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# POLYCYSTIC OVARIAN SYNDROME

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## ABSTRACT

*Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder affecting individuals assigned female at birth, characterized by hormonal imbalances, ovulatory dysfunction, and the presence of polycystic ovaries. The condition is driven by an interplay of genetic, environmental,and lifestyle factors, leading to elevated levels of androgens (hyperandrogenism), insulin resistance, and inflammation. PCOS manifests through symptoms such as irregular menstrual cycles, hirsutism, acne, obesity, and infertility. It is closely associated with metabolic disturbances, increasing the risk of Type 2 diabetes, cardiovascular diseases, and mood disorders.*

*Recent research highlights the heterogeneity of PCOS, suggesting it comprises several distinct phenotypes with varying severity and presentations. These phenotypes can range from cases dominated by hyperandrogenism to those primarily exhibiting insulin resistance or menstrual irregularities. The complexity of PCOS pathophysiology suggests that a "one-size-fits-all" approach is ineffective, necessitating a personalized model of care to address individual symptoms and underlying mechanisms*

*Management of PCOS involves a combination of lifestyle interventions, pharmacological treatments such as hormonal contraceptives and insulin-sensitizing agents, and fertility treatments where necessary. The disorder also poses psychological challenges, with increased rates of anxiety, depression, and body image issues reported. Comprehensive, multidisciplinarycare is essential for improving the overall well-being of those affected, emphasizing early diagnosis, patient education, and ongoing support.*

## REVIEW OF LITERATURE

1. **L. Konrod's :** L. Konrod's literature review on endometriosis outlines key aspects of the condition, emphasizing its prevalence, biological processes, and management strategies. Endometriosis is characterized by the growth of endometrial-like tissue outside the uterus, affecting 6-10% of women. Symptoms typically include pain and infertility, and diagnosis is confirmed through laparoscopy and histological analysis. While mild cases are managed with medical treatments such as contraceptive steroids and anti-inflammatory drugs, surgery can offer relief, though symptoms often recur within two years. The review categorizes endometriosis into six stages of biological processes that resemble metastasis, including shedding of cells, survival, immune evasion, adhesion, angiogenesis, and bleeding**.** The role of transforming growth factor-beta (TGF-β) in these stages is highlighted, suggesting its involvement in both menstrual initiation and the carless regeneration of the endometrium post-menstruation. Increased expression of TGF-β during menstruation may indicate its pivotal role in these processes, providing potential targets for future research on endometriosis treatment.
2. **Lars R. McNaughton :** Lars R. McNaughton is a leading figure in exercise physiology, focusing on areas like stretching, supplementation, and heat adaptation in athletic performance. His research reveals mixed results on static stretching, showing it may reduce stiffness but potentially impair explosive performance, with uncertain benefits for endurance athletes ResearchGate: He has extensively studied sodium bicarbonate as a performance enhancer, highlighting its role in buffering lactic acid during high-intensity exercise. Selected Works : Additionally, McNaughton's work on heat shock proteins explores how heat stress during exercise drives cellular adaptations, which is crucial for athletes training in extreme environments Selected Works:. His contributions provide valuable insights for optimizing sports training and recovery strategies.
3. **Sardul S Guraya :** Both functions of the mammalian ovary, the endocrine and (synthesis and secretion of steroid hormones) and exocrine (production of ova), depend upon the presence and cyclic growth of follicles, as the depletion of primordial follicles from the ovary leads to cessation of these f- unction's or female reproduction in mammals, or to postmenopausal period in humans. Actually, various fertility and sterility problems at the ovarian level are related to follicles. Therefore, a thorough understanding of the biology of ovarian follicles in mammals is of fundamental interest to a wide variety of academic and scientific disciplines. Study of their structure, function, and control involves mor phology, including ultrastructure, cell biology, physiology, endocrinology, biochemist try, immunology, neurobiology and pharmacology. Zoologists take interest in comparative and evolutionary aspects of

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biology of ovarian follicles in many different groups of mammals. Agricultural scientists and wildlife biologists need a thorough knowledge of the biology of follicles to control more effectively fecundity in domestic animals and endangered species of mammals

4. **Michael J. Buckenmeyer :** Michael J. Buckenmeyer's research in bioengineering focuses on innovative approaches for ovarian health, particularly in the context of fertility preservation. His work has pioneered the development of bioengineered ovarian-specific extracellular matrix (ECM) hydrogels, which serve as supportive scaffolds for follicle delivery. This technology has been instrumental in creating in situ ovarian environments, enabling sustainable follicle engraftment and natural pregnancy in preclinical models. These methods hold promise for addressing infertility caused by chemotherapy and other ovarian dysfunctions by integrating advanced biomaterials and regenerative medicine strategies

## INTRODUCTION

Poly Cystic Ovarian Syndrome is a relatively common endocrine disorder in women of reproductiveage group. It is found in around 70% of women who have ovulation difficulties leading to subfertility (1)

Poly Cystic Ovarian Syndrome is a condition that has cysts on the ovaries that prevent the ovaries from performing normally. (2)Symptoms of Poly Cystic Ovarian Syndrome include Amenorrhea or infrequent menstruation, irregular bleeding, infrequent or no ovulation, multiple immature follicles, increased levels of male hormones, male pattern baldness or thinning hair, excess facial and body hair growth, acne, oily skin or dandruff, dark colored patches of skin specially on neck, groin, underarms, chronic pelvic pain, increased weight or obesity, diabetes, lipid abnormalities and high blood pressure(3)

Fertility problems experienced by women with Poly Cystic Ovarian Syndrome may be related to theelevated hormone, insulin or glucose levels, all of which can interfere with implantation as wellas development of the embryo1.(4) Increased Luteinizing hormone reduces the chance of conception and increase miscarriage. Additionally, abnormal insulin levels may also contribute to poor egg quality, making conception more difficult

The World Health Organization (WHO) stated that PCOS affected over 116 million women worldwide in 2012. One in five Indian women are affected by PCOS. Globally, 1.55 million incident cases of PCOS in women of reproductive age (15–49 years) were reported, representing an increase in the rate of 4.47%(2.86–6.37%) from 2007 to 2017 A large-scale survey conducted across India in 2020 showed that around 16% of female respondents between the ages of 20 and 29 years suffered from PCOS(5)

### Herbal Drug

Currently, herbal remedies are playing a prominent role in treating various chronic disorders, including PCOS. The use of herbal medicines and modifications to the diet may help in treating PCOS more effectively Different herbs will exert their activity against PCOS through a variety of mechanisms, including the suppression of prolactin levels, anti-androgenic activity, promoting follicle stimulating hormone (FSH), decreasing luteinizing hormone (LH), the induction of ovulation andrestoration of glucose sensitivity, estrus cyclicity and enzyme activity

(**Figure 3**).

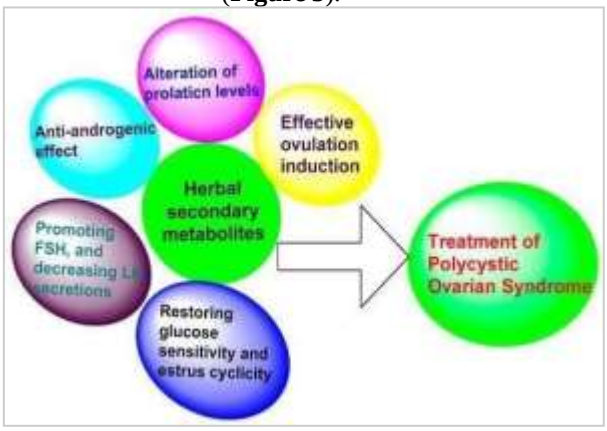


**Figure 3. Mechanisms through which different herbal secondary metabolites are active in the treatment of PCOS.**

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Among various herbs, *Glycyrrhiza glabra* (liquorice), *Linum* (chaste berry), *Vitex negundo*(Chinese chaste tree), *Foeniculum vulgare* (fennel) and *Curcuma longa*(Turmeric) are potentialplantsources that have shown effective action against PCOS(6 ).

### *3.1 Herbs That Increase Ovulatory Cycles*

Changes in prolactin levels and hormonal imbalances will have a significant impact on ovulatorycycles. Decreasing prolactin levels or improving the hormonal balance have a positive impact on ovulatory cycles and the treatment of PCOS. These two activities have the potential to reducecyst formation, dissolve cysts and improve ovulatory cycles. Vitex and turmeric are two herbs that show a beneficial effect in PCOS by increasing the ovulatory cycles(7)

### *3.2Herbs with Anti-Androgen Properties*

Elevated blood levels of androgens are also the one of the major etiologies behind PCOS. Hence,drugs with anti-androgen activity are used in the treatment of PCOS. Herbs including *Glycyrrhiza glabra*, *Linum usitatissimum*, *Mentha spicata*, *Cocus nucifera* and *Punica granatum*have anti- androgenic action and these herbs could be useful for the management of PCOS(08)

### *3.3 Herbs That Restore Glucose Sensitivity, Estrus Cyclicity and Enzyme Activity*

Decreasing insulin sensitivity and elevated blood glucose levels are also two of the major Symptomsobserved in women suffering from PCOS. As a result, drugs that increase insulin sensitivity Are included in PCOS treatment. Herbs such as Cinnamomum cassia and Aloe vera,which have the Samemechanism, can reduce blood glucose as well as regulate the estrus cycleand could be useful(09)

### *3.4Herbs That Promote FSH and Decrease LH Secretions*

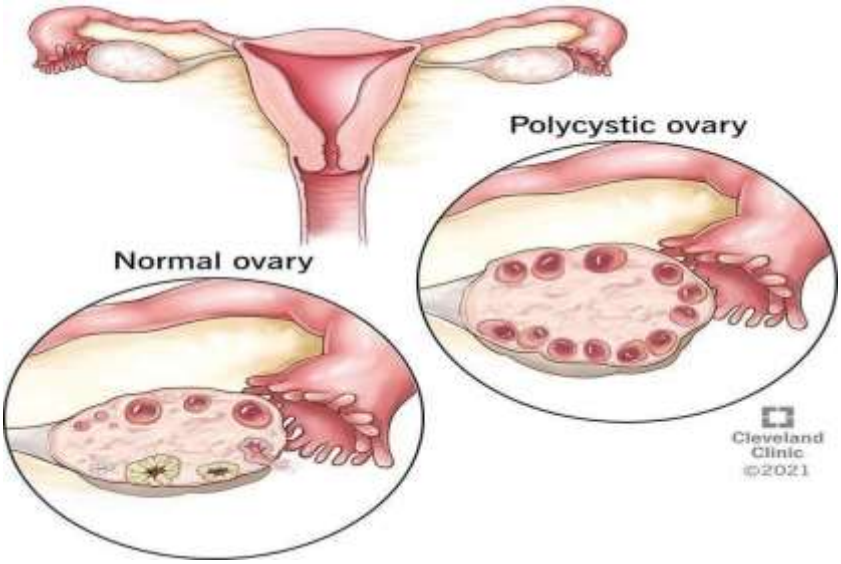
In PCOS, a common complication is elevated levels of LH and decreased levels of FSH. Hence, drugsthat have the ability to elevate the levels of FSH and reduce the concentrations of LH are beneficial in the treatment of PCOS. Herbs including *Foeniculum vulgare*, *Panax ginseng* and *Cimicifuga racemosa*have such actions; hence, they are useful for the treatment of PCOS(10)

### *3.5Effective Ovulation Induction Agent*

The most common complication of PCOS is infertility or frequent pregnancy termination due tothe patient's lack of carrying capacity. As a result, drugs used to stimulate ovulation are included in PCOStreatment. Herbs such as *Zingiber officinalis* and *Tribulus terrestris*, which have the same action and promote ovulation, might be useful for the treatment of PC(11)

**Etiology**

**Differentiation between normal and poly cystic ova**



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- External Factors
  1. Epigenetic mechanism
  2. Environmental toxicants
  3. Physical and emotional stress
  4. Diet
- Insulin resistance
  1. Hyperandrogenism
  2. Oxidative stress
  3. Obesity

**External Factors**

**1. Epigenetic Mechanism**

Epigenetic refers to inheritable alterations in genome and gene expression without any changesin DNA sequence These changes involve adding or omitting chemical components on DNA or histone Increased LH activity is a seen phenomenon in PCOSwomen. It may relateto the problems in follicle development and HA, which are common among PCOS patients LH/choriogonadotropin receptor (LHCGR) is responsible for the steroidogenesis process in thecacells This receptor hypomethylation leads to higher gene expression and sensitivity to LH [A study on PCOS patients approved that hypomethylated sites are related to overexpressionof LHCGR n theca cells surface In addition, epoxide hydrolase 1 (EPHX1) isan active enzyme in degrading aromatic compounds Its gene promoter hypomethylation increases enzyme Overproduction of EPHX1 reduces the transformation of testosterone to estradiol, which can contribute to PCOS [12]. Furthermore, peroxisome proliferator-activated receptor gamma (PPAR-γ) plays a role in ovaries' function Hypermethylation of PPARγ, hypomethylation of nuclear co-repressor and alteration inacetylation of histone deacetylase 3, for which both are PPARγ co-repressors are observedin PCOS patients showing HA These alterations were noticed in PCOS women's granulosa cells (13)

**2. Environmental Toxicants**

The United States Environmental Protection Agency (USEPA) defines endocrine-disrupting chemical (EDC) as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsiblefor the maintenance of homeostasis, reproduction, development and/or behavior" [14].

EDCs may act as hormones' agonists or antagonists in binding to their receptors EDCsarealmost parts of everything we use in our daily life Their structures consist of phenols or halogens like chlorine and bromine, so they imitate steroid hormones' actions Studies have approved the higher serum concentration of EDCs in PCOS suffering women Prolonged and continuous exposure to EDCs from prenatal to adolescence can cause susceptibility to PCOS As an example, bisphenol A (BPA) BPA is a synthetic compound used in polycarbonate plastics,epoxy resins dental filling, food and drink packages baby bottles, and polyvinyl chloride (PVC) which affects metabolism through different pathways. BPA directly affects oogenesis by interacting with estrogen receptor (ER) α and β, non-classical membrane ER,and G-protein coupled receptor 30 (GPCR30) It also triggers androgen secretion and restrains testosterone catabolism in theca cells (15)

Another effect of BPA on interstitial theca cells is the overproduction of androgens by dysregulation of 17β-hydroxylase (P450c17) cholesterol side-chain cleavage enzyme (P450scc), and steroidogenic acute regulatory protein BPA's influence on granulosa cells refers to reducing the expression of aromatase enzyme and production of estrogen
Lastly, it disturbs the intrafollicular environment and damages the oocyte development and maturation . BPA's indirect effect on HA involves downregulation of testosterone 2a-hydroxylase and testosterone 6b-hydroxylase enzymes in liver level, and thus a higher concentration of testosterone [16].

In addition, BPA is a potent ligand for sex hormone-binding globulin (SHBG) and replacestestosterone; thereby, free testosterone concentration increases. Androgen and BPA have a two-way relation; high androgen inactivates the uridine diphosphate-glucuronosyl transferaseenzyme and reduces BPA clearance in the liver. This processcauses a high concentration offree BPA in blood and worsens its negative effects on the ovaries.Additionally, it is believed that BPA may act as an obesogen Its obesogenic influence includes upregulation of adipogenesis-related genes stimulation of adipocytes differentiation potentiation of the accumulation of lipid in cells incorporated in medical syndrome, and triggering the conversion of target cells to adipocytes via phosphatidylinositol 3- kinase pathway [17].

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Adipogenesis due to BPA happens because of the activation of the glucocorticoid receptor. Activation of the receptor upregulates the enzyme involved in the conversionof cortisone to cortisol, thus inducing Moreover, BPA prompts the release of interleukin-6(IL-6) and tumor necrosis factor α (TNF-α) , both involving adiposity and IR In addition, it restrains the release of adiponectin and the beneficial compound in protecting against IR [18].

It can also change glucose homeostasis by directly influencing the pancreatic BPA causes a chronic increase in insulin and further IR in long byaffecting the mitochondrial activity and metabolic pathways of β-pancreatic cells BPAreduces glucagon secretion by inhibiting the intracellular calcium ion fluctuating pattern with a lack of glucose condition [19].

Advanced glycation end products (AGEs), also called gliotoxins, are another chemical group affecting body health. AGEs are pro-inflammatory molecules that interact with their surface receptor called RAGE (receptor for AGE)] and stimulate pro-inflammatory pathways and oxidative stress AGEs can be absorbed into the body as exogenous compounds or derived from nonenzymatic glycationand oxidation of proteins and lipids Increased concentration of AGEs in serum has been detected in PCOS patients AGEsinterrupt pre-ovulatory follicles growth via ERK1/MAPK pathway and damage follicles by oxidative stress caused by interaction with This interaction increases intracellular inflammatory molecules [20].

In vitro studies on 3T3-L1 cell lines showed that gliotoxins are likely to trigger adipogenesis On the other hand, a higher body mass index corresponds to a lower extent of soluble RAGEs, which is responsible for gliotoxin clearance and deposition of AGEs in th reproductive system, especially in ovaries This bilateral relation worsens inflammatory processes and metabolic syndrome in PCOS AGEs also play a role in IR These compounds disrupted glucose transport in the human granulosa KGN cell line and reduced glucose uptake by adipocytes in previous research They also involve IR by causing oxidative stress, inflammation, and glycation of proteins, whichconsiderably diminishes insulin sensitivity Moreover, increased concentration of AGEs changes the insulin signaling pathway and interferes with glucose transporter 4 (GLUT-4) translocation [21].

**3.Physical and Emotional Stress**

Although there is minimal information on the role of stress in PCOS, it is known that PCOS possesses adverse effects on self-esteem and mental health. Chronic stress resultsin hypertrophy and hyperplasia of adipocytes. This phenomenon happens as a result of glucocorticoids' effect on pre-adipocytes maturation. Chronic stress is also associated with adipokine secretion, attraction, and activation of stromal fat immune cells In addition, it is responsible for making an inflammatory condition by leading to high levelsof inflammatory cytokines like IL-6 and TNF-α, along with disrupting oxidant-antioxidantbalance In addition, chronic stress plays a vital role in IR. Stress triggers the hypothalamic-pituitary-adrenal (HPA) axis to release cortisol Cortisol leads to IR by stimulating visceral fat accumulation, gluconeogenesis, and lipolysisMoreover, cortisol arouses glucose production in the Stress is also involved in enhancing insulin levels Other stress influences on PCOS may refer to inference with anti-mullerian hormone (AMH) and changing sex hormone levels [22].

**4.Diet**

Although nutrition contributions to PCOS is unclear, studies showed a relationship between somenutrient levels and PCOS indices.Saturated fatty acids (SFAs) intake plays a role in PCOS by producing an inflammatory status and reducing insulin sensitivity Taking SFAs induces inflammation bytriggering anincrease in TNF-α level in circulation and expressing a specific cytokine suppressor Vitamin D deficiency may exacerbate PCOS or the comorbidities induced by PCOS.Calcitriol upregulates insulin receptors at mRNA and protein levels. It also increases insulin sensitivity directly and indirectly. The direct effect occurs by activating PPAR-δ, theinvolved receptor in fatty acids metabolism in adipose tissue and skeletal muscle. The indirect impact is the regulation of intracellular calcium, which is vital for insulin-mediated signaling in fat and muscle On the other hand, vitamin D deficiency may result in insulinresistance by causing an inflammatory response Furthermore, vitamin D downregulates the AMH promoter [23]

- **Internal Factors**

**1.Insulin Resistance**

IR means an insufficient cells response to insulin IR is independent of patients' adiposity,body fat topography, and androgen levels i.e., it has been reported in lean patients aswell It should be mentioned that IR is tissue-selective in PCOS women althoughskeletal muscles adipose tissue, and liver lose their sensitivity to insulin, adrenalglands and ovaries remain sensitive
Insulin directly triggers androgens production in ovarian theca cells and growinsulin effectively stimulates ovarian follicle growth and hormone secretion by stimulating its receptors in the follicle membrane It also triggers ovarian P450c17and P450scc enzyme

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activity to promote ovarian steroidogenesis and increases them with the synergistic effect of chorionic gonadotropin This hormone, as well as insulin-like growth factor 1 (IGF-1) [18], synergizes with luteinizing hormone [18,45].Hyperinsulinemia increases LH-binding sites and androgen-producing response to LH [44].LH and insulin interaction enhancesteroidogenic acute regulatory enzyme and CYP450c17 mRNA expression CYP450c17 is involved in androgen production Likewise, IR independently enhancesCYP17A1 activity, the productive enzyme in androstenedione and testosterone production (24)On the other hand, hyperinsulinemia reduces hepatic SHBG increasing free testosterone levels in blood In addition, hyperinsulinemia inhibitsIGF-1 binding protein production in the liver. IGF-1 is responsible for triggering the production ofandrogens in thecal cells. Inhibition of the production of IGF-1 binding proteinsleads to a higher concentration of this substance in blood circulation and then higher production of androgens in thecal cells Moreover, IGF-1 upregulation decreases a specific miRNA and thus accelerates granulosa cells apoptosis and inhibits folliculogenesisHA andhyperinsulinemia both play a role in stopping follicles growth This stoppage isattributed to menstrual irregularity, anovulatory sub-fertility, and amassing of immature follicles Furthermore, hyperinsulinemia contributes to PCOS by affecting the pituitary gland. Excessiveinsulin stimulates its receptors in the pituitary gland to release LH Accumulation of insulin stimulates GnRH and LH pulse secretion via influencing both amplitude and frequency insulin's indirect effect on PCOS is augmented by pituitary gonadotropin sensitivity to GnRHand hyperinsulinemia increases GnRH neuron activity The insulin's influence on adipose tissue and inflammation is another essential PCOS pathogenesis topic. Insulin stimulates adipogenesis and lipogenesis and inhibits lipolysis resulting in fat accumulationIR leads to enhanced plasma levels of free fatty acids(FFAs), affecting the liver and adipose tissue Moreover, IR causes a reduction in omentin level independent of the patient's body mass index (BMI). In addition, hyperglycemia can lead to inflammation by producing TNF-α from mononuclear cells (MNCs) [23].

**2.Hyperandrogenism**

Generally, hyperandrogenism (HA) reduces the SHBG level, leading to a higher concentration of free testosterone It was observed that PCOS women have higherconcentrations of testosterone in plasma which can convert to estrone in adipose tissue.Increased alteration of estrone to estradiol affect follicle growth and increases the LH to FSH ratio causing ovulatory dysfunction HA can result in AMH upregulation, which inhibits ovulation and the development of folliclesby a different mechanism. Furthermore, the IGF-II level is negatively related to androgenlevels, and HA reduces IGF-II infollicular fluid. IGF-II positively relates to follicle diametersand estradiol concentration in follicular fluid In addition, HA increases LH indirectly Estradiol and progesterone are responsible for GnRH and LH secretion via negative feedbackHA disrupts the negative feedback on secretion resulting in increased LH levels Interaction of androgen and its receptor interferes with progesterone receptor transcription. Moreover, this receptor is involved in converting high levels of androgens to compounds that modulate the gamma-aminobutyric acid A(GABAA). Modulation of the GABAA receptor triggers GnRH neurons and weakens the response to negative progesterone feedback [58]. In addition, it is assumed that androgens might decrease hepatic nuclear factor-4α (HNF- 4α) levels by inhibiting lipid synthesis. HNF-4α stimulates SHBG expression by binding to its promoter [24].

HA contributes to other influential factors of PCOS, including IR, inflammation, and oxidativestress.HA aggravates IR via different routes; it reduces the insulin sensitivity, expression of GLUT-4 and inhibits insulin degradation in the liver Moreover, HA increases a type of skeletal muscle fibers that have lowinsulin On the other hand, HA worsenscentral adiposity, which is involved in Additionally, it was observed that testosterone increases inflammatory chemicals such as lipopolysaccharide-induced IL-6 in3T3-L1 adipocytes by activating some signaling pathways [64]. One way androgen resultsinoxidative stress is by increasing MNC sensitivity to glucose and aggravating glucose- stimulated oxidative stress It is worth mentioning that dehydroepiandrosterone as anandrogen decreases interferon-ˠ (IFN- γ), an essential regulator in normal ovarian physiology and cell function In addition, it should be mentioned that studies on PCOS women approved the resemblanceof their fatty tissue to men, and hence the effect of HA on adipose tissue dysfunction In addition, HA is a cause of adipocyte hypertrophy and consequential damages to adipokine secretion [25].

**3.Inflammation**

Appropriate inflammation is a vital cause of oocyte growth and ovulation However, highlevels of white blood cell C-reactive protein (CRP) and other inflammatory biomarkers in peripheralblood are associated with PCOS

Inflammation is a cause of HA TNF-α is a pro-inflammatory chemical that can worsen IR. Contribution to IR happens due to interference of pro-inflammatory molecules with insulinsignaling pathways andreduction of GLUT-4 expression Some studies showedthat the insulin receptor substrate (IRS) serine residue phosphorylation inhibits insulin receptor signaling This phenomenon results in the prevention of GLUT-4 translocation and glucose reuptake In addition, TNF-α showed the ability to prompt theca cells proliferation in vitro Furthermore, IL-1 hinders the FSH and LH receptors. Inhibition of these receptors leads to inhibition of follicular development

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and ovulation Both TNF-α and IL-1β inhibit activation of HNF- 4α by different mechanisms. In addition,NLRP3 inflammasomes induce follicular pyroptosis, ovarian fibrosis, and disturbance of follicular formation An increase in CRP level is another cause of IR in insulin-
sensitive tissues. IR occurs because of increased pro-inflammatory factors secreted by theliver and monocytes. CRP stimulates this increase in secretion Moreover, another study approved the higher- than-normal level of IL-6 mRNA in granulosa cells (26)

**4.Oxidative Stress**

Oxidative stress (OS) is an imbalance between pro-oxidants and antioxidants Oxidative molecules include different chemicals such as reactive oxygen species (ROS) (e.g., O2−, H2O2, and OH−) and reactive nitrogen species (RNS) ROS plays a role in different mechanisms like signaling pathways cell growth and differentiation, as well as RNS RONS also acts on ovaries functions like steroidogenesis and affects neurons responsible for feeding behavior to induce hunger Overproductions of oxidative chemicals cause various damage to vital molecules such as lipids, proteins, and DNA Increased OS has been seen in PCOS patients in different studies Increased levels of OS activate the nuclear factor-kappa B (NF-κB) NF-κB is involved in inflammatory pathways and affects the production of pro-inflammatory cytokines like TNF-α and IL-6 the effect in IR and PCOS was explained above. A high level of OS also increases the release of TNF-α On the other hand, increasedOS actuates some protein kinases that trigger serine/threonine phosphorylation instead of normal tyrosine phosphorylation of IRS. Thus, the insulinsignaling pathway is inhibited, and OS leads to IR OS also plays a role in obesity. It increases mature adipocyte size and consequently stimulates pre- adipocyte proliferation and adipocyte differentiation. OS alsoimposes a major effect on obesity (27)

**5.Obesity**

Obesity is a key in low-grade chronic inflammation Accumulation of adipocytes in visceral fat leads to hypoxia and consequent necrosis, which causes inflammatory cytokinesproduction [66]. Adipocyte death dueto hypertrophy causes an inflammatory state The mononuclear cells of adipose tissue produce pro- inflammatory cytokines Excess abdominal fat is also responsible for the inflammatory condition Obesity also plays a role in hyperinsulinemia, IR, and HA occurrence. Visceral obesity arouses an increasein non-esterified fatty acids (NEFAs) levels in the blood. Skeletal muscles uptake NEFAs as the energy source instead of glucose. This hyperglycemia leads to a pancreas rapid reaction and hyperinsulinemia In addition, the lipolytic response of visceral fat to catecholamines causes lipotoxicity and impairment ofinsulin clearance and activity FFA stimulates IRS-1 serine/threonine phosphorylation and reduces tyrosinephosphorylation. Increased FFAs reduce insulin and glucose uptake sensitivity in intramyocellular lipids Notably, that visceral fat is weightier in IR than abdominal and subcutaneous fat asthe visceral fat lipolytic response to catecholamines is more severe The reason isthe increased function of the β3 and higher expression of β1 and β2 receptors Moreover, the type 1 isoenzyme of 11β-hydroxysteroid dehydrogenase (11β-HSD) is involved in converting cortisone to active cortisol, which is highly expressed in adipose tissue, especially in adipose tissue visceral ones. Glucocorticoids reduce glucose uptake and insulinsignaling in omental adipocytes Inaddition, visceral fat's adiponectin secretion is less than subcutaneous fats, and this phenomenon leads to decreased adiponectin secretion in obesity .In addition to all adipose tissue's functions mentioned above, this tissue has endocrine function and secreteschemicals called adipokines or adipocytokines. Adipocytes produce leptin, a high concentration of which inhibits the expression of aromatase mRNA in granulosa cells—thus interrupting androgens to estrogen In addition, it is suggested that increased leptin levels are related to the absence of folliculogenesis Moreover, adiponectin, secreted by adipocytes has insulin-sensitizing, anti-diabetic, and anti-inflammatory effects The adiponectin insulin-sensitizing effect causes a reduction in FFA uptakeand gluconeogenesis. It also plays a role in progesterone and estrogen production, ovulation, and decreased GnRH secretion Furthermore, adiponectin reduces LH secretion from the pituitary, triggers estradiol secretion in granulosa, and is associated with androgen production in ovaries Omentin-1, another adipose tissue secreted chemical, improves IGF-1-induced progesterone and estradiol secretion in different ways, including increasing the steroidogenic acute regulatory protein and CYP450 aromatase expression and enhancingIGF-1 receptor signaling Adipose tissue also has several enzymes responsible for converting androstenedione to testosterone and testosterone to dihydrotestosterone 17β-HSD converts androstenedione to testosterone and estrone to estradiol This enzyme is expressed in adipose tissue As a result of this process, excess adiposity exacerbates HA Furthermore, the accumulation of lipid in non-adipose tissues, called lipotoxicity, causes oxidative/endoplasmic reticulum stress linked with inflammation and IR. Excess fatty acidsin muscles and liver induce IR via serine phosphorylation of insulin receptor by diacylglycerol In addition, lipid accumulation in the liver diminishes HNF-4α levels leading to reduced SHBG production (28)

**Symptoms**

**1. Acnevulgaris**

Patients with PCOS complain of inflammatory acne minimally responsive to conventional line of treatment. Even if responsive,

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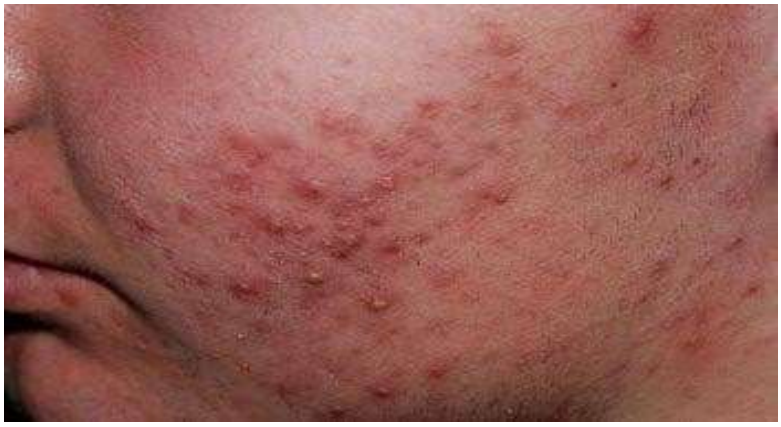
lesions promptly recur on stopping treatment, necessitating treatment with oral isotretinoinand/or hormonal therapy. An important featureseen in these patients is the development of multiple closed comedones which rapidly transform into tender, lumpy nodules, distributed in the lower half of face and jaw-line (V distribution) These tend to persist beyond the usual course of 5-7 days. A pre-menstrual flare is also common. Acne lesions may not only be localized to the face, but may also bepresent on the chest, shouldersand back. Prompt relapse after stopping the treatment, strongly suggests a hormonal basis.

Patients may in addition, have a history of irregular periods, and evidence of hirsutism, alopecia, or a positive family history of PCOS. The severity of hirsutism may not be matching the severity of acne, and would be dependent on the balance of activity betweenthe alfa-hydroxy type 2 vis- a-vis type 1.



**2. Hirsutism**


Excessive facial hair is a racial trait for the Indian sub-continent, running within families andespecially strongin certain ethnic groups. This should be kept in mind while evaluating patients complaining of excessive facial/body hair. Androgens affect various aspects of follicular activity. Acting via androgen receptors and secretory factors, they increase the growth rate, diameter and melanization of hair in androgen-sensitive areas. It is these thick, coarse, terminal hair, in androgen-dependent areas which are unsightly on a female and point to an underlying hyper-androgenic state . Evaluation of the degree of hirsutismis done by adopting a modified Ferriman-Galway score

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which evaluates 9 body areas ona scale of 1 to 4. The total scores are significant if more than 6 to 8. (29)

### 3. Alopecia

Not all cases of female pattern hair loss (FPHL) may be of androgenic origin. Patternedhair loss in PCOS may be difficult to distinguish from those secondary to other hyperandrogenic states [Figure - 5]. Various clinical presentations include those describedby Ludwig (diffuse), Hamilton (male pattern), and Olsen (frontalaccentuation). Womenwith early onset FPHL are much more likely to have an associated hyperandrogenism. Hormonal influences convert terminal to vellus hair, making the scalpappear bald.

### 4. Acanthosis Nigricans

Typically thick dark velvety skin situated on the nape of the neck, axillae, groins and other frictional areas may often be the first clue of insulin resistance [Figure - 6]. The thickeningoccurs due to the stimulation of tyrosine kinase growth factor - signaling pathways in the epidermis. Insulin - like growth factor receptor 1 (IGF1R) is present in many tissues including the epidermis and ovary. High levels of insulin directly or indirectly stimulate theIGF1R resulting in the skin changes. Skin tags in the frictional areas like the neck, axillae, groins, infra mammary or even under a pendulous abdominal fold are common, especiallyin obese individuals.(30)

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