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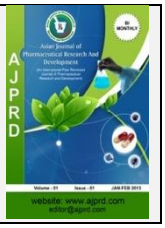

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Review Article

Polycystic Ovary Syndrome Is a Challenging Problem in Women

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A B S T R A C T

A diverse endocrine condition, polycystic ovarian syndrome is characterised by ovarian cysts, anovulation, and endocrine variance in women. As from the World Health Organisation, PCOS affects more than 116 million women globally. Patients with irregular periods and clinical indications of hyperandrogenism, such as acne, seborrhea, hirsutism, irregular menses, infertility, and alopecia, are suspected of having polycystic ovarian syndrome, a "multispeciality" illness. It is now widely acknowledged that oxidative stress plays a crucial part in the pathogenesis of numerous illnesses, including PCOS. OS is thought to have close interactions with PCOS characteristics, including insulin resistance (IR), hyperandrogenemia, and chronic inflammation. Although highly complicated antioxidant enzyme and non-enzymatic systems regulate intracellular reactive oxygen species formation and propagation, knowing the mechanisms that underlie oxidative stress is crucial to the development of PCOS prevention and treatment options. Management should prioritise encouraging employees, educating the public, resolving psychological issues, and highlighting a healthy lifestyle with appropriate medical treatment. Long-term metabolic problems need to be monitored and managed as part of standard therapeutic care. To help with early diagnosis, appropriate investigation, routine screening, and treatment of this common illness, comprehensive evidence-based guidelines are required. The research suggests that phytoestrogen rich herbal extracts reduce hyperandrogenism, insulin resistance, and ovarian weight while increasing ovulation. As a result, these plants may have some effect on the levels of various hormones in the serum as well as ovarian weight and morphology, which presents a chance to research and find novel bioactive compounds.

Key words: Polycystic ovarian syndrome, oxidative stress, clinical Problems, Medicinal plants

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INTRODUCTION

Polycystic ovary syndrome is a frustrating condition for women, frequently a challenge for medical practitioners to treat, and a challenging scientific issue for academics. Given how swiftly PCOS research is evolving, it is essential that study findings are applied to knowledge and action among women, healthcare providers, and policy makers. PCOS is the most prevalent endocrine disorder among women of reproductive age [1].

Ovarian cysts, anovulation, and endocrine variation are the hallmarks of the heterogeneous endocrine illness known as polycystic ovarian syndrome (PCOS), which has a significant negative influence on a woman's quality of life [2]. The normal menstrual cycle is disrupted by disturbances

in the reproductive hormones LH, FSH, oestrogen, and testosterone, which can also cause oligomenorrhoea and irregularities resembling amenorrhea.

Over 116 million women globally are estimated to have PCOS, according to estimates from the World Health Organisation (WHO) [3]. PCOS is characterised by hyperandrogenism, irregular menstruation, and ovarian cysts of various sizes, albeit there are significant individual variations. Adolescents who are at high risk of developing a number of comorbidities, such as obesity, type-II diabetes, infertility, endometrial dysplasia, cardiovascular problems, and mental disorders, initially acquire this multifactorial condition [1].

Pathophysiology

Although the aetiology of PCOS is yet unknown, there is strong evidence that the disorder is complex, with interactions between endocrine, metabolic, genetic, and environmental variables acting in concert to produce a similar outcome [4-5].Additionally, PCOS' heterogeneity emphasises the fact that it is complex. The majority of the susceptibility genes and single-nucleotide polymorphisms for this syndrome have yet to be identified, despite the familial segregation of cases suggesting a genetic component [6-7].The two most prominent phenotypes of PCOS are recognised to be hyperandrogenism and ovarian dysfunction [8,7].The increased androgen biosynthesis, usage, and metabolism in PCOS is known as hyperandrogenism. The ovary can develop an aggregation of many follicles or cysts when the ovaries are induced to produce excessive levels of androgen. Through increasing ovarian androgen secretion and decreasing hepatic sex hormone-binding globulin (SHBG) synthesis, hyperandrogenism in PCOS is mostly caused by insulin resistance. [9].PCOS affects 80-85% of women who have clinical hyperandrogenism [10-11]. Acne, aberrant folliculogenesis, and/or excessive hair growth are possible symptoms in women with PCOS and hyperandrogenism. There have been three main pathophysiological routes identified, however they are not exclusive. They are insulin resistance, abnormal gonadotropin release, and ovulatory dysfunction.

Oxidative stress & its biomarkers

Oxidative stress is defined as an imbalance between oxidants and antioxidants as well as an excess of reactive oxygen species (ROS). Numerous studies have shown that oxidative circulating indicators are much higher in PCOS patients than in controls, and they are thought to be a potential initiator of PCOS pathogenesis.It is now widely acknowledged that oxidative stress plays a crucial part in the pathogenesis of numerous illnesses, including PCOS.

To examine the role of oxidative stress in the onset of diseases, we have mostly focused on oxidative stress biomarkers like MDA and NO as well as anti-oxidative biomarkers including TAC, SOD, GPx, and glutathione (GSH). In order to assess the likelihood of oxidative damage and associated diseases [12] and to help manage and prevent oxidative disorders, antioxidant biomarkers and the assessment of oxidative stress have been advocated as useful strategies.

Malondialdehyde

MDA is a persistent biomarker that is produced when polyunsaturated fatty acids undergo lipid peroxidation. Several studies have reported MDA levels in PCOS. One meta-analysis revealed that, compared to controls, women with PCOS had circulating mean MDA concentrations that were 47% higher based on age and BMI [12].Different study has been done one study blood MDA levels in PCOS patients and healthy controls were compared. It demonstrated that, despite being unrelated to fat, the MDA level was remarkably greater in the PCOS group.

Nitric oxide

Free radical NO is a key player in numerous physiological and pathological processes. However, it can be dangerous in excess. Numerous nitric oxide synthase (NOS) enzymes use L-arginine, oxygen, and nicotinamide adenine dinucleotide phosphate to create NO in the body. An alternate method of producing NO involves sequentially reducing nitrate obtained from plant-based meals [13].It is also produced during immunological reactions by neutrophils, macrophages, and monocytes using phagocytes. Numerous studies have reported NO level in PCOS. Recent meta-analysis research revealed that there was no statistically significant difference in the mean NO level between controls and PCOS-afflicted women.According to one study by Hassani et al., Nitric oxide could have a big impact on PCOS pathogenesis. L arginine, a precursor of NO, was administered to Wistar rats, and the results revealed that the treated rats' ovaries were more polycystic than those of the control group [12].

Superoxide dismutase

Superoxide anions (O2-), the main oxygen radical, are eliminated by SOD, an enzyme and crucial antioxidant defence, which catalyses their conversion to H2 O2 and subsequent conversion to water by GPx. There are several popular kinds of SOD, including the Cu/Zn type, the Fe and Mn type, and the Ni type, depending on the metal cofactor and the protein structure. SOD activity in PCOS has been discovered in several investigations. One study compared the blood SOD levels of polycystic ovarian syndrome patients with healthy controls to establish the antioxidant status of PCOS patients. They demonstrated that compared to healthy participants, women with PCOS exhibited greater levels of SOD. Additionally, Zhang et al. demonstrated that PCOS patients had considerably lower serum SOD levels than the control group [12].

Glutathione peroxidase

The GPx enzyme family protects the organism from oxidative damage by converting H2O2 to water and lipid hydroperoxides to their corresponding alcohols. The GPx activity evaluation for anti-oxidant defence assessment in PCOS has been the subject of numerous studies. The oxidant and antioxidant status of PCOS-afflicted women was assessed by Sabuncu et al. They showed that there was no difference in GPx between the PCOS group and the healthy control group. Savic Radojevic et al.'s research, however, revealed that PCOS women's GPx activity considerably declines when compared to controls [16]. To

better understand how GPx acts as PCOS's antioxidant defence, more research is required.

Reduced glutathione

GSH is produced in the cytosol in two processes that both call for ATP as an essential antioxidant. Glutamylcysteinesynthetase first converts glutamate and cysteine into glutamylcysteine, which is then transformed into GSH, which is present in the endoplasmic reticulum, nucleus, and mitochondria. Glutathione is crucial for controlling the disulfide linkages in proteins as well as for getting rid of electrophiles and oxidants [12].The antioxidant activity of GSH is mediated by its redox active thiol group, which is oxidised when GSH lowers target molecules. In various researches, the antioxidant impact of GSH in PCOS was evaluated. One study revealed that PCOS-afflicted women's mean GSH levels were 50% lower than those of controls [17].

Oxidative Stress in Polycystic Ovary Syndrome

When two of the following three criteria have been found, polycystic ovarian syndrome (PCOS) would be identified in accordance with the amended criteria established at the Rotterdam meeting: (1) clinical and/or biochemical evidence of androgen excess after the exclusion of other related disorders; (2) oligoovulation or anovulation; (3) ultrasound appearance of the ovaries: presence of more than 12 follicles in each ovary measuring 29 mm and/or increased ovarian volume (>10 mL).Hyperandrogenism and insulin resistance (IR) are usually involved with PCOS, despite the fact that its whole aetiology is still unknown. It's possible that PCOS's dysfunctional ovaries, adrenal glands, peripheral fat, and hypothalamus-pituitary compartment are to blame for the accompanying hyperandrogenemia. Insulin resistance, which is usually present in PCOS as well, causes a compensatory hyperinsulinemia that increases the synthesis of androgens driven by luteinizing hormone (LH) either through its own receptors or through insulin growth factor (IGF-1) receptors.

PCOS is often treated as a syndrome based on specific clinical symptoms, with the primary therapy regimens being ovulation induction, lowering levels of androgen and LH, reducing IR, and surgery. OS is also deeply entwined in PCOS aetiology, as PCOS patients have more severe OS than the norm.However, when different markers are used, the same marker is assessed in various sources, and even when using various inquiry techniques, the results won't necessarily be consistent. Additionally, OS contributes to the clinical conditions of IR, hyperandrogenemia, and obesity, which frequently but not always accompany PCOS. As a result, the proper markers for the situation should be chosen to assess the OS levels in PCOS. Homocysteine, malondialdehyde (MDA), asymmetric dimethylarginine (AMDA), superoxide dismutase (SOD), glutathione (GSH), and paraoxonase-1 (PON1) are the most often used circulating indicators today. The complex connections between OS and PCOS will be discussed below from the primary nodes connecting OS and PCOS. This is due to the significant cross-link between OS and the physiological and clinical aspects of PCOS [18].

Clinical problems

The patient visits a dermatologist for advice on one or more issues, such as acne, hirsutism, alopecia, acanthosisnigricans, skin tags, or occasionally, a darkening of the skin as a result of weight gain. The patient may contact a gynaecologist if the major problems are irregular menstrual periods or primary infertility. In cases of metabolic syndrome with hirsutism, an endocrinologist may be contacted. Rarely do people exhibit all of the clinical symptoms and indications of PCOS, and some patients might not be honest about receiving concurrent treatment from a gynaecologist or an endocrinologist. An astute physician should be able to connect the symptoms, pointing to a potential hyperandrogenism-related underlying problem figure 1.

Acne vulgaris

Inflammatory acne that is poorly responding to standard treatment is a common complaint among PCOS patients. Even when responsive, lesions quickly return after ceasing treatment, needing hormone therapy or oral isotretinoin medication. Multiple closed comedones that grow into tender, lumpy nodules quickly in the lower half of the face and jaw line are a significant characteristic of these people. These frequently last longer than the typical duration of 5 to 7 days. Premenstrual flare-ups are also typical. Not only can acne lesions appear on the face, but they can also appear on the chest, shoulders, and back. Rapid relapse upon therapy discontinuation strongly supports a hormonal cause. Additionally, patients may have a history of irregular menstrual cycles, as well as hirsutism, alopecia, or a positive family history of PCOS. The balance of activity between the alpha hydroxy types 2 and 1 will determine whether the severity of hirsutism matches the severity of acne [19].

Hirsutism

A racial characteristic of the Indian subcontinent is excessive facial hair, which runs in families and is particularly prevalent in some ethnic groups. When evaluating patients who complain of having excessive facial or body hair, keep this in mind. Different facets of follicular activity are impacted by androgens. They accelerate hair growth, diameter, and melanization in areas that are sensitive to androgens by acting through androgen receptors and secretory factors. On a woman, these thick, coarse, terminal hairs in androgen-dependent areas are ugly and indicate an underlying hyperandrogenic condition. By using a modified Ferriman Galway score, which rates nine body regions on a scale of 1 to 4, the degree of hirsutism is assessed. If the overall scores range from 6 to 8, then they are important [19].

Alopecia

Female pattern hair loss (FPHL) may not always have an androgenic cause. Patterned hair loss associated with PCOS may be challenging to distinguish from secondary hyperandrogenic conditions. The clinical manifestations mentioned by Ludwig (diffuse), Hamilton (male pattern), and Olsen (frontal accentuation) are just a few examples [19].Hyperandrogenism is substantially more prevalent in women with early-onset FPHL. Hormonal effects change

terminal hair into vellus hair, giving the appearance of a bald scalp.

Irregular menses and infertility

Chronic menstrual abnormalities or alterations in the menstrual cycle along with decreased fertility are characteristics of PCOS. Endometrial hyperplasia and endometrial stimulation with oestrogen as a result of anovulatory or oligoovulatory cycles raise the risk of endometrial cancer [19].

Diagnosis

There was no widely accepted clinical definition of PCOS prior until recently. Research has shown that PCOS is a heterogeneous disorder throughout the past three decades. In 2003, the Rotterdam or ESHRE/ASRM diagnostic criteria added PCO at ultrasonography to the original NIH diagnostic criteria based on oligomenorrhoea/amenorrhoea and clinical or biochemical hyperandrogenism. According to ultrasounds of young women, 25% of them have PCOS, and since PCOS was added to the list of diagnostic criteria, PCOS prevalence has increased. Recent research suggests that the prevalence of PCOS may be doubled on application of the ESHRE/ASRM criteria, with a prevalence of 12% (without imputing the existence of polycystic ovaries) to 18% (imputing the presence of polycystic ovaries) documented in a community sample [1].

In order to exclude people without symptoms (PCO on ultrasonography and oligo/amenorrhea but no hyperandrogenism), the Androgen Excess PCOS Society advised further altering the diagnostic criteria in 2006 [20]. It should be noted that PCOS is a diagnosis of exclusion, therefore less common disorders like Cushing's syndrome and virilizing tumours should be ruled out clinically while more unusual ones like hyperprolactinemia and thyroid dysfunction should be ruled out biochemically. Cardiometabolic traits or insulin resistance are not yet part of the PCOS diagnosis criteria. This is partially caused by the lack of adequate methods for assessing insulin resistance, as these tests are not currently recommended in clinical practise [21].

With the four primary diagnostic criteria (oligomenorrhoea/amenorrhoea, clinical or biochemical hyperandrogenism, and PCO on ultrasonography), there are various potential morphologies. The heterogeneity of the illness is influenced by a number of variables, including the degree of obesity, insulin resistance, ethnicity, and others [1]. The variability of PCOS and the lack of understanding of its aetiology are the two factors that contribute to the fluctuating diagnostic criteria and fierce dispute. The ESHRE/ASRM or Rotterdam criteria are currently the standard international PCOS diagnosis criteria, while further research is still necessary.

TREATMENT

Weight, exercise and lifestyle changes

In an evidence-based approach, changing one's lifestyle is the primary line of treatment for the majority of PCOS women who are overweight [1]. Additionally, it's important to underline the prevention of excessive weight gain in PCOS patients with both normal and increasing body weight. When compared to diet alone, weight loss from even a 5% to 10% loss of body weight has better clinical effects on psychological outcomes [22], reproductive characteristics and activity including structured exercise (30 minutes/day), and exercise increases weight loss in PCOS [1]. Clinical results are also improved by exercise alone. Like in the general population, the focus of exercise should be on total health benefits rather than just weight loss.

Fad diets are discouraged because they rarely result in sustained weight loss over the long run. More study is required to determine the benefits of particular dietary strategies over calorie restriction alone. Specific dietary strategies for PCOS have been suggested, such as high protein, low carb, and low glycaemic load diets. One study found that adding a highprotein supplement to a conventional energy reduced diet improved weight loss, and numerous smaller studies examining specific dietary approaches in PCOS have found similar advantages for diets that have a moderate increase in dietary protein or carbohydrate. Two brief trials for PCOS have looked at very low-carbohydrate diets, while one research looked at low-glycaemic-load diets used in clinical care. Even when reductions in weight, BMI, waist circumference, fasting insulin, or testosterone were seen in these trials, there was no control group. As long as they are safe, nutritionally adequate, and long-lasting, a variety of dietary strategies will all aid PCOS patients in losing weight and improving their reproductive and metabolic features, according to the existing research [23, 1].

Pharmacological treatment

There is currently no perfect medical cure for PCOS that addresses all clinical symptoms and totally corrects underlying hormonal imbalances. In PCOS patients, the OCP does reduce hyperandrogenism, and Metformin and other insulin sensitizers reduce insulin resistance. Generally speaking, pharmacological treatment for PCOS focuses on symptoms and shouldn't be substituted with lifestyle coaching. In PCOS patients, the OCP has long been used to treat hyperandrogenism, safeguard the endometrium, and induce regular cycles. Among the mechanisms of action are a potent first pass hepatic effect and an increase in hepatic protein synthesis, including sex hormone binding globulin. This reduces the levels of free circulating testosterone, even with low dose OCPs. This essential antiandrogenic action mechanism is not produced by progestin alone or by non-oral oestrogen-containing contraceptives. The OCP also reduces the production of ovarian androgen. The OCP may decrease glucose tolerance and encourage insulin resistance, according to alarming findings. However, the cardiometabolic adverse effects of pharmaceutical therapy should be taken into account. Low dose OCP formulations may be a better option because they have equal efficacy and fewer cardiometabolic side effects. Additional study is necessary because studies are limited and data are inconsistent [1].

The use of metformin has grown in the management of PCOS, enhancing clinical characteristics with favourable cardiometabolic consequences. Although studies in DM2 suggest that it may help prevent future weight gain, It

doesn't seem to lead to weight loss. Metformin plays a function in diabetes prevention where lifestyle management is insufficient, according to recommendations from the International Diabetes Federation [1, 24]. Given the elevated risk of DM2 and increased insulin resistance, PCOS is also at risk, especially if additional risk factors including being overweight, having a family history of Diabetes mellitus2, the metabolic syndrome, or pre-diabetes are present. Metformin's role in infertility is still debatable. Although it does lessen hyperstimulation in people using other reproductive treatments, this area needs additional study. Metformin is best tolerated if taken twice daily in doses of 500 mg delayed release and raised over the course of several weeks or months to 2 g. A rare adverse effect in people with serious diseases, such as renal impairment, is lactic acidosis. It is crucial to remember that the majority of regulatory agencies have not formally approved metformin or the OCP for PCOS. The OCP and metformin are both advised for the treatment of diabetes. However, both therapies are supported by data and are advised by both national and worldwide endocrine associations [1] table 1.

CONCLUSION

The assessment makes it abundantly evident that PCOS is a difficult issue for women. It's challenging to comprehend and articulate the central mechanism. In both animal and human reproductive medicine, the link between oxidative stress and PCOS is a significant concern. The most significant functions played by oxidative stress in the pathophysiology of PCOS are covered in our summary of the most recent research on the subject. Measurement of numerous antioxidant and oxidant biomarkers may be a reliable diagnostic of oxidative stress. Although the Rotterdam criteria are still the most often used, diagnostic standards are continually changing. As a result, no treatment can be hailed as a miracle cure because it only addresses the clinical symptoms rather than the underlying illness. Knowing the mechanisms of action of herbal or medicinal plants should be considered as alternatives to pharmaceuticals. It is important to conduct additional research on the pathophysiology and the medications that affect it in order to better predict the long-term effects on the patient's health. Changing one's lifestyle may help with PCOS-related symptoms.

AUTHOR'S CONTRIBUTION

Arifa Hassan, Afshana Bashir Reshi, Muzamil Muzaffar and Arooj all contributed equally to the manuscript's literature and design. Additionally, Maaz Naqvievaluates and edits the paper. The study plan, the literature, and the text design are all created by Mohd Rafi Reshi. The final review article was approved by all authors.

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