A Review Article On PCOD/PCOS

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ABSTRACT
Hyperandrogenism and persistent anovulation are two characteristics of the complex condition known as polycystic ovarian syndrome (PCOS). 6% to 20% of women in their reproductive years may be impacted, depending on the diagnostic criteria. Early in the pubertal years is when PCOS symptoms first appear. Period irregularities, 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 teenage girls, while the Rotterdam criteria are recognized for adult women. Menstrual irregularity, clinical hyperandrogenism, and/or hyperandrogenemia are diagnostic features for teenage girls. It is not necessary to use the results of a pelvic ultrasound to diagnose PCOS in teenage girls. Teenagers exhibiting the clinical indicators of androgen excess and oligomenorrhea/amenorrhea—two characteristics of PCOS—can be considered “at risk for PCOS” even in the absence of a formal diagnosis. Education, measures promoting a healthy lifestyle, and therapy aimed at symptom relief are all part of the management of PCOS, for both individuals at risk and those with a diagnosis that has been established. Metformin, combination oral contraceptive pills, spironolactone, and topical therapies for acne and hirsutism are examples of interventions. Management should involve planned transitions 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. Appropriate therapy interventions when implemented on time will enhance quality of life, reduce related comorbidities, and improve overall management of PCOS during adolescence.

Keywords: Polycystic ovarian syndrome; hyperandrogenism; insulin resistance; Metformin; anovulation; Metabolic Disorders; Medicinal Plants etc.

INTRODUCTION
Hyperandrogenic anovulation [HA] or Stein-Leventhal Syndrome are other names for polycystic ovarian syndrome [PCOS], one of the most common endocrine system disorders affecting women of reproductive age. Infertility, hirsutism, acne, obesity, and menstruation disruption are some of the manifestations of this chronic and diverse illness.
It depicts a syndrome in which at least one ovary develops an estimated ten tiny cysts, with diameters ranging from 2 to 9mm, and at least one ovary has an ovarian volume larger than 10ml. It is typically only identified when problems such as hair loss, alopecia, acne, and issues associated to infertility arise and substantially lower a patient’s quality of life.

A global screening program for PCOS using the National Institutes of Health (NIH) diagnostic criteria predicts that 4-10% of women of reproductive age have the condition. According to estimations from the World Health Organization (WHO), 116 million women worldwide suffered from PCOS in 2012.

Infertility, hair loss, and metabolic problems highlight the high financial cost of PCOS. While PCOS can strike at any age, starting at menarche, most cases are seen in people between the ages of 20 and 30. Globally, PCOS affects 1.55 million women who are fertile, accounting for 0.43 million DALs (disability-adjusted life years). In 2017, there was a 1.45% increase in the age-standardized incidence rate of PCOS among women who were of reproductive age, with 82.44 cases per 100,000.

It was previously believed that PCOS exclusively afflicted adult women, however recent study shows that it is a lifelong syndrome that initially appears during pregnancy. Hormonal imbalance, persistent low-grade inflammation, insulin resistance, and hyperandrogenism are the main pathophysiological factors of PCOS. These factors hinder folliculogenesis and raise the risk of associated comorbidities such as type 2 diabetes and endometrial cancer. International guidelines state that ovarian morphology, anovulation, and hyperandrogenism are the three primary characteristics used to diagnose PCOS.

Numerous environmental factors, including location, food and nutrition, socioeconomic level, and pollution from the environment, may play a role in the onset, progression, and treatment of PCOS.

The female hypothalamic-pituitary ovarian (HPO) axis is a finely tuned and synchronized network that is ultimately in charge of the species ability to reproduce and its ability to survive. The HPO axis reacts to both external [such as environmental effects] and internal signals [such as hormonal and neuronal impulses].

HPO axis function is disrupted by polycystic ovarian syndrome (PCOS), a condition predominantly defined by signs and symptoms of androgen excess and ovulatory failure. Between 6% and 20% of women who are reproductive age are affected by this illness, depending on diagnostic criteria.

Infertility, irregular menses, hirsutism, and persistent anovulation are typical clinical characteristics. Persistent hyperandrogenism is linked to abnormal oocyte maturation, LH hypersecretion, premature granulose cell luteinization, defective hypothalamic-pituitary feedback, and premature arrest of activated primary follicles.

A diverse endocrine illness that affects many women worldwide who are of reproductive age is called polycystic ovarian syndrome, or PCOS. This syndrome is frequently linked to insulin resistance, high
testosterone levels, oversized and malfunctioning ovaries, etc.\textsuperscript{17} One in ten women are thought to have PCOS before to menopause and struggle with its after affects\textsuperscript{18}

While the fundamental causes of PCOS are known to be elevated gonadotropin-releasing hormone\textsuperscript{[GnRH]} and a high ratio of luteinizing hormone\textsuperscript{[LH]} to follicle-stimulating hormone\textsuperscript{[FSH]}\textsuperscript{19}. The precise pathophysiology and causation are not fully understood\textsuperscript{19,20}

Research points to the involvement of a variety of internal and external elements, such as genetics, epigenetics, environmental factors, hyperandrogenism\textsuperscript{[HA]}, and insulin resistance\textsuperscript{[IR]}. Further, it is important to note that PCOS raises the risk of developing other issues, such as cardiovascular disorders\textsuperscript{20,21}, Diabetes Mellitus type 2\textsuperscript{20,21}, Metabolic syndrome\textsuperscript{21}, Anxiety and depression\textsuperscript{22}

As of right now, none of the pharmaceuticals listed above are FDA-approved for the treatment of PCOS; instead, they are all taken off-label\textsuperscript{23}. In addition to the critical need for advancements in the discovery and investigation of novel drug compounds, drug repurposing techniques may yield new therapeutics\textsuperscript{24}. The polycystic ovary has a denser center and more follicles in its layer than a normal ovary. This region, referred to as the stroma, is the source of testosterone\textsuperscript{25}

**ETIOLOGY**

- **External factors:**
  - **Epigenetic Mechanism**

  The term “epigenetic” describes heritable modifications to the genome and the expression of genes without affecting the sequence of DNA\textsuperscript{26,27}. These modifications entail introducing or eliminating from DNA or histones\textsuperscript{28}. In PCOS women, elevated LH activity is a common occurrence. It might be connected to the issues with HA and follicle development that PCOS patients frequently experience\textsuperscript{29}. The steroidogenesis process in theca cell is mediated by the LH/choriogonadotropin receptor\textsuperscript{[LHCGR]}\textsuperscript{30}. A greater sensitivity to LH and increased gene expression result from this receptor hypomethylation\textsuperscript{29,31}

  According to a study conducted on PCOS patients, hypomethylated regions are linked to overexpression of LHCGR\textsuperscript{26,30}, on the surface of theca cells\textsuperscript{30}. Moreover, epoxide hydrolase 1\textsuperscript{[EPHX1]} is a productive enzyme that breaks down aromatic compounds\textsuperscript{26,30,32}. The hypomethylation of its gene promoter\textsuperscript{26,30}, enhances the expression of enzymes\textsuperscript{26}. Reduced testosterone to estradiol conversion due to overproduction of EPHX1 may be a factor in PCOS\textsuperscript{26}. Moreover, the function of the ovaries is influenced by peroxisome proliferator-activated receptor gamma\textsuperscript{[PPAR-\gamma]}\textsuperscript{26,29,30,33}. These changes were observed in the granulose cells of PCOS women\textsuperscript{29,34}
Environmental Toxicants

According to the US Environmental Protection Agency, "endocrine disrupting chemicals" are exogenous substances that obstruct the body's natural hormones, which are necessary for homeostasis, reproduction, development, and behavior. These hormones can be synthesized, secreted, transported or eliminated. When EDCs attach to hormone receptors, they can function as either agonists or antagonists. Almost everything we use on a daily basis contains EDCs. They mimic the effects of steroid hormones since their structures are made of phenols or halogens like chlorine and bromine. Research has confirmed that women with PCOS have higher serum concentrations of EDCs. From pregnancy through puberty, prolonged and continuous exposure to EDCs can increase a person’s risk of developing PCOS. Using bisphenol A is a synthetic chemical found in epoxy resins and polycarbonate polymers. They influence metabolism via many channels direct effects of BPA on oogenesis.

In theca cells, it likewise inhibits the breakdown of testosterone and increases androgen production. Last but not least, it ruins oocyte growth and maturation by upsetting the intrafollicular environment. Downregulation of the liver-level testosterone 2a-hydroxylase enzymes testosterone 6b-hydroxylase enzymes results in a greater concentration of testosterone as a result of BPA’s indirect action on HA. The concentration of free testosterone rises as a result of BPA, s replacement of testosterone and strong ligand for sex hormone-binding globulin (SHBG). There is a reciprocal relationship between testosterone inhibits the uridine diphosphate glucuronosyl transferase enzyme and lowers the liver’s ability to remove BPA. This procedure increases the harmful effects of free BPA on the ovaries and raises its concentration in blood.

Physical and Emotional stress

While little is known about how stress contributes to PCOS, it is well recognized that PCOS negatively impacts mental and self-esteem. Adipocytes undergo hypertrophy and hyperplasia as a result of prolonged stress. The impact of glucocorticoids on the maturation of pre-adipocytes causes this phenomena. Additionally, adipokine release, stromal fat immune cell recruitment, and activation are linked to chronic stress.

Furthermore, it triggers an inflammatory cytokines such as TNF-α AND IL-6 and by upsetting the equilibrium between antioxidants and oxidants.

The hypothalamic-pituitary-adrenal (HPA) axis releases cortisol in response to stress. Cortisol causes IR by promoting lipolysis, gluconeogenesis, and visceral fat storage. Additionally, cortisol stimulates the liver’s synthesis of glucose. Additionally, stress contributes to raising insulin levels. Alterations in sex hormone levels and effects on anti-mullerian hormone (AMH) could be considered additional stressors on PCOS.
Diet

Studies have shown a correlation between certain nutritional levels and PCOS indices, despite the fact that the exact role of nutrition in PCOS remains unknown. Consuming saturated fatty acids [SFAs] causes an inflammatory state, which contributes to PCOS\(^{[46]}\) as well as decreasing insulin sensitivity\(^{[47]}\). By raising the quantity of TNF-α in the bloodstream and expressing a particular cytokine suppressor, taking SFAs causes inflammation\(^{[46]}\). A lack of vitamin D may make PCOS worse\(^{[47,48]}\). Or the PCOS-induced comorbidities\(^{[48]}\).

Insulin receptors are upregulated at the mRNA and protein levels by calcitriol. Additionally, it both directly and indirectly raises insulin sensitivity. By activating PPAR-δ, the receptor implicated in fatty acid metabolism in skeletal muscle and adipose tissue, the direct effect is achieved. The control of intracellular calcium, which is essential for insulin-mediated signaling in fat and muscle, is the indirect effect\(^{[48]}\).

Conversely, a lack of vitamin D can lead to an inflammatory response, which in turn can cause insulin resistance\(^{[47,49]}\). Moreover, vitamin D inhibits the AMH promoter\(^{[49]}\).

- **Internal factors:**

- **Insulin Resistance**

  IR stands for inadequate insulin-responsive cells\(^{[50]}\). IR is unaffected by a patient’s amount of androgen, body fat, or degree of obesity\(^{[29,51]}\). Additionally, reports of it in thin patients\(^{[29,52]}\) should be noted that in women with PCOS, IR is tissue-selective\(^{[29,53]}\), even so skeletal muscles\(^{[29,53,54]}\). Insulin and adrenal gland sensitivity is lost in fat tissue and the liver\(^{[29,53]}\), and the ovaries continue to be responsive\(^{[29,39,53,55]}\).

  Insulin directly stimulates the ovarian theca cells to produce androgens\(^{[54,56,57]}\). Insulin stimulates its receptors in the follicle membrane cells, which successfully promotes the growth of ovarian follicles and the release of hormones\(^{[58]}\). Moreover, it sets off ovarian P450c17\(^{[29,34,59]}\) and the ability of the P450scc enzyme to encourage ovarian steroidogenesis\(^{[29,60]}\) and raises them through chorionic gonadotropin, synergistic action\(^{[61]}\).

  Steroidogenic acute regulatory enzyme and CYP450c17 mRNA expression are enhanced by the interaction of LH and insulin\(^{[61,62]}\).

  Conversely, hyperinsulinemia lowers SHBG in the liver\(^{[29,50,58,61,63,64]}\), raising blood levels of free testosterone\(^{[29,61,63,64]}\). Furthermore, the liver’s synthesis of IGF-1 binding proteins is inhibited by hyperinsulinemia. The production of androgens in thecal cells is initiated by IGF-1, IGF-1 binding proteins are produced less frequently, which raises their quantity in the blood and increases the synthesis of androgens in thecal cells\(^{[29,56]}\). Further, IGF-1 over expression suppresses a particular mRNA, which quickens the death of granulose cells and prevents the growth of new cells\(^{[61]}\), as well as hyperinsulinemia\(^{[55,56,65]}\). Both contribute to the inhibition of hair development. Menstrual
irregularity, anovulatory sub-fertility, and the accumulation of immature follicles are the causes of this standstill\textsuperscript{55,56}.

**Hyperandrogenism**

Generally speaking, hyperandrogenism\textsuperscript{[HA]} raises the concentration of free testosterone by lowering the SHBG level\textsuperscript{29,66}. It has been noted that women with PCOS have greater plasma amounts of testosterone, which in adipose tissue can be converted to estrone. Follicle growth is impacted by increased estrone to estradiol change, which also raises the LH to FSH ratio and results in ovulatory failure\textsuperscript{34}. AMH overexpression brought on by HA can prevent ovulation and follicle growth through an other route. Moreover, HA lowers IGF-2 in follicular fluid, and there is a negative correlation between IGF-2 and androgen levels. Estradiol levels in follicular fluid and follicle diameters are favorably correlated with IGF-2\textsuperscript{34}. Furthermore, HA indirectly raises LH\textsuperscript{67,68}. GnRH and LH production is caused by progesterone and estrogen through negative feedback\textsuperscript{67,69,70}. The transcription of the progesterone receptor is hampered by the interaction between androgen and its receptor. Furthermore, this receptor is implicated in the conversion of elevated androgen levels into substances that alter GABAA\textsuperscript{[gamma-aminobutyric acid]}, GnRH neurons are activated by GABAA receptor modification, which also reduces the responsiveness to negative progesterone feedback\textsuperscript{67}. Furthermore, androgens are thought to suppress lipid synthesis, which could lower hepatic nuclear factor-4\textalpha\textsuperscript{[HNF-4\textalpha]} levels, HNF-4\textalpha binds to the promoter of SHBG to increase its expression\textsuperscript{77}. Furthermore, it has been noted that testosterone activates certain signaling pathways in 3T3-L1 adipocytes to increase inflammatory chemicals such lipopolysaccharide-induced IL-6\textsuperscript{72}. Increasing MNC sensitivity to glucose and exacerbating glucose-stimulated oxidative stress are two ways androgen causes oxidative stress\textsuperscript{73}. Furthermore, investigations on PCOS women have confirmed that their adipose tissue resembles that of men, supporting the hypothesis that HA affects adipose tissue malfunction\textsuperscript{74}. Furthermore, HA causes adipocyte enlargement and the ensuing impairments to adipokine secretion\textsuperscript{75}.

**Inflammation**

Oocyte development and ovulation are critically dependent on appropriate inflammation\textsuperscript{76}. However, elevated white blood cell counts\textsuperscript{56,76}, CRP or C-reactive protein\textsuperscript{56,59,76,77}, and other peripheral blood inflammatory indicators are linked to PCOS\textsuperscript{56,76,78}. One reason for HA is inflammation\textsuperscript{54,79}. TNF-\textalpha is an inflammatory cytokine that can exacerbate IR. Pro-inflammatory chemicals interfere with insulin signaling pathways, which contributes to IR\textsuperscript{77}. As well as GLUT-4 expression reduction\textsuperscript{34}. According to certain research, phosphorylation of the serine residue of the insulin receptor signaling\textsuperscript{180}. This process leads to the inhibition of glucose reuptake and GLUT-4 translocation\textsuperscript{180}. Furthermore, TNF-\textalpha demonstrated the capacity to stimulate the proliferation of
Theca cells in vitro\(^{[81]}\). Moreover, IL-1 inhibits the receptors for LH and FSH. The suppression of these receptors results in the suppression of ovulation and follicular growth\(^{[76]}\). TNF-\(\alpha\) prevent HNF-4\(\alpha\) activation through several mechanisms\(^{[34]}\). Furthermore, ovarian fibrosis, follicular pyroptosis, and disruption of follicular development are all brought on by NLRP3 inflammasomes\(^{[76]}\). Another reason for IR in insulin-sensitive tissues is an elevation in CRP levels. Increased pro-inflammatory substances released by the liver and monocytes generate an inflammatory response syndrome (IR). This increase in secretion is triggered by CRP\(^{[82]}\).

**Oxidative stress**

An imbalance between pro-oxidants and and antioxidants is known as oxidative stress (OS)\(^{[71,83]}\). Reactive Oxygen species (ROS) are among the several compounds that are considered oxidative molecules\(^{[83,84]}\). ROS is involved in a variety of processes, including signaling pathways\(^{[81,83,85]}\), cell division\(^{[81,83]}\), and distinction in addition to RNS\(^{[83]}\). It influences the neurons in charge of feeding behavior to make people feel hungry\(^{[81]}\).

Oxidative chemical overproduction damages essential molecules like proteins, DNA, and lipids in a number of ways\(^{[83,84,86]}\). Several studies have shown that PCOS patients have higher OS.\(^{[87,88,89]}\) OS levels that are higher trigger the nuclear factor-kappa B (NF-kB) pathway\(^{[82,84]}\). The mechanisms leading to inflammation involve\(^{[84]}\) and influence the synthesis of pro-inflammatory cytokines such as IL-6\(^{[82,90]}\). However, instead of the typical tyrosine phosphorylation of IRS, elevated OS activates certain protein kinases that cause serine/threonine phosphorylation. Thus, OS causes IR and the insulin signaling pathway is blocked\(^{[77]}\). OS contributes to obesity as well. It causes adult adipocytes to enlarge, which in turn promotes pre-adipocyte growth and adipocyte differentiation. OS has a significant impact on obesity as well\(^{[81]}\).

**Obesity**

A major factor in low-grade chronic inflammation is obesity\(^{[82]}\). The buildup of adipocytes in visceral fat results in hypoxia and subsequent necrosis, which triggers the release of inflammatory cytokines\(^{[76]}\). Hypertropic adipocyte death results in an inflammatory condition\(^{[54,79]}\). Adipose tissue mononuclear cells release cytokines that promote inflammation. Another factor contributing to the inflammatory condition is extra abdominal fat\(^{[54,91]}\). Additionally, obesity contributes to the development of IR, HA, and hyperinsulinemia. Blood levels of non-esterified fatty acids (NEFAs) are absorbed by skeletal muscles in place of glucose as an energy source. Hyperinsulinemia and a pancreatic fast response are caused by this hyperglycemia\(^{[75]}\). Moreover, lipotoxicity is brought on by visceral fat’s lipolytic reaction to catecholamines\(^{[54]}\), with a reduction in insulin activity and clearance\(^{[91]}\).

Adipokines, also known as adipocytokines, are substances secreted by adipose tissue that have endocrine properties. Adipocytes generate leptin, which in high concentrations prevents granulosa cells from...
expressing aromatose mRNA and so stops the conversion of androgens to estrogen\textsuperscript{[61]}. Furthermore, there is a suggestion that the lack of folliculogenesis and elevated leptin levels are connected\textsuperscript{[91]}. Additionally, adipocytes release adiponectin\textsuperscript{[61]}. FFA absorption and gluconeogenesis are decreased as a result of the adiponectin insulin-sensitizing action. It also contributes to the generation of progesterone and estrogen, ovulation, and decreased secretion of GnRH\textsuperscript{[61]}. Moreover, adiponectin causes the granulosa to secrete estrogen, lowers the pituitary’s release of LH, and is linked to the ovaries’ synthesis of androgen\textsuperscript{[91]}. Moreover, lipotoxicity, or the buildup of lipid in non-adipose tissues, results in oxidative/endoplasmic reticulum stress, which is connected to IR and inflammation. Diaglycerol serine phosphorylates the insulin receptor in muscles and the liver, causing IR\textsuperscript{[92]}. 

**Figure: 1 PCOS risk change factors**

**PATHOPHYSIOLOGY**

By the time ovarian, metabolic, and neuroendocrine abnormalities are taken into account, PCOS has manifested as a phenotype representing a self-sustaining vicious cycle. Regarding the proximate physiologic roots of PCOS, many theories have been put out over the years. PCOS is a result of interactions between several proteins and genes that are impacted by environmental and epigenetic factors\textsuperscript{[93]}.
This article breaks down the variables that lead to PCOS development in preclinical models and humans in particular sections. One of the main characteristics of PCOS is biochemical and clinical hyperandrogenism. The early years of puberty are when PCOS first appears\textsuperscript{[94]}. The majority of pertinent data, however, has come from clinical research involving adult women, where referral bias is concentrated on looking into the more severe phenotypes\textsuperscript{[95]}

![Figure: 2 Factors contributing to PCOS phenotype](image-url)
Neuroendocrine Disruption

Enhanced gonadotropin-releasing hormone pulse frequency and decreased hypothalamic negative feedback from sex steroids are the hallmarks of polycystic ovarian syndrome[96]. Increased luteinizing hormone secretion is the result of pulsatile release of gonadotropin-releasing hormone from neurons in the hypothalamic infundibular nucleus[97]. Raised luteinizing hormone levels lead to increased ovarian thecal androgen production in women with polycystic ovary syndrome, while relative follicle stimulating hormone deficit results in follicular arrest, polycystic ovarian morphology, and oligo-ovulation[97].

Because gonadotropin releasing hormone neurons lack progesterone or estrogen receptors, it is believed that the decrease in sex steroid feedback upon release of the hormone occurs upstream of the hormone itself[98]. Progesterone and estrogen receptors, which are necessary for the negative feedback on gonadotropin-releasing hormone pulsatility, are expressed by kisspeptin neurons[99,100] and while the exact cause of this excess is unknown, women with polycystic ovarian syndrome and oligomenorrhea may have elevated kisspeptin pulse frequencies, which may indicate a hypothalamic source[101].

Furthermore, these women no longer have the physiological link between kisspeptin and luteinizing hormone pulsatility[101]. Kisspeptin release is regulated autocrinely and paracrinely by neurokinin B and dynorphin, which are produced by KNdy neurons. The neurokinin 3 receptor, which is encoded by TACR3, is the preferred binding site for neurokinin B, which increases the pulsatility of gonadotrophin-releasing hormone[102]. It is an appealing target for treatment because the milder effect of neurokinin B blockage may prevent an excessive reduction in gonadotrophin releasing hormone pulsatility[97].

Ovarian granulosa cells release anti-mullerian hormone, where elevated levels interfere with ovulation and folliculogenesis in women with polycystic ovarian syndrome[103]. Recent research linking anti-mullerian hormone to gonadotrophin-releasing hormone neuronal migration[104], luteinizing hormone secretion, gonadotrophin-releasing hormone pulsatility[103].

Figure: 3 Polycystic Ovary

Ovary, Adrenal and Androgen Excess

Excess androgen release from the adrenal glands or ovaries is a hallmark of PCOS. The overproduction of androgens in the ovaries is caused by both external and intrinsic causes, including hyperinsulinemia and altered steriodogenesis. Compared to normal controls, women with PCOS have more developing follicles, and their antral follicles grow at an earlier stage, stopping at 5 to 8mm. The traditional ovarian phenotype, which consists of larger ovaries with a string-of-pearl morphology and theca interstitial hyperplasia, is indicative of...
exposure to testosterone; this morphology has also been noted in female transgender individuals and women with congenital adrenal hyperplasia [CAH] [105].

Variations in follicle form and development potential can be observed in ovarian tissue from prepubertal and early pubertal girls. In particular, a significant percentage of aberrant, non-growing follicles are present in prepubertal ovaries but not in pubertal ovaries [106]. Granulosa cells secrete a glycoprotein called Anti-Mullerian hormone (AMH), which denotes follicular reserve and inhibits initial follicular recruitment. AMH appears to encourage preantral follicle growth to the antral stage in the ovaries of non-human primates (NHPs), in contrast to mice where it inhibits preantral follicle growth and antral follicle maturation [107, 108].

Antral follicles contain the highest quantities of AMH. Estradiol inhibits the expression of AMH after FSH-stimulated granulosa cell estradiol concentrations reach the required threshold [109]. Contrary to previous beliefs, androgens have a positive effect on follicles. They are synthesized in preantral follicle theca cells, where they stimulate the formation of preantral and antral follicles and activate the expression of the FSHR (granulosa cell FSH receptor) in early antral follicles [110].

In granulosa cells, androgens stimulate the production of aromatase, which in turn stimulates the expression of the LH/chorionic gonadotropin receptor (LHCGR). Androgens seem to limit proliferation and encourage death in mature follicles. Initially, the marmoset, an NHP, was used to demonstrate this biphasic androgen activity. In small antral follicles, androgens increased FSH action, but in larger follicles, they had an inhibitory impact [111]. Androgens receptors (ARs), which are expressed in theca cells, granulosa cells, oocytes, and stromal cells, mediate androgen effects [1]
Figure 5 Pathophysiology Of PCOS
**DIAGNOSIS**

Introduction to different diagnostic criteria:

Approximately 8%-13% (changing across different populations) of women in the reproductive age bracket have PCOS, a recurring endocrinopathy \[113,114,115,116\]. Though it occurs frequently, there is comparatively little and inconsistent guidance among health professionals regarding the implementation of the diagnostic techniques for recognizing PCOS. Because of this, it is estimated that up to 70% of these women never receive a diagnosis \[115\]. Consensus-based worldwide guidelines identify ovulatory dysfunction, hyperandrogenism, and PCOM as the three unique characteristics of this endocrinologic disease \[117,118,119\]. Furthermore, hirsutism, oligo-anovulation, amenorrhea or an irregular menstrual cycle, and infertility are common manifestations of PCOS \[120\].

[1] National Institute of Health (NIH) criteria: It was founded in 1990 thanks to the consensus of an experienced panel and the development of the first set of diagnostic criteria in history. Two distinct traits have been approved by the NIH criteria as being indicative of PCOS: {a} clinical or biochemical evidence of hyperandrogenism, and {b} oligo-anovulation or oligomenorrhea \[117\]. Later, in 2012, this criterion was updated to comply with the Rotterdam criteria by integrating PCOM as the third determinant \[121\].

[2] Rotterdam criteria: The third PCOS determinant—the PCOM upon ultrasonogram imaging—was added to the proposal made in 2003 by the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Radiology (ESHRE). The Rotterdam criteria indicated that a diagnosis of PCOS might be made if any two of the three characteristics were present. By applying this criterion for diagnosis, patients can be further classified into four distinct phenotypes, ranging from A to D \[118\].

- **Phenotype A:** PCOM, Ovulatory Dysfunction, and Hyperandrogenism
- **Phenotype B:** Ovulatory Dysfunction + Hyperandrogenism
- **Phenotype C:** Hyperandrogenism + PCOM
- **Phenotype D:** Ovulatory Dysfunction + PCOM

Gynecologists, obstetricians, and other medical professionals frequently utilize the Rotterdam criteria; the 2018 International PCOS guideline and other recommendations embraced it \[122,123\].

[3] AE – PCOS Criteria: It was proposed by the society for Androgen Excess and PCOS in 2006. For the diagnosis of PCOS, the third criterion proposed the presence of hyperandrogenism in conjugation with any one or both of the other factors [Ovulatory Dysfunction or PCOM] \[113\]. For example, NCAH (Non-Classical congenital Hyperplasia) that shows up as hirsutism or irregular menstruation might be assessed by taking measurements 17-hydroxyprogesterone [17 OHP] levels in borderline instances along with an additional ACTH stimulation test \[124\].
Similarly, if a prolactin level above 500µg/L is discovered, presenting galactorrhoea, hyperprolactinemia can be identified\[125\]. Moreover, thyroid-stimulating hormone [TSH] levels can be determined to rule out thyroid disorders\[121\]. Conversely, cushing’s syndrome is a more severe illness characterized by amenorrhoea, obesity, and high blood pressure. Moreover, it is linked to excessive cortisol secretion. To differentiate this from PCOS, an overnight dexamethasone suppression test or a midnight salivary cortisol test will be helpful\[126\]

**Diagnostic features in Adults:**

Based on the three available diagnostic features - ovulatory Dysfunction, hirsutism, biochemical hyperandrogenism, and PCOM – data from a recent meta-analysis and systematic review painted a clear picture of the overall prevalence of PCOS, with these features being present in 12%, 13%, 11%, and 28% of women, respectively\[116\]

**Ovulatory Dysfunction:** Approximately 75% of people with PCOS are known to have ovulatory disruption, which is a startling statistic\[127\]. One way to explain it is as an irregular menstrual cycle\[121\]. During the 24th or 25th day of a regular ovulation cycle, menstruation starts\[121\]. An adult’s irregular menstruation may be indicated by a cycle lasting less than 21 or more than 35 days, or in a rare situation where the gynecologic age is substantially greater, less than eight menstrual cycles annually\[123,129\]. Prolonged irregular menstruation is a sign of anovulation, which can subsequently exacerbate PCOS\[121\].

On the other hand, women with PCOS have also been observed to have regular menstruation that reflects normal ovulatory cycles\[130\]. Subclinical ovulatory dysfunction is the term for the phenomenon, which hyperhydrogenism may help to explain. This makes diagnosing PCOS more difficult\[131\].

**Hyperandrogenism:** According to the Rotterdam criteria, an additional prominent characteristic of PCOS is an elevated serum androgen level. A sizable fraction (about 60%-100%) of women with PCOS are probably experiencing clinical or biochemical androgenism\[122\].

**Clinical hyperandrogenism:** The manifestation of hirsutism, acne, or alopecia in clinical hyperandrogenism often indicates low-to-average levels of androgen excess\[132\].

**Hirsutism:** About 80% of those with hyperandrogenism exhibit hirsutism more frequently than the other two. It describes terminal hair development that is visible to the unaided eye (hair that can grow longer than 5mm)\[133\]. With a score ranging from 0 to 4, this incorporates a visual assessment of the nine body parts (chin, chest, upper lips, upper arms, thighs, upper and lower abdomen, and back)\[134,135\].

**Comedonal acne:** Women frequently suffer from comedonal acne, particularly adolescent girls. It was estimated that a vulnerable PCOS condition could account for around 40% of the incidence of acne\[136\]. Despite the fact
that biochemical hyperandrogenism and acne are related, there is currently no specific measuring instrument to
evaluate this condition\[132\].

_Alopecia_: Out of the three, alopecia is the least frequent. During PCOS diagnosis, hair loss similar to that of men was found in just 22% of women. There are several variables besides hyperandrogenism that could contribute to alopecia. The Ludwig scale is a method for measuring hair loss around the scalp that assigns a visual assessment grade of 1 to 3 based on the extent of hair loss\[137\].

**Biochemical hyperandrogenism:** Women are evaluated for indications of biochemical hyperandrogenism when the clinical indicators of hyperandrogenism are unclear\[119\]. The condition can be identified by measuring total testosterone (TT), free androgen index (FAI), calculated free testosterone (fT), and/or calculated bioavailable testosterone, according to the evidence-based advice\[119\]. According to prior research, the most sensitive metric for identifying biochemical hyperandrogenism is serum-free testosterone\[122,132\]. Alternatively, the free alternative testosterone index (FAI) can also be calculated indirectly by multiplying the ratio of total testosterone by Sex Hormone Binding Globulin [SHBG] and then multiplying the result by 100\[138\]. High-quality assays such as mass spectrometry, liquid chromatography-mass spectrometry [LCMS], and extraction/chromatography immunoassays can be used to determine the levels of free or total circulating testosterone. The chemiluminescence assay [CLIA], radioimmunoassay [RIA], and enzyme-linked immune sorbent assay [ELISA] are other automated direct assays. But these tests show decreased sensitivity, which leads to imprecise results\[139,140,141\].

**PCOM:** It is acknowledged that PCOM is the feature most frequently utilized in PCOS diagnosis. It was initially included as the third PCOS characteristic in the Rotterdam criteria in 2003\[118\]. Follicle arrest causes the ovulation process to stop in adult PCOS women. The tiny follicles appear on transvaginal ultrasound as formations resembling cysts\[142,143,144,145,146\]. When FNPO/Antral Follicle Count [AFC] cannot be accurately determined due to technical imaging issues, like with transabdominal ultrasound, the ovarian volume is a major factor\[132\]. The suggested method for assessing FNPO suggestive of a polycystic ovary is transvaginal ultrasonography. But it should only be applied to women who are sexually active\[119\].

_Anti-Mullerian Hormone as an alternative diagnostic feature for PCOS_: Anti-Mullerian Hormone [AMH] has been proposed as a substitute for ultrasound in the detection of PCOM, given the uncertainty surrounding the use of ultrasound as a diagnostic technique\[122\]. Women with PCOS showed an increasing tendency in their antral follicle count in proportion to their AMH levels. This is due to the fact that AMH is generated by granulosa cells found in pre-antral and antral ovarian follicles, which are more numerous in PCOS\[147,148,149\].
Figure 6: Diagnosis of PCOS

**TREATMENT**

Since there isn’t a cure for PCOS that addresses all clinical manifestations and cures the hormone imbalances that cause it, medical care solely focuses on treating specific symptoms in conjunction with lifestyle modifications\(^{150}\).

[1] Diet regimen

A diet plan works to control weight while lowering the long-term risk of PCOS, cardiovascular illness, type 2 diabetes, etc.

[2] The following products should be avoided:

- Nicotine, caffeine, alcohol, and the addictive substance in each.
- Products made from soy: they prevent ovulation.
- Normal testosterone processing is limited by milk protein, which results in level syndrome.
- Red meat and dairy items are high in saturated fats, which boost the synthesis of estrogen.
- Highglycemic index foods, such as potatoes and white rice.

[3] The following products should be consuming:

- Whole grains: red rice, ragi.
- Rich in vitamins, minerals and nutrients are green leafy vegetables.
- Dry fruits-fig, dates.
- Whole fruits with low glycaemic index: pears, apples, grapes, oranges, and plums.
- Brightly coloured vegetables: such as salad, carrots, capsicum, and beets.
- Proteins and Carbohydrates.

Exercise: A 10-minute workout improves PCOS condition.

**Pharmacological management:**

**Clomiphene citrate**

For PCOS patients, it is the first-line medication for inducing ovulation. The oestrogen receptor antagonist increases the availability of FSH by interfering with the oestrogen signaling pathways negative feedback. Follicle growth is a result of elevated FSH.\(^{150}\). It includes the forst phase of the menstrual cycle\(^{151}\). Additionally, infertility is treated using it\(^{152}\).
Metformin

Insulin sensitizing medications, including metformin and troglitazone, work to counteract some hyperandrogenic symptoms by lowering the concentrations of both free and total testosterone\(^{[153]}\). It promotes ovulation, lessens insulin resistance-related issues, and controls abnormally high testosterone levels. It brings back fertility, ovulation, and the menstrual cycle\(^{[154]}\). Pregnancy-related conditions such gestational diabetes and gestational hypertension are less common when this occurs\(^{[155]}\).

Flutamide

It was suggested as a substitute for spironolactone, which works by blocking the androgen receptor. Pure non-steroidal antiandrogens work in a dose-dependent manner to block the androgen receptor, although they are not more effective than spironolactone\(^{[156]}\).

Glucocorticoids

To induce ovulation, prednisone and dexamethasone have been utilized. Patients with PCOS who have elevated adrenal androgen may benefit from taking low doses of dexamethasone (0.25-0.5mg) before bed\(^{[150]}\).

Gonadotropins

When clomiphene citrate is no longer effective, it is used as a second line of treatment. With the carefully regulated injection of FSH, it promotes follicle growth, maintains ovulation, and begins treatment with modest dosages\(^{[157]}\).

N-acetyl-cysteine [NAC]

It contains antioxidants needed by the body to produce glutathione, which reduces oxidative stress and keeps hyperinsulinemia from occurring\(^{[158]}\).

Surgery: Laparoscopic ovarian drilling [LOD] is a procedure used to eliminate androgen-producing tissues in women who do not respond to clomiphene treatment. Re-establishing hormonal balance and making corrections in ovarian activity. Treatment options for hirsutism and acne include suppressing hyperandrogenism\(^{[159]}\).

Therapy for Hirsutism:

**Cosmetic hair removal:** Permanent hair removal can be achieved using electrolysis and laser treatment, although temporary methods like shaving, waxing are considered in cosmetic removal.

**Pharmacotherapy:** The pharmaceutical management of hirsutism inhibits the growth of newly growing hair while having no effect on existing hair\(^{[154]}\).
Endocrinological effects of Herbal Medicines in Oligo/amenorrhoea, Hyperandrogenism and PCOS.

<table>
<thead>
<tr>
<th>Medicinal Plants</th>
<th>Family</th>
<th>Mechanism of action</th>
<th>Pharmacological Effects</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinosphora Cordifolia[Guduchi]</td>
<td>Menispermaceae</td>
<td>Root causes for Insulin Imbalane ovarian cysts. Boosting Metabolism</td>
<td>Hypoglycemic Effects</td>
<td>Anti-Inflammatory</td>
</tr>
<tr>
<td>Foeniculum Vulgare[Shatapushpa]</td>
<td>Apiaceae</td>
<td>Fennel helps in reducing resistance. Bringing down the Inflammation in PCOS.</td>
<td>Diabetes, Bronchitis, Kidney Stones</td>
<td>Anti-Inflammatory</td>
</tr>
<tr>
<td>Ocimum Tenuiflorum[Holy Basil, Tulsi]</td>
<td>Lamiaceae</td>
<td>Decreasing the Androgen Production</td>
<td>Obesity</td>
<td>Anti-Androgenic</td>
</tr>
<tr>
<td>Grifola Frondosa [Maitake Mushroom]</td>
<td>Meripilaceae</td>
<td>Changing blood sugar levels and increasing Insulin Sensitivity</td>
<td>Hypoglycemic Effects</td>
<td>Anti-Diabetic</td>
</tr>
<tr>
<td>Taraxacum Officinale[Dandelion Root]</td>
<td>Asteraceae</td>
<td>Stimulate the production of SHBG Helps in removal of toxin from the body.</td>
<td>Liver Detoxifier</td>
<td>Anti-Cleansing</td>
</tr>
<tr>
<td>Actaea Racemosa [Black Cohosh]</td>
<td>Ranunculaceae</td>
<td>Ability to induce ovulation in women.</td>
<td>Amenorrhoea, Leucorrhoea Dysmenorrhoea</td>
<td>Anti-Inflammatory</td>
</tr>
</tbody>
</table>
CONCLUSION

From the review, it is evident that PCOS is a complicated condition. It is challenging to identify and comprehend the primary mechanism. Therefore, as treatment focuses on treating clinical symptoms rather than curing the illness, no medication can be referred to as a miracle cure. It is important to understand the mode of action of alternative medications, such as herbal or medicinal plants. To improve the long-term effects on the patient’s health, more research on the pathophysiology and medications that affect it needs to be done. Changing one’s lifestyle could reduce the symptoms associated with PCOS.

References:


[143] Jonard S and Dewailly D. The follicular excess in polycystic ovaries, due to intra-ovarian hyperandrogenism, may be the main culprit for the follicular arrest. *Hum Reprod Update* 2004;10(2):107-117.


