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AN UPDATED IN DEPTH REVIEW ON POLYCYSTIC OVARY SYNDROME - PATHOGENESIS TO IT'S POSSIBLE TREATMENT

Uriti Sri Venkatesh[1], Ajit Kiran Kaur[2], Devesh Kumar[3], J. A. Soni[4], Syeda Fakrunnisa Begum[5], D. Sailaja[6], Utkarsh Verma[7], Subhasish Paul[8] and Dr. Anil Kumar[9]*

[1]Assistant Professor, Department of Pharmacology, Sri Sivani College of Pharmacy, Srikakulam, Andhra Pradesh, India.
[2]Professor, Department of Pharmacy, Accurate College of Pharmacy, Greater Noida, Uttar Pradesh, India.
[3]Assistant Professor, Department of Pharmacology, United College of Engineering and Research, KP-III, Greater Noida, Uttar Pradesh, India.
[4]Associate Professor, Department of Pharmacology, Arihant School of Pharmacy & Bio Research Institute, Adalaj, Gandhinagar, Gujarat, India.
[5]Lecturer, Department of Zoology, GDC (M), Cluster University, Kurnool, India.
[6]Lecturer, Department of Zoology, Government College (A), Rajahmundry East Godavari District, Andhra Pradesh, India.
[7]Assistant Professor, Faculty of Pharmacy, United University, Jhalwa, Prayagraj, Uttar Pradesh, India.
[8]Research Scholar, Department of Pharmaceutical Technology, School of Health and Medical Sciences, Adamas University, Kolkata, West Bengal, India.
[9]Head & Assistant Professor, Department of Chemistry (PG), Sahibganj College Sahibganj, Jharkhand, India.

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***Corresponding Author**
Dr. Anil Kumar
Head & Assistant Professor, Department of Chemistry (PG), Sahibganj College Sahibganj, Jharkhand, India.

ASTRACT

Hyperandrogenism and persistent anovulation are two characteristics of the complex condition known as polycystic ovarian syndrome (PCOS). Affected women range in age from 6% to 20%, depending on the diagnostic criteria. Early in the pubertal years is when PCOS symptoms first appear. Erratic menstrual periods, anovulation, and acne are features of both PCOS and normal female pubertal development. Because of the intricately entwined pathophysiology, identifying the causative factors is difficult. Most clinical data that are now accessible include findings and results for adult females. Different diagnostic criteria have been established for PCOS in adolescent girls, while the Rotterdam criteria are recognized for adult women. Periodic variation, clinical hyperandrogenism, and/or hyperandrogenemia are diagnostic features for teenage girls. Adolescent girls with PCOS can be diagnosed without the use of pelvic ultrasound findings. Adolescents exhibiting clinical manifestations of androgen excess and oligomenorrhea/amenorrhea—two characteristics of PCOS—may be considered "at risk for PCOS" even in the absence of a confirmed diagnosis. Treatment for PCOS involves lifestyle modifications, education, and symptom-specific therapies for both individuals at risk and those with a confirmed diagnosis. Metformin, combination oral contraceptive pills, spironolactone, and topical therapies for acne and hirsutism are examples of interventions. Management should involve planned transfer to adult care providers and routine follow-up visits in addition to screening for related comorbidities. A thorough understanding of the pathophysiology of PCOS will allow for the early detection of girls who are highly predisposed to the disease. This review's main goal is to highlight the pathophysiology of potential PCOS treatments.

KEYWORDS: Polycystic ovary syndrome, Obesity, Infertility, Ultrasound, Hirsutism.

INTRODUCTION

The complicated disorder known as polycystic ovarian syndrome (PCOS) is typified by high androgen levels, irregular menstruation, and/or tiny cysts on one or both ovaries.[1] The condition may be primarily biochemical (hyperandrogenemia) or morphological (polycystic ovaries). One of the clinical features of PCOS is hyperandrogenism, which can lead to anovulation, microcysts in the ovaries, follicular development suppression, and menstrual abnormalities.[2] While the basic causes of PCOS are known to be the high ratio of luteinizing hormone (LH) to follicle-stimulating

hormone (FSH) and increased frequency of gonadotropin-releasing hormone (GnRH)[3], the precise etiology and pathophysiology are still poorly understood.[3,4] Research points to the involvement of a variety of internal and external elements, such as genetics, epigenetics, environmental factors, hyperandrogenism (HA), and insulin resistance (IR). Furthermore, it is important to note that PCOS raises the chance of developing other issues such as metabolic syndrome, depression, anxiety, and cardiovascular illnesses.[4,5,6] The most important thing to do to control this illness is to decrease at least 5% of body weight; for this reason, any woman with PCOS should follow a regular exercise regimen and eat a diet low in fat and sugar. Additionally, because of their historical beliefs, reduced prices, etc., using complementary and alternative medical techniques in conjunction with established therapies may be beneficial in some circumstances. Doctors typically employ oral contraceptives, antiandrogens, insulin sensitizers, and ovulation inducers in combination. As of right now, none of the pharmaceuticals listed above are approved by the US Food and Drug Administration (USFDA) especially for PCOS, and all of them are taken off-label. In addition to the critical need for advancements in the discovery and investigation of new pharmacological compounds, drug repurposing techniques may yield newer pharmaceuticals.[7] There are many drugs available right now that the USFDA has previously approved for purposes other than PCOS, and there is a push to use them as therapeutic choices in the treatment of PCOS. These treatments include 3-hydroxy-3-methyl-3-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors like simvastatin and atorvastatin, mucolytics like N-acetyl cysteine, and anti-diabetic pharmaceuticals including pioglitazone, empagliflozin, sitagliptin, and liraglutide.[8]

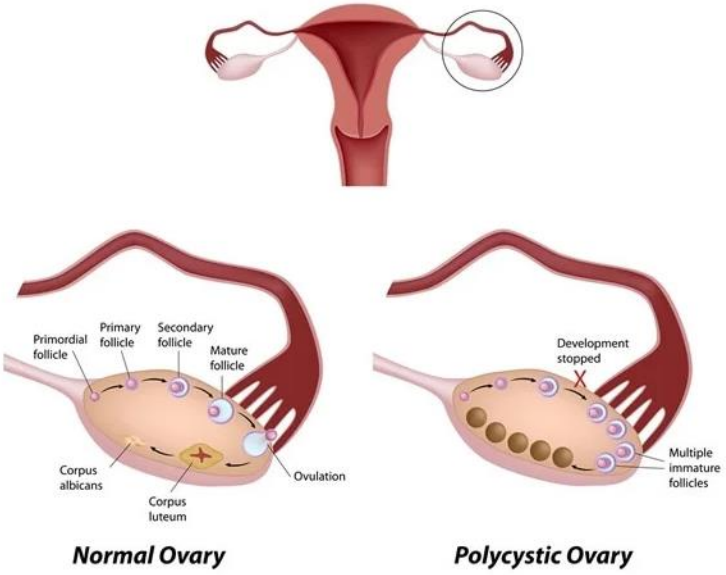

Figure 1: Normal Ovary Vs Poly-cystic ovary.

TYPES OF PCOS

(A) Type 1 PCOS
a) Insulin-resistant PCOS
b) Non-insulin-resistant types of PCOS

(B) Type 2 PCOS: Pill-induced PCOS or post-pill PCOS
(C) Type 3 PCOS: Inflammatory PCOS
(D) Type 4 PCOS: Hidden-cause PCOS.

Type 1 PCOS

Insulin-resistant PCOS

Because of the incorrect signaling from these metabolic hormones that suppress ovulation and lead the ovaries to generate testosterone, this kind of PCOS will result in insulin resistance and leptin resistance.[3] The primary reason of weight gain is an issue with the metabolic hormones. Once insulin and leptin sensitivity improve, signs of high testosterone, such as acne and facial hair, will also improve.

Non-insulin-resistant types of PCOS

There might be many immature follicles shown on the ultrasonography. The level of luteinizing hormone (LH) may be higher, and irregular periods are observed. You might have normal or high testosterone. If testosterone levels are normal, then low estrogen levels (in relation to testosterone) are the source of the acne and facial hair. A normal body weight is possible. Insulin stopped the ovaries in the insulin-resistant type from ovulating. Other forms of PCOS lead the ovaries to become incapable of ovulating for an unidentified cause.[9]

Type 2 PCOS: Pill-induced PCOS or post-pill PCOS

The contraceptive pill prevents ovulation. That is often a transient side effect for most women, and ovulation will resume somewhat quickly when the pill is stopped. On the other hand, ovulation suppression can last for months or even years in certain women. It is not rare to receive a PCOS diagnosis around that period. It is PCOS's second most prevalent kind.[10]

Type 3 PCOS: Inflammatory PCOS

Stress, pollutants in the environment, intestinal permeability, and inflammatory foods like gluten or A1 casein all contribute to inflammation or chronic immunological activation. Because it interferes with ovulation, damages hormone receptors, and increases adrenal androgens like dehydroepiandrosterone and androstenedione, inflammation is a concern for PCOS.[11]

Type 4 PCOS: Hidden-cause PCOS

There is one simple thing that is blocking ovulation. Once that single thing is addressed, this type of PCOS resolves very quickly, usually within 3-4 months.[12]

SIGN AND SYMPTOMS OF PCOS

The most common signs and symptoms of PCOS include[13,14]

- **Irregular periods:** Abnormal menstruation involves missing periods or not having a period at all. It may also involve heavy bleeding during periods.
- **Abnormal hair growth**: Patient may grow excess facial hair or experience heavy hair growth on arms, chest and abdomen (hirsutism). This affects up to 70% of people with PCOS.
- **Acne:** PCOS can cause acne, especially on back, chest and face. This acne may continue past teenage years and may be difficult to treat.
- **Obesity:** Between 40% and 80% of people with PCOS have obesity and have trouble maintaining a weight that's healthy for them.
- **Darkening of the skin:** Patient may get patches of dark skin, especially in the folds of neck, armpits, groin (between the legs) and under breasts. This is known as acanthosis nigricans.
- **Cysts:** Many people with PCOS have ovaries that appear larger or with many follicles (egg sac cysts) on ultrasound.
- **Skin tags:** Skin tags are little flaps of extra skin. They're often found in armpits or on neck.
- **Thinning hair:** People with PCOS may lose patches of hair on their head or start to bald.
- **Infertility:** PCOS is the most common cause of infertility in people. Not ovulating regularly or frequently can result in not being able to conceive.

Figure 2: Sign & Symptoms of PCOS.

ETIOLOGY/CAUSES OF PCOS

It is yet unknown what causes PCOS, however it most likely has several contributing factors. There is no one aetiologic component that completely explains the range of anomalies associated with polycystic ovarian syndrome.[15] Although hyperandrogenism and insulin resistance (IR) are the two main hormone abnormalities that cause PCOS, other factors include weight, genetic predisposition, way of life, and environment.[16] Hereditary components can be seen in polycystic ovaries, elevated testosterone levels due to ovarian cell defects, and insulin resistance. Congenital or acquired environmental influences include intrauterine factors like androgen exposure and prenatal nutrition, particularly intrauterine growth restriction, whereas acquired obesity is a significant postnatal factor that affects the phenotypic.[17] After a fetus is exposed to androgens in utero, epigenetic reprogramming of the reproductive

tissue may produce changes in the hypothalamic-pituitary-ovarian axis, which can modify folliculogenesis and result in PCOS.

The complex interactions between these contributing factors generally mimic an autosomal dominant trait with variable penetrance. Ethnic diversity also influences the syndrome's phenotypic diversity and its prevalence.[18]

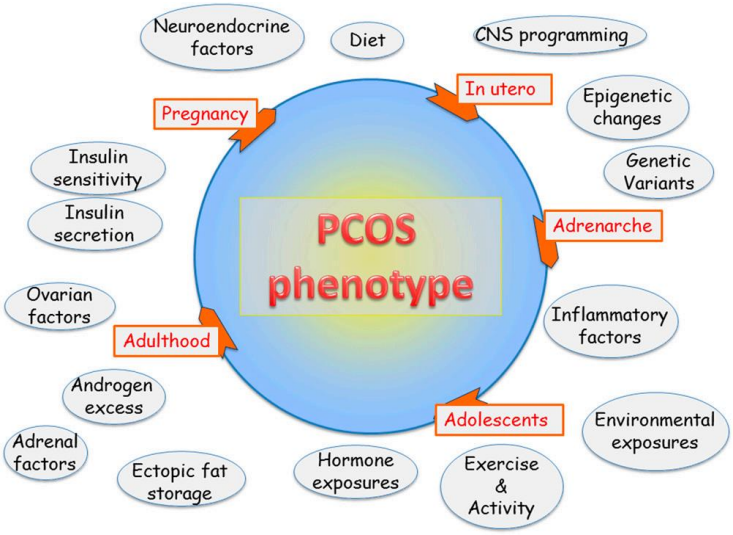

Figure 3: Etiology of PCOS.

Hyperandrogenism

When luteinizing hormone levels are elevated in PCOS, the ovarian theca cell is stimulated to generate an excessive quantity of androgens. The ovaries preferentially produce androgen when luteinizing hormone concentration rises in comparison to follicle-stimulating hormone concentration.[19] The ratio of luteinizing hormone to follicle-stimulating hormone decreases in women with polycystic ovary syndrome because of an increased luteinizing hormone pulse frequency that favors transcription of the β-subunit of luteinizing hormone over the β-subunit of follicle-stimulating hormone. This might be because these women ovulate infrequently, which results in relatively low progesterone levels, or it could be because of an inherent defect in the GnRH pulse generator.[20] Studies suggest that ovarian theca cells in PCOS women more efficiently convert androgenic precursors to testosterone than normal theca cells.

Insulin Resistance

Insulin Resistance (IR) or hyperinsulinaemia stimulates the theca cells of the ovary and acts synergistically with luteinizing hormone to produce excessive testosterone, which is responsible for the clinical symptoms of hyperandrogenism (acne, hirsutism,alopecia). Insulin also inhibits hepatic synthesis of sex hormone-binding globulin and thus increases the proportion of free testosterone while the total testosterone concentration is at the upper range of normal or only modestly elevated.[21,23]

Genetic Factors

There are several lines of evidence indicating a heritable component to polycystic ovarian syndrome. In addition to the 25% of sisters and 3%–35% of moms of PCOS-afflicted women, these individuals also have a high prevalence of metabolic syndrome. Researchers highlighted how some genes (such INSIG2 and MC4R) have a higher risk of insulin resistance (IR), and how the TCF7L2 SNP in particular affects the development of type 2 diabetes mellitus (T2DM) and body weight gain in PCOS patients (a per-allele weight gain of 1.56 kg/m2). Researchers determined that visceral obesity, decreased phosphatidylinositol-3-kinase levels in muscle tissue, and insulin receptor auto-phosphorylation were likely pathways. According to what is currently known about the syndrome's pathophysiology, it is a complicated multigenic condition.[24,26] However in rare instances, single-gene mutations can give rise to the phenotype of the syndrome.[27,30]

RISK FACTORS

- Diabetes
- 4-7 times higher risk of heart attacks

High blood pressure or hypertension

- High cholesterol
- High lipids
- Sleep apnea
- Risk of endometrial cancer
- Infertility
- Higher rate of miscarriages
- Higher risk of gestational diabetes
- Obesity which can also lead to low self-esteem and depression
- Liver disease.[31,33]

PATHOPHYSIOLOGY OF PCOS

Primary abnormalities in the hypothalamic-pituitary axis, insulin production and action, and ovarian function are involved in the pathogenesis of PCOS.[34] Despite having no recognized etiology, obesity and insulin resistance have been connected to PCOS. It makes sense that there would be a connection between insulin and ovarian function—excess insulin causes the ovaries to produce androgens, which can cause anovulation.8The primary indicator of an ovarian anomaly is follicular maturation arrest.

Elevated gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) levels are indicative of PCOS, whereas muted or unaltered follicular-stimulating hormone (FSH) levels are present. The activation of the ovarian thecal cells, which results in an increase in GnRH, creates more androgens.[35] It is possible to treat follicular arrest by either supplying exogenous FSH or increasing endogenous FSH levels. According to some research, young girls who are starting puberty and have a family history of PCOS may develop the illness as a main defect. Prolactin levels are high in about 25% of PCOS patients.[36]

The goal of therapeutic treatments is to lower ovarian androgen production and insulin levels, which will eventually raise or lower levels of sex hormone-binding globulin (SHBG).[37] It is possible to properly control PCOS symptoms with this rise in SHBG levels. According to studies, thecal cells of PCOS patients release more progesterone, testosterone, and 17-hydroprogesterone than those of normal people. Patients with PCOS who have high levels of the cytochrome P450 (CYP) 11A, 3-HSD2, and CYP17 genes have these cells changed. Although it is frequently present, obesity is not necessary for PCOS diagnosis.[38]

DIAGNOSIS OF PCOS

The precise diagnosis of polycystic ovarian syndrome (PCOS) lacks a single test. The health care professional will probably begin by going over your symptoms, prescriptions, and any other illnesses you may have.[39] The doctor may also inquire about any changes in weight and menstrual cycles. During a physical examination, symptoms of acne, insulin resistance, and excessive hair growth are looked for.

Health care provider might then recommend

- **Pelvic exam.** During a pelvic exam, provider can check your reproductive organs for masses, growths or other changes.[40]

- **Blood tests.** Blood tests can measure hormone levels. This testing can exclude possible causes of menstrual problems or androgen excess that mimic PCOS. A glucose tolerance test can measure your body's response to sugar (glucose).

- **Ultrasound.** An ultrasound can check the appearance of ovaries and the thickness of the lining of uterus. A wandlike device (transducer) is placed in vagina. The transducer emits sound waves that are translated into images on a computer screen.[41]

If candidate have a diagnosis of PCOS, doctor might recommend more tests for complications. These tests can include

- Regular checks of blood pressure, glucose tolerance, and cholesterol and triglyceride levels
- Screening for depression and anxiety Screening for obstructive sleep apnea.[42]

TREATMENT

The management of the relevant issues is the main goal of PCOS therapy. These could include obesity, hirsutism, acne, or infertility. Medication or lifestyle modifications may be part of a particular treatment plan.

Lifestyle changes

Your healthcare professional can advise losing weight by combining a low-calorie diet with mild activity. Even a small weight loss helps to enhance your health. Reducing weight can aid in infertility and perhaps boost the efficacy of PCOS drugs prescribed by the provider. A licensed dietician and a healthcare professional can collaborate to identify the most effective weight-loss strategy.[43,45]

Medications

To regulate periods, health care provider might recommend

- **Combination birth control pills:** Pills that contain both estrogen and progestin decrease androgen production and regulate estrogen. Regulating hormones can lower risk of endometrial cancer and correct irregular bleeding, excess hair growth and acne.[46,32]
- **Progestin therapy:** Taking progestin for 10 to 14 days every 1 to 2 months can regulate periods and protect against endometrial cancer. This progestin therapy doesn't improve androgen levels and won't prevent pregnancy.[47,49]
- **Clomiphene:** This oral anti-estrogen medication is taken during the first part of menstrual cycle.[50]
- **Letrozole (Femara):** This breast cancer treatment can work to stimulate the ovaries.
- **Metformin.** This medicine for type 2 diabetes that is taken by mouth improves insulin resistance and lowers insulin levels. If don't become pregnant using clomiphene, health care provider might recommend adding metformin to help you ovulate.
- **Gonadotropins:** These hormone medications are given by injection.[51]

To reduce excessive hair growth or improve acne, health care provider might recommend

- **Birth control pills:** These pills decrease androgen production that can cause excessive hair growth and acne.

- **Spironolactone (Aldactone):** This medication blocks the effects of androgen on the skin, including excessive hair growth and acne.[52] Spironolactone can cause birth defects, so effective birth control is needed while taking this medication. This medication isn't recommended if you're pregnant or planning to become pregnant.[53]
- **Eflornithine (Vaniqa):** This cream can slow facial hair growth.[54]
- **Hair removal:** There are two methods for hair removal: electrolysis and laser hair removal. Each hair follicle is punctured with a small needle during electrolysis. An electric current pulse is released by the needle. The follicle is damaged by the current before being destroyed. A focused light beam is used in a medical technique called laser hair removal to eliminate unwanted hair. It is possible that you will require several electrolysis or laser hair removal sessions. Other choices include shaving, plucking, or applying treatments that destroy unwanted hair. However, these are transient, and when the hair grows back, it can get thicker.[55,59]
- **Acne treatments:** Medications, including pills and topical creams or gels,may help improve acne. Talk to your health care provider about options.[60]

CONCLUSION

Even while the exact cause of PCOS is unknown, a variety of variables, including obesity, inflammation, and inactivity, as well as epigenetic modifications, are thought to exacerbate the illness. Since there is currently no proven treatment or cure for this illness, the standard course of treatment is functional therapy with a variety of medications, such as oral antidiabetics, antiandrogens, or contraceptives, after offering lifestyle change advice and additional pointers. Regarding repurposing, there's a strong possibility that more authorized medications might help PCOS. The process of discovering new medicines gets a bit easier because the full profiles of these drugs are available, and their safety and efficacy have previously been thoroughly investigated. To target the mechanism with appropriate treatment, however, and to gain a better knowledge of the etiology, there is still much to learn and investigate.

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