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Review Article

Polycystic ovarian syndrome: an updated review of pathophysiology, clinical features, biomarkers, and management

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine and metabolic disorders affecting women of reproductive age and represents a major global public health challenge. PCOS is a heterogeneous condition characterized by reproductive dysfunction, hyperandrogenism, insulin resistance (IR), and metabolic abnormalities, frequently accompanied by psychological distress that significantly reduces quality of life. Despite its high prevalence, diagnosis, treatment, and long-term management remain challenging due to its complex, multifactorial pathophysiology. This review provides a comprehensive overview of the epidemiology, diagnostic criteria, clinical manifestations, and etiological factors associated with PCOS, with particular emphasis on genetic susceptibility, epigenetic regulation, environmental exposures, dietary habits, and lifestyle factors contributing to disease onset and progression. Key pathophysiological mechanisms are explored, including IR, hyperandrogenism, follicular arrest, chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, and adipose tissue dysregulation. The clinical manifestations of PCOS reproductive, metabolic, hyperandrogenic, and psychological along with long-term complications such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), endometrial disorders, infertility, and adverse pregnancy outcomes, are discussed. Emerging hormonal, inflammatory, metabolic, genetic, and molecular biomarkers are highlighted for their potential to improve diagnosis, phenotypic classification, and personalized therapy. Current treatments, including lifestyle modification, pharmacological interventions, nutritional supplementation, and emerging targeted therapies, are also summarized. A deeper understanding of the molecular mechanisms underlying PCOS is essential for enabling early diagnosis, optimizing individualized management, reducing long-term health risks, and improving outcomes through precision medicine, multidisciplinary care, evidence-based decision-making, and continued therapeutic innovation.

Keywords: Polycystic ovary syndrome, Insulin resistance, Ovarian dysfunction, Biomarkers, Metabolic syndrome

INTRODUCTION

One of the most common endocrine illnesses in women, PCOS, often referred to as Stein-Leventhal syndrome or syndrome "O," affects 6-15% of the population and is a major contributor to female infertility. Three criteria are usually used to diagnose the condition like irregular menstrual cycles caused by chronic anovulation, biochemical or clinical signs of hyperandrogenism, such as hirsutism, acne, or elevated testosterone, and the presence of ten or more follicles visible on an ovarian ultrasound. Despite the fact that its precise cause is still unknown, it is regarded as a complex metabolic disease in which IR and compensatory hyperinsulinemia play a major role by promoting excess androgen synthesis in the ovaries and adrenal glands while inhibiting sex hormone-binding globulin (SHBG). Women with PCOS face serious long-term health risks, such as T2DM, CVD, and elevated psychological distress, in addition to reproductive difficulties like infertility and repeated miscarriages. Individual symptoms are the main focus of the syndrome's management, which combines pharmacological treatments

like metformin or clomiphene citrate to restore hormonal balance and avoid further complications with lifestyle changes like particular dietary plans and frequent exercise.[1] Oestrogen, progesterone, and androgens are examples of sex hormones that are crucial in controlling a number of functions, including metabolism and fertility. Ovulation is disturbed and immature follicles build up in the ovaries when women's androgen hormone levels rise abnormally, resulting in cysts and hormonal imbalances. This condition's precise cause is still unknown. Nonetheless, a number of significant factors, such as IR, obesity, and heredity, have been linked to the development of this syndrome based on the information now available. Additionally, it raises the chance of mental illnesses like depression, high blood pressure, and T2DM. To better represent its complex pathogenesis and systemic metabolic ramifications, researchers have suggested renaming PCOS to polyendocrine metabolic ovarian syndrome (PMOS). With this new nomenclature, the clinical focus is now on central metabolic disorders such oxidative stress, IR, and chronic inflammation rather than solely ovarian morphology. The authors contend that a variety of systemic problems, such as visceral obesity, T2DM, and elevated cardiovascular risk, are specifically included in PMOS and are frequently overlooked in conventional diagnostic frameworks. The ultimate goal of the switch to PMOS is to lessen diagnostic ambiguity and advance a multidisciplinary care strategy that incorporates long-term metabolic health and reproductive health.[2]

EPIDEMOLOGY AND GLOBAL BURDEN

As demonstrated by a clinical study of women with endometriosis in Zabol, Iran, where the prevalence of PCOS was 24.5%, surpassing previously recorded rates of 16.5% in other cohorts, its epidemiology is especially important when taking into account its co-occurrence with other disorders. There is a substantial correlation between endometriosis and PCOS, as evidenced by the 74% incidence of probable endometriosis in certain high-risk groups, such as women with pelvic pain or infertility.[3]

IMPACT ON WOMEN'S HEALTH AND QUALITY OF LIFE

Research using the PCOSQOL scale shows that the mood domain frequently reflects the greatest impairment among women with the syndrome, as patients struggle with the emotional burden of the condition. PCOS is a multisystem endocrine disorder that significantly impairs health-related quality of life, particularly impacting psychological well-being through symptoms like anxiety, depression, and reduced self-esteem. Infertility, hirsutism, mood, and overall life impact are all negatively impacted by body mass index (BMI), which is a reliable independent predictor of lower quality of life. Other factors that worsen emotional distress include living in an urban area and the chronic nature of the illness, underscoring the urgent need for holistic management that combines lifestyle interventions with regular psychological support.[4]

DIAGNOSTIC CRITERIA AND PHENOTYPES OF PCOS

Rotterdam standards (2003)

It is the most often utilised criteria in use today. Any two of the following three are necessary for diagnosis: Anovulation or oligo-hyperandrogenism, both clinical and biochemical on ultrasonography, polycystic ovarian morphology (PCOM) (≥12 follicles 2-9 mm or ovarian volume >ten millilitres.

It is necessary to rule out other endocrine diseases. Women with ovulatory PCOS, non-hyperandrogenic PCOS, or ultrasound-dominant PCOS are included in this larger description, which specifies four phenotypes. Because typical puberty can mimic PCOS symptoms, recent guidelines advise against identifying teenagers too soon.

NIH criteria (1990)

the first generally recognised rule. Diagnosis requires, chronic anovulation/oligo-ovulation and clinical or biochemical hyperandrogenism.

Other causes must be excluded. Ultrasound appearance is not required Women with more "classic" and severe PCOS are identified by these criteria; they usually exhibit considerable irregular menstruation, hirsutism, and elevated metabolic risk.

The 2006 AE-PCOS society criteria

Emphasises the overabundance of androgens. Diagnosis necessitates: Clinical or biochemical hyperandrogenism that is required in addition to ovarian malfunction (PCOS or anovulation).

Women with more consistent and frequently more severe metabolic manifestations are identified by this more restrictive criterion. For population consistency, it is frequently employed in research.[5]

Clinical phenotypes of PCOS

Based on menstrual cycle status and the existence or lack of neuroendocrine dysfunction, the Doi-Alshoumer classification distinguishes three different clinical phenotypes of PCOS. Infertility is often the outcome of phenotype A, which is characterised by neuroendocrine dysfunction, irregular cycles, and the highest levels of testosterone, androstenedione, and oestradiol. Phenotype B, which is mostly linked to metabolic problems like obesity, IR, and acanthosis nigricans, also has irregular cycles but does not have neuroendocrine dysfunction. Patients with phenotype C often have hirsutism, acne, and the greatest molar ratios of progesterone to oestradiol. They also have regular menstrual cycles and no neuroendocrine dysfunction. This phenotypic approach, in contrast to standard diagnostic criteria, attempts to assist

doctors in more accurately identifying certain risks for metabolic or reproductive malfunction in order to direct more focused treatment approaches.[6]

SCOPE AND OBJECTIVES OF THE REVIEW

The goal of this review is to present a thorough and current overview of PCOS, a complex endocrine and metabolic condition that affects women of all reproductive ages. This review's coverage includes the most recent research on the multifactorial aetiology, clinical phenotypes, diagnostic criteria, and epidemiology of PCOS, with a focus on lifestyle, environmental, and epigenetic factors. It also looks at the main pathophysiological mechanisms that underlie the condition, such as IR, ovarian dysfunction, hyperandrogenism, and abnormalities of adipose tissue, and investigates how these mechanisms contribute to the various reproductive, metabolic, and psychological symptoms of PCOS. The review also examines existing and developing therapy methods, emphasises established and new biomarkers for diagnosis and risk stratification, and summarises the key comorbidities and long-term health implications associated with the condition. In order to support development of more individualised, evidence-based strategies for enhancing clinical outcomes and quality of life in people with PCOS, this review concludes by identifying current knowledge gaps, difficulties in diagnosis and treatment, and potential research directions.

ETIOLOGY OF PCOS

Genetic factors

A significant genetic component is suggested by the fact that PCOS patients frequently have a family history and exhibit some degree of familial clustering. PCOS is a polygenic syndrome with X-linked inheritance patterns rather than a monogenic disorder, according to twin investigations on small cohorts of monozygotic and dizygotic twins. PCOS patients' hyperandrogenemia has a hereditary basis, according to familial analysis, which supports the condition's reported familial clustering. Our knowledge of PCOS genetics has significantly improved thanks to developments in genomic research. The 29 susceptibility loci have been found by genome-wide association studies that connect PCOS to metabolic diseases, especially those linked to elevated BMI. PCOS pathogenesis has also been linked to rare variations in DENND1A and anti-Müllerian hormone (AMH). Additionally, illness susceptibility may be increased by genetic variants that impact insulin signalling, hormone control, and inflammatory pathways. All of these results highlight how PCOS is polygenic and complex, with genetic predisposition interacting with endocrine and metabolic variables to drive disease development.[7]

Environmental influences

Materials like Bisphenol A (BPA) can interfere with hormone regulation and ovarian steroidogenesis, frequent use of plastic tableware is a major environmental contributor to PCOS. There is a clear gradient trend linked to an increased risk of ovulatory dysfunction when exposed to indoor decoration, such as recent home painting or moving large furniture. Decorative materials contain organic solvents that are thought to cause pro-inflammatory cytokines like TNFα, which can interfere with follicle formation and reduce insulin sensitivity. The hypothalamic-pituitary-ovarian axis is disrupted by these environmental endocrine disruptors (EEDs), which function as steroid agonists or antagonists. Although the preliminary results indicated associations with the cooking oil fumes and air fresheners, these characteristics were shown to be less significant after controlling for age and the BMI.[8]

Lifestyle and dietary factors

In women with PCOS, lifestyle factors, especially a diet high in calories or meat, are strongly linked to an increased risk of ovulatory failure. According to epidemiological data, smoking both actively and passively disrupts folliculogenesis and oocyte maturation in a dose-dependent way. Additionally, snoring is associated with obstructive sleep apnoea, which may worsen hormone imbalances in this population, and it is a crucial lifestyle predictor of neuroendocrine disruption. While some behaviours, like drinking tea, are positively correlated with the syndrome, other factors, including alcohol use and the amount of time spent exercising, did not reveal statistically significant differences in this particular cohort. The major therapeutic approach to reduce systemic metabolic disorders and restore normal ovulatory function is still the adoption of extensive lifestyle changes.[8]

Epigenetics contribution

By modifying gene expression without changing the underlying DNA sequence, epigenetic processes such as DNA methylation and microRNA (miRNA) dysregulation play a fundamental role in the development of PCOS. In particular, methylation of genes like PPARG and PPARGC1A is linked to increased IR, whereas DNA methylation in the promoter regions of genes like CYP19A1 and LHCGR contributes to typical hormonal abnormalities. Furthermore, by suppressing GLUT-4 expression in adipose tissue, the overexpression of some miRNAs, like miRNA-93 and miRNA-223, upsets metabolic equilibrium. Intrauterine "programming," in which prenatal exposure to maternal androgen excess or foetal distress develops lasting adaptations that emerge as PCOS features in adulthood, frequently initiates these epigenetic alterations.

The substantial phenotypic variety seen even within the same familial lineage is ultimately explained by these transmissible phenomena, which enable a complex interaction between genetic predisposition and environmental circumstances.[9]

PATHOPHYSIOLOGICAL MECHANISMS OF PCO

Hyperandrogenism and androgen excess

In about 60-80% of instances of PCOS, hyperandrogenism (HA) is a major pathogenic factor that causes symptoms like hirsutism, acne, and androgenic alopecia. Pathophysiologically, HA creates a self-sustaining vicious cycle with IR in which hyperinsulinemia suppresses the synthesis of hepatic SHBG to raise bioactive free testosterone while directly stimulating the production of androgens in the ovaries and adrenal glands. By causing visceral obesity, skeletal muscular resistance, and hepatic steatosis, this hormonal excess contributes to systemic metabolic dysfunction, which can lead to metabolic dysfunction-associated steatotic liver disease (MASLD). Phenotype A, which has the greatest amounts of testosterone, androstenedione, and oestradiol in comparison to other phenotypic groups, is the most severe hyperandrogenic profile according to the Doi-Alshoumer phenotypic framework. In order to shift therapeutic therapy toward long-term risk mitigation for T2DM and CVD, it is essential to acknowledge HA as a fundamental metabolic driver rather than just a reproductive consequence.[10]

IR and hyperinsulinemia

IR and subsequent compensatory hyperinsulinemia are recognized as fundamental components of PCOS that significantly exacerbate hyperandrogenemia. Pathophysiologically, IR promotes systemic metabolic dysfunction and serves as a primary driver for the development of T2DM and atherosclerosis by inducing dyslipidemia and chronic low-grade inflammation. Within the Doi-Alshoumer classification, Phenotype B is explicitly defined by the presence of significant IR and obesity, often presenting with the highest HOMA2 IR values and acanthosis nigricans compared to other subgroups. Evidence suggests that this metabolic dysfunction may be linked to specific genetic variants, such as mutations in the Grb14 region, which impair insulin receptor signaling and increase extraovarian estrogen production.[11]

Ovarian dysfunction and follicular arrest

The definition of ovarian dysfunction in PCOS encompasses a range of problems, such as considerably lower oocyte quality, decreased follicular development, and chronic anovulation. These symptoms often result in permanent infertility due to faulty responses in target organs or aberrant modulation of the hypothalamic-pituitary-ovarian (HPO) axis. At the cellular level, follicular maturation arrest and excess steroid hormone synthesis are largely caused by decreased granulosa cell proliferation and functional abnormalities in theca cells. Furthermore, it is becoming more widely acknowledged that the underlying molecular mechanisms behind these follicular developmental abnormalities and related endocrine changes include aberrant DNA methylation patterns.[12] One of the main characteristics of PCOS is follicular arrest, which happens when growing follicles fail to attain ovulation despite ongoing recruitment. According to research, these follicles usually stop growing in the mid-antral stage, which is a direct cause of infertility and chronic anovulation. Systemic metabolic disorders such as obesity, hyperinsulinemia, and dyslipidaemia often worsen this follicular dysfunction by impairing normal folliculogenesis. This condition shows up on ultrasound as aberrant follicular recruitment and a sustained build-up of many tiny antral follicles.[13]

Adipose tissue dysfunction and obesity

Dysregulation of the hypothalamic-sympathetic nerve-adipose tissue (HSF) axis, which presents as a clear dichotomy of sympathetic overactivation in white adipose tissue (WAT) and decreased excitation in brown adipose tissue (BAT), is the main cause of adipose tissue dysfunction in the context of PCOS. Pathological WAT remodelling, which is marked by adipocyte hypertrophy, persistent low-grade inflammation, and the overproduction of non-esterified fatty acids (NEFAs) that directly impede insulin signalling, is encouraged by this sympathetic imbalance. Moreover, this condition is made worse by hyperandrogenemia, which suppresses the expression of vital thermogenic genes in BAT while activating androgen receptors in WAT to promote the early differentiation of preadipocytes into defective cells. A self-reinforcing loop of metabolic and reproductive misery is maintained by poor adipokine signalling, where decreased adiponectin levels and central leptin resistance interfere with hypothalamic energy sensing.[14] The prevalence of PCOS is almost four times higher in women of childbearing age who are overweight or obese than in those who have lean body mass. IR and hyperinsulinemia are the two main physiological mechanisms that contribute to the development of PCOS in the context of obesity. Additionally, being overweight might aggravate the syndrome's hallmark symptoms, such as reduced glucose tolerance and increased infertility. Due to these correlations, lifestyle modification including dietary changes and consistent exercise is recognised by international recommendations as the crucial first-line management approach to lessen the clinical burden of both disorders.[15]

CLINICAL PRESENTATION OF PCOS

Reproductive manifestations

The most prevalent clinical manifestation was irregular menstruation, with 76% of women reporting either amenorrhoea or oligomenorrhea. These irregular cycles are closely associated with chronic anovulation, which is frequently caused by follicular arrest and aberrant LH pulsatility. Oligomenorrhea is the strongest independent predictor of infertility, increasing the risks by almost four times, according to multivariable analysis. The great

frequency of these abnormalities highlights their importance as a primary diagnostic characteristic of PCOS, frequently coexisting with additional indicators such as obesity and hyperandrogenism.[16]

The main cause of female infertility is PCOS, which is primarily caused by hyperandrogenism and persistent ovulatory dysfunction. About 80% of women in the clinical population who come with anovulatory infertility have PCOS as their underlying aetiology. The disorder reduces the quality of oocytes and hinders the formation of mature ovulatory follicles by causing aberrant follicle growth. Medical management frequently uses ovulation induction with pharmaceuticals like letrozole or clomiphene citrate as a first-line therapeutic option for patients trying to conceive. Additionally, resolving underlying metabolic problems and greatly enhancing reproductive outcomes require the incorporation of lifestyle improvements, such as dietary changes and frequent exercise.[17]

HYPERANDROGENIC MANIFESTATIONS

Hirsutism

Approximately 70% to 80% of women who present with hirsutism are also diagnosed with PCOS, making hirsutism a defining clinical characteristic of the disease. High amounts of androgens, especially dihydrotestosterone (DHT), bind to pilosebaceous unit receptors in these patients, changing fine vellus hair in male-pattern regions into coarse, pigmented terminal hair. The modified Ferriman-Gallwey (mFG) score is used clinically to evaluate the severity of this growth; a score of eight or higher across nine body areas is considered diagnostic. Oral contraceptive pills (OCPs) are the first-line treatment for PCOS-related hirsutism. They inhibit ovarian androgen production and are frequently used in conjunction with mechanical removal techniques like laser therapy.

Acne

In PCOS, acne vulgaris is a chronic inflammatory disorder caused by follicular hyperkeratinization and androgen-induced hyperactivity of the sebaceous glands. Increased sebum production and a favourable environment for Cutibacterium acnes colonisation result from elevated androgens activating the mTor pathway and promoting lipogenesis in sebocytes.

PCOS is a crucial diagnostic factor for patients with resistant or late-onset lesions because studies show that 55% of women with adult acne had elevated androgen concentrations. To address the multiple endocrine and metabolic causes of the disease, management regimens for these patients frequently combine hormonal medicines like OCPs with insulin-sensitizing drugs like metformin. In addition to these main characteristics, PCOS patients may also have androgenetic alopecia, which is characterised by a generalised thinning of the hair on the crown as a result of follicular miniaturisation brought on by DHT. Acanthosis nigricans, which manifests as velvety, hyperpigmented plaques and is closely linked to the extreme IR exhibited in the HAIR-AN syndrome subphenotype of PCOS, is another important symptom. The condition is also associated with a higher incidence of hyperhidrosis and acrochordons (skin tags), both of which are correlated with the disorder's local androgen sensitivity and systemic hyperinsulinemia.[18]

Androgenic alopecia

About 20-35% of women with PCOS experience androgenetic alopecia (AGA), also known as female pattern hair loss, which is a well-known clinical indicator of systemic metabolic and endocrine dysfunction. Finer, shorter, and less pigmented hairs are produced as a result of the condition's gradual miniaturisation of hair follicles, which shortens the anagen growth phase. The "synergistic pathology" concept states that hyperandrogenism, chronic inflammation, and systemic IR combine with a person's local genetic propensity to cause AGA. Interestingly, even women with normal amounts of circulating testosterone can experience this hair loss, indicating that metabolic signalling and local follicular sensitivity are equally important as systemic hormone concentrations. Therefore, an integrated strategy is needed for optimal therapy, starting with lifestyle changes to address underlying metabolic factors before using targeted pharmaceutical medications like minoxidil or anti-androgens.[19]

METABOLIC MANIFESTATIONS

IR

About 70-80% of obese women and 30-40% of women with normal weight have IR, which is thought to be a key pathophysiological cause of PCOS. This disorder causes compensatory hyperinsulinemia, which worsens hyperandrogenism by increasing the production of androgens in the ovaries and adrenal glands while also interfering with normal ovarian function. According to clinical research, women with PCOS frequently have HOMA-IR levels that are almost twice as high as those of healthy controls. This metabolic burden is strongly associated with adipocyte malfunction and persistent low-grade inflammation. Reduced dietary antioxidant consumption may worsen insulin sensitivity, according to research, underscoring the possibility of using antioxidant-rich nutritional approaches to lessen metabolic disorders in those who are impacted.[20]

Metabolic syndrome

In women with PCOS, metabolic syndrome (MetS) is a common condition that is mostly caused by IR and an excessive build-up of fatty acids. It manifests as a collection of symptoms that include dyslipidaemia, central obesity, and hypertension. These particular ultrasound morphologies do not have a statistically significant

relationship with the rate of MetS, glucose levels, or lipid profiles, according to recent research on the follicular distribution pattern (FDP), specifically comparing the peripheral cystic pattern (PCP) to the general cystic pattern (GCP). The most significant predictors were found to be a history of oligomenorrhea and a high IR index rather than ovarian patterns; irregular menstruation increased the risk of MetS by 2.9 times, and each unit increase in IR increased it by 1.6 times.[21]

Obesity

About 50% of people with PCOS have obesity, a relatively common comorbidity that greatly increases the risk of long-term metabolic and reproductive issues. In terms of pathophysiology, visceral adipose tissue buildup creates a self-sustaining "vicious cycle" by aggravating IR, which in turn promotes excessive androgen production in the ovaries and adrenal glands. A more severe clinical phenotype marked by hirsutism, chronic anovulation, and an increased risk of T2DM and CVD is frequently the outcome of this metabolic burden. Therefore, the main therapeutic intervention for reducing these systemic hazards and re-establishing hormonal balance continues to be extensive lifestyle changes that emphasise calorie restriction and frequent exercise.[22]

PSYCHOLOGICAL AND NEUROBEHAVIORAL MANIFESTATIONS

Compared to the general population, women with PCOS are three to five times more likely to have anxiety and depression symptoms. Patients are almost four times more likely to acquire a clinical diagnosis for disorders like binge eating or bulimia, and the disease is often associated with problems with body image and a markedly increased risk of eating disorders. Along with certain cognitive vulnerabilities impacting attention and executive function that may be made worse by hormonal and metabolic abnormalities, many women also report lower sexual satisfaction and decreased desire. Additionally, there is a known risk of schizophrenia spectrum disorders and psychotic symptoms, underscoring the significance of an integrated, multidisciplinary treatment approach that attends to both physical and mental health.[23]

Anxiety

Compared to women without PCOS, those with the illness are five times more likely to experience severe anxiety symptoms, among other mental health issues. Research shows that adult separation anxiety is common in this population, affecting about 28.9% of patients and manifesting as persistent worry regarding relationships or life transitions. Intolerance of uncertainty, which refers to an individual's inability to cope with the unpredictable or ambiguous nature of the syndrome's symptoms, is a primary psychological driver. Elevated testosterone levels may physiologically worsen these symptoms by affecting the brain's amygdala and other emotional processing regions. Anxiety is further exacerbated by psychosocial variables, such as body image dissatisfaction and social stigma associated with outward symptoms like the hirsutism.[24]

Depression

The likelihood of developing depression is more than 2.5 times higher in women with PCOS than in healthy controls, indicating a markedly increased risk of mental health problems. It is acknowledged that this link is bidirectional and complicated, including a complex interaction between different psychological stressors and biological mechanisms such chronic inflammation. Hyperandrogenism and IR are pathophysiological factors; studies show that higher IR scores are independently linked to a higher incidence of depressive symptoms. Additionally, concerns about infertility and the subjective perception of outward signs like hirsutism and acne greatly increase psychological anguish and lower health-related quality of life.[25]

Sleep disorder

Women with PCOS are more than six times as likely to experience sleep difficulties than women without the condition, making sleep disorders a very common comorbidity. Although nearly 20% of patients have obstructive sleep apnoea (OSA), which is the most prevalent symptom, many also experience persistent sleep disruptions, poor sleep quality, and severe trouble falling asleep. Because IR and obesity have been found to be independent predictors for the development of OSA, these disruptions are fundamentally linked to metabolic complications. Regular sleep screenings are crucial for providing comprehensive, patient-centered care because poor sleep can worsen psychological comorbidities like anxiety as well as metabolic health.[26]

COMORBIDITIES AND LONG-TERM CONSEQUENCES

T2DM

In women with PCOS, prediabetes is a prevalent metabolic comorbidity. It is an intermediate, potentially reversible state of dysglycemia that greatly raises the risk of developing T2DM. Prediabetes prevalence was found to be 30.7% in a study of 150 women with PCOS, suggesting a significant burden of poor glucose regulation in this population. IR, a defining characteristic of PCOS that affects up to 70% of patients and leads to both metabolic and reproductive problems, is largely responsible for the development of prediabetes. When it comes to identifying early glucose problems, the 2-hour oral glucose tolerance test (OGTT) has proven to be more sensitive than either fasting plasma glucose or glycated haemoglobin (HbA1c). In order to lower long-term cardiovascular risk and stop prediabetes from developing into T2DM, regular metabolic tests and prompt lifestyle changes are crucial.[27]

T2DM is around three times more common in women with PCOS than in the overall female population. The disease usually manifests more earlier in this cohort, with a median diagnostic age of 33 years as opposed to 62 years in women without the syndrome. The increased risk is mostly associated with intrinsic abnormalities in post-receptor insulin signalling in muscle and adipose tissue, which are frequently made worse by co-occurring obesity or overweight. A countrywide cohort study discovered that women with PCOS and T2DM actually have a lower risk of diabetes complications, especially with relation to cardiovascular and eye problems, despite the longer duration of the disease. This reduced risk profile might be the outcome of proactive use of drugs like metformin, which can lessen tissue damage from dysglycemia, and systematic glucose screening that results in early identification.[28]

CVD

The pooled relative risk of CVD for women with PCOS is estimated to be 1.41 times higher than that of women without the illness. This elevated risk seems to be unrelated to BMI, indicating that PCOS's metabolic and endocrine environment rather than merely being overweight is what causes cardiovascular problems. Systemic inflammation, coagulation problems, and abnormal glucose and lipid metabolism are important mediators that have been linked to this increased risk. These variables can eventually cause coronary artery calcification, endothelial dysfunction, and atherosclerosis, which raises the risk of serious illnesses like myocardial infarction, heart failure, and coronary heart disease.[29]

Endometrial hyperplasia

Because chronic oligomenorrhea or amenorrhoea results in prolonged, unopposed oestrogen exposure of the uterine lining, women with PCOS are more likely to develop endometrial hyperplasia (EH) and endometrial cancer (EC). A 30% prevalence of abnormal endometrial biopsies was found in clinical data from a prospective study of 208 women with PCOS. Specifically, nonatypical EH was found in 9% of participants, endometrial intraepithelial neoplasia (EIN or atypical EH) in 15%, and EC in 6% of patients. Increasing age, nulliparity, and elevated HbA1c levels the latter of which is a marker for hyperinsulinemia and IR are important risk factors for these disorders.[30]

NAFLD

NAFLD is highly prevalent among young women with PCOS (31.2%), and 65.1% of those affected also fulfil the more recent criteria for metabolic dysfunction-associated fatty liver disease (MAFLD). The overweight-MAFLD (OW-MAFLD) subtype accounts for 98% of these individuals, whereas "lean-MAFLD" instances are conspicuously rare in this group. Because hyperandrogenism (HA) and oligoanovulation (OA) promote hepatic fat accumulation through mechanisms like IR and androgen-induced adipocyte hypertrophy, people with both of these PCOS phenotypes have the highest independent risk of developing MAFLD.[31]

Pregnancy-related complications

Due to its fundamental pathophysiology of hyperandrogenism, IR, and obesity, PCOS significantly increases the risks to both the mother and the foetus. Higher rates of early pregnancy loss, such as miscarriage and implantation failure, are caused by several systemic disorders and are frequently linked to poor egg quality and decreased endometrial receptivity. Because pregnant women with PCOS are more likely to develop gestational diabetes mellitus and hypertension conditions like pre-eclampsia, metabolic problems are also common. The syndrome is linked to an increased risk of ovarian hyperstimulation syndrome (OHSS) in patients receiving reproductive therapies; this risk is exacerbated by elevated levels of AMH.[32]

BIOMARKERS ASSOCIATED WITH PCOS

A wide range of hormonal, metabolic, inflammatory, and newly developed molecular biomarkers are used in the clinical therapy of PCOS to treat the disorder's systemic and reproductive consequences. Hormonal biomarkers include 11-oxygenated androgens, the free androgen index (FAI), which is used to measure hyperandrogenemia and hirsutism, and AMH, which is roughly three times higher in women with PCOS and may eventually replace ultrasound for diagnosing polycystic morphology. The focus of metabolic assessment has shifted to functional markers such as the visceral adipose index (VAI) and lipid accumulation product (LAP), which are superior to BMI in predicting IR in all phenotypes. Elevated ceramides and decreased IGFBP-1 are indicators of deep-seated dysregulation of the metabolic and IGF-1 systems.[33]

CURRENT THERAPEUTIC APPROACHES

Lifestyle modification

By combining systematic dietary changes, increased physical activity, and behavioural techniques to address the underlying IR and hyperandrogenism of PCOS, lifestyle modification provides a crucial, non-pharmacological basis for controlling the condition. Achieving a moderate 5-10% weight loss with these therapies can greatly improve metabolic status, restore menstrual regularity, and improve general quality of life for overweight or obese women. According to data from systematic reviews, these programs improve insulin sensitivity and lower circulating testosterone levels while also significantly reducing BMI, weight, and waist circumference. Additionally, it has been demonstrated that exercise-based therapies are essential for improving hormonal balance, considerably raising ovulation rates, and restoring reproductive function.[34]

Pharmacological interventions

The combined oral contraceptive pill (COCP) is typically the first-line pharmacological intervention for managing symptoms of irregular periods and clinical hyperandrogenism, including hirsutism and acne. Metformin is recommended as a first-line treatment for managing excess body weight and metabolic effects like IR, showing synergistic benefits when combined with lifestyle modifications. Antiandrogens may be prescribed as second-line therapy for patients with persistent hirsutism or GLP-1 receptor agonists for adults, and inositol as a third-line insulin sensitizer.[35]

Nutritional supplementation

By focusing on metabolic, hormonal, and inflammatory disorders, nutritional supplements are a useful supplementary technique in the treatment of PCOS. Research indicates that important supplements, such as myo-inositol, vitamin D, and omega-3 fatty acids, can significantly enhance lipid profiles, insulin sensitivity, and general hormonal balance. These nutrients lessen oxidative stress and persistent low-grade inflammation by modifying important biochemical pathways including AMPK and NF-κB. Further high-quality trials are necessary to develop standardised dose procedures and guarantee long-term safety, even though they provide a promising personalised alternative to traditional medications.[36]

Emerging therapeutic strategies

By increasing insulin sensitivity and simultaneously preventing ferroptosis in trophoblasts and reducing pro-inflammatory cytokine cascades, metformin functions as a major dual-action treatment. By focusing on the redox-inflammation cycle and regulating the AR-NRF2 regulatory axis to restore mitochondrial function, antioxidants like N-acetylcysteine and anti-androgens like flutamide provide further benefits. Low-dose aspirin and low-molecular-weight heparin (LMWH) combination regimens are used to treat vascular remodelling abnormalities, enhance placental blood flow, and promote immunological tolerance in patients with recurrent pregnancy loss. Furthermore, GLP-1 receptor agonists, selenium nanoparticles, and stem cell-based regeneration therapies are new but understudied approaches; nonetheless, more thorough human clinical trials are now needed to verify their effectiveness in reducing miscarriage.[37]

FUTURE PERSPECTIVES AND RESEARCH GAPS

Novel biomarkers and therapeutic targets

Leukotriene A4 hydrolase (LTA4H), fibroblast growth factor binding protein 1 (FGFBP1), and meteorin-like protein (METRNL) are recently discovered potential circulating protein biomarkers for PCOS. The PHOEBE study is the first to prospectively validate these candidates in adolescents and young adults to address the diagnostic challenges caused by the overlap of PCOS symptoms with normal pubertal development. These blood-based tools offer a non-invasive, objective, and scalable triage method that could significantly reduce diagnostic delays and help prevent long-term comorbidities like T2DM and metabolic dysfunction-associated steatotic liver disease. It has been demonstrated that using these markers in relative ratios, such as FGFBP1:METRNL and LTA4H:METRNL.[38]

Current therapeutic approaches

Because their release initiates signalling pathways that induce hyperandrogenemia, IR, and anovulatory dysfunction, advanced glycation end products (AGEs) are recognised as important therapeutic targets. MicroRNAs (miRNAs) represent a promising frontier for precision medicine, as they can be targeted using synthetic mimics or inhibitors to correct dysregulated steroidogenesis and improve oocyte quality. Together, these molecular pathways provide a scientific foundation for developing next-generation drugs that address the underlying pathogenic mechanisms of the syndrome rather than just its clinical symptoms. Another crucial target is SHBG.[39]

The fact that PCOS is often misdiagnosed as a primary gynaecological issue rather than a multisystem metabolic and endocrine disorder presents a significant diagnostic difficulty and has prompted a global consensus call to rename the syndrome. Furthermore, because detectable alterations in serum glucose may not appear until decades after the first development of hyperinsulinemia, the prevalent glucose-centric model frequently fails to identify IR during its early, "silent" phase. A major psychological burden, where high levels of anguish and perceived stress frequently do not correlate with obvious clinical symptoms, makes management even more difficult. This makes it difficult to stick to crucial lifestyle changes. Lastly, many of the syndrome's clinical characteristics match with typical pubertal development, making it challenging for medical professionals to diagnose teenagers. This underscores the critical need for the validation of trustworthy, non-invasive biomarkers.[40]

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

The high clinical heterogeneity of PCOS and the crucial need to rule out mimicking disorders, including non-classic congenital adrenal hyperplasia (NCAH), which might be mistaken for PCOS based only on clinical indications, make diagnosing the syndrome challenging. Because cardinal characteristics like irregular menstrual cycles and PCOM often overlap with normal pubertal physiology, diagnosing adolescents is particularly difficult. According to guidelines, PCOM should not be used for diagnosis within eight years of menarche. The operator-dependent nature of ultrasound and the absence of standardised, age- and ethnicity-specific cutoffs for

AMH and androgen assays are among the technical challenges that clinicians must overcome.[41]

CONCLUSION

Genetic vulnerability, environmental exposures, lifestyle variables, and epigenetic alterations combine intricately to cause PCOS, a complex and heterogeneous endocrine-metabolic illness. A wide range of reproductive, metabolic, and psychological symptoms are caused by interrelated mechanisms in its pathophysiology, such as hyperandrogenism, IR, ovarian malfunction, and abnormalities of adipose tissue. The combination of several phenotypes and the diversity in clinical presentation continue to be major obstacles to prompt diagnosis and efficient treatment. PCOS is linked to significant long-term risks, such as T2DM, CVD, NAFLD, endometrial pathology, and unfavourable pregnancy outcomes, in addition to its effects on reproductive health. This highlights the importance of early detection and all-encompassing care. Growing knowledge of hormonal, metabolic, inflammatory, and molecular biomarkers present significant prospects for better risk assessment, diagnosis, and individualised treatment plans. While changing one's lifestyle is still the mainstay of care, new therapeutic approaches and precision medicine techniques may improve patient outcomes. Clarifying the intricate mechanisms underlying PCOS, confirming new biomarkers, standardising diagnostic techniques, and creating customised, interdisciplinary treatment plans should be the main goals of future research. To lower the illness burden, enhance quality of life, and maximise long-term health outcomes for women with PCOS, a better understanding of the condition and the incorporation of patient-centered care paradigms will be crucial.

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REFERENCES

1. Muhas C, Nishad K, Naseef P, Vajid KA. An overview on polycystic ovary syndrome (PCOS). Technol Innov Pharm Res. 2021;6:19-30.
2. Tewari S, Khalua RK, Parida S. Redefining polycystic ovary syndrome (PCOS) as Polyendocrine Metabolic Ovarian Syndrome (PMOS): implications for diagnosis, pathophysiology and clinical management. Int J Gynaecol Sci. 2026;8(1):17-25.
3. Kaveh M, Moghadam MN, Iranpour Z, Chaichian S, Kashi AM, Afshari M, et al. Epidemiological study and clinical consequences of endometriosis and PCOS co-occurrence in a clinical population of women: a cross-sectional study. BMC Women's Health. 2026;26(1):182.
4. Bokka SL, Maktha VK. Impact of Polycystic Ovary Syndrome on Health-Related Quality of Life: A Cross-Sectional Study Using the PCOSQOL Scale. National J Community Med. 2026;17(03):182-6.
5. Koshti A, Jadeja J, Vaja M, Soni R, Yadav P, Patel D. Current Trends in the Diagnosis and Therapeutic Approaches To PCOS. J Pharmaceut Res. 2026;15(1):1243-70.
6. Elsayed AM, Al-Kaabi LS, Al-Abdulla NM, Al-Kuwari MS, Al-Mulla AA, Al-Shamari RS, et al. Clinical phenotypes of PCOS: a cross-sectional study. Reproduct Scie. 2023;30(11):3261-72.
7. Chen Y, Sun X, Xia X, Chen K, Zeng F. The pathogenesis, therapeutic targets and drugs of polycystic ovary syndrome. Front Endocrinol. 2026;16:1722649.
8. Zhang B, Zhou W, Shi Y, Zhang J, Cui L, Chen ZJ. Lifestyle and environmental contributions to ovulatory dysfunction in women of polycystic ovary syndrome. BMC Endocrine Disord. 2020;20(1):19.
9. Bruni V, Capozzi A, Lello S. The role of genetics, epigenetics and lifestyle in polycystic ovary syndrome development: the state of the art. Reproduct Sci. 2022;29(3):668-79.
10. Xu J, He B. The central role of hyperandrogenism in driving metabolic dysfunction in polycystic ovary syndrome: from pathophysiological mechanisms to targeted therapies. J Ovarian Res. 2026;NA
11. Goodarzi MO, Korenman SG. The importance of insulin resistance in polycystic ovary syndrome. Fertil Steril. 2003;80(2):255-8.
12. Hu R, Jin L, Li Q, Fan P, Fan W, Xu J. Epigenetic regulation by DNA methylation in PCOS and POI: mechanisms of ovarian dysfunction and implications for clinical research. J Ovarian Res. 2026;13:123.
13. Shahzadi Z, Rehman L, Maryam A, Malik HA. Lifestyle Factors and Sonographic Characteristics in PCOS: A Systematic Review. Pak J Med Cardiological Rev. 2026;5(2):4248-55.
14. Zhang S, Jiang N, Liu G, Zhang B, Xu H, Xu Y, et al. New perspectives on polycystic ovary syndrome: hypothalamic-sympathetic-adipose tissue interaction. J Ovar Res. 2025;18(1):145.
15. Mu Y, Zou Y, Chen C. Knowledge, attitude and practice toward obesity and polycystic ovary syndrome among women of childbearing age with overweight or obesity. Arch Gynecol Obstet. 2026;313(1):9.
16. Ashraf S, Shakeel Q, Mumtaz S, Iqbal S, Afzal R, Ashraf T. Phenotypic Spectrum, Menstrual Irregularity, and Reproductive Outcomes Among Women with PCOS Attending Public Hospitals in Gujranwala: A-Participant Cross-Sectional Study. J Health Wellness Community Res. 2025;3(7):e907.
17. Azam SS, Vasudevan S, Bukhari WS, Thadhani J, Tasneem H, Singh S, et al. Reproductive endocrine disorders: a comprehensive guide to the diagnosis and management of infertility, polycystic ovary syndrome, and endometriosis. Cureus. 2025;17(1):10.
18. Magkou S, Sali E, Paschou IA, Dimopoulou SM, Tagka A, Chasapi V, et al. Skin manifestations of hyperandrogenism: an update. Hormones. 2026;1-2.
19. Motafeghi F, Naz MS, Tehrani FR, Behboudi-Gandevani S. Androgenetic alopecia in polycystic

ovary syndrome: a cutaneous marker of systemic metabo-inflammatory and endocrine dysfunction. Endocrine Connections. 2026;15(5):10.
20. Alataş H, Arslan N, Keskin L, Ağralı C. Dietary Antioxidant Capacity, Inflammation, and Insulin Resistance in Women with Polycystic Ovary Syndrome: An Integrated Metabolic and Nutritional Assessment. Diabetes Metabol Synd Obesity. 2026;586793.
21. Pourkhani Z, Jahanian Sadatmahalleh S, Moini A, Nasiri M. The association between the follicular distribution pattern of polycystic ovaries and metabolic syndrome development in patients with polycystic ovary syndrome a prospective cohort study. Scient Rep. 2025;15(1):5284.
22. Bila J, Dotlic J, Andjic M, Ivanovic K, Micic J, Tulic L, et al. Obesity as a Part of Polycysric Ovary Syndrome (PCOS)-A Review of Pathophysiology and Comprehensive Therapeutic Strategies. J Clin Med. 2025;14(16):5642.
23. Adamczak A, Głowińska A, Banaszewska B, Wysocka E, Remlinger-Molenda A. Psychological aspects of polycystic ovary syndrome. Neuropsychiat Neuropsychol. 2003;20(1):178-85.
24. Gül Ö, Akkuş M, Akkuş F. Depression, anxiety, and stress in polycystic ovary syndrome: understanding the impact of adult separation anxiety and uncertainty intolerance. BMC Women's Health. 2025;25(1):377.
25. Karampela AI, Druce M. The Relationship Between Polycystic Ovary Syndrome (PCOS) and Depression. Clin Endocrinol. 2026;105(2):131-40.
26. Decrinis C, Hofmann K, Bitterlich N, Singer A, Tropschuh K, Lozza-Fiaco S, et al. Sleep disorders and psychological comorbidities in women with polycystic ovary syndrome-a cross-sectional study. Arch Gynecol Obstet. 2025;312(2):573-82
27. Ollila MM, Arffman RK, Korhonen E, Morin-Papunen L, Franks S, Junttila J, et al. Women with PCOS have an increased risk for cardiovascular disease regardless of diagnostic criteria-a prospective population-based cohort study. Europ J Endocrinol. 2023;189(1):96-105.
28. Pourahmad B, Majidnia M, Saniee N, Riyahifar S, Moradi Y. Polycystic ovary syndrome with stroke, hypertension, and cardiovascular diseases: a systematic review and meta-analysis. BMC Women's Health. 2025;25(1):385.
29. Ollila MM, Hautakoski A, Arffman M, Morin-Papunen L, Koivikko M, Ebeling T, et al. Diabetic complications in women with type 2 diabetes and polycystic ovary syndrome. Eur J Endocrinol. 2025;192(3):202-9.
30. Agarwal R, Stanczyk FZ, Mandelbaum R, Paulson RJ, McGinnis LK, Winer SA. Prevalence of endometrial hyperplasia and carcinoma in women with polycystic ovarian syndrome. F and S Rep. 2025;6(3):394-8.
31. Hong SH, Sung YA, Hong YS, Song DK, Jung H, Jeong K, et al. The association between phenotypes of polycystic ovary syndrome and metabolic dysfunction-associated fatty liver disease. Front Endocrinol. 2025;16:1480528.
32. Odunvbun WO, Ukoba O, Isogun JK, Ekoh A. A systematic review of pregnancy outcomes and management in polycystic ovary syndrome. Afr J Reproduct Health. 2026;30(10):1.
33. Huffman AM, Rezq S, Basnet J, Romero DG. Biomarkers in polycystic ovary syndrome. Curr Opin Physiol. 2023;36:100717.
34. Kaleeswari G, Rajalakshmi S. Life Style Modification For PCOS: Systematic Review and Meta Analysis. Int J Innovat Res Health Sci. 2025;1(12):19-27.
35. Ee C, Tay CT. Pharmacological management of polycystic ovary syndrome. Aust Prescriber. 2024;47(4):109.
36. Andres-Montenegro N, Molina-Gutierrez S, Núñez-Murillo O. Evidence-Based Nutritional Supplementation in Polycystic Ovary Syndrome: A Comprehensive Review of Clinical Outcomes, Mechanisms, and Recommendations. BioNatura J. 2025;2(2):23.
37. Zhang F, Wu J, Ge L, Huang Y, Huang Y. A review of immunometabolic crosstalk in PCOS-related pregnancy loss: mechanisms and emerging therapeutic strategies. Gynecological Endocrinol. 2025;41(1):2600160.
38. Lotz L, Sillman J, Hund M, Di Domenico A, Buck K, Dittrich R. Validation of novel biomarkers for the detection of polycystic ovary syndrome in adolescents and young adult women-the PHOEBE study. Research Square. 2025.
39. Chen Y, Sun X, Xia X, Chen K, Zeng F. The pathogenesis, therapeutic targets and drugs of polycystic ovary syndrome. Front Endocrinol. 2026;16:1722649.
40. Parker J, Hitch V. New Challenges and Perspectives in Polycystic Ovary Syndrome. J Clin Med. 2025;14(24):8867.
41. Joham AE, Tay CT, Laven J, Louwers YV, Azziz R. Approach to the patient: diagnostic challenges in the workup for polycystic ovary syndrome. J Clin Endocrinol Metabol. 2025;110(7):e2298-308.

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