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## **AN OVERVIEW OF HYPERANDROGENISM IN PCOS AND THE PROSPECTIVE UNDERLYING FACTORS**

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**ABSTRACT:** Poly Cystic Ovary Syndrome (PCOS) is an endocrine disorder with an increased prevalence worldwide. The rate of incidence of PCOS has been alarmingly getting amplified among the women of reproductive age. It is a major contributor of infertility/subfertility in global population. The patients with PCOS often present heterogeneous symptoms like irregular menses, hyperandrogenism, ovulatory disorders, presence of ovarian cysts etc. The symptoms are often underestimated or ignored and they are diagnosed only at a later stage. The etiology of PCOS is still unclear as it is a multifactorial condition. There are different scientific societies that have framed guidelines for diagnosis of PCOS and they have classified 3 different phenotypes. All the phenotypes has hyperandrogenism as a main symptom of PCOS where there is an excess of androgen production. This review focuses on hyperandrogenism and various factors that are responsible for the hyperandrogenic state in PCOS patients.

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**KEYWORDS:** PCOS, Hyperandrogenism, Testosterone, Gynecologic disorders, Environmental factors.

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### **1. INTRODUCTION**

Poly Cystic Ovary Syndrome (PCOS) is an endocrine disorder commonly found in women during their reproductive age [1]. The history of PCOS dates back to the 18th century based on some scientific evidences, though Stein and Leventhal defined it during 1935 [2]. But, the existence of genetic traits similar to this disorder is considered to be as ancient as nearly 50,000 years ago [3].

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The manifestation of this condition usually begins in adolescence. Clinical or biochemical hyperandrogenism is the most commonly presented symptom along with ovulation problem, menstrual irregularities and presence of multiple cysts in their ovaries. It has been reported that 5 – 20% of the women in the reproductive age have PCOS. Nearly 70% of the women are left undiagnosed [4]. The diagnosis of PCOS is defined based on the presence or absence of three major symptoms (Hyperandrogenism, Ovulatory disorders and presence of polycystic ovaries) and the PCOS condition has been differentiated into four different phenotypes. The incidence of PCOS is caused by a number of genetic, metabolic and environmental factors. Increased level of stress, sedentary lifestyle, intake of junk food and exposure to various environmental toxicants. PCOS has an increased risk of associated morbidities like insulin resistance leading to type 2 diabetes like condition, obesity, ovarian cancer and cardiovascular diseases. At present there is no specific medication or cure for PCOS. Rather, the patients will be treated according to the presentation of symptoms by the individual patients. The fine line of treatment includes fertility medicines like clomiphene citrate, hormonal therapy, oral contraceptives, surgery, in vitro fertilization along with life style modifications.

### **Prevalence of PCOS**

The global prevalence of PCOS is similar. It has been roughly estimated to be in the range somewhere between 5 – 20%. The prevalence of PCOS varies based on ethnicity which has been revealed by Genome Wide Analysis Studies in different geographical locations [5, 6].

### **Symptoms and diagnostic criteria**

PCOS is a heterogeneous condition with a wide range of signs and symptoms varying based on the age or reproductive phase of the individual. The symptoms may be mild to severe. Based on the presence of the aforesaid signs in different combinations the PCOS has been categorized into four different phenotypes of PCOS. Though Stein and Leventhal introduced PCOS in 1935 the consensus meeting by NIH was held in 1990. The NIH criteria for PCOS includes Clinical and/or biochemical hyperandrogenism and associated ovarian dysfunction. Later in 2003, a conference was organized in Rotterdam, Netherlands which was partly sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and The American Society for Reproductive Medicine (ASRM) where a broader classification was done including the symptoms said in NIH and the presence of Poly Cystic Ovarian Morphology (PCOM). More recently, the Androgen Excess society met in 2006 and made the presence of hyperandrogenism as a mandatory criteria of PCOS along with ovulatory disorders with/without PCOM.

### **Hyperandrogenism**

The term hyperandrogenism refers to the condition where the level of androgens (male hormones) are present above the normal range in females. In PCOS ovarian and extra-ovarian hyperandrogenism is considered as a major symptom. The hyperandrogenic condition in the ovary

is contributed by the androgen synthesis that occur in the theca cells of the ovarian cells [7]. The most common hyperandrogenic disorders include PCOS, idiopathic hyperandrogenism and the non-classic 21 hydroxylase deficiency. In PCOS condition the level of testosterone will be much higher than that of the normal range. Hyperandrogenism is generally diagnosed by the levels of total testosterone, free testosterone, SHBG, androstenedione and dehydroepiandrosterone (DHEA). The free androgen index (FAI) can be calculated ( $FAI = (Total\ Testosterone / SHBG) \times 100$ ) [8]. Though testosterone is a male reproductive hormone, females too secrete androgens in smaller quantities as part of normal metabolic function. Normally, in women both adrenal glands and ovaries produce androgens in almost similar levels [9]. Elevated levels of ovarian androgen is considered as staple manifestation of hyperandrogenism in PCOS leading to impaired follicular maturation as the elevated levels of androgens may have a negative impact on follicular development leading to atresia. Generally, ovaries are considered as the main contributor of androgen excess in PCOS condition, but it has been found that 20 – 30% of patients with PCOS exhibit increased adrenal androgen levels [10, 11]. It is evident from some scientific reports that, the ovarian androgen excess influences adrenal androgen excess in PCOS condition and they are often correlated. Only a very few patients present adrenal hyperandrogenism alone [9]. Adequate research have proved the ovarian androgen excess as major criteria in PCOS women at molecular level but, the adrenal hyperandrogenism couldn't be explored at molecular level due to the risks involved in obtaining the adrenal glands from the patients [12, 13]. Hyperinsulinaemia leads to hyperandrogenism by increasing the level of free testosterone in circulation as a result of decreased production of sex hormone binding globulin SHBG by the liver [14]. Some studies make it clear that insulin may be attributable to the increased level of adrenal androgens in women with PCOS [15]. The source of androgens vary in different hyperandrogenic conditions. In PCOS condition, ovary acts as the main androgen source [16] whereas, in idiopathic hyperandrogenism both ovary and adrenal glands are known to contribute to the androgen excess [17] In the non-classic 21 hydroxylase deficiency the adrenal gland seems responsible for androgen excess [9,18].

### **Hirsutism**

Hirsutism is a remarkable clinical symptom of hyperandrogenism common in PCOS which can be visually diagnosed [19]. It is a major consequence of androgen excess. Hyperandrogenism leads to the presence of masculine features in the females with PCOS. The presence of excessive facial hairs on the side of the face, upper lip, chin and it is also observed in chest region in individuals with severe conditions of PCOS. Hirsutism is defined by the FG score (Ferriman - Gallwey) though it has certain limitations [20]. It is a common symptom of PCOS due to androgen excess and it also depends on the individual hair growth patterns. The enzymatic conversion rate of testosterone to dihydrotestosterone has been reported to influence the androgenic effects in the hair follicle. Researchers have identified the role of 5  $\alpha$  reductase on variation of hair growth. 5  $\alpha$  reductase is

known to exist in 2 isoforms viz., type 1 and type 2 where the type 2 is predominant in the masculine hair (Beard and genitals) apart from testes and prostate. But, there is no adequate information pertaining to this in PCOS women. It has been proved under in vitro conditions that the expression of 5  $\alpha$  reductase mRNA was higher in the follicles obtained from the PCOS women compared to that of normal follicles [21, 22]. A study on patients with functional hyperandrogenism and PCOS showed that, the patients with hyperandrogenism who consulted physicians were more hirsute with presentation of both clinical and biochemical hyperandrogenism. Further they were more obese with increased incidence of PCOS than the normal population [23].

### **Ovulatory dysfunction**

Ovulatory dysfunction is one of the remarkable hallmarks of PCOS in spite of its heterogeneous nature [24]. It has been reported that ovulatory dysfunction affects nearly 25% couples [25]. Ovulation disorders are classified into 3 categories by WHO as group I, II and III. Hypothalamic pituitary failure is said to be the cause of Group I. It has been found that nearly 10% women with ovulatory dysfunction come under group I. Whereas, 85% of women with ovulatory dysfunction have group II disorder which arise due to the hypothalamic - pituitary – ovarian axis dysfunction. PCOS comes under group II ovulation disorders. The group III ovulation disorders includes about 5% women due to ovarian failure.

### **Polycystic ovaries**

In PCOS condition, the ovarian follicular arrest has been observed commonly where the maturation of follicles is inhibited and leads to the formation of fluid filled sacs called cyst. The presence of polycystic ovaries is a remarkable feature in the diagnosis of PCOS. The diagnosis of PCOS condition is not just based on the presence of enlarges cysts but the presence of excessive number of growing follicles [26]. Presence of poly cystic ovarian morphology (PCOM) is a diagnostic criteria for PCOS, though PCOM is excluded in some PCOS phenotype. Many studies have reported that ovarian size considering the ovarian volume and ovarian area are significant criteria for diagnosis of PCOS. In some cases women presenting polycystic ovaries are non – PCOS [27].

### **Day-day factors that may lead to PCOS**

Men and women across the globe are increasingly exposed to various known and unknown pollutants in their day-day life due to progressive industrialization and ever blooming technologies. Environmental and workplace pollution have nowadays play a significant role in causing fertility related disorders. A multitude of chemicals are generated into environment through various sources. The emerging pollutants or persistent organic pollutants impose adverse health effects in humans and they are unbiased towards age, sex or geographical location. Among them the female factors for infertility is often bothered and causes psychological distress in women particularly in developing countries and the women often bear the brunt. There are various female factors that lead to infertility. Among them the incidence of PCOS is in the rise in the recent decade due to environmental and life

style changes. PCOS is a multifactorial condition with an unclear etiology and a myriad of underlying causes. Generally, the contributing factors of PCOS include genetic, endocrine, metabolic and environmental factors. Environmental factors are less concerned but are ambient contributors to infertility related issues. There are many scientific reports postulating the possible role of various pollutants that act as endocrine modulators leading to infertility [28]. Endocrine disruptors are a class of chemical compounds or molecules that cause a significant change in the hormonal levels leading to various disorders in different classes of organisms. The effect of these chemicals have reported to cause a wide range of diseases like infertility to fatal ones like cancer. They also cause developmental disorders. The toxicity of endocrine disruptors have been established both in vitro and in vivo. Bisphenol A (BPA) is synthetic compound used found in polycarbonated plastics and epoxy resins. It is present in an umpteen number of products we use in our day-day life including storage containers to hygiene related personal care products and also dental fillings. The exposure to BPAs has almost been unavoidable as they occupy a maximum space in a wide range of commercial products. Takeuchi et al., (2004) has reported the presence of Bisphenol A in the serum samples of women included in their study [29]. They have reported a strong correlation between the levels of BPA in the serum and the androgen levels. The level of BPA was higher in the serum of men than women and interestingly, in hyperandrogenic women the BPA level were much higher and led to the speculation of androgen's influence on BPA metabolism. The presence of various pollutants in biological samples have been surfacing in various scientific investigations [30].

## **2. CONCLUSION**

In recent decades the incidence of PCOS has been significantly increased. The genetic and pathologic factors are mostly considered as underlying cause for fertility related disorders and the environmental factors contributing to infertility are often of least concern. Hence, this review focused on environmental factors that we get exposed to in our day-day life that lead to infertility related issues and highlights the alarming influence of them in PCOS.

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## **CONFLICT OF INTEREST**

The authors hereby declare there is no conflict of interest.

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