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Polycystic Ovary Syndrome, a modern epidemic: An overview

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting women, but can be very difficult to diagnose and treat due to vague presentation of symptoms and a lack of standardization in treatment. PCOS is characterized by hyperandrogenic manifestation like acne, hirsutism and chronic anovulation and is associated with metabolic derangement such as hyperlipidemia, hyperinsulinemia, insulin resistance and Type 2 diabetes mellitus.The cause of polycystic ovary syndrome is still unclear due to its multifactorial complexity; however, it has been observed and understood that there are several environmental and genetic factors, such as genetic variations like mutations and polymorphisms, differential regulation of genes, and pathways, may contribute to the pathogenesis of PCOS.The occurrence of considerable heterogeneity in clinical symptoms and endocrine features associated with PCOS implies that some women with Polycystic Ovaries on ultrasound scan may even exhibit none of the other features of PCOS.There is a spectacular increase in the prevalence of PCOS all over the world especially in Asia. The condition seems to be on a rise in Kashmir valley although systematic studies on the subject are still underway. In this review article, we will briefly provide an overview about the polycystic ovary syndrome.

Keywords: Polycystic ovary syndrome, Genetic basis, clinical presentation.

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Introduction

Polycystic ovary syndrome (PCOS) is an exceedingly prevalent metabolic disorder and possibly constitutes the most frequently encountered endocrinopathy to affect women. There is considerable heterogeneity of symptoms and signs among women with PCOS, and for an individual these may change over time. The extreme end of the spectrum, once known as Stein-Leventhal syndrome, encompasses the combination of hyperandrogenism (hirsutism, acne, alopecia and elevated serum testosterone concentrations), severe menstrual disturbance (amenorrhea or oligomenorrhea) and obesity[1].The prevalence rate of PCOS appears to be higher in countries where obesity and type 2 diabetes are common[2]. Not all PCOS women are obese and hence they vary in degrees of thinness to fatness, 30-75% of PCOS cases contend with being overweight or obese[3]. Within the past two decades, the developing nations as India and China[2] began relying on Westernized diets and lifestyle. It is predicted that there may be up to a six fold increase in obesity prevalence in the next ten years especially for India who already has the highest rates of diabetes in the world[4].Most of the symptoms associated with PCOS appear to be linked with either high androgen or insulin hormone levels [5, 6]. The clinical presentation and expression of PCOS symptoms viz. polycystic ovaries, high levels of androgens and irregular periods are variable from patient to patient. It is a fact that not all women with polycystic ovaries have PCOS and not all women with PCOS have polycystic ovaries. The symptoms may vary from mild to more severe, and some women may only have a few symptoms, while others have more. This complexity has made it very difficult for clinicians to find a clear cut way to diagnosis a patient with PCOS and to account for exact prevalence rates [7, 8].

Clinical Presentation of PCOS

The clinical presentation of PCOS differs widely. Women with PCOS often seek curative treatment for menstrual disturbances, hyperandrogenism (clinical features), and infertility. Menstrual irregularities commonly observed in PCOS are oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding [9]. However, 30% of women with PCOS will have normal menses[10]. Approximately 85%–90% of women with oligomenorrhea have PCOS while 30%–40% of women with amenorrhea will have PCOS [11]. Hirsutism is a common clinical presentation of hyperandrogenism occurring in up to 70% of women with PCOS [12]. It is evaluated using a modified Ferriman–Gallwey scoring system (mFG score) [13]. This tool is used to evaluate hair

growth at nine body sites: upper lip, chin, chest, upper abdomen, lower abdomen, upper arms, upper back, lower back and thighs [14]. Over 90% of normally menstruating women with hirsutism are identified through ultrasound to have polycystic ovaries (PCO)[15]. In addition, PCOS occurs in 50% of women with less severe distribution of unwanted hair growth [16]. Acne is also a manifestation of hyperandrogenism but is less prevalent in PCOS and less specific than hirsutism. Approximately 15%–30% of adult women with PCOS present with acne [17, 18]. The variations in prevalence of hirsutism and acne may be related to the difference in expression of 5α-reductase in the sebaceous gland and the hair follicle, and resulting in higher dihydrotestosterone in the hair follicle [19]. Out of these women presenting with severe acne, over 40% were diagnosed with PCOS [20]. Some experts suggest that women presenting with acne be asked about their menstrual history and be evaluated for other signs of hyperandrogenism[21]. Infertility affects 40% of women with PCOS [22]. PCOS is the most prevalent reason for an ovulatory infertility. Approximately 90%–95% of an ovulatory women attending infertility clinics have PCOS. PCOS women have a normal number of primordial follicles where as primary and secondary follicles are significantly increased. However, due to disorders in factors involved in normal follicular development, the follicular growth becomes arrested as follicles reach a diameter of 4–8 mm. As a result dominant follicle does not develop, ovulation does not ensue [22, 23]. In addition, spontaneous abortion occurs more frequently in PCOS with incidences ranging from 42%–73% [24, 25].

Molecular alterations in PCOS

The exact cause of polycystic ovary syndrome is still unknown due to its multifactorial complexity; however, it has been observed and understood that there are several environmental and genetic factors, like genetic variations like mutations and polymorphisms, differential regulation of genes, and pathways, may contribute to the pathogenesis of PCOS [26-28]. Various studies elaborate, association of differential regulation of genes at various levels , which includes, genes that are increasingly regulated and decreased in PCOS and the associated effects of differential regulation of genes were studied [29]. The detailed literature study revealed that the differential expression of genes involved in various biological process such as androgen biosynthesis, angiogenesis, follicular development, and at different stages of the embryonic development, contributes to the several changes of the gene regulation at the molecular level [30], including the differential regulation of genes and mRNAs in the PCOS and its serious effects, including endometrial receptivity, implantation failure, early pregnancy loss, PTB, insulin resistance, hyperandrogenesim in women with PCOS [31, 32]. On the note of mutations and polymorphisms, it's been studied that the genetic variations play an important role in the pathogenesis of PCOS across various populations or ethnicities. Although several studies have been performed and several hundreds of articles are published in the public domain on PCOS, the information is highly scattered or dispersed in the literature, which is the most specific challenge for researchers. Hence, the need to have a comprehensive coverage of scientific, evidence-based information on PCOS-associated genes and its molecular mechanism becomes essential and critical [33].The detailed literature study revealed several genes and the genetic variations in PCOS and its critical effects, such as ovary failure [34], obesity [35], spontaneous abortion[36], recurrent pregnancy loss [37]etc. The causal genetic variants were grouped at various levels, including mutation, single nucleotide polymorphism, etc., and the associated phenotypic effects of those variations or alterations were captured. Despite a number of candidate genes being identified, a primary pathological cause of PCOS has still not been identified.

Diagnosis of PCOS

Three main diagnostic criteria employed for diagnosis of PCOS are as follows;

A. The National Institute of Health/National Institute of Child Health and Human Development consensus conference criteria is the most commonly employed diagnosis for the PCOS and is as follows[38] ;

1. Clinical and/or biochemical hyperandrogenism.

2. Oligo-anovulution (oligomenorrhea/amenorrhea) Exclusion of disorders like non-classical congential adrenal hyperplasia (NCAH), hyperprolactinemia, androgen producing tumors, thyroid dysfunction and cushing syndromes.

B. ROTTERDAM CRITERIA 2003 [39]

The Rotterdam criteria for the diagnosis of PCOS (2003) states 2 of the 3 features need to be present to make the diagnosis and with the exclusion of other etiologies (like congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors). These features include;

(1) Oligo- or anovulation.

(2) Clinical / biochemical signs of hyperandrogenism and

(3) PCO (either 12 or more follicles measuring 2–9 mm in diameter, or an ovarian volume of >10 cc).

C. ANDROGEN EXCESS SOCIETY (AES) [40]

Diagnostic criteria laid down by include hyperandrogenemia and or hyperandrogenism plus one out of 2 remaining criteria of oligo/amenorrhea and polycystic ovaries on ultrasonography.

Treatment Guidelines and Recommendations for PCOS[41, 42]

Endocrine Society Clinical Practice Guideline (Ligro et al, 2015) for treatment of polycystic ovaries recommends:

1. HCs (ie, oral contraceptives, patches, or vaginal rings) as the first-line management for the menstrual abnormalities and hirsutism/acne of PCOS.
2. Use of exercise therapy in the management of overweight and obesity in PCOS. Weight loss strategies should begin with calorie-restricted diets (with no evidence that one type of diet is superior) for adolescents and women with PCOS who are overweight or obese.
3. Suggest against the use of Metformin as a first line treatment of cutaneous manifestations, for prevention of pregnancy complications, or for the treatment of obesity.
4. Recommend metformin in women with PCOS who have T2DM or IGT who fail lifestyle modification. For women with PCOS with menstrual irregularity who cannot take or do not tolerate HCs, suggest metformin as second-line therapy.
5. Recommend Clomiphene citrate (or comparable estrogen modulators such as letrozole) as the first-line treatment of anovulatory infertility in women with PCOS.

6. Suggest the use of Metformin as an adjuvant therapy for infertility to prevent ovarian hyperstimulation syndrome (OHSS) in women with PCOS undergoing in vitro fertilization (IVF).
7. Recommend against the use of insulin sensitizers, such as inositols (due to lack of benefit) or thiazolidinediones (given safety concerns), for the treatment of PCOS.
8. Suggest against the use of statins for treatment of hyperandrogenism and anovulation in PCOS until additional studies demonstrate a favorable risk benefit ratio. However, guideline suggests statins in women with PCOS who meet current indications for statin therapy.

Evidence-based guideline for the assessment and management of polycystic ovary syndrome recommends[43]:

1. Lifestyle intervention as the first line non-pharmacological treatment and management for PCOS. Lifestyle management, including diet and exercise programs should be used throughout the lifespan in women with PCOS to optimise health generally and to alleviate PCOS clinical severity including infertility.

2. Clomiphene citrate as a first-line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility, with no other infertility factors.

3. Recommends against the use of aromatase inhibitors e.g., Letrozole as the firstline pharmacological therapy in women with PCOS who are anovulatory and infertile, with no other infertility factors.

4. Recommends Gonadotrophins as a second-line pharmacological therapy in women with PCOS who have clomiphene citrate resistance and/or failure, are anovulatory and infertile, with no other infertility factors.

5. Recommends CC + Metformin or Metformin alone (if BMI 30kg/m2) as the 2nd line pharmacological agents for infertility.

Conclusion

In view of PCOS encompassing multiple specialities, a holistic approach involving general practitioners, endocrinologists, gynaecologists and health educators remains the most pragmatic approach. Hyperandrogenism and insulin resistance appear to be central cause to the pathophysiology of the disease, which appears to be multi-factorial and polygenic in nature involving multisystem dysfunction, namely reproduction, endocrine and metabolic. Though, a plethora of treatment options have arrived for PCOS in recent years the lifestyle modification including a structured meal plan and exercise schedule remains the cornerstone and the most effective modality of treatment till date. As a general rule all other treatment options are added to this depending upon the gravity of the presenting problems.

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