Unravelling Polycystic Ovary Syndrome: From Pathophysiology to Personalized Treatment

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Abstract:

Polycystic Ovary Syndrome (PCOS) is a prevalent, multifaceted endocrine-metabolic pathology that impacts approximately 5% to 20% of women of reproductive age on a global scale. It is primarily delineated by chronic anovulation or oligo-ovulation, biochemical and/or clinical hyperandrogenism, and the manifestation of multifollicular ovarian morphology as visualized through transvaginal ultrasonographic imaging. The condition exhibits a broad phenotypic spectrum and interindividual variability in clinical presentation and severity, reflecting its underlying pathophysiological heterogeneity. The etiology of PCOS is multifactorial encompassing a complex interplay of genetic, epigenetic, environmental, and lifestyle determinants that disrupt normal hormonal balance and ovarian function, often leading to metabolic disturbances as well. Various diagnostic criteri like NIH (1990), Rotterdam (2003), and AES (2006)—have led to differing definitions and phenotypic classifications (A–D), influencing both diagnosis and treatment approaches. PCOS is associated with a diverse array of comorbid

conditions, including infertility, metabolic syndrome, and related endocrine and cardiometabolic abnormalities, and various psychological diseases. Management is tailored to symptomatology and includes lifestyle modifications, pharmacological therapies, and assisted reproductive technologies. A holistic understanding of PCOS's pathophysiology and associated comorbidities is crucial for timely diagnosis and effective treatment, thereby potentiating favourable long-term prognostic trajectories and augmenting the holistic biopsychosocial well-being of afflicted individuals.

Keywords: Polycystic Ovary Syndrome, worldwide statistics, treatment, etiology

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) represents the most prevalent endocrine, reproductive, and metabolic disorder among women of reproductive age. Its global prevalence is estimated to range from 4% to 21%, contingent upon the diagnostic criteria employed—primarily the NIH 1990 and Rotterdam 2003 definitions. Although epidemiological data from Pakistan remain limited, PCOS appears to have a disproportionately high prevalence among women of South Asian descent [1]. Diagnostic frameworks that mandate the presence of hyperandrogenism tend to delineate a phenotype associated with more severe reproductive and metabolic complications. The phenotypic expression of PCOS is influenced by racial and ethnic variation, is challenging to characterize in both premenarchal and perimenopausal populations, and is notably worsened by the presence of obesity. The underlying pathophysiology is multifactorial, involving aberrant gonadotropin secretion driven by impaired hypothalamic sensitivity to circulating sex steroids, along with structural and functional alterations in ovarian morphology. Additionally, dysregulated insulin signaling across multiple target tissues contributes substantially to the metabolic component of the syndrome. PCOS demonstrates a familial aggregation pattern, with both female and male relatives often exhibiting clinical or subclinical features, including metabolic abnormalities. Genome-wide association studies (GWAS) have identified several susceptibility loci; however, the precise functional implications of these genetic variants in PCOS pathogenesis remain incompletely understood [2]. From fetal development through adulthood, androgen excess appears to play a central and unifying role in the onset, progression, and perpetuation of the disorder—creating a self-reinforcing cycle of hormonal and metabolic dysregulation. This continuous loop of androgen-driven disruption underscores the need for deeper mechanistic insights [3]. Advancing our understanding of the molecular and physiological underpinnings of PCOS will be essential for developing targeted interventions aimed at normalizing androgen levels, restoring ovulatory function, and reestablishing metabolic homeostasis [4].

ETIOLOGY

Insulin Resistance

Polycystic Ovary Syndrome (PCOS) is a multifactorial metabolic-endocrine disorder in which insulin resistance (IR) plays a pivotal role in its pathophysiology. A significant proportion of individuals with PCOS exhibit hyperinsulinemia, largely attributed to a combination of increased pancreatic insulin secretion and diminished hepatic insulin clearance. Approximately 10% of affected women develop type 2 diabetes mellitus (T2DM), while 30–35% demonstrate impaired glucose tolerance (IGT), highlighting the syndrome's strong metabolic dimension [5,6]. Among PCOS phenotypes, anovulatory women tend to exhibit greater degrees of insulin resistance and hyperinsulinemia compared to their ovulatory counterparts. A defining feature of PCOS pathogenesis is selective insulin resistance, wherein insulin's metabolic signaling is impaired, yet its mitogenic and steroidogenic effects on the ovaries and adrenal glands remain preserved or even exaggerated.

As a result, compensatory hyperinsulinemia contributes to decreased levels of sex hormone-binding globulin (SHBG), thereby increasing the bioavailability of circulating androgens. Additionally, insulin exerts a direct stimulatory influence on ovarian theca cells and adrenal steroidogenesis, leading to excess androgen production. It also interacts with the central nervous system, particularly the hypothalamus, dysregulating appetite control and gonadotropin secretion, thereby exacerbating ovulatory dysfunction. On a molecular level, insulin resistance is associated with reduced insulin receptor signaling in peripheral tissues, contributing to widespread endocrine disruption [7,8]. Obesity acts as a compounding factor, further intensifying insulin resistance and hyperinsulinemia, and potentiating the hyperandrogenic state characteristic of PCOS. Furthermore, hyperinsulinemia impairs hepatic synthesis of SHBG, leading to elevated concentrations of free testosterone. The ovaries, in turn, exhibit increased sensitivity to insulin, perpetuating a cycle of androgen excess. Independent predictors of insulin resistance in PCOS include elevated body mass index (BMI), biochemical hyperandrogenemia, and clinical signs of hyperandrogenism.[11] Disruption in the negative feedback regulation of luteinizing hormone (LH) secretion, in conjunction with persistent hyperinsulinemia, contributes to aberrant folliculogenesis and chronic anovulation—central features in the reproductive dysfunction seen in PCOS [9]

Hormonal Imbalance

Hormonal dysregulation is a hallmark feature of Polycystic Ovary Syndrome (PCOS), involving alterations in several key endocrine pathways:

- Elevated testosterone levels contribute to clinical and/or biochemical hyperandrogenism, manifesting as hirsutism, acne, and alopecia.
- Increased luteinizing hormone (LH) concentrations, particularly when disproportionately elevated relative to follicle-stimulating hormone (FSH), disrupt normal folliculogenesis and ovulatory function.
- Reduced levels of sex hormone-binding globulin (SHBG) enhance the bioavailability of circulating androgens, thereby intensifying hyperandrogenic symptoms.
- Elevated prolactin levels (hyperprolactinemia), though observed in a minority of patients, may interfere with gonadotropin regulation and contribute to anovulation.[6]
- Increased serum concentrations of androstenedione and dehydroepiandrosterone sulfate (DHEA-S), both adrenal androgens, further contribute to the androgen excess frequently seen in PCOS.

These hormonal abnormalities collectively impair ovarian function and contribute to the diverse clinical manifestations of PCOS. [6]

Genetic Factors

Excessive androgen exposure during intrauterine life is believed to exert long-lasting effects on gene expression, contributing to the developmental origins of PCOS and predisposing individuals to subsequent insulin resistance. Rather than being attributable to a single-gene mutation, PCOS is widely considered to be a polygenic or oligogenic disorder, involving the interplay of multiple genetic variants. Additionally, low birth weight and prenatal androgen excess have been implicated in the early programming of the PCOS phenotype [10].

Several environmental and lifestyle factors further modulate the clinical manifestation and severity of PCOS:

- Bisphenol A (BPA), an endocrine-disrupting compound commonly found in plastics, has been associated with ovarian dysfunction and may exacerbate hormonal imbalances in PCOS.[6]

- Chronic psychological stress and associated disorders can disrupt the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated levels of cortisol and prolactin, both of which interfere with normal gonadotropin release and menstrual cycle regulation.
- Aberrant androgen signaling is implicated in both the increased number of ovarian follicles and their impaired maturation, potentially due to defective intraovarian growth factors—collectively termed as the ovarian follicular defect [11,12].
- Lifestyle-related elements such as a sedentary routine, irregular dietary patterns, lack of physical activity, or conversely, excessive physical exertion, along with extreme weight fluctuations, endocrine disorders, and intrinsic ovarian pathologies, are all recognized as contributing factors in the development and progression of PCOS [13].

Together, these genetic, epigenetic, environmental, and lifestyle influences underscore the multifactorial nature of PCOS and its heterogeneous clinical expression.

Pathophysiology

Multiple interrelated hypotheses have been advanced to elucidate the underlying mechanisms of Polycystic Ovary Syndrome (PCOS) pathogenesis. These include:

- Endometrial progesterone resistance, which may impair endometrial receptivity and contribute to menstrual irregularities and infertility.
- A distinct defect in insulin action and secretion, leading to systemic insulin resistance and compensatory hyperinsulinemia, which in turn amplifies ovarian androgen production.
- A primary neuroendocrine abnormality characterized by an exaggerated luteinizing hormone (LH) pulse frequency and amplitude, disrupting the normal hypothalamic-pituitary-ovarian axis regulation.
- An intrinsic defect in ovarian steroidogenesis, resulting in excessive androgen biosynthesis from theca cells, independent of gonadotropin stimulation.
- Altered cortisol metabolism, potentially involving impaired 11β-hydroxysteroid dehydrogenase activity, which may favor increased adrenal androgen production, further contributing to hyperandrogenism.

These diverse yet interconnected mechanisms reflect the complex, multifactorial nature of PCOS and its broad spectrum of clinical presentations [14].

Diagnosis

In November 2015, the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the Androgen Excess and PCOS Society (AES) jointly issued updated clinical guidelines for the diagnosis and management of Polycystic Ovary Syndrome (PCOS). These guidelines reflect an integrated approach to both diagnostic evaluation and therapeutic intervention. Key recommendations include:

- ✓ The diagnostic framework for PCOS necessitates the presence of at least two of the following three cardinal features: persistent anovulation, clinical and/or biochemical manifestations of hyperandrogenism, and sonographically confirmed polycystic ovarian morphology.
- ✓ In addition to standard clinical assessment, measurement of serum 17-hydroxyprogesterone and anti-Müllerian hormone (AMH) levels is recommended to assist in differential diagnosis, particularly for distinguishing PCOS from non-classic congenital adrenal hyperplasia and other etiologies of ovulatory dysfunction.
- ✓ Free testosterone concentrations, assessed via equilibrium dialysis, are considered more sensitive and accurate indicators of androgen excess compared to total testosterone levels and should be prioritized during biochemical evaluation.
- ✓ Comprehensive clinical evaluation should include assessment of reproductive function, hirsutism, androgenic alopecia, and acne, all of which may manifest due to underlying hyperandrogenism.
- ✓ The diagnosis and management of adolescent PCOS pose particular challenges due to overlapping features with normal pubertal physiology. Oligomenorrhea persisting beyond 2–3 years post-menarche warrants investigation for potential ovarian or adrenal dysfunction.
- ✓ In adolescents, first-line therapy may include metformin monotherapy or combination therapy using oral contraceptive agents and anti-androgenic agents, depending on the severity and constellation of symptoms.
- ✓ These guidelines underscore the importance of a multidisciplinary, individualized approach in the accurate diagnosis and effective management of PCOS across different age groups [15].

Signs and Symptoms

- ✓ The clinical manifestation of PCOS is highly variable and tends to differ with age. Younger women predominantly present with reproductive and psychological disturbances, such as menstrual irregularities, infertility, and mood disorders, whereas older women more commonly report metabo**lic complications**, including insulin resistance, dyslipidemia, and obesity [16]

- ✓ Mostly seen symptoms are hirsutism or hair loss, acne, androgenic alopecia, and acanthosisnigricans, obesity, excessive sweating, fatigue, altered mood, poor sleep, oligomenorrhea (irregular periods), amenorrhea (absence of periods), infertility, high circulating levels of testosterone or androstenedione, high levels of luteinizing hormone, polycystic ovaries on ultrasound (>/=12 follicles in each ovary, follicle size between 2 and 9 mm +_>10 ml ovarian volume [17-20]

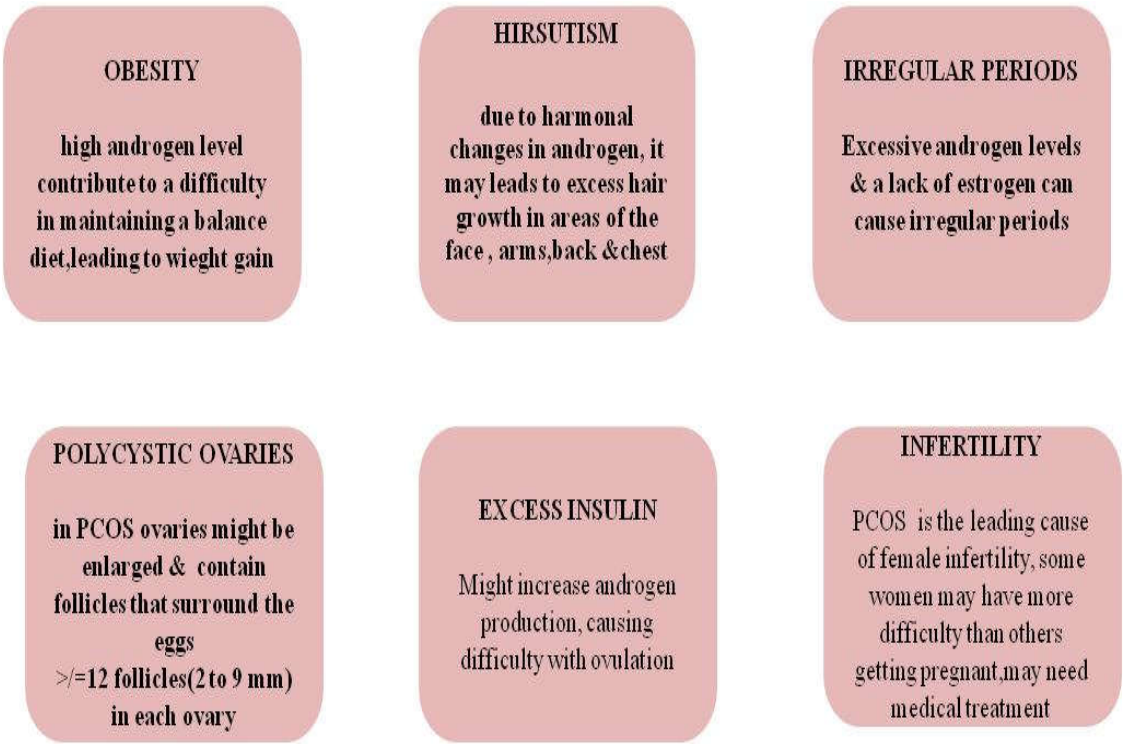

Figure 1: Signs and Symptoms of PCOS

Phenotype

Since PCOS tends to show as a spectrum of disease, the Rotterdam criteria classify disease into fourphenotypes .

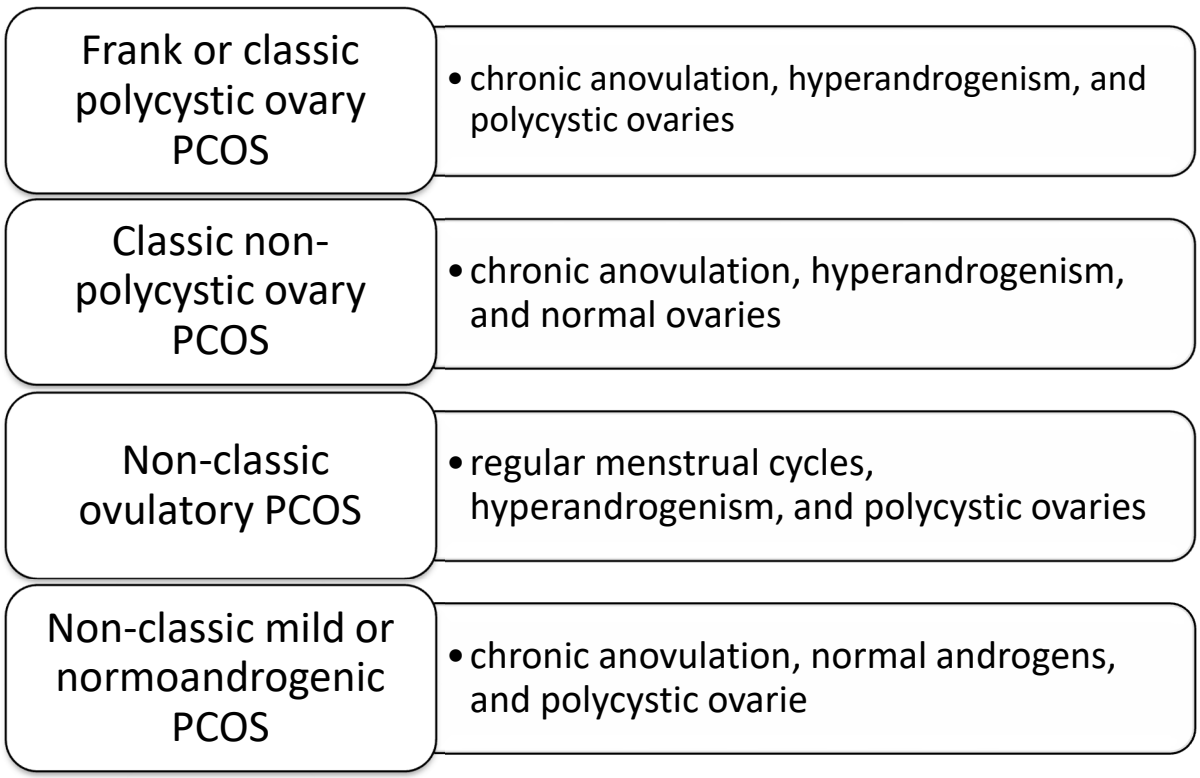

Figure 2: Classification of PCOS

Women exhibiting the classic or frank phenotype of polycystic ovary syndrome (PCOS) are at an elevated risk of developing metabolic and cardiovascular complications, including insulin resistance and dyslipidemia, compared to individuals presenting with the non-classic phenotype—even when matched for body mass index (BMI). In contrast, women with a non-classic androgenic presentation tend to exhibit a lower degree of insulin resistance and are less likely to manifest the metabolic disturbances typically associated with PCOS.

To facilitate a more precise clinical characterization of PCOS, the 2012 National Institutes of Health (NIH) consensus panel proposed a phenotypic classification system, delineating subtypes based on specific combinations of clinical, biochemical, and ultrasonographic criteria [21].

According to the phenotypic classification established by the 2012 NIH consensus panel, PCOS is classified into four phenotypes based on the presence of hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovarian morphology (PCO):

- Phenotype A (HA + OD + PCO): Classic form with all three features.
- Phenotype B (HA + OD): Non-PCO variant; lacks polycystic ovaries.
- Phenotype C (HA + PCO): Ovulatory PCOS; ovulation preserved.
- Phenotype D (OD + PCO): Non-hyperandrogenic type; no elevated androgens.

This phenotypic framework facilitates a more precise diagnostic and therapeutic approach by acknowledging the heterogeneity inherent in PCOS presentation.

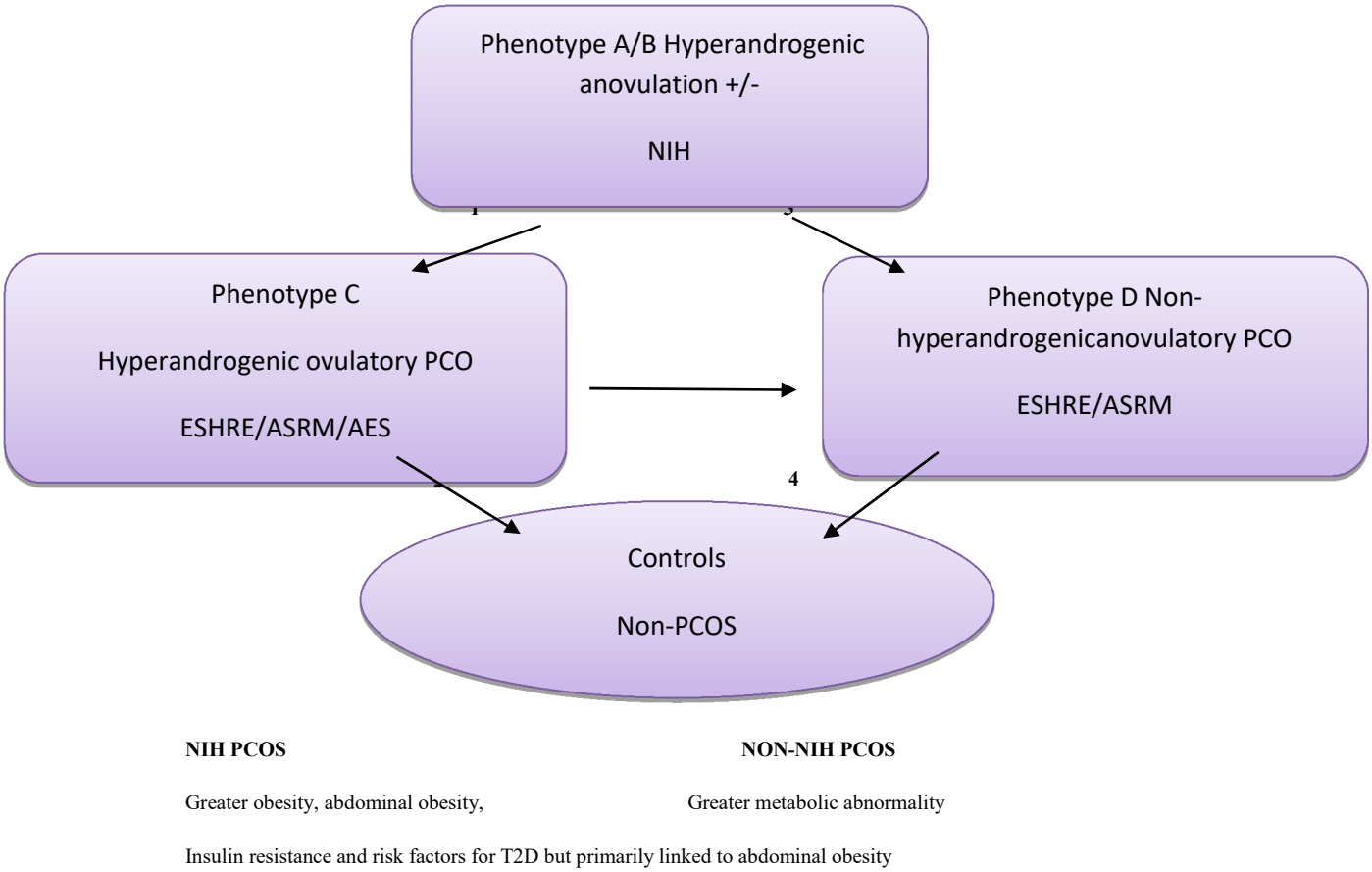

Figure 3: Phenotypic classification

Recent diagnostic parameters

Anti-Müllerian hormone (AMH) has been proposed as a potential surrogate biomarker for the ultrasonographic evaluation of polycystic ovarian morphology, given its strong correlation with antral follicle count. An additional diagnostic indicator includes the quantification of ovarian stromal volume, often expressed as the stromal-to-total ovarian area ratio (S/A ratio), which may enhance the assessment of ovarian architecture [22].

A comprehensive physical examination should be undertaken, encompassing the measurement of blood pressure, body weight, and height. This should be complemented by a general systemic evaluation with particular attention to the development of secondary sexual characteristics. Clinical palpation of the thyroid gland is also warranted to identify any nodular formations or glandular enlargement.

Further diagnostic refinement can be achieved via endocrine profiling, including serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin, dehydroepiandrosterone (DHEA), and total testosterone, to elucidate the underlying hormonal dysregulation. Additionally, lipid profiling, including total

cholesterol and high-density lipoprotein (HDL) levels, should be performed to evaluate associated metabolic risk factors [23].

Transvaginal or transabdominal ultrasonography remains a key diagnostic modality, with polycystic ovarian morphology defined by the presence of ≥12 peripheral follicles in each ovary, each measuring 2–9 mm in diameter, and/or an increased ovarian volume exceeding 10 mL [24].

Associated morbidities

- **Obesity**

  Obesity, marked by excessive fat accumulation, is a major comorbidity in PCOS, affecting 61% to 76% of women [20]. Its development is influenced by genetic, environmental, and lifestyle factors, not just PCOS alone. Obesity contributes significantly to the metabolic symptoms of PCOS. While ovarian cysts are a feature, they are not the cause, and some symptoms persist even after ovary removal. Cysts appear in only about 15% of PCOS cases linked to metabolic issues. Prenatal and environmental exposures may also worsen PCOS and promote obesity. Obese women with PCOS often exhibit high LDL, triglycerides, and cholesterol, along with low HDL, increasing their risk of cardiovascular disease [25,26].
- **Cardiovascular Diseases**

Hyperinsulinemia is recognized as a central pathophysiological contributor to the elevated cardiovascular risk observed in women with polycystic ovary syndrome (PCOS). Insulin resistance, a hallmark metabolic disturbance in PCOS, is implicated in two principal mechanisms that potentiate cardiovascular disease (CVD) in this population. The first involves the direct pro-atherogenic effects of hyperinsulinemia on vascular endothelium, while the second pertains to its deleterious impact on lipid metabolism, resulting in an atherogenic lipoprotein profile [27].

Hypertension represents a critical cardiovascular comorbidity in PCOS, with numerous studies demonstrating a positive correlation between elevated plasma insulin levels and increased arterial blood pressure, underscoring the role of insulin resistance in the pathogenesis of hypertensive states. Notably, the risk of preeclampsia is significantly amplified—by approximately fourfold—in pregnant women with PCOS who are also obese, relative to the general obstetric population.

Collectively, these findings suggest that women with PCOS are predisposed to the early onset of major cardiovascular risk factors, including atherosclerosis, hypertension, and myocardial infarction, often manifesting at a younger age compared to their non-PCOS counterparts.

Diabetes

Cumulative evidence indicates that beyond the age of 30, over 20% of obese women exhibit impaired glucose tolerance (IGT), reflecting early disturbances in glucose homeostasis [28, 29]. Numerous studies have established a strong association between obesity and the development of type 2 diabetes mellitus (T2DM) among women diagnosed with polycystic ovary syndrome (PCOS) [29]. Although the risk of T2DM is markedly elevated in obese women with PCOS, emerging data also suggest that non-obese PCOS patients are not exempt from this metabolic vulnerability, as they too demonstrate a significantly increased predisposition to glucose dysregulation and insulin resistance, albeit to a lesser extent.

Furthermore, a notable correlation has been observed between gestational diabetes mellitus (GDM) and subsequent diagnosis of PCOS, with a higher prevalence of PCOS identified in women with a prior history of GDM, suggesting a bidirectional metabolic interplay between these two endocrinopathies [30,31].

Ovarian Cancer

The risk of ovarian cancer has been found to be elevated among nulliparous women, particularly those with a history of early menarche and late menopause, conditions that cumulatively contribute to a greater number of lifetime ovulatory cycles. This association is further reinforced by observations that women experiencing infertility, particularly those with frequent ovulation, also exhibit an increased risk of ovarian malignancy. In contrast, women with polycystic ovary syndrome (PCOS), who typically exhibit chronic anovulation and thereby a reduced lifetime ovulatory burden, may possess a comparatively lower risk of developing ovarian cancer. However, this protective effect may be attenuated or altered with the use of ovulation-inducing agents [32].

Epidemiological data suggest that the use of combined oral contraceptives confers a substantial protective effect against ovarian cancer, with an estimated 20% reduction in risk for every five years of use, culminating in an approximate 50% reduction after 15 years of continuous administration. This protective benefit generally becomes evident following at least one year of consistent oral contraceptive use.

In the context of PCOS, anovulatory women treated with oral contraceptives may experience chemopreventive effects not solely due to the interruption of incessant ovulation, but rather through the suppression of gonadotropin stimulation. This mechanism may mitigate oncogenic

processes such as inclusion cyst formation, excessive epithelial proliferation, and subsequent genetic instability—factors implicated in ovarian carcinogenesis [33].

Breast Cancer

The pathogenesis of breast cancer may be influenced by factors commonly associated with PCOS, such as obesity, hyperandrogenism, and infertility. While some studies suggest a higher prevalence of family history of breast cancer in women with PCOS, a direct causal link remains unproven [33]. Overall, evidence does not show a significant increase in breast cancer risk in PCOS patients compared to the general population. However, the high obesity rate in PCOS may indirectly raise breast cancer susceptibility. [34,35].

Moreover, emerging data indicate that metformin, an insulin-sensitizing agent commonly used in the management of PCOS, may exert a protective effect against breast cancer. This is thought to occur through mechanisms involving improved insulin sensitivity, modulation of circulating androgen levels, and potential antiproliferative effects on breast epithelial cells.

Endometrial Cancer

Chronic anovulation, a hallmark feature of polycystic ovary syndrome (PCOS), is widely regarded as a principal pathophysiological mechanism underlying the sustained, unopposed estrogenic stimulation of the endometrium, thereby significantly elevating the risk of endometrial carcinoma [36,37]. The absence of regular progesterone-mediated endometrial shedding facilitates a proliferative environment conducive to neoplastic transformation.

Additional risk factors that have been strongly associated with the development of endometrial cancer include obesity, prolonged use of unopposed estrogens, nulliparity, infertility, hypertension, and type 2 diabetes mellitus—all of which are frequently comorbid with PCOS [38]. These overlapping metabolic and hormonal derangements underscore the heightened vulnerability of this population to endometrial pathology.

Endometrial hyperplasia, particularly in its atypical forms, is recognized as a precursor lesion to endometrioid adenocarcinoma. In women with PCOS, prolonged intermenstrual intervals—especially those exceeding three months—have been correlated with a greater likelihood of developing endometrial hyperplasia, which may progress to carcinoma if left unaddressed.

Treatment

At present, there is no definitive cure for polycystic ovary syndrome (PCOS); however, its clinical manifestations can be effectively managed through a combination of therapeutic lifestyle interventions and pharmacologic strategies. Evidence supports that enhancement of daily physical activity, coupled with adherence to a high-fiber, low-glycemic index diet rich in vegetables, whole grains, and fruits, contributes to weight reduction, improved insulin sensitivity, and mitigation of metabolic complications associated with PCOS [39].

Sustaining a healthy waist circumference is critical, as central adiposity is closely linked with insulin resistance and cardiometabolic risk [40-48]. Dietary modifications should also include the minimization of processed foods and the reduction of trans and saturated fat intake to promote glycemic control and prevent exacerbation of hyperinsulinemia and dyslipidemia [49]. Professional dietary counseling by a registered dietitian or nutritionist is recommended for individualized nutrition planning and optimization of metabolic outcomes.

Moreover, smoking cessation—or avoidance of tobacco use altogether—is strongly advised, as smoking is known to exacerbate cardiovascular risk and negatively influence endocrine and reproductive health parameters in women with PCOS.

In addition to lifestyle modification, pharmacologic interventions play a critical role in the individualized management of polycystic ovary syndrome (PCOS), with therapeutic regimens tailored according to the patient's clinical presentation, metabolic profile, reproductive intentions, and long-term health goals [50].

Hormonal Contraceptives: Combined oral contraceptives (COCs) with low-androgenic progestins like drospirenone, or progestin-only pills, are used to regulate periods, lower androgen levels, and treat acne and hirsutism.

Inositol supplements (myo- and D-chiro-inositol), alone or combined, help improve insulin resistance, ovulation, acne, and hirsutism by enhancing insulin sensitivity and supporting ovarian function. [51, 52].

Metformin: Metformin, a biguanide class insulin sensitizer, exhibits multiple metabolic benefits including the reduction of hepatic gluconeogenesis, improvement in peripheral insulin sensitivity, and attenuation of hyperandrogenism by decreasing circulating insulin and androgen levels [49–51]. Its therapeutic impact on ovulation and menstrual cycle regulation may become evident after a minimum of six months of consistent use. However, its role as a first-line ovulation-inducing agent remains controversial and may be best considered as part of a combination strategy in selected patients [53].

Lipid-Lowering Agents: In women with PCOS who present with dyslipidemia, statins and other lipid-modifying agents may be indicated to mitigate cardiovascular risk [54].

Aromatase Inhibitors (AIs): Selective aromatase inhibitors (e.g., letrozole, anastrozole) have emerged as potent, reversible ovulation-inducing agents with a favorable pharmacokinetic profile. Unlike clomiphene citrate (CC), which has a prolonged half-life of approximately 5–7 days and anti-estrogenic effects on endometrial and cervical mucus, AIs possess shorter half-lives (mean ~45 hours) and lack anti-estrogenic peripheral activity [55-57]. Letrozole, in particular, has been extensively studied and widely adopted in assisted reproductive protocols due to its superior safety profile and ovulation rates, especially in CC-resistant cases. Mechanistically, letrozole inhibits aromatase-mediated estrogen biosynthesis within the hypothalamic-pituitary axis, thereby relieving negative feedback inhibition and enhancing the secretion of gonadotropin-releasing hormone (GnRH) and follicle-stimulating hormone (FSH), thus promoting follicular development and ovulation [58].

Combined Oral Contraceptives (COCs): Estrogen–progestin combination therapy, particularly in the form of combined oral contraceptive pills (COCPs), constitutes the cornerstone of pharmacologic management for clinical manifestations of hyperandrogenism in women with polycystic ovary syndrome (PCOS), such as hirsutism and acne. The estrogenic component of COCPs exerts a suppressive effect on pituitary luteinizing hormone (LH) secretion, thereby diminishing ovarian androgen synthesis. Concurrently, estrogen promotes hepatic synthesis of sex hormone–binding globulin (SHBG), leading to a reduction in circulating free testosterone levels—thus decreasing androgen bioavailability and activity at the target tissue level.

Progestin Profiles: The selection of progestin is critical in determining the overall androgenic burden of the contraceptive regimen. Norgestimate and desogestrel are considered minimally androgenic, whereas drospirenone—an analogue of the aldosterone antagonist spironolactone—possesses unique antiandrogenic and antimineralocorticoid properties. When combined with ethinylestradiol, drospirenone represents an optimal therapeutic option for PCOS patients by addressing androgen-mediated dermatologic symptoms while offering endometrial protection against unopposed estrogenic stimulation.

Antiandrogens: Cyproterone acetate, a steroidal antiandrogen, exerts its effects via competitive antagonism at the androgen receptor, inhibiting the binding of both testosterone and its more potent metabolite, 5α-dihydrotestosterone (DHT). Although not available in the United States, it is widely used in Europe, Canada, and Mexico for the effective treatment of hirsutism and acne in PCOS. Spironolactone, a potassium-sparing diuretic with antiandrogenic activity, may be used in synergy with COCs to enhance clinical efficacy. Given the teratogenic potential of antiandrogens,

their use is contraindicated in women attempting to conceive and should be accompanied by effective contraception.

Glucocorticoids: A subset of women with PCOS may exhibit elevated adrenal androgen secretion (e.g., dehydroepiandrosterone sulfate, DHEAS). While glucocorticoids can suppress adrenal androgen production, their utility in PCOS is generally limited due to the modest contribution of adrenal hyperandrogenism to the overall pathophysiology of anovulation in most patients. Consequently, prolonged glucocorticoid therapy is not routinely recommended unless there is compelling evidence of significant adrenal androgen excess.

Additional Therapeutic Agents: Finasteride, a synthetic 4-aza-steroid compound, acts as a selective and competitive inhibitor of the type 2 isoform of 5α-reductase, an enzyme responsible for the peripheral conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT). Although it has demonstrated some clinical efficacy in ameliorating hirsutism [59], its therapeutic potential may be limited due to the predominance of type 1 5α-reductase isoenzyme in the pilosebaceous units of the skin—an anatomical site closely associated with androgen-mediated cutaneous manifestations.

Eflornithine hydrochloride is a topically administered, irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme in polyamine synthesis within human skin. This agent has received regulatory approval for the management of facial hirsutism in women, where it acts by impeding hair growth at the follicular level. Its clinical efficacy typically becomes evident after 6–8 weeks of consistent use and may be augmented through adjunctive laser therapy.

Laparoscopic Ovarian Diathermy (LOD): In women with clomiphene citrate-resistant polycystic ovary syndrome who are either unable or unwilling to undergo intensive gonadotropin monitoring protocols, laparoscopic ovarian drilling—achieved via monopolar electrocautery or laser-induced multiple ovarian perforations—constitutes an efficacious alternative for ovulation induction. This minimally invasive surgical intervention yields comparable ovulatory and pregnancy outcomes to gonadotropin therapy, while significantly reducing the risk of multifetal gestation [60].

Insulin-Sensitizing Agents: Pharmacologic agents that reduce insulin resistance, including metformin (a biguanide) and thiazolidinediones (e.g., rosiglitazone, pioglitazone), may attenuate ovarian androgen production primarily through their insulin-lowering effects. A Cochrane systematic review indicated limited evidence, based on small patient populations, to suggest any significant difference in the efficacy of metformin versus combined oral contraceptives for the management of hirsutism and acne in PCOS. Clinical studies have shown that rosiglitazone can

modestly improve clinical signs of hyperandrogenism, while troglitazone—withdrawn due to hepatotoxicity—previously demonstrated beneficial effects in PCOS-associated hirsutism [61].

Topical Therapies: Eflornithine hydrochloride remains the primary topical pharmaceutical intervention for facial hirsutism. As an irreversible inhibitor of ornithine decarboxylase, it curtails polyamine synthesis necessary for hair follicle proliferation. Clinical efficacy becomes apparent within 6–8 weeks of initiation, and its effect is often enhanced when used in combination with laser epilation procedures for long-term hair reduction.

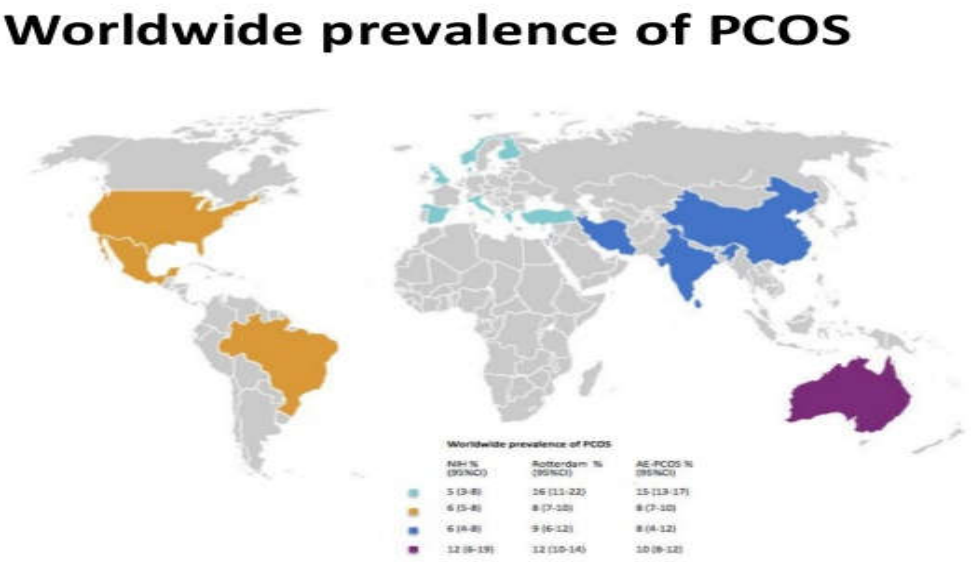

Figure 4: Worldwide Prevalence of PCOS

Epidemiological evidence underscores the widespread prevalence of Polycystic Ovary Syndrome (PCOS) across diverse geographical regions, with notable incidence reported in India, China, Australia, Middle Eastern nations, the United States of America, Mexico, Brazil, and various European countries.

According to WHO estimates, PCOS affected around 116 million women worldwide in 2012, representing 3.4% of the female population. However, prevalence rates vary widely (2.2%–96%) depending on diagnostic criteria, population differences, and study methods.

In the Indian context, PCOS is emerging as a significant public health concern. The prevalence among women of reproductive age has been reported to range between 9.13% and 36%, reflecting both urbanization-related lifestyle shifts and increasing awareness [63]. A recent study focusing on adolescent and young adult females in Mumbai documented a prevalence rate of 22.5%,

highlighting the growing burden of PCOS in younger populations and the need for early intervention strategies.

Conclusion

Polycystic Ovary Syndrome (PCOS) persists as a major global public health concern, owing to its high prevalence and multifaceted clinical sequelae. Characterized by phenotypic heterogeneity, PCOS arises from a complex interrelationship between endocrine dysregulation, genetic predisposition, and environmental influences, thereby necessitating a patient-specific and interdisciplinary model of care for accurate diagnosis and optimal therapeutic intervention. Although existing diagnostic frameworks—such as the NIH, Rotterdam, and AE-PCOS criteria—offer structured clinical guidelines, the evolving insights into the syndrome's pathophysiology underscore an urgent need for harmonized and universally endorsed diagnostic standards. Given its strong associations with metabolic dysfunction, subfertility, and adverse psychological outcomes, early identification and timely, individualized management are paramount. An integrative approach incorporating lifestyle modification, pharmacologic interventions tailored to symptomatology and risk profiles, and long-term surveillance can substantially reduce morbidity and enhance both reproductive and metabolic outcomes. Advancing our understanding of the etiological mechanisms through ongoing translational and clinical research remains critical for the development of precision medicine-based strategies in the management of PCOS.

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