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Clinical Presentation, Risk Assessment and Management of Polycystic Ovary Syndrome [PCOS]

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by chronic anovulation, hyperandrogenemia, hyperinsulinemia and insulin resistance. It is the most common endocrine disorder in women of reproductive age with an enigmatic pathophysiology. The current proposed diagnostic criteria for PCOS include a number of disorders with similar phenotypes but radically different etiologies. Since there is no universally accepted clinical definition for PCOS identification, clinical associations and assessment of treatment is delayed. It is the most frequently encountered endocrine disturbance in women of reproductive age with prevalence from 5% to 10% affecting all ethnic groups, and it is not only a reproductive disorder but a metabolic one. Recognition of this syndrome makes management of symptoms such as acne, hirsutism, infertility and also reduces the development of type 2diabetes mellitus (T2DM) subsequent strokes and myocardial infarction much easier. Once a diagnosis is made, a thorough investigation of the propensity to developT2DM, noting features of the MS and markers of risk factors for cardio vascular disease (CVD), should be made in both obese and non-obese women. Studies of PCOS in India carried out in convenience samples reported a prevalence of 3.7% to 22.5%, with 9.13% to 36% prevalence in adolescents only. The wide variation in prevalence might be due to diagnostic criteria practiced, limitations in diagnosis, heterogeneous presentation of symptoms, age groups, and ethnic populations studied. This article will discuss the clinical presentation, risk assessment and management of polycystic ovary syndrome.

Keywords: PCOS, Insulin resistance, Obesity, Hirsutism, BMI.

1. Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting women of the reproductive age and is a heterogeneous disorder of unknown etiology resulting in overproduction of androgens, primarily from the ovary, and is associated with insulin resistance (IR) [1]. The most common symptoms of PCOS range from menstrual disorders, infertility, hyperandrogenemia to metabolic syndrome (MS). Elevated insulin levels due to IR may lead to development of PCOS by contributing to complex physiological dysfunction produced by interrelated metabolic and hormonal factors that predisposes patients with PCOS to different complications like endometrial hyperplasia and cancer, cardiovascular disease (CVD), miscarriage, and acanthosis nigricans (AN) [2]. These complications besides affecting the social and emotional health of the patients add to the burden in adolescents, who are under the impression of being afflicted by a 'disease'.

Table 1: Diagnostic Criteria for PCOS

National Institute of Health Criteria [NIH 1990]	Rotterdam Consensus Criteria [2003]	Androgen Excess and PCOS Society [2006]
Must Include All	2 out of 3 required	Must Include All
Chronic anovulation	Oligo/anovulation	Ovarian dysfuction
		Oligo/anovulation
	Polycystic Ovaries on USG	Polycystic Ovaries on USG
Clinical and/or Biocehmical signs of Hyperandrogenism	Clinical and/or Biocehmical signs of Hyperandrogenism	Androgen Excess
		Hirsutism
		Hyperandrogenimia
Exclusion of possible related disorders	Exclusion of possible related disorders	Exclusion of possible related disorders
First developed	Formulated to expand NIH definition and Commonly used	Formulated to provide evidence based definition

National Institute of Health Criteria (NIH 1990) was the first developed diagnostic criteria for PCOS (Table 1). Chronic anovulation and Clinical and/or Biocehmical signs of Hyperandrogenism were defined as the criteria for diagnosis of PCOS. The Rotterdam [2003][3] meeting, sponsored by the European society of Human reproduction and Embryology [ESHRE] American society for reproductive medicine, suggested that the definition PCOS should include two of the following three criteria: (i) Oligo- and/or anovulation, (ii) clinical and / or biochemical signs of hyperandrogenism, (iii) Polycystic ovaries on ultra-sonography, and exclusive of related disorders. In 2006, the Androgen Excess and PCOS Society [4] was an attempt to defined evidence based criteria for PCOS diagnosis and included ovarian dysfunction, oligo/anovulation, polycystic ovaries on ultra sonogram and androgen excess. ESHRE/ASRM consensus criteria defined polycystic ovary morphology as a presence of at least one ovary with ≥ 12 follicles of 2–9mm [between day 2-5 of cycle] or ovarian volume >10mL in the absence of a cyst or dominant follicle > 10 mm [5], established with ultrasound examination of ovaries. This morphology was also endorsed by the Rotterdam criteria and NIH. It is important to distinguish PCO from multi-follicular ovaries to make an appropriate diagnosis of PCO morphology [6]. Multi-follicular ovaries contain larger (up to 10 mm diameter) and fewer (up to 6 each ovary) cysts, without hypertrophic echogenic stroma. Thus currently three main criteria for diagnosis of PCOS are androgen excess (AE), chronic anovulation, and presence of PCOS (Figure 1) [7].

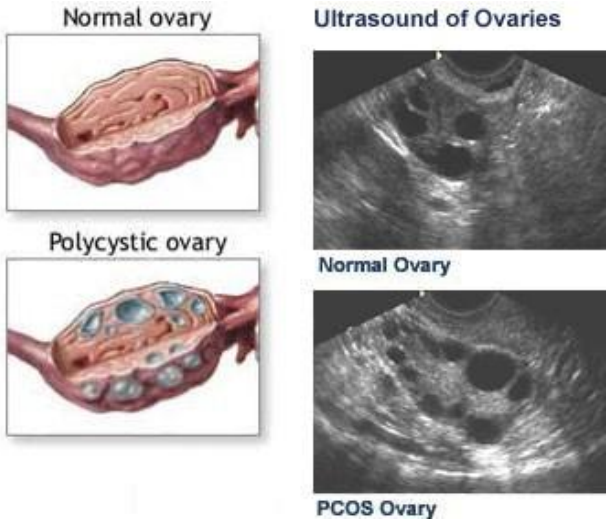

Figure 1: Normal Vs polycystic Ovary

2. Risk factors in the assessment of PCOS

Body Mass Index (BMI) is a key risk factor associated with the incidence of PCOS (mean BMI: 29.3 ± 7.5 vs. 25.6 ± 5.8 kg/m2, $p < 0.001$ in women with and without PCOS); higher BMI has been implicated as an important indicative marker of PCOS status. Development of IR and dysregulation of lipid metabolism are seen even in the early stages of PCOS. A family history of PCOS or diabetes or an inadequate lifestyle has also been shown to be important risk factors for incidence of PCOS [8].

Table 2: Diagnostic Criteria for Grade A, EL 3 Malik et al, 2014

Biochemical characteristics	Clinical symptoms
BMI >23 kg/m2 for adults and > 97.5th percentile for age in adolescents	Pubertal deviations [early or late]
Insulin Resistance (aconthosis nigricans as clinical marker)	Disturbances in periodicity/ timing of menstrual cycle
Family history of diabetes, PCOS, obesity and inadequate lifestyle	Presence of PCO
Marker of lipid metabolic dysregulation: • elevated serum total cholesterol, • triglyceride • LDL-C levels	Clinical signs of hyperandrogenism: • Early acne or hirsutism • Persistent severe acne • Frequent relapse in acne • Acne in facial 'V' area • Persistent acne and hirsutism for more than two years

The Indian Fertility Society recommended that an Indian specific grading should be performed and the possibility of other aetiologies like thyroid dysfunction, hyperprolactinemia, hypercortisolism, non-classic/late-onset congenital adrenal hyperplasia as well as hormonally active adrenal or ovarian tumors should be excluded (Grade B, EL 3) [8].

Indian women showing at least one biochemical characteristic in conjunction with one clinical symptom should be considered for further evaluation for the likelihood of PCOS (Table 2).

3. Diagnostic criteria for PCOS in adults and adolescents

Since there is a prevalence of acne and the immaturity of HPO (hypothalamic-pituitary-ovarian) axis during the first two years following menarche care must be taken in the diagnosis of PCOS among adolescents. For adolescents, a diagnosis of PCOS should follow a method based on a combination of persisting menstrual irregularity beyond the first two years of menarche and biochemical hyperandrogenism, with or without clinical symptoms of androgen excess [9].

Ovarian morphology on ultrasound is not routinely recommended because it is not an established criterion in adults. Table 3 gives the diagnostic criteria for PCOS in adult women and adolescents. The Rotterdam Criteria of androgen excess, ovulatory dysfunction and polycystic ovary on ultrasound are the main criteria for diagnosis additional criteria have been defined to categorise the PCOS patients into different grades (Table 3).

The prevalence of PCOS in India is reported as 3.7% to 22.5% in adults [10], and 9.13% to 36% in adolescents [11].

Studies have suggested a wide variation in the prevalence rates and this might be due to heterogeneous presentation of symptoms, under defined diagnostic criteria practiced, different age groups and ethnic populations studied. The risk in PCOS prevalence in populations where the gene pool has been relatively constant confirms that environment factors are assuming an ever more important role.

4. Factors that contribute to PCOS

4.1 Overweight and Obesity

Obesity is a serious and prevalent condition constituting a significant economic burden in western countries and is considered a global epidemic by the world health organization [12]. It is defined as a condition where the amount of adipose tissue is increased to a point where it can adversely affect health [13]. Body mass Index (BMI, weight in kg per height in m^2) is a useful clinical tool that correlates reasonably well with adiposity. The modern living conditions are characterized by low daily energy expenditure and an abundance expensive food supply, making positive energy balanced common. As more developing countries adapt western lifestyles and diets, this trend is likely to spread.

Exposure to unrecognized environmental toxins may also play a role. Abdominal visceral fat correlates more strongly with IR and metabolic and reproductive fitness than subcutaneous fat [13] although the subcutaneous depots likely to also contribute to metabolic abnormalities [14] Waist – hip ratio (WHR) or waist circumferences (measured midway between the lowest rib and the iliac crust) provide a reasonable estimate of abdominal fat. In women, a WHR > 0.8 or 9 waist circumferences >80cm indicates increased risk of obesity associated metabolic complications and > 88cm indicates substantially increased risk.

This rising prevalence is an important health issue due to the clear association of obesity and abdominal obesity with an increased risk of IR, impaired psychosocial health, T2DM, cardiovascular tissue [CVD], Osteoarthritis, sleep apnoea and breast and uterine cancer. The development of obesity is linked to the development of the PCOS in susceptible individuals. Abbott et al[16] suggested prenatal risk factors for the post pubertal expression of the PCOS phenotype found two distinct groups of patients with polycystic ovaries; (i) those that had above average birth weight and (ii) those born to overweight mothers (women of normal weight who had high plasma LH but normal testosterone concentration. The authors point out two forms of PCOS have different origins in intrauterine life i) obese, hirsute women with polycystic ovaries have higher than normal ovarian secretion of androgens, associated with high birth weight and maternal obesity ii) lean women with polycystic ovaries have altered hypothalamic control of LH release resulting from prolonged gestation.

Table 3: Diagnostic Criteria for Adults and Adolescents based on Indian specific grading recommended by Malik et al, 2014

Diagnosis	Additional	Rotterdam Criteria [2 Out of 3]		
Adult women				
Grade A, EL 4		Androgen excess Biochemical: serum total testosterone Clinical: persistent acne, hirsutism, female pattern hair loss	Ovulatory dysfunction	Polycystic ovary
Grade B, EL 4	-Presentation of acanthosis nigricans with or without obesity -Mild prolactinemia and subclinical hypothyroidism are			
Grade B, EL 3	Peri-menopausal/ menopausal women -prolonged periods - androgen exces -oligomenorrhea -PCO -log ovarian volume -follicle number -testosterone			
ADOLESCENTS				
Grade B, EL 4	Oligomenorrhea or amenorrhea beyond two years of menarche	Androgen excess Biochemical: serum total testosterone Clinical: persistent acne, hirsutism, female pattern hair loss	Ovulatory dysfunction	Polycystic ovary
Grade A, EL 4	-Serum total testosterone [cut off 60 ng/dL] -OGTT [at zero and two hours after 75 g glucose load] -Serum 17– hydroxy progesterone [assessed at 8 am] -Serum TSH -Serum prolactin levels			

4.2 Insulin Resistance and PCOS

Studies have reported that 70% of PCOS women could be insulin resistant and 10% have Diabetes Mellitus (DM) [17-19]. Even in PCOS women with normal glucose metabolism 25% of them may convert to abnormal glucose metabolism in over just three years. More alarming, insulin abnormalities are highly prevalent in adolescents with PCOS. Glucose levels alone lack the sensitivity to predict metabolic risk in PCOS patients since the overall normal glucose levels on an Oral Glucose tolerance test (OGTT) do not predict Insulin Resistance (IR) and IR despite normal glucose levels, is correlated with chronic respiratory problem (CRP), dyslipidemia and other CAD risk factors. IR can be just as severe in diabetics and non diabetics indicating that this metabolic impairment as a precursor and not a separate disease that culminates in end organ disease. Some human data shows a high degree of correlation between hyperandrogenism and IR and the relationship between hyperandrogenism and IR seem to be different between PCOS and non PCOS women. Reproductive dysfunction in PCOS women may also be a manifestation of IR. Post receptor insulin abnormalities and reduced peripheral insulin receptor binding have been found in PCOS women. Proposed mechanisms for insulin reproductive abnormalities include abnormalities of ovarian steroid genesis, excessive LH secretion and abnormalities in glucose uptake. Studies on PCOS from India reported a prevalence rate of 37.5% [20] to 62.5% [21] for obesity in patients with PCOS. A family history of obesity is also associated with PCOS phenotype [22]. Obese women with PCOS have a higher incidence of showing hypertension, impaired glucose tolerance (IGT) and type 2 diabetes Mellitus (T2DM) as well as higher odds of irregular menstrual cycles and clinical hyperandrogenism than lean women with PCOS [20].

5. Management of PCOS

5.1 Non Pharmacological Interventions: Exercise and Diet

Some controlled studies have reported the benefits of physical activity (at least 150 minutes of per week) in improving metabolic status and reducing the incidence of diabetes in high risk groups but these studies lack large

Randomised Control Trials [23]. In women with PCOS and obesity, weight loss through diet control has been shown to improve pregnancy rates, normalize hyperandrogenemia, and improve insulin sensitivity, menstrual functions, and hirsutism[24]. However, no PCOS- specific diet has been reported. Therefore, it is essential to consult a dietician for optimal weight management in women with PCOS.

5.2 Pharmacological Interventions

5.2.1 Menstrual Irregularity and Hyperandrogenis

In women with menstrual irregularity (MI), proliferation of endometrium can be inhibited using either cyclic progestin or combined oral contraceptives (COCs: estrogen + progestin). The main treatment for MI patients with PCOS not willing to conceive has been Low-dose COCs (< 50 mcg of estrogen in combination with a progestin0. Progesterone withdrawal bleeds are generally accepted as first line therapy to restore cycle regularity in women with PCOS and to reduce the risk of endometrial proliferative disorders. The progestins commonly used in India are drospirenone, desogestrel, and cyclic progestin or COCs like natural micronized progesterone, dienogest, nor-ethisterone and the levonorgestrel- intrauterine system (LNG-IUS) [24].

The Androgen Excess [AE] in women with PCOS is linked to IR and consequent hyperinsulinemia, necessitating the use of insulin sensitizers such as metformin and thiazolidinediones in the management of PCOS. Metformin in combination with a low dose anti-androgen (spironolactone) was more beneficial than either drug alone in improving MI in adult women with [18]. COCs are common agents for pharmacologic treatment of hirsutism in women not willing to conceive [25]. COCs with anti-androgenic progestins such as cyproterone acetate (CPA), drospirenone, desogestrel are generally used for the management of hirsutism in women with PCOS. Corresponding administration of direct mechanical hair removal methods improves the condition and reduces the time required. Hormone therapy is suggested as first-line therapy for androgenic acne in women with PCOS, SAHA syndrome (seborrhea, acne, hirsutism, alopecia), HAIRAN syndrome (hyperandrogenism, IR, AN), or cutaneous hyperandrogenism. Cosmetic treatment of hirsutism, acne, and alopecia is an option for women dealing with the hyperandrogenic manifestations of PCOS. Alopecia can be treated topically or with oral antiandrogens like spironolactone, flutamide and finasteride [26]. Contraception is recommended when patients are using antiandrogens for the treatment of PCOS since there is an increased risk of teratogenicity to the male fetus (opposing genital formation).

5.2.2 Anovulation

The drug of choice for inducing ovulation in PCOS is clomiphene citrate, although the precise mechanism of action is unknown [24]. Antidiabetic drugs like metformin can be used to improve fertility, decrease insulin resistance, and reduce circulating androgen levels [25]. Human menopausal gonadotropin (HMG) and FSH can also be used to induce ovulation if clomiphene and/or metformin therapy fails. Homburg et al., 2012 [26] reported that pregnancy rates were higher with FSH than with clomiphene, and there were more live births with FSH.

6. Conclusion

Polycystic ovary syndrome (PCOS) is not only a reproductive endocrine disorder but also a metabolic disorder associated with hyperinsulinemia, glucose intolerance, obesity and altered lipid profile. The heterogeneous nature of PCOS necessitates a sustained multi-pronged strategy with inter-disciplinary expertise for the effective management of PCOS. However, in contemporary clinical practice in India there is lack of awareness about PCOS, guidelines addressing its diagnostic criteria and management makes successful interdisciplinary cross-linking of efforts a huge task. Further, the relative lack of medical infrastructure to deal with the chronic outcomes of PCOS and the higher risk of PCOS in Indian women makes effective evidence based treatment guidelines for India an immediate necessity.

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