

**A REVIEW OF POLYCYSTIC OVARIAN SYNDROME: IMPLICATIONS FOR NON-COMMUNICABLE DISEASES****Irum Ismail<sup>1</sup>, Rahman Gul<sup>1,2\*</sup>, Safia Mengal<sup>1</sup>, Ghulam Farooq<sup>1</sup>, Kashmala Khan<sup>3</sup>, Abdul Qadir<sup>2</sup> and Wajid Khan**<sup>1</sup>Institute of Public Health Quetta, Balochistan, Pakistan.<sup>2</sup>Faculty of Pharmacy University of Balochistan, Pakistan.<sup>3</sup>Fatima Jinnah Medical University, Lahore, Pakistan.**\*Corresponding Author: Rahman Gul**

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**ABSTRACT**

The review article provides a comprehensive overview of polycystic ovarian syndrome (PCOS) and its connection with various non-communicable diseases. The article discusses the clinical features, diagnostic criteria, genetic predisposition, and environmental triggers of PCOS. It highlights the extensive risk of metabolic issues, with dyslipidemia and type 2 diabetes, as well as abdominal obesity metabolic syndrome. The review also explores the association of PCOS with non-alcoholic fatty liver illness, hypertension, coagulation disorders, and increased cardiovascular risk. Furthermore, the article discusses the potential link among PCOS and ovarian, endometrial, and breast cancers, as well as the higher prevalence of depression among women through PCOS. The conclusion emphasizes the importance of lifestyle modifications and further research to better understand and manage PCOS.

**KEYWORDS:** PCOS, androgen, insulin, animal models, cardiovascular diseases, depression, obesity, lifestyle.**1. INTRODUCTION**

Polycystic ovarian syndrome is hormonal disease in reproductive age group women under 18-44 age, with prevalence of 6-20% depending on criteria used.<sup>[1,2]</sup> Clinical features include menstrual irregularities, acne, increased facial hair growth, weight gain and infertility. The diagnosis is usually made by Rotterdam criteria with 2 out of 3 features as diagnostic for PCOS.<sup>[3]</sup>

- Chronic anovulation
- Clinical hyperandrogenemia Biochemical
- Polycystic ovarian morphology

PCOS is affecting women with different clinical presentations from menstrual irregularities, infertility, cosmetic dilemma, weight gain to metabolic disorders like non-insulin dependent diabetes mellitus, cardiovascular diseases, anxiety depression to various types of cancers.

PCOS is multifactorial disease with evidence of genetic predisposition triggered by environmental agents. The genetic susceptibility is different between families but having common biological pathway. Recently intrauterine programming has been hypothesized for PCOS. It has been published that, "Genes like CAPN10, insulin gene, FTO, cytochrome family P450, AR, FSHR are documented to take part in role in its etiology".<sup>[4]</sup>

Maternal PCOS may affect the developing offspring inside the womb as evidence is provided by various animal studies like mice, rats, sheep and rhesus macaques.<sup>[5]</sup>

Cure through testosterone during the prenatal period in sheep and macaques and late prenatal and early postnatal in rodents outcome in adult onset PCOS like character.<sup>[6,7]</sup> Lifestyle changes like obesity contributes to PCOS development, as women are encouraged to simply reduce weight to notice improvement in their symptoms; it can be due to improved insulin levels, androgens and gonadotropins.<sup>[7,8]</sup> Usage of high calorie food, unprocessed grains, and larger portion sizes is contributing to increased incidence of PCOS.<sup>[9,10]</sup> Environmental toxins such as organ chlorine compounds found in pesticides accumulate in fat are estrogenic and hormone disrupter, they can contribute to development of PCOS and breast cancer.

Epileptic drug valproic acid may contribute in PCOS development that can be reversed with discontinuation of medicine.<sup>[11]</sup> substances like perfumes and cosmetic agents are also thought to trigger development of PCOS.<sup>[12]</sup> No studies are available on infectious agents causing PCOS.

A retrospective cross sectional study was done recently in UAE understanding association of PCOS and chronic diseases like asthma and high cholesterol, it was found that understanding of association may get better the observation of chronic disease in PCOS women.<sup>[13]</sup>

## 2. METHODS

Google Scholar, PubMed, TRIP database, ScienceDirect, and UpToDate were searched for publications with PCOS related keywords in diverse areas, focusing on the new ones.

## 3. Diagnostic Criteria

Historically in 1935, Stein and Leventhal named PCOS as syndrome due to its wide presentation of symptoms, diagnosis been done on hormonal assays like raise in serum androgen and luteinizing hormone level among amplified LH/follicle-stimulating hormone ratio. presently the Rotterdam classification is mostly used according to this criteria 2 out of 3 criterias are required to diagnose PCOS.

- Oligo-and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovarian morphology and exclusion of other etiologies.<sup>[14]</sup>

## 4. Management

Treatment options vary according to presenting symptoms ranging from weight reduction, menstrual regularities to infertility treatment hence it is customized according to patient.

Lifestyle modification and dietary changes like increase fiber diet and low in saturated fat and carbohydrates and regular exercise to reduce and maintain weight.<sup>[15]</sup>

Currently used supplements in the treatment of PCOS vitamin D,  $\alpha$ -lipoic acid resveratrol, omega-3, folic acid, berberine, myoinositol, and d-chiro-inositol.<sup>[16]</sup>

Patients not willing to get pregnant, mostly complains concerning her menstruation irregularity, progestins or combined oral contraceptives are the drugs of selection. for example, Yaz<sup>®</sup>, may show antiandrogenic property and can, on the other side, effects in the decrease of androgen production, infact they might be caring in those with acne complications or hirsutism.<sup>[17]</sup>

Metformin, is given along with the (COCs) to restore the ovulation cycle in PCOS women because of its insulin sensitivity-increasing properties.<sup>[18]</sup>

In patients who desire assistance from skin manifestation because of hyperandrogenism drugs, aldosterone receptor antagonists like 5-alpha reductases, spironolactone and finasteride can be extra helpful treatment choice modify for persons with infertility who must take agents for ovulation induction similar to aromatase inhibitors and/or clomiphene citrate.<sup>[19]</sup>

## 5. Pcos as Risk Factor of Non-Communicable Disease

### 5.1. The metabolic consequences

There is increased risk of insulin resistance and glucose intolerance in PCOS and higher body index further exacerbates insulin resistance leading to hyperinsulinemia that augments androgen production, this androgen increases visceral fat in women. Prevalence of defective glucose tolerance and non-insulin dependent diabetes is 23-35% and 4-10 % respectively. The risk in women among PCOS for developing T2DM increases with body weight and are at increased risk to develop gestational diabetes mellitus.<sup>[20,21]</sup>

In addition there is 70% prevalence of developing dyslipidemia i.e. increased level of small density lipoprotein cholesterol, very low density lipoprotein cholesterol, high serum triglyceride, free fatty acid concentration and low level of high density lipoprotein cholesterol. This atherogenic profile is exacerbated by increased body weight and insulin resistance. These are risk factors for developing cardiovascular diseases.<sup>[22-23]</sup>

### 5.2. Abdominal obesity metabolic syndrome

It is a cluster of metabolic abnormalities with hyperglycemia abdominal obesity, hypertension and dyslipidemia among insulin resistance the key factor involved. It is posing 5 times risk for type 2 Diabetes mellitus and 2 times cardiovascular diseases. Prevalence of MetS is higher in PCOS compared with common population and it is still higher in hyper androgenic than non-hyper androgenic an ovulatory women with PCOS. There is fatty tissue useful derangement in PCOS patients i.e. adipose hypertrophy associated with hyperandrogenemia leading to insulin resistance.<sup>[24-26]</sup>

### 5.3. Non- alcoholic fatty liver disease

Increased prevalence of NAFLD i.e 27-62% in PCOS women.<sup>[27]</sup> Insulin resistance has been connected among developing NAFLD independent of obesity. Serum androgens also contribute and hence prevalence of complex liver disease in women with Polycystic disease higher than general population.<sup>[28]</sup>

### 5.4. Hypertension

The prevalence of hypertension is 9-27% higher than the general population, its postulated that androgen activates the renin-angiotensin system.<sup>[29]</sup>

### 5.5. Coagulation disorder

PCOS leads to prothrombotic state, there are increased levels of plasminogen activator inhibitor 1 and fibrinogen irrespective of BMI.<sup>[30]</sup>

### 5.6. Increased cardiovascular risk

Most prospective studies indicate association of hyperinsulinemia with atherosclerosis and coronary heart diseases.<sup>[31]</sup> there are several studies showing increased subclinical hardening and narrowing of coronary vessels in PCOS by various parameters like coronary artery

calcification, coronary artery media thickness and endothelial dysfunction.<sup>[32]</sup> Arterial stiffness is also increased in PCOS. In a retrospective cohort study PCOS women had more hospitalization for IHD & cardiovascular diseases compared to non-PCOS.<sup>[33]</sup>

Another retrospective cohort study conducted for 20 years period indicated higher ischemic heart diseases compared with local female population.<sup>[34]</sup>

Meta-analysis studies have shown that RR for coronary heart disease or stroke was 2.02 (95% CI 1.47 – 2.76) that was still considerable 1.55 after adjusting for BMI.<sup>[35]</sup>

Another meta-analysis showed OR for cardiovascular disease in PCOS was 1.30 (95% CI 1.09-1.56) the OR for Coronary heart disease (1.44; 95% CI 1.13-1.87) all three studies indicate a potential cardiovascular risk for coronary heart disease.<sup>[36-37]</sup>

### 5.7. Cancer

PCOS may increase risk for endometrial, ovarian and breast cancers. Confounders like hyperglycemia, obesity, and an ovulation among resulting infertility creates difficulty to describe absolute risk of these cancers attributions to PCOS.<sup>[38]</sup>

Association of PCOS with endometrial cancer is helped by biologic plausibility and preponderance of evidence suggesting 2-3 fold increase risk of endometrial cancer due to anovulation, menstrual irregularity and PCOS.<sup>[39]</sup> Measures like endometrial ultrasound or sampling, periodic induction of uterine bleeding through progesterone withdrawal, progesterone releasing intrauterine devices, use of oral contraceptives. Pregnancy has protective role against all three cancer types.<sup>[40]</sup>

Ovulating agents combat unrestricted estrogen and less risk of endometrial hyperplasia and cancer. Use of insulin sensitizing agents, dietary changes and weight reduction have contributed towards reversing pathology for endometrial and breast cancers.<sup>[41-42]</sup>

### 5.8. Depression

There is 8 times higher prevalence of depression among women with PCOS,<sup>[43]</sup> this could be due to releases of pro inflammatory markers further intensified by aesthetic issues of acne, increased facial hair, increased body weight, androgenic alopecia and infertility. PCOS has been mentioned as thief of woman hood.<sup>[36]</sup> as it steals the femininity and attractiveness of women.

A RCT by Greenwood et al suggested insulin resistance as causative factor for PCOS associated depression.<sup>[44]</sup> A cross-sectional study in India used Hamilton rating scale for depression and showed prevalence of depression was 25.7 % in women with PCOS.<sup>[45]</sup> Weight loss and dietary changes with oral contraceptive pills may prevent

complications of PCOS, such as hyperandrogenism related clinical features and metabolic complications like T2DM.<sup>[46]</sup>

### CONCLUSION

PCOS is evolving as an epidemic itself and as risk factor for many non-communicable diseases that is impairing quality of life and putting financial burden on community. Although it can be controlled by promotive and preventive measures of lifestyle modification. Research is required to further clear. Diagnostic criteria, epidemiology, genetics and molecular mechanisms of PCOS. As there is risk of developing cancers like endometrial, ovarian and breast cancers due to unopposed estrogen exposure but proper surveillance measures and screening can lead to early detection and treatment. Encouragement to conceive simple measures of progesterone support and use of intrauterine devices can protect against endometrial cancers. By controlling PCOS we can lower the burden of non-communicable disease too. Latest studies have revealed use of myo-inositol in improving PCOS symptoms, ovulation, fertility, hyperandrogenism, metabolic profile and thus has become novel treatment option for treating PCOS.<sup>[47]</sup> Also there are some challenges relating to age like diagnosis of PCOS in adolescents as the normal physiological changes overlap with signs of PCOS such as menstrual irregularities and multifollicular ovaries.<sup>[48]</sup> Positive effects of resistance training on health outcomes of women among PCOS in improving their symptoms and also in chronic diseases but further clinical trials are required to establish clinical dose to implement it as therapeutic regime.<sup>[49-50]</sup>

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