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UNDERSTANDING PCOS: CONTEMPORARY INSIGHTS AND APPROACHES TOTREATMENT

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ABSTRACT

A hormonal imbalance describes polycystic ovarian syndrome (PCOS), as it is more often known. Polycystic ovarian syndrome (PCOS) is classified as a heterogeneous condition with acombination of excess androgen and hormonal imbalance. Growing evidence suggests that PCOS is a complex multigenic illness with important environmental and epigenetic factors,including dietary and lifestyle decisions, even if the actual etiology of the condition is still unknown. An ovulation or oligo ovulation, indications of excess androgen such as hirsutism, acne, and many ovarian cysts in the ovaries, are common symptoms of polycystic ovarian syndrome. The goal of therapy is to induce conception, bring about normal menstruation, and diminish hyperandrogenism's symptoms. When it comes to treating infertility brought on by polycystic ovarian syndrome, letrozole, looks to be more effective than clomiphene citrate, an anti-estrogen, and the standard fertility medication. It can assist patients with maintaining important modifications to their lifestyles, such as reducing fat deposits, improving metabolic processes, and improving reproductive health when provided by a multidisciplinary team. The most prevalent type of androgen inhibitor is an oral compound contraceptive, which is the chosen treatment for PCOS patients who do not want to become pregnant. Women with PCOS should focus on reducing weight because a healthy diet and regular physical activity can boost metabolism, improve insulin sensitivity, and effectively induce loss of weight. PCOS symptoms other than reproductive issues include chronic mild to moderate inflammation, metabolic syndrome, and insulin resistance (IR). The pathophysiological mechanism, diagnosis, and treatment of PCOS are now better understood.

KEYWORDS: Etiology, modification lifestyle, PCOS, medication.

INTRODUCTION

Polycystic ovarian syndromes are extremely complicated problems. This impacted at least 7% of the world's adult female population. According to a report from the National Institutes of Health Office of Disease Prevention in the United States, PCOD affects roughly 5 million women aged 25 to 35. Which can be identified by the evolution of androgen amount. Menstrual irregulating and small cysts on both or single ovaries indicate polycystic ovary diseases. The PCOD may be morphological or predominantly biochemical.[1] Polycystic ovary problems can be seen in healthy women, but it is more common in women with abnormal cycles and hyperandrogenism. The polycystic appearance of the ovary can be known as polycystic ovary syndrome but there isa wide range of clinical and biochemical features.[2] It is the most frequent female endocrine disorder. In 1935, Stein and Leventhal published the first description of it. The prevalence fluctuates between 5% and 15% based on the criteria for diagnosis utilized.[3] The presence of at least two of the following three criteria is commonly accepted by specialized society guidelines for the diagnosis of PCOS. It is the most common endocrine disease to afflict reproductive females globally. Diagnosis of PCOS requires ovulation, clinical or biological hyperandrogenism, and polycystic ovaries.[4] Conditions that share clinical characteristics with PCOS must be ruled out because this assessment is an exclusionary one for instance, thyroid illness, hyperprolactinemia, and non-classical congenital adrenal hyperplasia. If clinical characteristics point to another cause, some individuals may require a more complete workup.[5] PCOS is a condition caused by the combination of various environmental and genetic variables. The cause of PCOS is unclear, however, genetic factors are present. In the case of PCOS, for example, family histories are highly frequent. However, family ties are also hazy in this case. The path of formal division is prevented by a lack of phenotypic data. Recent research investigations have shown that PCOS tends to cluster in families like an autosomal dominant tendency.[6] Certain environmental variables are linked to PCOS. As an example, consider obesity. Poor food habits and physical inactivity might aggravate it. Infectious diseases and poisons may also be to blame. Sometimes, with lifestyle adjustments, the condition's reproductive and metabolic aspects can be reversed. Regular physical activity and weight reduction are a couple of instances.[7] Basic anomalies in the hypothalamic-pituitary axis are what define the pathophysiology of PCOS. Moreover, ovarian function, insulin action, and secretion. Although the cause of PCOS is unknown, obesity and insulin resistance have been linked to the condition.[8] The control of ovarian function is aided by insulin. Excess insulin causes the ovaries to produce androgens, which might result in anovulation. Follicular maturation arrest is a tell-tale symptom of an ovarian disorder.[9] The clinical symptoms involve an assessment of Luteinizing Hormone (LH) and gonadotropin-releasing hormone (GnRH), but follicular-stimulating levels of hormones are muted. The stimulation of the ovarian thecal cells results in a rise in androgens because of the increased gonadotropin-releasing hormone (GnRH). Increases in endogenous or exogenous Follicle follicle-stimulating hormones (FSH) can be used to reverse a follicular halt.[10] According to several studies, PCOS is a serious abnormality in young girls who are about to enter puberty and have a family history of the condition. Patients with PCOS make up about 25% of those with elevated prolactin levels.[11]

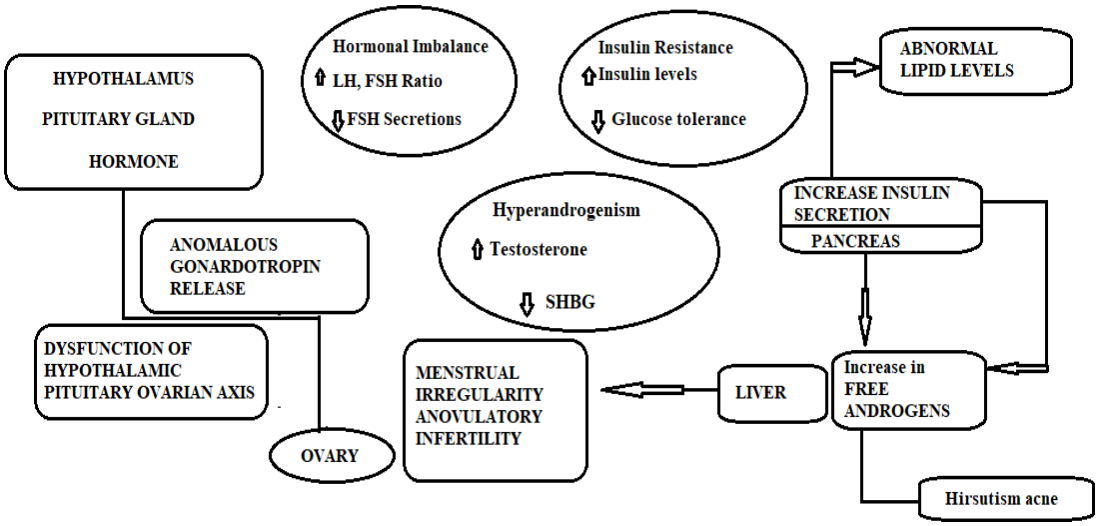

Figure 1: Schematic illustration of the mechanism connected to PCOS (1, 13).[11]

Etiology

In PCOS, there are a lot of androgens, and ovulatory failure affects how well the hypothalamus- pituitary-ovarian axis works.[12,13] Hirsutism, persistent anovulation, abnormal menstrual periods,and infertility are the most common clinical symptoms. Chronic hyperandrogenism is associated with abnormal oocyte maturation, hypothalamic-pituitary dysfunction, LH overproduction, early primary follicle activation, and precocious granulose cell luteinization.[14] Chronic hyperandrogenism is associated with early primary follicle activation, early granulose cell luteinization, abnormal oocyte maturation, hypothalamic-pituitary dysfunction, and LH hypersecretion.[15] Making changes to your lifestyle like decreasing weight and exercising can help these issues.[16]

Pathophysiology

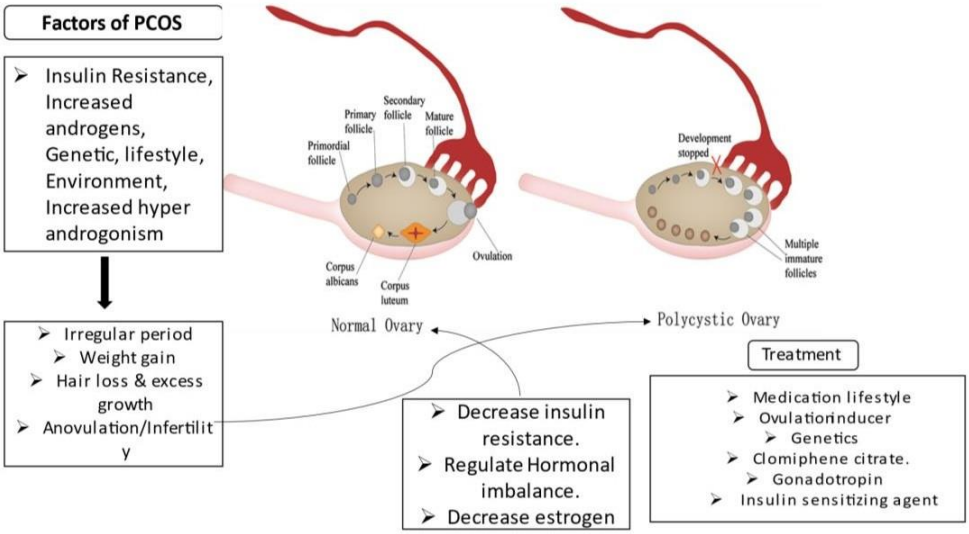

Figure 2: Represents Pathophysiology of PCOS.

The intricacy of PCOS is influenced by unregulated ovarian steroidogenesis, unexpected glucose expression, higher levels of oxidative stress, and environmental as well as hereditary variables.[17] In figure 2 showing the details pathology of pcos. PCOS patients' increased levels of androgen are caused by endocrine cells as intrinsic factors because of the intrinsic steroidogenesis process. Individuals with PCOS are more common when the

apoptotic procedures of mature follicles are altered, and PCOS women with more follicles are more likely to have pre-antral and petite antral follicles.[18] Internally, the post receptor's binding component in the insulin signaling pathways causes decreased insulin sensitivity, which is a major contributor to PCOS.[19] Furthermore, related to PCOS is a rise in secondary glycol oxidative stress for mitochondrial malfunction.[20] Microarray genomic profiling revealed that other athletes' genes were expressed differently in insulin signaling pathways.

Treatment Options for PCOS Modification in Lifestyle

Over half of the population who are suffering from polycystic ovarian syndrome are stout or fat, as a result, women with PCOS are frequently urged to lose weight since doing so can boost their metabolism and improve their sensitivity to insulin while also enabling safe weight loss.[21,22] Patients with PCOS have severe obesity, increased blood cholesterol levels, and hormonal irregularities. They must realize that a workout is not going to adequately help them shed pounds. A balanced diet is even more necessary.[23] Diet is rarely a high concern for Indian women. The nutrient-dense diet must include the right amount of protein and fiber according to body weight. Obese persons can lose weight, and PCOS-affected infertile women respond better to ovulation induction medications and experience irregular ovulation, which increases the likelihood of conception and live delivery. The study found that reducing extra weight may significantly decrease symptoms associated with PCOS and the overall risk of long-term illnesses in overweight women. Even a small weight decreases of 5% can significantly help PCOS.[24]

Genetics

Hyperandrogenism, irregular ovulation, and polycystic ovarian shape are the hallmarks of polycystic ovary syndrome or PCOS. Insulin resistance and disruption of the equilibrium of glucose are among the abnormalities in metabolism commonly observed in affected women. There is a phenotypic variation in PCOS situations because PCOS is identified using two separate sets of diagnostic standards. Genetic connections to cardiovascular disease, being overweight, diabetes type 2, rapid insulin release, levels of lipids, and coronary heart disease, suggesting a similar genetic foundation between metabolic disorders and PCOS. Variants linked to a person's body mass index, fasting insulin levels, menopausal timing, depressive disorders, and baldness in men may be causally involved in PCOS, according to a Mendelian randomization analysis.[24]

Ovulation Inducers

Fertility stimulation is an essential therapy for polycystic victims, those who desire to conceive as most of the patients suffering from this disorder have anovulation or irregular ovulation.[25]

Clomiphene citrate is a SERM (selective estrogen receptor modulator)

Oral anti-estrogen clomiphene citrate (CC) is the chosen therapy for ovarian stimulation in children with PCOS. By inhibiting the receptors for estrogen in the brain, it increases the rhythmic width of the anterior pituitary's gonadotropin-releasing hormone (GnRH) and encourages the production of follicle-stimulating hormone.[26] It is normally used for five days, commencing at 50 mg per day and progressively increasing to 150 mg per day, from the second day of the period until day five. For patients with polycystic ovarian syndrome who cannot take Clomid, metformin can be added. Tiredness, enlarged ovaries, sweating too much, ectopic pregnancies, and ovarian hyperstimulation syndrome are among the typical side effects.[27]

Inhibitors of aromatase (AI) and letrozole

A woman with PCOS, which impacts around five percent to twenty percent of women around the globe, is the most prevalent cause of irregular or nonexistent cycles of menstruation. Anovulatory infertility, or infertility caused by failure to conceive, is frequently the result of it. Ovulation also is induced by aromatase inhibitors (AIs). Regarding whether (AIs) letrozole is at least as successful as the most widely used medication, clomiphene citrate, for treating infertility,scientific research has produced conflicting results since approximately the year 2001. When letrozole is used to induce ovulation and scheduled sexual activity, it seems to increase the number of live births and pregnancy rates in comparison to clomiphene citrate. The rates of miscarriages and multiple births didn't seem to change.[28]

Gonadotropins

A female patient on gonadotropin medication for PCOS who is not ovulating. Patients who have not responded to first-line oral ovulation stimulation medicines are prescribed aromatase inhibitors and selective estrogen receptor inhibitors as substitutes.[29]

Insulin sensitizing agents

Insulin secretion and function are impaired in women with polycystic ovary syndrome. There hasbeen research on how androgen levels in PCOS women are affected by insulin resistance and hyperinsulinemia. Ovarian functions are regulated by insulin and a high amount of insulin may damage the ovaries. Excess amounts of androgens are produced by the muscle cell responding to high insulin, inhibiting ovulation & leading to changes in polycystic ovarian appearance seen in PCOS. Because of insulin resistance, PCOS patients are more prone to Chronic diseases like Diabetic mellitus and cardiovascular disease. Thus, PCOS therapy must address insulin resistance with drugs and changes in lifestyle.[30]

Metformin for PCOS

Metformin is an effective and safe biguanide drug that is used to treat diabetes mellitus in addition to being one of the most popular insulin sensitizers in the treatment of PCOS. By reducing the amount of glucose produced by the liver, increasing glucose absorption, and blocking glucose synthesis in the liver, it improves peripheral insulin sensitivity.[31] Women with PCOS are initially given metformin at a dose of (500–850) mg daily; if well tolerated, the dosagemay be increased to 2000 mg daily. It has been shown to reduce the prevalence of type 2 diabetes mellitus in people with PCOS, and diabetes mellitus prevention is crucial in thispopulation. Because metformin has a considerable impact on dyslipidemia even if it does not affect total cholesterol levels, treatment for dyslipidemia in PCOS is essential.[32] Abdominal discomfort, diarrhea, nausea, vomiting, and significant weight loss are the common manifestations of metformin intolerance, and several treatment solutions for metformin- intolerant women should be investigated.[33]

Inositol

The nutritional supplement called inositol helps insulin regulation. Its function in controlling the metabolic and biochemical elements of PCOS is not fully understood. Menstrual cycles and ovulation can be improved, claims recent research. Inositol has few benefits; thus, this suggestion recommends using it, but it also has a minimal risk of side effects and is cost- effective.[34]

Antiandrogens

Hirsutism and acne problems in PCOS patients can be reduced by using antigens like spironolactone, flutamide, and finasteride. For six months, the efficacy of three medicines was studied in 40 women with hirsutism.[34] All three

medicines were successful, even though there were no notable variations among these groups. The most effective antiandrogen is spironolactone (25–100 mg two times per day), which is safe, readily accessible, and affordable.[35]

Medroxyprogesterone acetate

Medroxyprogesterone acetate may be administered to manage PCOS in people who cannot reproduce but are not at risk of pregnancy, amenorrhea, or abnormal uterine bleeding.[35] Monthly progestogen treatment reduces ovarian androgen production, but not aberrant endometrial growth. Medroxyprogesterone acetate enhances PCOS patients' plasma lipids and insulin levels.[36]

Analogue of the glucagon-like peptide-1 receptor

Glucagon-like peptide-1 (GLP-1) and glucose-dependent unguided polypeptides are Proteinogenesis that stimulate the release of glucose-dependent insulin, particularly post-meal. Incretin reaction Particularly in diabetes mellitus, a change in incretin function is associated with insulin tolerance.[37] The enhanced glycemic control and weight loss in diabetic patients have made this system as a therapy for the disease a realistic choice. A potential medication called Mimetics cures PCOS in a wide range of individuals by effectively targeting a certain metabolic target.[38]

Oral contraceptive pill

The main mode of action of oral contraceptives in the management of PCOS is menstrual regulation. Modern estrogen and progesterone formulations have improved the therapy of androgenic symptoms.[39] Most women with hirsutism have a clinical improvement over six months of Oral contraceptive treatment, suggesting that antigens and Oral contraceptives may work together to produce a synergic effect. Antigens and oral contraceptives are commonly prescribed by physicians to reduce testosterone levels, treat symptoms, and shield the endometrium. Ethinylestradiol and cyproterone acetate should be kept to a minimum and should not be used as first-line Combined oral Contraceptive Pill treatments.[40]

Weight loss medications for PCOS

The benefits of the weight-loss drug orlistat have been established, despite some skepticism. Orlistat therapy resulted in statistically significant decreases in body weight and blood levels in trials evaluating the impact of orlistat vs. metformin treatment on biochemical and endocrine parameters in women with PCOS.[41] It also decreased IR indicators, testosterone, and total cholesterol. However, it has been linked to a rise in lipodystrophy, gas, diarrhea, stomach discomfort, and a lack of fat-soluble vitamins.[42] Visceral adiposity index (VAI) values were higher in PCOS individuals who were overweight or obese, and they were associated with several inflammatory and metabolic indicators.[43]

Sibutramine ($C_{17}H_{26}ClN$)

IUPAC name of Sibutramine (N, N,3-trimethylbutan-1-amine substituted by a (4-chlorophenyl) cyclobutyl group at position 1).

Sibutramine, a desire suppressant, is used to treat obesity together with dietary and lifestyle modifications. It prevents monoamines from reuptake. It blocks the absorption of dopamine, serotonin, and other neurotransmitters.[44]

Rimonabant

Rimonabant is obtained by formal condensation of the carboxy group of 5-(4-chlorophenyl)-1- (2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid with the amino group of 1- aminopiperidine.

A cannabinoid 1 receptor blocker called rimonabant is used for the treatment of the initial drug to be established that selectively blocks the CB1 (cannabinoid receptor 1) is rimonabant. It suppresses appetite centrally and regulates lipid and glucose metabolism peripherally in adipose tissue, the liver, muscles, and the GI tract. Rimonabant significantly lowers weight and has weight-independent effects on cholesterol and high-density cholesterol levels in addition to decreasing weight. It lessens the risk of developing a condition called metabolic syndrome. eight and anorexia in obese women with PCOS who do not have nonalcoholic fatty liver disease to lower alanine aminotransferase (ALT) and body weight.[45]

Naltrexone/bupropion

By lowering the release of dopamine, the opioid receptor antagonist naltrexone has been demonstrated to decrease food intake, use, and binge eating behavior. It just received Food Drug Administration approval for the therapy of alcohol and drug addiction.[46] Antidepressant bupropion can be used to treat mental disorders and aid in quitting smoking. In clinical studies, weight reduction was the most frequent adverse effect.[44] PCOS may benefit from weight loss while using naltrexone and bupropion. Consider postponing childbearing until you've established nutritional stability if you're a surgical patient. It can also benefit those who have comorbid conditions such as type 2 diabetes, hypertension, dyslipidemia, gestational diabetes, and large- for-gestational-age babies.[47]

Vitamin D

There is growing evidence that PCOS can begin during pregnancy in people who are genetically predisposed to it, manifest clinically in adolescence, and continue throughout a woman's reproductive years.[48] 45 to 90% of reproductive-age women have inadequate or insufficient vitamin D levels. Vitamin D insufficiency has been associated with noticeably decreased levels of ovulation, pregnancy, and the likelihood of live birth in PCOS women receiving ovarian stimulation for infertility.[49] Vitamin D-containing drugs may be helpful for persons with metabolic problems, ovulation dysfunction, and polycystic ovarian syndrome. Randomized, prospective, and controlled trials are necessary to draw definitive findings on the impact of additional vitamin D on the health of female reproduction.[50]

CONCLUSION

PCOS is a clinical disorder with complex hormonal, metabolic, and psychological symptoms. It is one of the most common reasons for infertility. Before contemplating any pharmaceutical options, the primary therapy recommendations for infertility caused by PCOS should be lifestyle modifications, PCOS increases the risk of endometrial cancer in women of all ages but does not affect the risk of ovarian or breast cancer. These findings imply that PCOS may raise the morbidity of gynecological cancer. Even though the actual origin of PCOS is still largely unknown, accumulating research suggests that the disorder is a complex multigenic one with major environmental and epigenetic effects, including diet and other lifestyle decisions. The metabolic condition PCOS has long been treated with metformin and other insulin sensitizers, modern drugs like incretin mimics and Sodium Glucose co-transporter-2 inhibitors (SGLT2) have been proven to be more effective in reducing obesity and cardiovascular risk.

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Conflict of Interest

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