome is associated
Serum FSH	Normal or decreased	
LH (Luteinising hormone)	Elevated	Both pulse and amplitude
LH/FSH ratio	Elevated	
AMH (Anti-mullerian hormone)		A new diagnostic marker • AMH – correlates well with AFC • Correlates best with 2–5 mm follicles proposed as most accurate biochemical marker for PCOS • Serum AMH 35 pmol/L (5 ng/mL) was more sensitive than U/S to detect PCOM • Not used due to lack of standardisation

Investigations in PCOS[1] (contd.)

Investigation	Findings	Remarks
Test for insulin resistance • OGTT (Oral glucose tolerance test) • Ratio of fasting glucose/ insulin • Ratio of 2h fasting glucose/ insulin after 75 gm glucose challenge • Homa – IR • QUICKI	Deranged	• Hyperinsulinism • ADA criteria for diagnosis of type 2 diabetes mellitus • FPG 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h. Or • 2h PG 200 mg/dL (11.1 mmol/L) during an OGTT. * Or • A1C 6.5% (48 mmol/mol)** Or • In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose 200 mg/dL (11.1 mmol/L). This feature is best associated with metabolic syndrome and cardiovascular disorder (CVD) risk
Lipid profile	Deranged	Dyslipidemia
Thyroid stimulating hormone	Abnormal	Thyroid disorders
Vitamin D levels	Decreased	

The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

** The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

References:

1. Rosenfield RL. Diagnostic evaluation of polycystic ovary syndrome in adolescents. UpToDate. 2016. Available at: https://www.uptodate.com

Detecting Insulin Resistanc (IR) Clinically

Familial, clinical and physical features as risk factors for IR

Family history	Patient history	Physical features
Glucose intolerance	Birth weight- small or large for gestational age	Acanthosis nigricans
Obesity	Precocious puberty	Striae
Hypertension	Evolution of obesity	Centripetal obesity
Metabolic syndrome	Dietary habits	Adipomastia
Hyperuricemia	Physical activity	Hypertension
Coronary heart disease	Medication/drugs which affect appetite, glucose or lipid metabolism	Acne
Stroke		Hirsutism
Chronic pancreatitis		Alopecia
Gestation diabetes		Precocious puberty
PCO and hirsutism		Genu valgum
Non-alcoholic fatty liver disease		

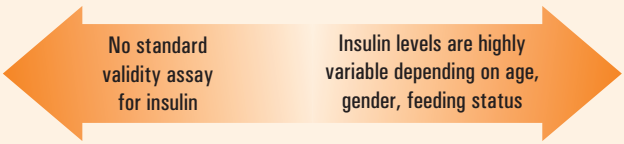
References:

1. Eyzaguirre F, Mericq V. Insulin resistance markers in children. *Horm. Res*. 2009;71:65–74.

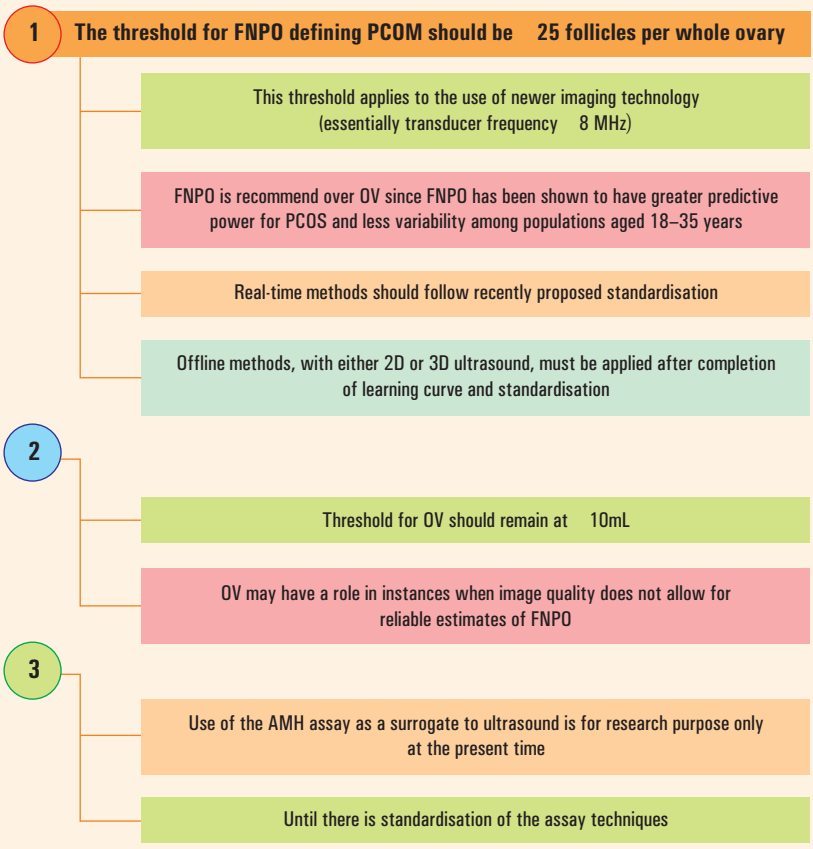
Medications Associated with Insulin Resistance (IR)

Hormones	HIV therapy	Anti-psychotic drugs	Immune suppressants	Others
Glucocorticoids	HIV nucleosides reverse transcriptase inhibitors	Clozapine	Tacrolimus	Tiazides
Growth hormone	HIV protease inhibitors	Clanzapine	Cyclosporine	Valproate
		Risperodone	Sirolimus	Glucosamine

Why Insulin Levels Should Not Be Used to Diagnose PCOS



Newer Developments in Diagnosis of PCOS



OV: Ovarian volume; FNPO: Follicle number per ovary; AMH: Anti-mullerian hormone

Newer Developments in Diagnosis of PCOS (contd.)

- Ultrasonography – For PCOS diagnosis, increasing the threshold of AFC to 19 or even 26 follicles[1,2]
- Anti-mullerian hormone (AMH) levels accurately reflect the ovarian follicular reserve and may be considered as an extremely sensitive marker of ovarian ageing
- Serum AMH level alone, with a cut-off value as 3.8 ng/mL is a useful marker for diagnosing PCOS
- Combination of the serum AMH level with hyperandrogenesim and/or oligo-anovulation markedly increases the diagnostic capability for PCOS
- AMH is currently not included in the Rotterdam criteria. [3] However the following has been proposed

Newer Developments in Diagnosis of PCOS (contd.)

Oligo-anovualtion	Clinical and/or biological HA	FN > 19 and/or serum AMH [a] > 35 pmol/L (5 ng/mL)	Diagnosis
+	+	(+/–)[b]	PCOS
+	–	+	PCOS
–	+	+	PCOS
–	–	+	Normal woman with PCOM
+	–	–	Idiopathic anovulation
–	+	–	Idiopathic hyperandrogenism

HA: Hyperandrogenism; AMH: Anti-mullerian hormone; FN: Follicle number
As with the previous classification, other causes of oligo-anovulation and/or HA must be excluded before applying this classification
[a] to be used preferentially
[b] not necessary for diagnosis

- A lot of research is being done around the diagnostic criteria of PCOS
- In this regard authors have put forth the use of serum AMH as a sensitive marker of ovarian ageing
- The serum concentrations of AMH are increased in most patients with PCOS. Also, there is an association between the performance of serum AMH and antral follicle count (AFC). This has led to compare the performance of AMH levels and AFC in diagnosis of PCOS

References:

1. Ionescu C, Tircomnic I, Dimitriu M, *et al*. New trends in diagnose of polycystic ovarian syndrome. *Romanian Society of Ultrasonography in Obstetrics and Gynecology*. 2015;11(42): 196–198.
2. Mohammad MB, Seghinsara AM. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. *Asian Pac. J. Cancer. Prev*. 2017;18(1):17–21.
3. Dewailly D, Gronier H, Poncelet E, *et al*. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. *Hum. Reprod*. (2011) 26 (11): 3123–3129.

Conclusions

- Androgen testing in suspected cases of PCOS is for differential diagnosis
- Biological hyperandrogenism in PCOS is inconstant and has no specific profile
- Serum AMH as a surrogate to follicle count seems promising, but issues about assays must be solved
- Follicle excess is the best criteria for PCOS but threshold is highly dependent on technology used with newer technologies, threshold may be as high as 25
- There will never be a single criteria to define PCOS

Key Points

- There are multiple reproductive and metabolic features that define PCOS as a disorder
- The origin of PCOS starts from intra uterine life and extends throughout life
- Hyperandrogenemia and hyperinsulinemia are the main pathology in PCOS
- The exact aetiology is not known but various genetic and environmental factors are involved in its pathogenesis
- Establish accurate diagnosis of PCOS /Identify the phenotypes
- ACOG/AEPCOS recommends 75 gm 2 hr OGTT
- Lipid profile (cholesterol, triglycerides, HDL, LDL)
- Identify metabolic syndrome, use TG/HDL > 3.2 to target subjects
- No test for insulin resistance is needed to make diagnosis of PCOS or to select treatment
- Obese women with PCOS (and/or those with abdominal obesity) should have an OGTT (or fasting glucose) and lipid profile
- Utility of these tests in non-obese women with PCOS is not yet known
- SHBG as a screening test for metabolic abnormalities?

NOTES

NOTES

NOTES

POST TEST

1. **What features of PCOS were identified by Stein Leventhal in 1935, during their first description of the syndrome?**
   a. Hirsutism, oligoamenorrhea
   b. Enlarged cystic ovaries, oligoamenorrhea and subfertility
   c. Subfertility, hirsutism, oligoamenorrhea
   d. Polycystic ovaries, oligoamenorrhea and, hirsutism
2. **Which of the following are clinical features of insulin resistance?**
   a. Acanthosis nigricans
   b. Metabolic syndrome
   c. Sleep disordered breathing
   d. a and b
   e. All of the above
3. **Which is correct?**
   a. Polycystic ovaries represent ovaries with multiple true cysts
   b. More than one cyst in the ovary is termed polycystic ovary
   c. Polycystic ovaries have no true cysts instead these are antral follicles with arrested development
   d. All the above
4. **Reducing insulin resistance (IR) helps in-**
   a. Restoring hormonal balance
   b. Ovulation induction
   c. Treating subfertility
   d. All of the above
5. **The Rotterdam diagnostic criteria includes**
   a. All the following characteristics:
      i. Clinical hyperandrogenism and/or hyperandrogenemia
      ii. Oligoanovulation
      iii. Polycystic ovaries on ultrasound

b. At least 2 of the above mentioned criteria

c. Any one of the above criteria

d. None of the above

6. For detecting the polycystic ovaries, preferred technique is-

a. Ultrasound

b. MRI

c. Laparoscopy

d. Any of the above

7. Which of the following statement is untrue?

a. Adolescents have higher ovarian volume than adults

b. Considerable number of adolescents have multi follicular ovaries

c. A persistent observation of oligo-/amenorrhea beyond two years of menarche in children/adolescents is a normal feature

d. All of the above

8. Ultrasound criteria for diagnosis of PCOS warrant-

a. 2–7 follicles less than 10 mm in size

b. 12 or more follicles in each ovary measuring 2 to 9 mm in diameter

c. Increased ovarian volume (> 10 mL)

d. a and c

e. b and c

9. Which of the following can cause hyperandrogenism?

a. PCOS

b. Late onset congenital adrenal hyperplasia

c. Cushing's syndrome

d. All of the above

10. Regarding anti-müllerian hormone (AMH), which of the following statement is incorrect?

a. AMH predicts the number of antral follicles in the ovary

b. It is the promising biomarker for diagnosis of PCOS

c. It is included in the Rotterdam diagnostic criteria

d. It can substitute for polycystic ovarian morphology

Suggested readings

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