Understanding PCOS: A Review of Its Causes, Symptoms, Pathogenesis, and Management Strategies

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Abstract ***The aim of this review is to provide an overview on the polycystic ovarian syndrome (PCOS) including its causes, symptoms and management. The most prevalent endocrine and metabolic conditions affecting women in their reproductive years is PCOS. About 116 million women worldwide (3.4%) may be impacted by PCOS, according to data from the World Health Organization (WHO). This is a heterogeneous endocrine condition that manifests as insulin resistance, increased testosterone levels, swollen and malfunctioning ovaries, and other symptoms. This paper covers the information about the polycystic ovary syndrome, its causes, symptoms, pathogenesis and its management in brief. External causes include genetic mechanism, diet and environmental factors while insulin resistance, inflammation, hyperandrogenism and obesity are the internal causes. Irregular periods, hirsutism, acne & oily skin, mood swings, weight gain, heavy bleeding, hair thinning, diabetes, pelvic pain, sleep problems and skin darkening are the main signs and symptoms of the PCOS. Pathogenesis of PCOS involves alteration in insulin secretion, change in gonadotropin – releasing hormone and excess androgen level. When treating PCOS, more focus should be placed on the patient's adherence to treatment.***

Index Terms: - polycystic ovary syndrome, hyperandrogenism, insulin resistance, molecular mechanisms, management, repurposing drugs.

I. INTRODUCTION

Polycystic ovarian syndrome (PCOS) was formerly known as Stein-Leventhal syndrome. [1] PCOS is the most common endocrine and metabolic disorder in women of reproductive age. This syndrome is a heterogeneous endocrine disorder characterized by enlarged and dysfunctional ovaries, excess androgen levels, resistance to insulin, etc. Approximately 10% of women are thought to have PCOS before to menopause and experience difficulties from it. [2] The World Health Organization (WHO) data suggests that approximately 116 million women (3.4%) are affected by PCOS globally. [4] According to the National Health Portal of India, the prevalence rate of PCOS in Maharashtra was found to be 22.5%. Another previous report from South India, which included adolescents, showed an incidence of 9.13%. [5]

Why the topic is important to discuss:
PCOS is a high impact, underdiagnosed condition with clear reproductive, metabolic, and psychosocial consequences—researching it can change clinical practice, public health screening, and patient quality of life in places like Kolhapur and across India. Choosing PCOS as your research topic is justified by its prevalence, long term health risks, treatment gaps, and strong need for locally relevant evidence.

- High prevalence and underdiagnosis. PCOS affects an estimated 10–13% of reproductive age women globally, and up to 70% may be undiagnosed, so many people never receive care
- Dual reproductive and metabolic burden. PCOS is a leading cause of anovulatory infertility and is strongly linked to insulin resistance, type 2 diabetes, dyslipidaemia, and cardiovascular risk, making it a chronic condition beyond reproductive years.

Causes of PCOS
There are various external, environmental and internal factors that cause the PCOS.

1.1. External factors Genetic mechanism:
The gene types implicated in the development of PCOS are classified as follows: genes involved in the steroidogenesis of the ovary and adrenal glands, genes involved in the actions and regulation of steroid

hormones, genes involved in the action and secretion of insulin, genes affecting energy homeostasis, and genes implicated in chronic inflammation. [6] Thus some particular alterations in some genomes are the reason for development of PCOS. Some examples of genes involved in development of PCOS are Calpain 10 (CAPN10), Cytochrome p450, Insulin gene, Androgen Receptor (AR), Fat Mass Obesity (FTO), and Follicular stimulating hormone receptor (FSHR). [7]

1.2. Environmental factors

Exposure to Endocrine Disrupting Chemicals (EDC) may also play a role in development of PCOS. The Endocrine Society defines Endocrine Disrupting Chemicals as "an exogenous chemical, or mixture of chemicals, that interfere with hormonal action." These chemical substances can affect the endocrine system and results in adverse effects. [14] Bisphenol A (BPA), perchlorate, dioxins, phthalates, phytoestrogens, polychlorinated biphenyls (PCB), polybrominated diphenyl ethers (PBDE), triclosan, perfluoroalkyl and polyfluoroalkyl substances (PFAS), pesticides such as dichlorodiphenyltrichloroethylene (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), organophosphorus compounds, alkyl phenols (surfactants), parabens, methoxychlor, diethylstilbestrol (DES), fungicide vinclozolin, and natural hormones are the commonly used EDC. [14,15] EDCs work as agonists or antagonists by binding to hormone receptors and leading to increase, decrease, or prevent the activity of the hormones. [16] Women who are exposed to air pollutants, such as particulate matter (PM) 2.5, sulphur dioxide, nitrogen oxides, and polycyclic aromatic hydrocarbons (PAHs), may have an increase in inflammatory mediators, which alters normal steroidogenesis and causes PCOS to develop. [17]

Diet Diet rich in fat, mainly saturated fatty acids and intake of foods with a high glycemic index increases the risk of insulin resistance and its related complications including obesity and PCOS. [8]

1.3 Internal factors

• Insulin resistance: PCOS is frequently characterized by insulin resistance and compensatory hyperinsulinemia. Some studies indicate that hyperinsulinemia contributes to the hyperandrogenism of the condition by raising ovarian androgen production and impairing ovulation. This is the effect of insulin inducing ovarian cell, called as theca cell, that are responsible for androgen biosynthesis to produce testosterone. [10]

• Hyperandrogenism: It results from overproduction of androgens produced due to abnormal ovarian function and insulin resistance. Hyperandrogenism hinders the growth of follicles, which are the sacs in the ovaries where eggs get develop, and inhibits normal ovulation [9]

• Inflammation: The imbalance between pro-inflammatory and anti-inflammatory cytokines, as well as cytokine gene polymorphisms, may influence etiology of PCOS. Thus, inflammatory reactions serve as mediators in the development and aggravation of the metabolic features of PCOS. Adipocytes have the ability to increase the production of pro-inflammatory chemicals, which can result in chronic inflammation. [11] Inflammation directly stimulates overproduction of androgens in the ovaries. The degree of hyperandrogenism may have an effect on the development of abdominal adiposity, which contributes to the inflammatory load in PCOS.[21] Research has linked elevated levels of androgen to inflammation [15]

• Obesity: Obesity activates the theca cells that stimulate luteinizing hormones which leads to ovarian androgen excess. High androgen levels lead to improper periods and obesity. [14]

Symptoms of PCOS

1. Irregular periods: This is the most typical PCOD symptom. PCOD first manifests as irregular or frightening periods. Observe your monthly cycle closely in order to identify PCOD. [16, 17]

2. Excessive facial and body hair (Hirsutism): Excessive facial hair growth is known as Hirsutism. Women with PCOD have excessive hair growth because their ovaries secrete a large amount of the masculine hormone androgens. [16,17] Up to 70% of women with PCOS experience Hirsutism, a frequent clinical manifestation of hyperandrogenism. The face, arms, back, chest, thumbs, toes, and abdomen are among the areas that may be impacted by excessive hair growth, which is linked to PCOS because of hormonal fluctuations. [16]

3. Acne and Oily Skin: Acne and other facial issues are caused by hormone disruption in PCOD. Acne is a result of an overabundance of male hormones. PCOD causes severe cystic acne in certain women. [17]
4. Heavy Bleeding: The uterine wall has increased accumulation since the periods are irregular. This causes more bleeding each time a period occurs. [15, 16]
5. Pelvic Pain: Along with severe bleeding and headaches, pelvic discomfort can also happen during menstruation. [16]

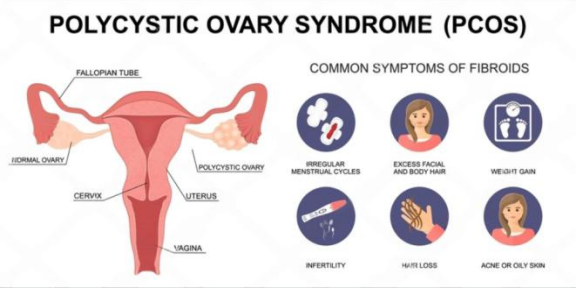

Fig. 1 symptoms of PCOS

II. PATHOGENESIS

A. Review

Excessive adrenal androgen secretion and/or ovarian secretion are the characteristics of PCOS. The overproduction of ovarian androgen is caused by both intrinsic ovarian factor such as altered steroidogenesis and external factor hyperinsulinemia.[18] Theca cells in the ovary support developing follicles physiologically, aiding in the production of mature oocytes. Patients with PCOS experience ovarian hyperthecosis due to the hyperresponsiveness of theca cells to stimulatory actions of insulin. The symptoms of PCOS are exacerbated by insulin resistance in peripheral tissues, which increases the androgenic potential in theca cells. Furthermore, an additional factor contributing to hyperandrogenism in PCOS is the increased sensitivity of theca cells to gonadal steroid gonadotropin activation. [19] A number of factors, including changes in adipose cell activity, inflammatory factors, neuroendocrine function, metabolism, steroidogenesis, ovarian folliculogenesis, insulin production, and insulin sensitivity may have impact on the pathophysiology of this illness. [20]

B. Irregular Cycles and Ovulatory Dysfunction

The average menstrual cycle in adults lasts 28 days, with a normal range of 21–35 days, with typically a relatively constant luteal phase lasting 14 days, and a more variable follicular phase length.[21] Even among those with ovulatory cycles, however, there can be significant heterogeneity between individuals and within a single individual in overall cycle, follicular phase, and luteal phase length. [22]

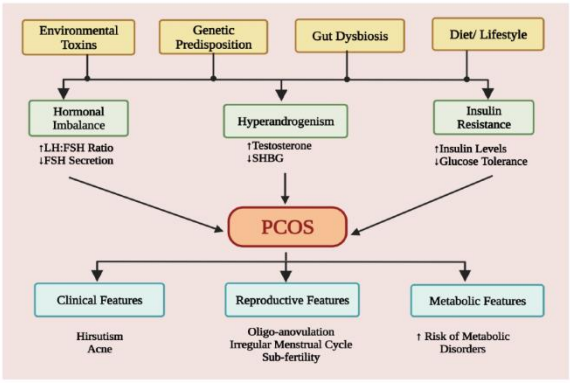

Fig.2 Pathogenesis of PCOS

Generally, the presence of regular monthly menses occurring within this normal range can be used as a surrogate marker of ovulatory function. [23] It is not uncommon, however, even among women with regular 28-day cycles to have one or more anovulatory cycles in a year. [24] Menstrual dysfunction among patients with PCOS is typically characterized by oligo-amenorrhea (cycles > 35 days apart or <8 cycles per year). Polymenorrhagia (cycles occurring < 21 days apart) is relatively uncommon among patients with PCOS [25] however this feature has been included in some guidelines for the diagnosis of PCOS. Irregular menses are normal within 1 year post-menarche, and in 1 to 3 years, post-menarche irregular menses should be defined as <21 or >45 days apart. [26]

C Insulin Resistance and Polycystic Ovary Syndrome

Insulin resistance and the associated compensatory hyperinsulinemia are common findings in women with PCOS, and may play a key role in this condition. It has been estimated that approximately 70% of these women are insulin resistant, but this figure is affected by frequent referral bias. In addition, there is metabolic heterogeneity between clinical phenotypes of PCOS. A fundamental issue is the role that hyperinsulinemia plays in androgen overproduction, which is enhanced by bidirectional links between insulin resistance and hyperandrogenism. Available data suggest that women with PCOS may have insulin action alterations of heterogeneous origins, which

induce specific abnormalities in these subjects due to the presence of intrinsic defects. Obesity is a common finding in these patients and contributes to the association between PCOS and insulin resistance, combining with the effect of PCOS per se. Insulin sensitization shows several beneficial effects in the treatment of this condition. However, clinical response is heterogeneous.[27]

Current Recommendation

Oligo-amenorrhea (cycles > 35 days apart or <8 cycles per year) may be used as a marker for ovulatory dysfunction to diagnose PCOS.

Ovulation can be confirmed in those with uncertain menstrual history with serum progesterone evaluation or luteinizing hormone testing.

III. MANAGEMENT

The management approach and selection of the best therapy option depend on the target patient and her priorities. [43] The complications may vary from seeking fertility, regulation of menstrual disturbances to weight reduction or relief from hyperandrogenic symptoms, including acne, hirsutism, or androgenic alopecia [44] Indeed, the approach should be individualized for each person to meet the optimal result [45]. There is no one ideal treatment for all women diagnosed with PCOS, which leaves physicians no choice but symptomatic therapy. [46]

1. Nutraceutical Supplementation

Women with PCOS often show a deficiency of many common nutrients, vitamins, and minerals associated with the psychological sequelae of the condition such as depression or anxiety, as well as physiological sequelae such as insulin resistance, diabetes, and infertility. [28] Specifically, two stereoisomers of inositol, the myo-inositol, and D-chiro-inositol (DCI), seem to play a main role in exerting several pleiotropic actions, including insulin-dependent androgen synthesis, [30] modulation of insulin transduction, and glucose metabolism. [29] Another molecule of interest is alpha-lipoic acid (ALA), largely present in potatoes, broccoli, spinach, tomatoes, Brussel sprouts, peas, brown rice, and red meat. Humans absorb only a few ALA amounts in biologically active form; it is, indeed, rapidly metabolized and therefore does not accumulate in human tissues. [31] ALA is a potent-free radical scavenger and exerts insulin-sensitizing activity and could be useful in the PCOS treatment [32] even if its beneficial effects are only regarding metabolic features of the syndrome. [33] The worth of interest is the promising therapeutic strategy that involves the combination of inositol plus ALA, exerting a synergistic action in improving glycaemic control, IR, and metabolic and endocrine features in PCOS patients. [34,35,36]

2. Probiotics, Prebiotics, and Synbiotics

Treatment options for the altered gut microbiome causing PCOS include probiotics, prebiotics, synbiotics, and more recent therapies, including faecal microbiota transplantation (FMT).[37] Probiotics naturally occur in fermented foods and are “live microorganisms that, when administered in appropriate amounts, confer a health benefit to the host”. [38] In women with PCOS, therapy with probiotics results in an improved metabolic profile. In fact, it has been seen that supplementation with L. casei, L. acidophilus, and B. bifidum for 12 weeks is capable of leading to a reduction in BMI with favourable effects on glycemia and very-low-density lipoprotein (VLDL), and triglycerides in PCOS patients. [39] Prebiotics are fermented substances that cause specific changes in the composition and/or activity of a host’s gut microbiota; the most known ones are inulin, lactulose, fructooligosaccharides (FOS), and galactooligosaccharides (GOS).[38] Since prebiotics induce the growth of both Bifidobacterium and Lactobacillus, they produce positive effects on immunomodulatory properties and metabolic markers by producing an important reduction in the levels of glucose, triglycerides, total cholesterol, and LDL. [40] Synbiotics refer to dietary supplements composed of probiotics and prebiotics: compounds in food that stimulate the growth and activity of probiotics. [41] In 2020, Cozzolino M.et.al., in a meta-analysis, showed that probiotic/symbiotic administration can improve metabolic, hormonal, and systemic inflammatory factors in women with PCOS. [42]

Challenges and Future Perspectives

1. One of the main challenges in the diagnostic–therapeutic course of PCOS is the identification of phenotype and the main cause of the disorder. This is a multifactorial etiology condition, often accompanied

by signs and symptoms that cannot be directly ascribed to a metabolic alteration.

For example, it is important to screen women with PCOS for all complications, including dyslipidaemia and psychological distress. [47]

2. An additional challenge is choosing the most appropriate nutritional strategy for weight loss, as well as maintaining weight loss. Women with PCOS, indeed, have additional difficulties in weight loss and maintenance, including insulin resistance, androgen excess, and impaired appetite regulation. Furthermore, there are normal-weight women with PCOS who, however, have been shown to have greater visceral adiposity than normal-weight controls without PCOS [48]; hence, body re-composition and weight gain prevention interventions should be carried out [49]. Thus, nutritional intervention or the synergistic effect of diet and supplementation with probiotics, prebiotics, or synbiotics to promote bacterial diversity and enrichment of beneficial species such as Bifidobacterium and Lactobacillus could help improve the clinical picture in women with PCOS. [50]

IV. CONCLUSION

PCOS is most common and complex disorder in women of reproductive age. It is caused due to various factors including environmental factors, genetic mechanism, diet, obesity, insulin resistance, hyperandrogenism, etc. and manifests as irregular periods, hirsutism, increased testosterone levels, weight gain, acne, mood swings etc. Depending on the cause of PCOS, multiple techniques are used to treat this condition. This review provides the information about PCOS, its causes, symptoms, pathogenesis and its management to raise the awareness among women to prevent and manage this complicated condition.

Since there is still no certain medication or definite cure for this condition, the routine approach after advising on some lifestyle modification and supplementary tips is symptomatic therapy with plenty of agents, including contraceptives, oral antidiabetics, or antiandrogens.

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