DR.AMUZEGAR

متخصص زنان وزایمان وفلوشیپ نازایی


بسم الله الرحمن الرحيم

Diagnostic Criteria of PCOS

PCOS is considered the most common endocrine disorder among reproductive age

Polycystic ovary syndrome (PCOS) is a heterogeneous and complex disorder that has both metabolic and hormonal implications and represents one of the major causes of infertility in women

DEFINITION OF PCO

- Polycystic ovary syndrome (PCOS) is a complex heterogeneous endocrine disorder, occurring due to synergistic interaction of genetic, epigenetic, and environmental factors, associated with both reproductive and metabolic abnormalities resulting in short- and long-term consequences in women's health.
- 1 Anovulatory disorders account for about 30–40% of female infertility, with PCOS accounting for 80–90% of World Health Organization (WHO) group 2, normogonadotropic, normoestrogenic anovulation (hypothalamic-pituitaryovarian dysfunction).
- The first description was given by Stein and Leventhal (1935) in seven women with variable clinical characteristics (i.e., obesity, hirsutism, acne, amenorrhea, sterility, and occasional menometrorrhagia) associated with bilateral enlarged polycystic ovaries (PCO) with thickened capsules and designated their name for the syndrome.
- 3 Later in the1960s, the term "polycystic ovary syndrome" and its abbreviation PCOS appeared, gradually replacing the Stein– Leventhal syndrome designation.

- It is now well-recognized that PCOS is not necessarily a disease [earlier known as a polycystic ovarian disease (PCOD)], but rather a cluster of features that may predispose to various diseases in different stages of life, such as anovulatory infertility, type 2 diabetes mellitus (T2DM), and metabolic syndrome .
- PCOS is known now as an endocrine, metabolic, and chronic inflammatory disorder, with hyperandrogenemia, insulin resistance (IR), and obesity as the key factors that influence the expression and symptoms of the condition.
- The syndrome is associated with a heterogeneous collection of signs and symptoms forming a spectrum, with a mild presentation in some at one end, to the other end of the spectrum causing severe disturbance of reproductive, endocrine, and metabolic function

How to diagnose PCO patient?

- The diagnosis of PCOS has remained controversial for many years, as the symptoms and signs are heterogeneous, depending on the population and life stage of the women affected.
- For many years, PCOS was only diagnosed in those with increased I (LH) or altered LH/ (FSH) ratio6 and in those with chronic anovulation.
- Later, the diagnosis was based on the finding of hyperandrogenism (HA) and chronic anovulation after the National Institutes of Health consensus conference in the United States (NIH criteria)
- . Again this criterion excluded many subjects, previously diagnosed with PCOS, as in the United Kingdom and other parts of Europe, NIH criteria were never used and the diagnosis was based on ultrasound morphology (and HA).

- ■ The global use of varying diagnostic criteria raised issues of compatibility for PCOS research worldwide and confusion within clinical practice.
- Therefore, the NIH 2012 undertook an Evidence-Based Methodology PCOS Workshop to address the "benefits and drawbacks" of existing diagnostic criteria
- .The panel then recommended the use of the broader European Society of Human Reproduction and Embryology (ESHRE) or American Society for Reproductive Medicine (ASRM) 2003 criteria,

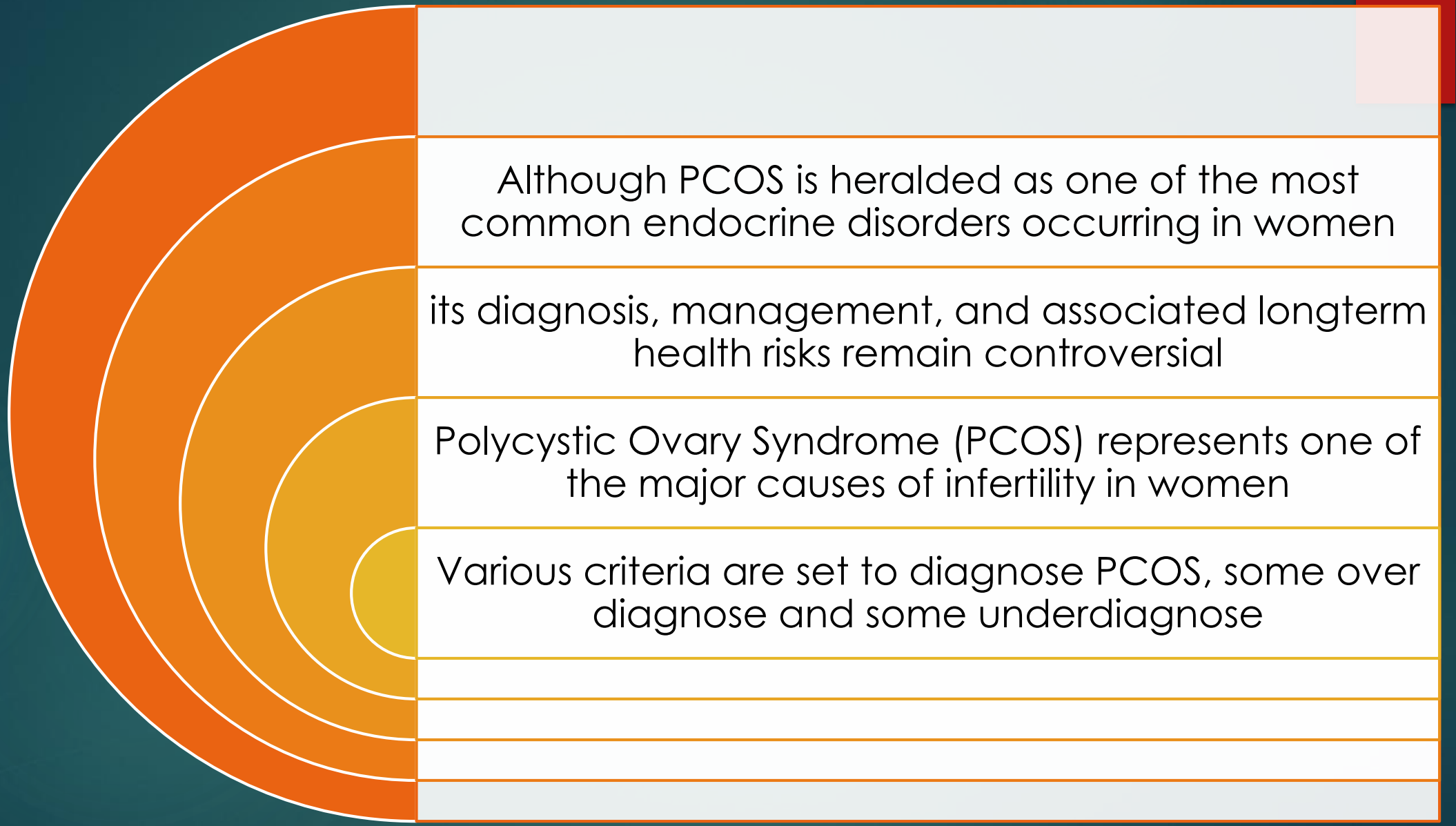
PREVALANCE

- ■ The prevalence of PCOS is determined by the diagnostic criteria used, ethnic origin, and population of women studied.
- The overall incidence varies from 8% to 10%.
- The prevalence among women of fertile age is 6–10% using the NIH criteria, 10% using the Androgen Excess and PCOS Society (AEPCOS) criteria, and 14–20% using the broader Rotterdam criteria
- The incidence is higher in the South Asian population which is about 50%, as against the Caucasian population, where the incidence is 5–25%.

POLYCYSTIC OVARY SYNDROME—PHENOTYPES

Four phenotypes have been identified, which may be influenced by genes, nutrients, physical activity,: Defining polycystic ovary syndrome (PCOS)—the evolution of the diagnostic criteria.

Diagnostic Criteria and Epidemiology of PCOS


Although PCOS is heralded as one of the most common endocrine disorders occurring in women
its diagnosis, management, and associated longterm health risks remain controversial
Polycystic Ovary Syndrome (PCOS) represents one of the major causes of infertility in women
Various criteria are set to diagnose PCOS, some over diagnose and some underdiagnose

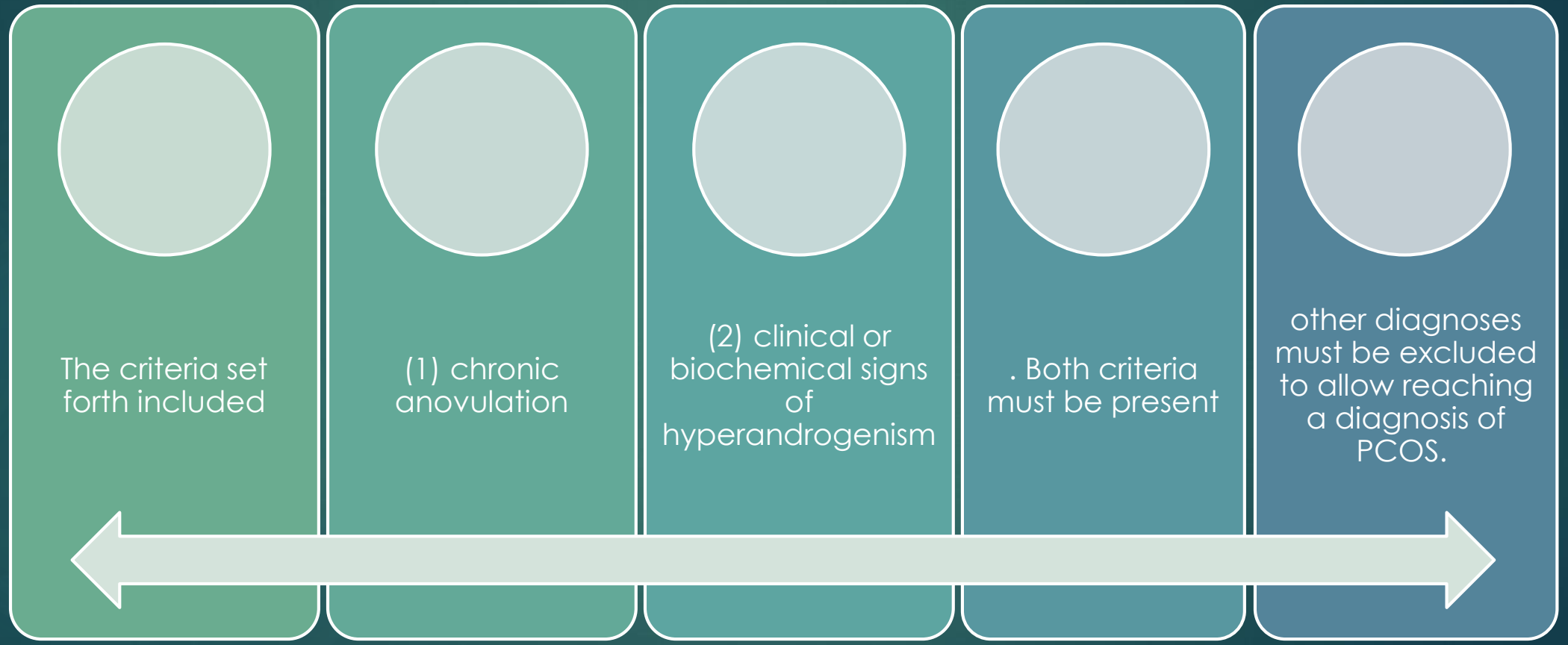
NIH criteria (1990)

Rotterdam criteria(2003)

More recently, in 2009, the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society outlined its own set of criteria

It is important to appreciate that the subtle heterogeneities within the various diagnostic criteria utilized by investigators impacts upon the reported prevalence of PCOS in a given population

NICHE CRITERIA OF PCO

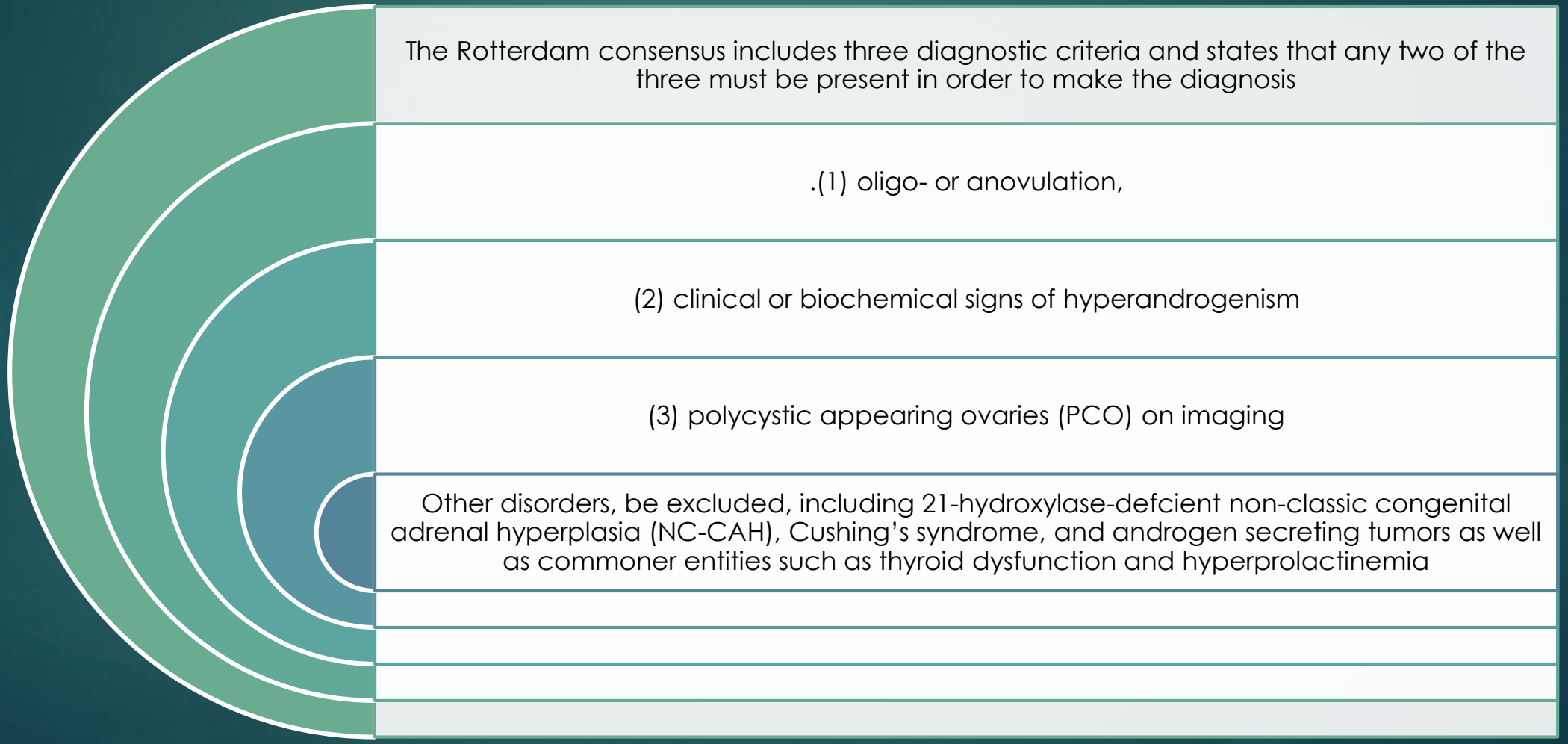


hyperandrogenism and or hyperandrogenemia and anovulation or oligo-ovulation. Hence, based on this, three principal phenotypes were identified hirsutism,

Hyperandrogenemia was defined by testosterone (T) and/or free testosterone (FT) and/or dihydroandrostenedione (DHEA) higher than 75% of the upper limits of each hormone

Hirsutism, defined by the FG score (Ferriman - Gallwey) is the presence of excessive facial hairs on the side of the face, upper lip, chin and it is also observed in chest region in severe PCOS

The Rotterdam consensus OF PCO



The stated rationale for incorporating these additional phenotypes included the recognition that PCOS does not represent a single entity

but rather occurs on a spectrum of heterogeneous disorders, as well as the associated long-term health risks such as of type 2 diabetes mellitus

and cardiovascular disease, commonly encountered in women diagnosed with PCOS.

The Rotterdam consensus statement advocated widening the inclusion criteria to avoid missing patients with the potential for these increased health risks.

The addition of polycystic morphology evolved based on improving ultrasound resolution

subcategories within PCOS

women with ovulatory dysfunction and polycystic ovaries

but without hyperandrogenism

and ovulatory women with hyperandrogenism and polycystic ovaries

Deeper explorations reveal that these subcategories within PCOS identifed based on the Rotterdam diagnostic criteria manifest subtle but distinct hormonal and metabolic milieu when compared to cases of PCOS identifed based on the more stringent NIH criteria

Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS)CRITERIA

A slightly modifed version of the criteria for the diagnosis of PCOS emerged:

(1) hyperandrogenism, including hirsutism and/or hyperandrogenemia

(2) ovarian dysfunction, including oligo-anovulation and/or polycystic appearing ovaries

(3) exclusion of other androgen excess or related disorders.

The AE-PCOS criteria also acknowledge that related disorders of hyperandrogenism must be excluded but allow that the clinician may take into account the prevalence of these differential diagnoses when deciding what tests to order

The AE-PCOS Society criteria (2006) attempted to make a balance between the NIH and Rotterdam definitions and recognized three unique clinical phenotypes

(1) Frank PCOS - oligomenorrhea, hyperandrogenismPCO

(2) Ovulatory PCOS - hyperandrogenism, PCO, and regular menstrual cycles

(3) non-PCO PCOS - oligomenorrhea, hyperandrogenism, and normal

Ovaries

However, all include hyperandrogenism.

TABLE 1: Defining polycystic ovary syndrome (PCOS)—the evolution of the diagnostic criteria.

Parameter	*NIH Consensus 1990*[7]	*ESHRE/ASRM/Rotterdam Consensus 2003*[9]	*AEPCOS definition 2009*[11]	*NIH 2012 extension of ESHRE/ASRM 2003*[12]
Criteria	• Clinical and/or biochemical HA • Oligo/amenorrhea, anovulation	• Clinical and/or biochemical HA • Oligo/amenorrhea, anovulation • PCO appearance on ultrasound	• Clinical and/or biochemical HA • Oligo/amenorrhea, anovulation • PCO appearance on ultrasound	• Clinical and/or biochemical HA • Oligo/amenorrhea, anovulation • PCO appearance on ultrasound
Limitations	Two of two criteria required	Two of the three criteria required	Androgen excess and one other criterion	Two of three criteria are required; and identification of specific phenotypes **(Table 2)**

(AEPCOS: Androgen Excess and PCOS Society; ESHRE/ASRM: European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; HA: hyperandrogenism; Excluding all causes for androgen excess and anovulation; NIH: National Institutes of Health; PCO: polycystic ovaries)

TABLE 2: Classification of polycystic ovarian syndrome phenotypes.[13,17]

Parameter	*Phenotype A*	*Phenotype B*	*Phenotype C*	*Phenotype D*
PCOS features	HA/OD/ PCOM	HA/OD	HA/PCOM	OD/PCOM
HA	+	+	+	–
OD	+	+	–	+
PCOM	+	–	+	+
NIH 1990 criteria	X	X		
Rotterdam 2003 criteria	X	X	X	X
AEPCOS 2006 criteria	X	X	X	

(AEPCOS: ANDROGEN Excess and PCOS Society; HA: hyperandrogenism; NIH: National Institutes of Health; OD: ovulatory dysfunction; PCOM: polycystic ovarian morphology)
Source: Lizneva, et al.[17]

- Approximately, 75% of PCOS have the classic type and the remaining 25% are evenly divided between ovulatory and nonhyperandrogenic PCOS phenotypes
- . Phenotypes A and B (classic or hyperandrogenic PCOS) have greater menstrual irregularity, HA, total and abdominal obesity, and IR, and are at risk for T2DM, MebS, and cardiovascular disease (CVD)
- . Phenotype D (nonhyperandrogenic PCOS), who do not demonstrate overt evidence of androgen excess, have little risk of metabolic dysfunctions.
- Phenotype C (ovulatory PCOS) have lower body mass index (BMI), lesser degrees of HA and HI, milder forms of dyslipidemia, and reduced incidence of MebS

- Also, few ovulatory women present with all the features of PCOS, including HA and hyperinsulinemia (HI), and hence there is no reason to make the diagnosis of PCOS only in those with chronic anovulation
- Finally, the Rotterdam criteria was adopted, and both NIH and the Endocrine Society have endorsed the Rotterdam criteria, which is the most widely adopted criteria
- While the Rotterdam criteria are simple and easier to follow, problems in diagnosing PCOS using these criteria often occur

- Changing ultrasound criteria for the definition of PCO y Polycystic morphology on scan is seen in about 25–30% of normal women without any clinical features of PCOS.

The AE-PCOS criteria also acknowledge that related disorders of hyperandrogenism must be excluded but allow that the clinician may take into account the prevalence of these differential diagnoses when deciding what tests to order

Disorders to consider in the differential diagnosis of PCOS include androgen-secreting neoplasms, Cushing's syndrome, 21-hydroxylase-defcient congenital adrenal hyperplasia, thyroid disorders, hyperprolactinemia, and premature ovarian failure.

androgen excess is a necessary component of the diagnosis by AES criteria. Therefore, the phenotype of ovulatory dysfunction and PCO alone—permissible under Rotterdam—does not qualify for a diagnosis of the syndrome by AES criteria

Table 1.1 Tests to rule out other potential diagnoses

Differential diagnoses	Tests to differentiate from PCOS
Cushing's	Dexamethasone suppression test 24-hour free urine cortisol
Congenital adrenal hyperplasia	17-hydroxyprogestrone
Thyroid disorders	TSH, T3, T4
Hyperprolactinemia	Prolactin
Premature ovarian failure	FSH, AMH
Androgen-secreting tumor	DHEAS, testosterone

. The combination of menstrual dysfunction and PCO, in the absence of features of hyperandrogenism or evidence of hyperandrogenemia

in fact, been shown to have the most similar anthropometrics, hormonal profle, and metabolic risks to the control subjects. The AES consensus criteria for defning PCOS are thus more inclusive than the NIH version but less so than the Rotterdam criteria.

, in part because of the natural clinical desire to move to discreet categorical criteria for the ease of diagnosis

In truth, there is a continuum of presentation from those persons minimally affected, with regular menses and only mild excess of androgens to those who have a unilateral PCO, to those who manifest more severe grades of androgen excess

Efforts to include hyperandrogenemia as diagnostic criteria will remain inadequate until the sensitivity of androgen assays is better refned because of our current inability to accurately quantify circulating androgens in women.

Anti-Müllerian hormone (AMH)

AMH levels correlate independently with both PCO morphology and androgenic profle

Although a cutoff value is not agreed upon, a level of 4.7 ng/mL has a specifcity of 79.4% and sensitivity of 82.8% in diagnosing PCOS in symptomatic women

. Some propose AMH be used as a substitute for ovarian morphology on ultrasound.

This would be especially useful in a setting where ultrasound is not readily available.

When used in addition to ultrasound, it may also identify more cases of PCOS than ultrasound fndings alone

AMH may not identify all phenotypes of PCOS equally but does show promise for a new possible objective test for PCOS.

ovarian stromal volume

Another parameter proposed as an adjunct to PCO morphology is an assessment of the ovarian stromal volume, measured as a ratio of the stromal area to total area of the ovary (S/A ratio).

Although this S/A ratio performed well when discriminating between women with and without PCOS, and correlated with androgen levels,

it has not been adopted as part of any of the existing diagnostic criteria

. In addition, follicle count per ovary is suggested as a better ultrasonographic marker for diagnosis of PCOS

Patients may initially present to a multitude of potential providers prompting a diagnosis of PCOS

Some may present as early as adolescence; however diagnosis can be diffcult as menstrual irregularities and acne are common during this time

Many women present to obstetrician-gynecologists with oligo/anovulation or infertility; however, they also may present to a dermatologist with acne or hirsutism

It is prudent that primary care providers are able to recognize the symptoms of PCOS as it is associated with other health disorders.

Diagnosis provides an opportunity to implement appropriate screening and prevention strategies for these women

. As women are diagnosed in their reproductive years, it is important to note PCOS is associated with an increased risk for obstetric complications including gestational diabetes and hypertensive disorders

Research has also shown a strong association with PCOS and non-alcoholic fatty liver disease among other signifcant chronic medical conditions

Hyperandrogenism

Determination of hyperandrogenism in females can be problematic, both during clinical and biochemical assessment

Laboratory assays for androgens were initially designed for detection in males and have been calibrated accordingly

total testosterone assays are typically calibrated for normal male levels, the lower end of which is 250 ng/dL.

The upper end of normal female total testosterone ranges between 45 and 80 ng/dL (inter-laboratory differences exist, and clinicians should familiarize themselves with the assay range for the laboratories serving their patient population).

Both the above specifed values are well below the ffth percentile for the assay detection range

where assay results may become unreliable; notably, calibration studies have not been done to develop a commercial female assay

An additional diagnostic dilemma is that the reporting of clinical hyperandrogenism is examiner-dependentand can be subjective

While a standardized tool such as the Ferriman-Gallwey score can help objectify evaluation

this method has been shown to have good intraobserver reliability but poor inter-observer reliability

Furthermore, a universal application of such tools across all ethnic groups may discount the normal ethnic variation in the appearance of body hair.

Inclusion of ultrasonographic evidence of PCO morphology into the defnition of PCOS is controversial.

The various sets of criteria place different degrees of emphasis on an isolated phenotypic PCO component not uncommonly encountered in the general reproductive-age population

the NIH criteria do not address ovarian morphology

the Rotterdam criteria in 2003 include PCO as a phenomenon distinct from menstrual irregularities

the AES lumps ovarian morphology into an “ovarian dysfunction” category along with oligo-anovulation and requires only one or the other to suffce as a diagnostic criterion

It is important to appreciate that PCO morphology is not specifc to PCOS and can be found in 20–30% of the general population of women 20–25 years of age

isolated PCO therefore should not be considered an indication of the syndrome in the absence of menstrual irregularities, infertility, or complaints of hirsutism

In some ways, efforts to agree on diagnostic criteria are artifactual.

There continues to be controversy and lack of complete agreement for what elements constitute optimal criteria for PCOS diagnosis

Prevalence of Polycystic Ovary Syndrome: Regional and Ethnic Variation

Although the prevalence of PCOS in any specifed population is dependent upon the diagnostic criteria used, there is regional and ethnic variation. While most reports on the prevalence of PCOS range between 2 and 20%, the chosen diagnostic criteria are recognized to infuence the determined prevalence.

In Iran the estimated prevalence of PCOS was 7% based on the NIH criteria, 15.2% using Rotterdam criteria, and 7.92% using AES criteria

These discrepancies highlight not just an ethnic diversity in the prevalence of the disorder but also the signifcance of lifestyle in the occurrence of PCOS. Likely prevalence is underestimated

A meta-analysis published in 2016 reported an overall prevalence of PCOS at 6% using NIH criteria and 10% using Rotterdam or AES criteria

By any measure, PCOS is one of the most prevalent endocrine disorders worldwide, with obvious regional and ethnic variation

Excess in facial and body hair and intractable acne are common reasons for women to seek evaluation with subsequent unmasking of PCOS. Rates of hirsutism vary among ethnic groups

Among women with hirsutism, up to one-third have an underlying diagnosis of PCOS. Around 27% of women presenting with acne were found in one study to have undiagnosed PCOS, compared to 8% of controls

Patients presenting with acne resistant to standard treatment have an even higher rate, near 50%

Among adolescents with irregular menses, after a 6-year follow-up period, 62% continued to have irregular menses, 59% of whom were diagnosed with PCOS.

In other words, approximately one-third of the original adolescent population with irregular menses was diagnosed with PCOS within the study period

PCOS is considered the most common endocrine disorder among reproductive-age women and is characterized by a chronic course, with features that suggest varying combinations of reproductive functional defcits (such as ovulatory dysfunction or PCO morphology) and androgen excess (such as acne and hirsutism)

The diagnosis of PCOS is based on well-defned criteria, and currently there are three major sets of diagnostic criteria available for utilization in clinical practice

Regional prevalence of PCOS can vary depending on the diagnostic criteria utilized as well as the ethnicity studied

Women with isolated symptoms of acne, hirsutism, and irregular menstrual cycles should be offered targeted screening

Beyond the symptom burden relating to PCOS that adversely impacts quality of life, and perhaps more clinically signifcant, is the higher prevalence of several medical comorbidities in the PCOS population

Identifying PCOS and screening for these adjunct disorders will allow for timely institution of preventive strategies aimed at minimizing the overall health risk in this population