Phenotypes and Complications of Polycystic Ovary Syndrome: A Rapid Update: a review

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Abstract:
Polycystic Ovary Syndrome (PCOS) is the most prevalent hormone disorder of fruitful-aged women in the entire world. This rapid review aims to highlight the essential clinical points face up to physicians and their patients in identify PCOS in different age stage and its complications in female's life.

Keywords: PCOs, hormone, complications, phenotypes


Introduction
Throughout the last 20th years, the issue of Polycystic ovary syndrome (PCOS) has risen as a genuine problem for women in the world. What is PCOS? PCOS is the most spreadendocrinopathy-metabolic irregularities in adult females of childbearing age, recognized by menstrual irregularity, androgenemia, and polycystic ovaries¹⁻⁴. Its morphology is seen on ultrasound in nearly 22% of women ⁵, with prevalence among females of reproductive age in the wide-ranging population has been estimated at 5.6%–16% reported by recent studies⁶. PCOS infertility cover more than one-fourth of the reason of infertility⁷. Additionally, it is valued that 90% of totally anovulation conditions are affected by PCOS⁸. Polycystic ovaries (PCO) are engage symptoms in patients with PCOS, hence the term of the syndrome. PCO are defined as an ovarian size of larger than 10 milliliters and/or existence of 12 or more follicles measuring 2–9 mm in diameter in both ovaries⁹. It is assessed that PCO are currently more than 75% of patients with PCOS¹⁰ even so, 20% of females in the overall population also have PCO¹¹.

A Historical Perspective
Stein and Leventhal who are the Americangynecologists, which firstly described it in 1935, so it is initiallyterminwas agree to names thosetwo gynecologists: Stein-Leventhal syndrome. While the earliest printingcase report about PCOS was in 1721 in Italy. Cyst-related variations to the ovaries were defined in 1844¹². Stein and Leventhal were taken seven ladies experiencing from amenorrhea, hirsutism, and inflation ovaries with multiple cysts at two-sided ovaries¹³,¹⁴. Later then more than 30,000 scientific reports on this subject have been issued¹⁵.

Etiology of PCOS
In spite of the etiology of PCOS is as yet misty, an interaction of gene variants and environmental factors have been contributed synergistically as the central contributor to its phenotypic expression¹⁶⁻¹⁹.

Symptoms with Metabolic, and Mental Complications at PCOS
The most frequently features of PCOS are chronic oligo/amenorrhea, infertility, hyperandrogenemia (HA), insulinresistance (IR), hirsutism, acne, androgenic alopecia, and increased luteinizing hormone (LH)¹⁰⁻²². Three of them are chief characters of PCOS that are anovulation, hyperandrogenism and insulin resistance. Anovulation consequences in irregular cycle's period, amenorrhea, ovulation-linked poverty and polycystic ovaries. HA consequences in acne and hirsutism. Insulin resistance is frequently linked with obesity, Type 2 diabetes mellitus (T2D), gestational diabetes mellitus (GDM), and elevation cholesterol levels. The prevalence rate of T2D and GDM with was greater in PCOS than with non-PCOS in recent investigations²³⁻²⁶. The signs and
acuteness of this syndrome differ really amongst the PCOS females. Furthermore, it can affect daily physical activities and cover to the life of women with disturbs them from the embryonic stage to death, thus generates many health risks that destroy the efficiency of life, this can weaken the quality of life and increase morbidity and mortality\(^{27-30}\). Moreover, the incident rate of cardiovascular disease (CVD) that containing hypertension and dyslipidemia was greater in PCOS than to non-PCOS women\(^{31}\). In additional to that, many articles associated with recent meta-analysis studies determined the relationship between PCOS and (CVD) risk markers and hypertension\(^{32-36}\).

In another hand, many studies have been searched about the associations of more than 70 candidate genes, and assessed for a contributory role in PCOS; however, because of genetic and phenotypic heterogeneity and underpowered studies, the results of many of these studies remain inconclusive.

**Diagnosis and Differential Diagnostic Criteria for PCOS**

**A. Criteria in Adult Women**

Three groups of diagnostic criteria have been suggested over the previous periods\(^{37-40}\)(Table 1). The starting was with the first PCOS diagnostic criteria by the National Institute of Health (NIH) in 1990 estimated that:

- Chronic oligo/anovulation.
- Clinical or biochemical hyperandrogenism.
- The elimination of correlated disease such as non-classical congenital adrenal hypertrophy, Cushing syndrome, hyperprolactinemia and malfunctions of the thyroid gland\(^{37}\).

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<th>Table 1: Comparison between the Three Sets of PCOS Diagnostic Criteria</th>
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Then, the additional classification was established on the agreement attitude of 27 PCOS specialists, who convened in Rotterdam, the Netherlands, May 2003. The Rotterdam European Society of Human Reproduction and the Embryology/American Society for Reproduction Medicine or (ESHRE/ASRM) support the PCOS Consensus Workshop group (Rott-PCOS) that suggested the presence of polycystic ovarian morphology (PCOM) (ultrasound) in addition to the NIH criteria, setting that PCOS could be diagnosed when any two of these three criteria were existing\(^{9}\)(Table 1). Notably, the overview of Rotterdam criteria produced to an extensive PCOS, as well as expanded the heterogeneity of PCOS phenotypes as matched with the NIH definition\(^{41}\). Latest updates, the Androgen Excess Society (AES) in 2006 recommended new indicative norms and catalogued that the syndrome must only be diagnosed in the occurrence of hyperandrogenism (HA) in associated with ovulatory dysfunction (OD) and/or PCOM (Figure1)\(^{42}\). Recently, a new meta-analysis study is a display of statistically significant differences in the collected prevalence assessment between the NIH criteria and the Rotterdam, with no statistically significant difference between NIH and AE-PCOS or Rotterdam and AE-PCOS\(^{43}\). Presently known four phenotypes of PCOS: 1) phenotype A: HA + OD + PCOM; 2) phenotype B: HA + OD; 3) phenotype C: HA + PCOM; 4) phenotype D: OD + PCOM. All of them with various extended-period trouble on health and metabolic function. Endocrinologists must clearly point a patient’s phenotype while the diagnosis of PCOS\(^{44,4}\).

Therefore, an heighten clinical signs recommended that HA appeared to be the strongest factor of the PCOS pathophysiology and a crucial auguring of the accompanying metabolic syndrome\(^{45-47}\). Subsequently, it has been suggested that non-HA PCOS patients (i.e., those with chronic anovulation and PCOM) do not truly
represent patients with the syndrome and are etiologically distinct from HA of PCOS. Systematic review of published literature to identify the link between PCOS phenotypes and independent morbidity. They concluded that PCOS is a disorder predominantly of androgen excess and that a concise diagnosis of PCOS should be based on the presence of clinical or biochemical HA in combination with ovarian dysfunction (i.e., ovulatory dysfunction or polycystic ovarian morphology), excluding other causes as congenital adrenal hyperplasia, Cushing’s syndrome and androgen secreting tumors. Therefore, AES-PCOS 2006 criteria excluded the non-HA phenotype (i.e., phenotype D, including polycystic ovarian morphology plus ovulatory dysfunction) that was proposed by the 2003 Rotterdam definition.

b. PCOS Criteria in Adolescents

While the definition of PCOS primarily in teen-agers monitors the universal ideologies of mature females, there are a number of warnings to troy and caution at judging this stage group, mainly girls who do not see the total symptoms in adults. This is an interval of hormonal and reproductive switch, so that while some of these girls will provide visibly adult PCOS symptoms, others will provide less obvious and less accurate signs of the disturbance. Nevertheless, at the age of 18 years, the massive common of adolescents with PCOS had obviously advanced the phenotype.

Lately, two groups of pubertal PCOS criteria were recommended, one by an ESHRE/ASRM working group and the additional by Endocrine Society in a clinical practice guidelines committee. Affording to these endorsements, while PCOS is not visibly apparent by mature criterion, in adolescents the defect could be gaze on the essential of the appearance of excess serum androgens levels and/or accumulative hirsutism, in assembling with present oligo/amenorrhea for at minimum 2 years next menarche and/or primary amenorrhea by age 16 years, and/or an ovarian size >10 cm3, in accordance with an exception, of side reasons. It should be clear, anywise, that neither of the project criteria has yet to be prove.

c. PCOS Criteria in the Pre- and Post menopause

PCOS diagnosing in the pre- and post-menopause is a challenging. The menopausal turnover of females with PCOS is not fully understandable. In spite of it appears that as a female with PCOS age many gaining menstrual periodicity, suffer a reduction in the ovarian size and issue of ovarian follicles, and keep serum androgen levels, whole of that can get better the clinical appearance of PCOS.

In 2013, an Endocrine Society-appointed committee of scientists, on the rules of exclusive proof, educated the first hypothetical PCOS qualifier for post menopause. The will proposes that the PCOS diagnosis in postmenopausal women could be established on a past medical record of menstrual disturbance and the HA appearance at the reproductive age. The entity of PCOM believed a supportive mark; while, it was far to be diagnosing at age-linked variations in ovarian morphology.

Epidemiology and Prevalence of PCOS

The incidence of PCOS relies on the select of diagnostic criteria. The World Health Organization appraisals that it affects 116 million females universal as of 2010 (3.4% of the society). One society-established incidence investigation employing the Rotterdam criteria found that about 18% of females had PCOS and that 70% of them were before undiagnosed. In latest years there has been an interest in conducting meta-studies to prove the validity of the relationships between many factors that are related to diseases, including the studies of PCOS and its prevalence among females of reproductive age in the wide-ranging population has been estimated at 5.6%—16% reported by recent studies.

Predisposing factors for PCOS

The influencing causes for PCOS contain the next: A) Genomic causes: the family past of PCOS. B) Rise maternal androgen: prenatal exposure to androgens unwell monitored maternal congenital adrenal hyperplasia, Androgen secreting neoplasms, decreased childbirth weightiness for gestational age, premature adrenarche. C) Endocrinial causes: a starter of type1 diabetes before the first occurrence of menstruation (menarche), IR, and obesity. C) Medication: like antiepileptic drugs (e.g., Valproate). One day after another appears powerful proof that it is a genetically infirmity. this proof contains the familial group of patients, maximal occurrence in monozygotic than in dizygotic twins and genetic of hormonal and metabolic features of PCOS. The genetic constituent seems to be hereditary in an autosomal predominant mode. That refers to that; every infant has a 50% possibility of receiving the predisposing heredity variant(s) from a father or mother. The heredity variant(s) can be received from a parent and may be moved into both children (who probably asymptomatic conveys or can have signs like early alopecia and/ or immoderate hair) and girls who will be symptoms of PCOS. The genetic variant proves itself at minimal by rising androgen scales.
produced via ovarian follicle theca cells. The precise gene influenced has not still been fixed. The clinical acuity of PCOS features seems to become mostly fixed via causes such as obesity.

**Hyperandrogenism**

Hyperandrogenism (HA) is often looked to be the crucial chief characteristic stamp of PCOS and was relevant to early events of this disturbance in 1935 by Stein and Leventhal. It is 3 features by either heighten serum androgens (hyperandrogenemia) or connected clinical appearances relating to androgen activity’s which happens in around 60-80% of the PCOS residents. Separately, hyperandrogenism has indicated a relationship to fluctuating monthly periods, obesity, and sterility in precocious researches of the disorder. Additionally, a positive relationship with hyperandrogenism and IR has been recognized.

In the background of PCOS, the word, androgen mentions to the group of hormones; dihydrotestosterone (DHT), testosterone (T), androstenedione and dehydroepiandrosterone (DHEA). Testosterone T is the greatest often used clinical indicator of HA in PCOS and can be recognized in many formulas with raised freetestosterone (unbound to protein), bioavailable testosterone or total testosterone. Ovarian resulting androgens, androstenedione and testosterone version for about half of whole androgen creation in females, with androgens too resulting from adrenal glands (DHEA) and to a reduced amount adipose tissue. Modern investigation is furthermore display that the altered forms of HA can affect the phenotype of PCOS particularly while matching adrenal and ovarian HA, however more study in that zone is necessary. Clinical symptoms linked to HA mainly contain hirsutism which is the extreme growing of androgen dependent hair and happens in 70% of females with PCOS. Though, proof of HA may moreover be gotten in acne and mandesign hairlessness (alopecia). Those clinical outcomes in females with PCOS might share, at minimum in part, to the raised occurrence of depressing and nervousness disorders due to dropped self-appreciation.

**The Obesity and PCOS**

Overweight and obesity are distinct as irregular or extreme lipid increasing that offerings a danger to health. The body mass index (BMI) is a plain indicator of weight-for-height that is frequently applied to group underweight, overweight and obesity in individuals. It is stated as the weight in kilograms divided by the square of the height in meters (kg/m2). An individual with a BMI of 25 or more is estimated by WHO to be overweight, while obesity is scoped as having a BMI of 30 or more. In the total population, obesity increased from 15.7% to 38.8% in the US. Overweight are likely to advance comorbidities, chiefly T2D, metabolic syndrome (MetS), a multiplicity of cancer, and CVD. These metabolic defects are spectacularly mounting amongst adults in the Eastern Mediterranean area. The datum for adults aged 15 years and older from 16 nations in the region offer the greatest levels of overweight and obesity in Egypt, Bahrain, Jordan, Kuwait, Saudi Arabia, and United Arab Emirates. The prevalence of overweight and obesity in those nations extent from 74% to 86% in females and 69% to 77% in males. This information marks a considerably higher prevalence of obesity amongst adult females, whilst overweight is extra noted amongst adult males. Increase rapidly levels of overweight and obesity amongst children and adolescents is of appointed worry offered new proof relating childhood and adolescent obesity to an elevated danger of obesity and morbidity in puberty.

In most circumstance, the threat of PCOS increases with growing obesity. Obesity is prevalence in 50% to 80% of females with PCOS. Ventral and visceral fat shows a chief character in the progress of this syndrome, by way of amplified abdominal adipose tissue is noticed in usual weight PCOS females also. Therefore, a meta-analysis and a systematic review study displayed that impaired glucose tolerance (IGT) and T2D are mainly effected by abdominal adipose tissues in PCOS, even in those have a usual weight, concentrated on body mass index (BMI) values. While HA and menstrual inconsistencies signify crucial protests in adolescence with the PCOS, signs associated to androgen extra, oligo amenorrhea or amenorrhea, and sterility are the core afflictions of childbirth-age women. Obesity had a serious effect on the intensity PCOS especially in the existence of excess abdominal adipose tissue. Fat irregularities have moreover existed to have an important and free connotation with PCOS, and are precisely branded via a noteworthy decreasing of high-density lipoprotein cholesterol (HDLc), and an rise of triglycerides (TG), those are frequently related with both extra weight and obesity. They can similarly have hormonal reliant comorbidities and sterility generally linked to PCOS-associated anovulation. The probability to become pregnant in obese women with PCOS is less than in those with typical weight. Moreover, obese PCOS women need rising doses of ovulation-promote drugs to reach ovulation. The results are particular features of obesity that may be co-influencer share into sterility.
The strong connection between fatty mass and insulin, estrogen, and androgen levels is closely proven. Females with central obesity have elevated T and DHT output rates than those with peripheral obesity. Those factors are specific for ladies with central obesity might be causing to raised free androgen driving to HA and decreased fertility. That truth is relevant for ladies with PCOS; even those with normal BMI might have increased abdominal obesity. The recent cohort study conclusions offered that waist to height ratio but not a body pattern indicator was a useful diviner of IR, MetS with PCOS and sanitary females. Waist to height ratio may be suggested as a checking marker for IR and MetS danger rating amongst PCOS females as a sensible, cheap, not nested, easy to estimate and simple to calculate by measuring tape.

**Management of PCOS**

Therapeutic management of PCOS purposes to dropping insulin heights, repair fertility, medicate hirsutism or acne, return constant menstrual cycle and avoid endometrial hyperplasia and endometrial cancer. All-purpose mediation that aid to decrease greater quantity of weight or IR be able to become helpful for totally these goals as they are supposed to be the primary roots.

**Conclusions**

PCOS remains the most prevalent syndrome among women in the world and causes millions of cases of childlessness in women across the globe. Although it is difficult to diagnose this syndrome in its early stages in the age of young females, researchers have proven the possibility of a clinical diagnosis of it, which gives hope stronger in avoiding its health complications represented by chronic diseases such as T2DM and CVD. Despite the many studies that dealt with many clinical aspects of this syndrome for more than a decade, the causes of PCOS are still not clear. Therefore, we recommend more research in the genetic direction in an attempt to explain some of the mysteries that still surround its causes.

**Keywords:** polycystic ovary syndrome, PCOS, BMI, obesity, insulin resistance IR, anovulation, infertility, hyperandrogenism, adolescents.

**Abbreviations:** PCOS, polycystic ovary syndrome; PCOM, polycystic ovarian morphology; CVD, cardiovascular diseases; T2DM, type 2 diabetes mellitus; TG, triglyceride; WHR, waist-to-hip ratio; HA, hyperandrogenemia; OD, Ovulatory Dysfunction; IGT, impaired glucose tolerance; HDLc, high-density lipoprotein cholesterol; T, testosterone; DHEA, androstenedione and dehydroepiandrosterone; MetS, metabolic syndrome.

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