



POLYCYSTIC OVARY SYNDROME (PCOS): A COMPREHENSIVE REVIEW OF ITS ETIOPATHOGENESIS, CLINICAL FEATURES, AND MULTIDIMENSIONAL MANAGEMENT STRATEGIES

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Abstract

Polycystic Ovary Syndrome (PCOS) is a widespread condition involving hormonal and metabolic imbalances, impacting approximately 8–13% of women during their reproductive years across the globe. It is mainly accompanied by excessive androgen levels, abnormal or absent ovulation, and polycystic ovarian morphology. The condition is arising due to genetic influences, environmental, lifestyle factors that disturb the normal hormonal balance and metabolism of the body. Insulin resistance, obesity, and inflammation play a major role in worsening the symptoms and future health risks linked to PCOS. Underlying mechanisms involve increased luteinizing hormone (LH) secretion, reduced follicle-stimulating hormone (FSH) activity, and overproduction of androgens by the ovaries. These changes lead to anovulation, infertility, acne, and excessive hair growth. Apart from reproductive problems, women affected by PCOS have an increased likelihood of developing metabolic disorders such as metabolic syndrome, type 2 diabetes, abnormal lipid levels, high blood pressure, and cardiovascular conditions. Emotional problems like anxiety, depression and low self-esteem are commonly seen, making PCOS a multidimensional health issue. The diagnosis is made by evaluating clinical symptoms along with hormonal assessments and ultrasound results. The Rotterdam and recent international guidelines recommend a comprehensive approach that also includes metabolic and psychological assessment. Management focuses on lifestyle modification such as balanced diet, regular physical activity, and weight control. Emerging options such as inositols, GLP-1 agonists, and nutraceuticals offer additional benefits. In conclusion, PCOS extends beyond a reproductive disorder and is a long-term metabolic condition that requires timely diagnosis, healthy lifestyle changes, and personalized treatment approaches.

Keywords : Polycystic Ovary Syndrome (PCOS), hormonal imbalance, hyperandrogenism, insulin resistance, ovulatory dysfunction, genetic predisposition, lifestyle factors, cardiovascular risk, psychological impact, diagnostic criteria, lifestyle-based management.

1. Introduction

Polycystic ovarian condition represents a main clinical and health of the population challenge due to its reproductive, metabolic, and psychological consequences. Initially described by **Stein and Leventhal (1935)** as a triad of amenorrhea, infertility, and enlarged polycystic ovaries, PCOS was once considered solely a gynecological disorder [5]. However, subsequent research revealed its multisystemic impact — involving not only ovarian dysfunction but also profound disturbances in insulin signaling, lipid metabolism, and hypothalamic–pituitary regulation [12,13].

1.1 Evolution of Conceptual Understanding

In the 1980s and 1990s, PCOS emerged as an endocrine–metabolic disorder when **Dunaif (1997)** demonstrated the intrinsic link between insulin resistance and hyperandrogenism [16]. The **NIH 1990 criteria** first formalized the diagnostic concept, requiring the presence of both hyperandrogenism (clinical or biochemical) and chronic anovulation, while excluding other endocrinopathies [7]. This definition, though stringent, provided diagnostic uniformity for classic PCOS.

The **Rotterdam ESHRE/ASRM consensus (2003)** later broadened the diagnostic framework, introducing polycystic ovarian morphology (PCOM) as an additional component and allowing any two of the three criteria to establish diagnosis [4]. This expansion significantly increased PCOS prevalence estimates and revealed multiple phenotypic variants. Subsequently, the **Androgen Excess and PCOS Society (AES, 2006)** reasserted androgen excess as the central hallmark of the syndrome [6], emphasizing its pathophysiological relevance to both reproductive and metabolic manifestations.

Most recently, the **International Evidence-Based Guidelines for the Assessment and Management of PCOS (2018–2023)** have adopted a comprehensive and globally harmonized approach integrating diagnostic, metabolic, and psychosocial care components [8,9]. These guidelines underscore the need for ethnic-specific diagnostic thresholds and long-term health surveillance in at-risk populations, particularly in South Asia, where metabolic manifestations often dominate clinical presentation [10,25].

1.2 Evolution of Diagnostic Frameworks

Table 1. Evolution of Diagnostic Frameworks

Criteria	Year	Core Diagnostic Components	Distinctive Attributes	Limitations
NIH	1990	Hyperandrogenism + Oligo-/Anovulation	First formal definition; pathophysiologic clarity	Excludes PCOM → under diagnosis of mild phenotypes
Rotterdam	2003	Any 2 of: HA/OD/PCOM	Broader inclusion; recognizes heterogeneity	May overestimate prevalence
AES	2006	Any 2 of: HA/OD/PCOM	Emphasizes androgen excess as core feature	Excludes non-HA variants
International (2018)	2018	HA/OD/PCOM + metabolic assessment	Evidence-based and globally applicable	Requires specialized testing and regional data

(HA = Hyperandrogenism; OD = Oligo-/Anovulation; PCOM = Polycystic Ovarian Morphology)

These evolving definitions illustrate how the concept of PCOS transitioned from a gynecologic condition to a systemic endocrinopathy involving genetic, metabolic, and psychological factors [11,18].

2. Etiology

PCOS cannot be attributed to a single causative factor; rather, it emerges from a network of dysregulated pathways affecting steroidogenesis, insulin signaling, and hypothalamic–pituitary control [11,18,19].

2.1 Genetic Factors

Genetic predisposition contributes significantly to PCOS pathogenesis, with familial clustering observed in 20–40% of cases [19,21]. Genome-wide association studies (GWAS) have identified over **20 susceptibility loci**, implicating genes such as **DENND1A**, **THADA**, **LHCGR**, **FSHR**, **INSR**, **YAP1**, and **HMG2** [19]. These genes modulate androgen biosynthesis, folliculogenesis, insulin receptor signaling, and gonadotropin action.

The **DENND1A** variant (2p16.3) enhances theca-cell androgen biosynthesis, while **LHCGR** mutations dysregulate LH receptor signaling, leading to persistent theca activation [19]. Similarly, **FSHR polymorphisms** impair FSH sensitivity, resulting in aberrant follicular maturation and ovulatory dysfunction [20,21].

Heritability estimates for PCOS range between **60% and 70%**, suggesting a strong genetic foundation that interacts with environmental modifiers. Studies also indicate polygenic inheritance patterns, with cumulative small-effect variants contributing to phenotype diversity [18,19].

2.2 Epigenetic Mechanisms

Beyond classical genetics, **epigenetic regulation** plays an emerging role in PCOS pathogenesis. DNA methylation, histone modification, and non-coding RNA (miRNA) interference influence gene expression involved in ovarian steroidogenesis, insulin signaling, and inflammation [21].

Notably, aberrant methylation of **CYP11A1** and **CYP17A1** promoters leads to increased androgen production, while miR-93 and miR-222 dysregulate **INSR** and **IRS-1**, exacerbating insulin resistance [21,22]. In animal models, maternal hyperandrogenism and obesity induce fetal epigenetic reprogramming, predisposing offspring to PCOS-like phenotypes—supporting the **Developmental Origins of Health and Disease (DOHaD)** concept [21].

Epigenetic plasticity also explains the observed phenotypic variability and environmental sensitivity in PCOS patients across populations [19,21].

2.3 Environmental and Lifestyle Influences

Environmental factors, particularly those influencing endocrine and metabolic homeostasis, significantly modulate PCOS expression. Early-life exposure to **endocrine-disrupting chemicals (EDCs)** such as bisphenol-A (BPA), phthalates, and organochlorines has been linked to altered ovarian steroidogenesis and insulin resistance [23]. BPA mimics estrogen and acts as an anti-androgen, binding to estrogen receptors and disrupting follicular maturation. Elevated serum BPA levels have been correlated with increased androgen and LH levels in PCOS women [24].

Additionally, **high-caloric diets**, **sedentary behavior**, and **obesity** exacerbate insulin resistance, leading to compensatory hyperinsulinemia that stimulates ovarian theca cells to produce androgens [16,20]. Conversely, weight reduction and exercise improve hormonal and metabolic parameters, demonstrating the modifiable nature of environmental contributions [3,8].

2.4 Developmental and Fetal Origins

Emerging evidence supports the hypothesis that PCOS may originate in utero. Excess maternal androgens during gestation can permanently program the fetal hypothalamic–pituitary–ovarian axis, predisposing female offspring to hyperandrogenism, insulin resistance, and anovulation in adulthood [21]. Animal studies demonstrate that **prenatal androgen exposure** increases LH pulsatility, disrupts folliculogenesis, and alters adipose gene expression [22]. Human data also suggest that **low birth weight and rapid postnatal weight gain** are associated with higher PCOS risk later in life [25].

Such findings position PCOS as a **developmental endocrine–metabolic disorder** that may be expressed or intensified by postnatal environmental and lifestyle triggers [21].

2.5 Combined influence of genetic makeup, epigenetic regulation, and environmental conditions

The convergence of genetic predisposition, epigenetic modification, and environmental exposure leads to **neuroendocrine and metabolic dysregulation**, forming the pathogenic core of PCOS. This interplay results in elevated GnRH and LH pulsatility, ovarian androgen excess, and insulin resistance—creating a self-perpetuating cycle of hormonal and metabolic imbalance [11,17,18].

3. Pathophysiology

Polycystic Ovary condition is underpinned by network of **neuroendocrine, ovarian and metabolic abnormalities** that interact bidirectionally. These disturbances create a self-reinforcing “vicious cycle” of **androgen excess, insulin resistance, and gonadotropin imbalance**, which drive both reproductive and metabolic features of the disorder [15–18]. The following subsections detail the major mechanistic pathways.

3.1 Neuroendocrine Dysregulation

At the neuroendocrine level, PCOS is characterized by **increased hypothalamic GnRH pulse frequency**, which preferentially stimulates luteinizing hormone (LH) secretion while suppressing follicle-stimulating hormone (FSH) release. This abnormal LH/FSH ratio (>2:1) enhances androgen biosynthesis by theca cells, while low FSH fails to support adequate follicular aromatization [17]. This dysregulation is maintained by **defective negative feedback** from estradiol and progesterone on GnRH neurons, leading to persistent LH hypersecretion and anovulation [18].

3.2 Ovarian Steroidogenesis and Follicular Arrest

The ovarian theca cells in PCOS exhibit up-regulated expression of CYP11A1 and CYP17A1, **key enzymes in steroidogenesis, resulting in excessive androgen synthesis** [18]. **Elevated androgens inhibit granulosa-cell aromatase activity, limiting the conversion of testosterone to estradiol. Consequently, follicular maturation arrests at the small antral stage, producing the classic “string of pearls” morphology on ultrasound** [4,11].

Furthermore, excessive androgens augment **anti-Müllerian hormone (AMH)** secretion, which in turn suppresses follicular sensitivity to FSH, reinforcing follicular arrest. Elevated AMH may also directly influence hypothalamic GnRH neurons, aggravating LH hyperpulsatility—a bidirectional feedback loop amplifying hyperandrogenism [18].

3.3 Insulin Resistance and Metabolic Dysregulation

Insulin resistance (IR) is one of the most consistent metabolic hallmarks of PCOS, affecting approximately **60–70%** of women, independent of obesity [16,20]. In peripheral tissues such as muscle and fat, insulin signaling after receptor activation is disrupted along the PI3K–Akt pathway, whereas the MAPK–ERK pathway continues to function normally. This “selective insulin resistance” allows insulin to continue stimulating ovarian theca cells to produce androgens while diminishing glucose uptake in skeletal muscle [16].

Hyperinsulinemia arising from this resistance exerts several pathophysiologic effects:

- **Enhances ovarian androgen production** by up-regulating CYP17A1.
- **Suppresses hepatic SHBG synthesis**, increasing free testosterone levels.
- **Stimulates LH secretion**, further compounding hyperandrogenism [16,17,20].

Chronic IR predisposes to **glucose intolerance, dyslipidemia, visceral adiposity, and endothelial dysfunction**, connecting PCOS to long-term cardiometabolic morbidity [2,20].

3.4 Adipose and Inflammatory Crosstalk

PCOS is now widely understood as a condition marked by chronic low-level inflammation. Visceral fat, in particular, releases pro-inflammatory adipokines such as TNF- α , IL-6, and leptin, while simultaneously decreasing the levels of the anti-inflammatory hormone adiponectin [2,35]. These cytokines impair insulin signaling, induce oxidative stress, and alter vascular endothelium function.

Inflammation also amplifies ovarian steroidogenesis via NF- κ B-mediated pathways, further linking metabolic stress to reproductive dysfunction. The chronic activation of inflammatory cascades explains the overlap between PCOS and the metabolic syndrome spectrum [2,18].

3.5 Integrative Pathophysiological Model

Table 2. Integrated model summarizing interrelated axes of PCOS pathophysiology.

Component	Primary Dysfunction	Secondary Consequences	Clinical Manifestations
Neuroendocrine Axis	Increased GnRH pulse frequency \rightarrow LH dominance	Theca-cell androgen excess	Anovulation, irregular menses
Ovarian Function	Overexpression of CYP17A1/CYP11A1	Elevated AMH \rightarrow follicular arrest	Infertility, polycystic morphology
Metabolic System	Insulin resistance, hyperinsulinemia	SHBG suppression, dyslipidemia	Obesity, type 2 diabetes
Inflammatory Axis	Cytokine activation (TNF- α , IL-6)	Endothelial stress, oxidative damage	Cardiovascular risk
Epigenetic Influence	DNA methylation, miRNA dysregulation	Altered gene expression	Intergenerational PCOS risk

3.6 Molecular Pathways Involved

Recent molecular analyses highlight involvement of key pathways such as **PI3K/AKT, MAPK, TGF- β , and Wnt/ β -catenin**, each influencing ovarian development and insulin response [18,21].

- The **PI3K/AKT** pathway governs glucose uptake and cell growth; its suppression leads to metabolic insulin resistance.
- The **TGF- β signaling** cascade influences granulosa-cell differentiation and AMH regulation, both altered in PCOS.
- **Wnt/ β -catenin** dysregulation may contribute to abnormal folliculogenesis. Cross-talk between these pathways defines PCOS as a systemic metabolic-inflammatory disorder rather than a purely reproductive syndrome [18,21].

4. Diagnostic Approaches

Diagnosis of PCOS requires a **multidimensional evaluation** incorporating **clinical, biochemical, and imaging findings**, while excluding other causes of hyperandrogenism and menstrual irregularity. Given the heterogeneity of presentation, comprehensive assessment ensures both accuracy and personalized management [4,7–9].

4.1 Clinical Evaluation

The **modified Ferriman–Gallwey (mFG) score** quantifies hirsutism; a score ≥ 8 (adjusted for ethnicity) indicates significant androgen excess [12]. **Menstrual history** remains critical: oligomenorrhea (cycle length >35 days) or amenorrhea (>3 months) reflects chronic anovulation. Anthropometric evaluation—including **BMI, waist-to-hip ratio, and waist circumference**—is essential to identify central obesity and metabolic risk [10,25].

4.2 Biochemical Assessment

Hormonal profiling differentiates PCOS from other endocrinopathies and quantifies metabolic derangements.

Table 3. Biochemical and metabolic indicators relevant to PCOS diagnosis.

Parameter	Reference Range / Diagnostic Indicator	Pathophysiologic Implication	Clinical Utility
LH / FSH ratio	$>2:1$	Reflects GnRH hyperactivity	Supports diagnosis [17]
Total / Free Testosterone	Elevated	Theca-cell androgen excess	Confirms hyperandrogenism [14]
DHEAS	Elevated	Adrenal androgen contribution	Distinguishes adrenal vs ovarian source
SHBG	Low	Increased bioavailable testosterone	Marker of insulin resistance [16]
AMH	>4.5 ng/mL	High follicle number / arrested growth	Correlates with PCOM severity
Fasting glucose, insulin, HOMA-IR	Elevated HOMA-IR >2.5	Insulin resistance quantification	Metabolic risk screening
Lipid profile	\uparrow TG, \downarrow HDL	Atherogenic dyslipidemia	Cardiovascular risk stratification

4.3 Imaging Techniques

Transvaginal ultrasound (TVS) remains the gold standard for detecting **polycystic ovarian morphology (PCOM)**, defined as ≥ 12 follicles (2–9 mm) or ovarian volume >10 cm³ in either ovary [4]. High-frequency **transabdominal ultrasound** is used for virginal or adolescent patients. Recent guidelines (2018) propose **≥ 20 follicles per ovary** using high-resolution (≥ 8 MHz) transducers, improving specificity [8].

4.4 Diagnostic Criteria in Special Populations

- **Adolescents:** Diagnosis requires persistent hyperandrogenism (clinical/biochemical) and menstrual irregularity ≥ 2 years post-menarche. Ultrasound criteria alone are discouraged due to normal pubertal multifollicular ovaries [9].
- **Perimenopausal women:** Diagnosis is retrospective, based on past menstrual irregularity and documented hyperandrogenism, since ovarian morphology becomes less distinctive with age [10].

4.5 Differential Diagnosis

Since PCOS is identified by ruling out other conditions, it is essential to exclude other disorders that cause hyperandrogenism or anovulation.

Table 4. Key differential diagnoses and distinguishing features.

Condition	Distinguishing Features / Tests
Non-classical Congenital Adrenal Hyperplasia (CAH)	Elevated 17-hydroxyprogesterone after ACTH stimulation
Cushing's Syndrome	Elevated cortisol, loss of diurnal rhythm, clinical stigmata (striae, moon facies)
Androgen-secreting Tumor	Rapid onset virilization, testosterone >200 ng/dL
Hyperprolactinemia	Elevated serum prolactin, galactorrhea
Thyroid Dysfunction	Abnormal TSH/T4, menstrual disturbance

4.6 Emerging Diagnostic Biomarkers

Beyond conventional hormones, several **novel biomarkers** have been proposed:

- **Adiponectin:** Reduced in PCOS; inversely correlates with insulin resistance.
- **Chemerin and Resistin:** Adipokines linked to metabolic inflammation.
- **Anti-Müllerian Hormone (AMH):** Correlates with follicle number and ovarian reserve.
- **MicroRNAs (miR-222, miR-93):** Potential non-invasive markers for metabolic and reproductive dysfunction [21].
- **Advanced ultrasound and MRI ovarian texture analysis** offer quantitative assessment of follicular distribution and stroma, improving diagnostic precision [8].

5. Epidemiology

Polycystic Ovary Syndrome is the most common endocrinopathy among women of reproductive age, but its prevalence varies widely depending on the diagnostic criteria, study design, and ethnicity [4,8,22]. Estimates using **NIH criteria** (the most restrictive) typically report **4–6%** prevalence, whereas **Rotterdam criteria**—which recognize broader phenotypes—yield estimates of **8–21%** worldwide [4,10,22].

5.1 Global Distribution

The global prevalence pattern of PCOS illustrates marked ethnic and geographic variability.

- **Europe and North America:** Approximately **6–10%** prevalence based on Rotterdam criteria.
- **East Asia (China, Japan):** **5–10%**, with lower obesity rates but comparable hyperandrogenism.
- **Middle East and Mediterranean regions:** Reported rates as high as **15–20%**, possibly reflecting both genetic and lifestyle contributors [10].
- **South Asia (India, Sri Lanka, Pakistan):** Prevalence up to **22–25%**, among the highest globally [25].

Socioeconomic transitions, sedentary lifestyle, and urbanization have contributed to increased metabolic expression of PCOS in these populations [9,25]. Women of South-Asian descent exhibit higher insulin resistance, abdominal adiposity, and dyslipidemia at lower BMI compared with Caucasians, underscoring ethnicity-specific metabolic vulnerability [10,25].

5.2 Indian Scenario

In India, PCOS has emerged as a **major reproductive-metabolic disorder** among young women. Urban prevalence estimates range from **18–22%**, while rural figures remain around **8–10%**—suggesting lifestyle and nutritional transitions as major determinants [25]. The **ICMR multicentric cohort (2022)** demonstrated that nearly **30%** of college-age women exhibited at least two PCOS criteria, with obesity and sedentary behavior as major risk factors.

Regional trends show higher prevalence in **Maharashtra, Karnataka, and Delhi**, where urban dietary habits, stress, and lack of physical activity exacerbate metabolic dysfunction.

Table 5. Prevalence of PCOS by Diagnostic Criteria and Population

Region	Diagnostic Criteria Used	Prevalence (%)	Distinct Observations
Europe	Rotterdam	6–8	Moderate obesity, classic phenotype predominance
China	Rotterdam	5–10	Lower BMI, higher lean PCOS cases
Middle East	AES	15–20	High androgen excess; familial clustering
India (Urban)	Rotterdam	18–22	High insulin resistance, early onset
India (Rural)	NIH	8–10	Underdiagnosis; less obesity, similar menstrual irregularity

5.3 Risk Factors Influencing Epidemiology

The expression of PCOS is influenced by both intrinsic and extrinsic factors:

1. **Genetic Predisposition:** Variants in androgen synthesis and insulin receptor genes [19].
2. **Obesity and Diet:** High glycemic-load diets and sedentary behavior potentiate insulin resistance [16].
3. **Endocrine-Disrupting Chemicals (EDCs):** Environmental exposure (BPA, phthalates) alters steroidogenesis [23,24].
4. **Urbanization and Psychosocial Stress:** Stress-mediated cortisol alterations may contribute to ovulatory dysfunction [25].
5. **Adolescent Onset:** Early menarche and excessive weight gain in adolescence predispose to lifelong hormonal imbalance [9].

6. Clinical Features

The clinical spectrum of PCOS extends across reproductive, dermatologic, metabolic, and psychological domains. Its presentation evolves over a woman's life cycle, reflecting dynamic hormonal and metabolic interactions [11,12].

6.1 Reproductive Manifestations

Anovulation is central to PCOS. Approximately **75–90%** of women with chronic anovulatory infertility meet diagnostic criteria for PCOS [11]. Menstrual disturbances include oligomenorrhea (cycles >35 days) or amenorrhea (>3 months), reflecting disrupted follicular maturation and absence of corpus luteum formation [17]. The unopposed estrogenic environment predisposes to **endometrial hyperplasia** and, in severe cases, **endometrial carcinoma** [18].

Ovulatory dysfunction stems from LH hyperpulsatility, reduced FSH, and granulosa-cell arrest, resulting in multiple immature follicles that fail to ovulate [11,18]. In adolescent PCOS, cycles may remain irregular for several years post-menarche due to persistent anovulation and androgen dominance [9].

6.2 Hyperandrogenic Symptoms

- Hirsutism affects 65–75% of women with PCOS and is evaluated using the modified Ferriman–Gallwey score, indicating the growth of androgen-sensitive terminal hair on the face and body [12,14].
- **Facial blemishes seborrhea** arise from increased sebaceous gland activity mediated by dihydrotestosterone (DHT).
- **Androgenic alopecia** presents as diffuse thinning over the vertex with frontal sparing, more common in phenotype A and B.

Table 6. Common Clinical Manifestations of PCOS

System	Symptoms / Signs	Underlying Mechanism
Reproductive	Oligomenorrhea, amenorrhea, infertility	Chronic anovulation, LH/FSH imbalance
Hyperandrogenic	Hirsutism, acne, alopecia	Elevated androgens (testosterone, DHT)
Metabolic	Weight gain, central obesity	Insulin resistance, altered adipokines
Psychological	Depression → low mood, persistent sadness, depressive symptoms	Neuroendocrine and body-image effects
Dermatologic	Acanthosis nigricans	Marker of hyperinsulinemia

6.3 Metabolic Abnormalities

PCOS is intricately linked to **metabolic syndrome**, with over **50%** of affected women meeting its diagnostic criteria by their 30s [16,20]. Insulin resistance, dyslipidemia, and central adiposity form the metabolic triad of PCOS.

- **Insulin resistance:** Observed in both lean and overweight women with PCOS, it plays a key role in increasing androgen levels and the risk of developing type 2 diabetes. [16].
- **Obesity:** Observed in 40–70% of PCOS patients, especially abdominal obesity, which aggravates insulin resistance and inflammatory stress [10,25].
- **Hypertension and CVD:** Endothelial dysfunction and oxidative stress predispose to hypertension and atherosclerosis, making PCOS a recognized cardiovascular risk condition [2,20].

6.4 Psychological and Neurobehavioral Impact

Beyond somatic symptoms, PCOS exerts significant **psychological morbidity**, often under-recognized in clinical practice [23,24]. Studies show up to **40–60%** of PCOS women experience **depression or anxiety**, attributed to hormonal imbalances, infertility stress, and body-image dissatisfaction.

Neuroimaging studies reveal altered functional connectivity in the amygdala and prefrontal cortex, suggesting a neuroendocrine basis for mood disturbances [23]. Chronic stress elevates cortisol, which exacerbates insulin resistance and weight gain, reinforcing the endocrine-psychological link [24].

6.5 Life-Stage Specific Presentation

Table 7. Age-specific clinical manifestations of PCOS.

Life Stage	Predominant Manifestations	Clinical Focus
Adolescence	Menstrual irregularity, acne, obesity, insulin resistance	Early diagnosis, lifestyle intervention [9]
Reproductive Age	Infertility, hirsutism, metabolic derangements	Ovulation induction, metabolic management
Perimenopause	Persistent obesity, dyslipidemia, diabetes, hypertension	Cardiovascular risk reduction, hormone evaluation
Post-menopause	Residual metabolic risk, endometrial changes	Cancer surveillance, continued lifestyle therapy

6.6 Phenotypic Correlation with Clinical Severity

Among the four Rotterdam phenotypes, **A (HA + OD + PCOM)** and **B (HA + OD)** represent “classic” PCOS with the most severe metabolic burden [4,12]. **C (HA + PCOM)** generally retains ovulation but shows dermatologic features; **D (OD + PCOM)** manifests mild hormonal imbalance yet comparable insulin resistance. **Phenotype A**, the most prevalent in Indian and Middle Eastern cohorts, exhibits the highest rates of obesity, insulin resistance, and metabolic syndrome [10,25].

6.7 Quality of Life and Social Implications

PCOS impacts not only physiological health but also psychosocial functioning. Studies demonstrate reduced **SF-36 quality-of-life scores**, particularly in domains of emotional well-being and social interaction [23,24].

Stigma surrounding hirsutism, infertility, and weight gain often leads to social withdrawal and low self-esteem. Integrating **psychological counseling and support groups** into PCOS care significantly improves treatment adherence and patient outcomes [3,23].

7. Management of PCOS

The management of Polycystic Ovary condition must be patient-specific, targeting dominant clinical domains — **reproductive, metabolic and psychological**. Given its chronic nature, the current paradigm emphasizes **multidisciplinary, long-term, and evidence-based care** combining **lifestyle modification, pharmacotherapy, and behavioral interventions** [3,8,13].

7.1 Lifestyle and Non-Pharmacological Management

Lifestyle modification forms the **cornerstone of PCOS therapy**. A reduction of **5–10% of body weight** can restore ovulatory cycles, reduce androgen levels, and improve insulin sensitivity [3,8].

Dietary interventions:

- **Calorie-restricted balanced diet (1200–1500 kcal/day)** with low glycemic index (GI) foods improves metabolic outcomes.
- **Mediterranean and polyphenols**, and fiber have demonstrated significant improvements in IR and lipid profiles [3,16].
- **Intermittent fasting and low-carbohydrate ketogenic diets** show emerging promise but require long-term validation.

Exercise:

Exercise enhances insulin sensitivity, promotes weight loss, and improves menstrual regularity [3,8].

Behavioral therapy:

Cognitive behavioral therapy (CBT) and mindfulness-based stress reduction address emotional distress and improve compliance with lifestyle programs [23].

Table 8. Non-pharmacologic strategies in PCOS management

Lifestyle Component	Recommended Approach	Physiological Benefit
Diet	Low-GI, calorie-controlled diet	Improves insulin sensitivity, reduces visceral fat
Exercise	Aerobic + resistance (150 min/week)	Reduces IR, improves ovulation
Sleep hygiene	7–9 hours/day, consistent timing	Normalizes cortisol and leptin balance
Stress management	Yoga, CBT, mindfulness	Reduces HPA-axis activation and cortisol levels

7.2 Pharmacologic Management

Pharmacotherapy is tailored according to patient goals — **cycle regulation, androgen reduction, fertility induction, or metabolic control** [3,8,13].

7.2.1 Hormonal Therapy

- **Mechanism:** Estrogen increases SHBG, lowering free testosterone; progestin suppresses LH-driven ovarian androgen production [13].
- **Preferred formulations:** Ethinylestradiol + drospirenone or desogestrel; drospirenone is favored for its anti-androgenic activity [3].

Potential drawbacks include weight gain and venous thromboembolism in obese patients; thus, risk stratification is essential [13].

7.2.2 Anti-Androgens

Spirolactone (50–100 mg/day) competes with DHT at androgen receptors, reducing hirsutism and acne; it is often co-prescribed with COCPs to prevent menstrual irregularity [14]. Other options include **flutamide** and **finasteride**, but their hepatotoxic and teratogenic risks limit long-term use [3].

7.2.3 Insulin Sensitizers

Metformin is widely used for metabolic and reproductive benefits:

- Decreases hepatic gluconeogenesis.
- Enhances peripheral glucose uptake.
- Reduces serum androgen concentrations and restores ovulatory cycles [16,20].

Typical dosage ranges from **1500–2000 mg/day**, titrated gradually to minimize gastrointestinal intolerance.

Myo-inositol and D-chiro-inositol, acting as insulin sensitizers and secondary messengers, are gaining popularity due to their favorable safety profile and comparable ovulation induction efficacy [3].

7.2.4 Ovulation Induction Therapy

For women desiring pregnancy, **ovulation induction** is key.

- **Letrozole (2.5–5 mg/day)** has surpassed **clomiphene citrate** as first-line therapy due to higher live birth rates and lower multiple pregnancy risk [8].
- **Gonadotropins (FSH, hMG)** are used for clomiphene- or letrozole-resistant cases, requiring careful monitoring to avoid ovarian hyperstimulation syndrome (OHSS).
- **Metformin combination therapy** enhances ovulatory response in insulin-resistant cases [3,8].

In refractory cases, **laparoscopic ovarian drilling (LOD)** remains a minimally invasive surgical alternative that restores ovulation in up to **80% of patients**, though recurrence may occur within 2–3 years [8].

7.2.5 Emerging Therapies

Recent research explores:

- **GLP-1 receptor agonists (liraglutide, semaglutide):** Promote weight loss and improve insulin sensitivity [3].
- **SGLT2 inhibitors:** Improve glycemic control and may reduce ovarian inflammation.
- **Selective estrogen receptor modulators (SERMs):** Optimize ovulatory response in resistant cases.
- **Targeted anti-inflammatory agents (resveratrol, omega-3 PUFAs):** Modulate cytokine imbalance [2,18].

7.3 Integrative and Alternative Therapies

Complementary medicine, including **Ayurveda, acupuncture, and herbal formulations**, has shown supportive roles in symptom management, though evidence quality remains variable.

- **Cinnamon extract** and **curcumin** exhibit insulin-sensitizing and anti-inflammatory properties.
 - **Yoga and pranayama** have demonstrated improvements in hormonal and psychological outcomes in Indian trials [25].
- However, integration must follow evidence-based validation to ensure safety and consistency [3].

8. Complications of PCOS

The long-term sequelae of PCOS extend beyond reproductive dysfunction, encompassing **metabolic, cardiovascular, and oncological risks**, as well as significant **psychological morbidity** [16,18,20].

8.1 Metabolic and Cardiovascular Complications

PCOS women have a **2–3 fold increased risk** of developing type 2 diabetes mellitus (T2DM), hypertension, and metabolic syndrome [20]. Endothelial dysfunction, low-grade inflammation, and dyslipidemia lead to premature atherosclerosis [2,16]. Visceral adiposity contributes to increased oxidative stress, vascular stiffness, and carotid intima-media thickness.

8.2 Reproductive and Oncological Complications

Prolonged anovulation and unopposed estrogen exposure increase the risk of **endometrial hyperplasia and carcinoma** [18]. Infertility, recurrent miscarriage, and pregnancy complications such as **gestational diabetes and preeclampsia** are significantly higher in untreated cases [8]. Additionally, polycystic ovaries exhibit altered oocyte microenvironment and mitochondrial dysfunction, leading to poor in vitro fertilization (IVF) outcomes [11].

8.3 Psychological and Social Complications

Depression, anxiety, body-image dissatisfaction, and decreased quality of life are recurrent findings in PCOS [23,24]. Untreated psychological stress worsens hormonal imbalance via activation of the hypothalamic–pituitary–adrenal (HPA) axis, establishing a vicious psychoneuroendocrine cycle [24]. Early counseling, social support, and peer networks are therefore integral to holistic PCOS management [23].

9. Future Perspectives

Emerging molecular and clinical insights are redefining PCOS as a **lifelong metabolic-endocrine disorder** rather than a purely gynecologic entity [18,21].

9.1 Precision Medicine

Advances in **genomics and epigenomics** enable phenotype–genotype correlation, identifying biomarkers for personalized therapy [19,21]. Single nucleotide polymorphisms (SNPs) in **DENND1A, THADA, and LHCGR** are potential molecular predictors of treatment response [19].

9.2 Epigenetic and Developmental Origins

The “**fetal programming hypothesis**” posits that in utero androgen exposure and maternal hyperinsulinemia induce persistent epigenetic alterations in daughters, perpetuating intergenerational PCOS risk [21]. DNA methylation and altered microRNA expression (miR-93, miR-222) are leading candidates for diagnostic and therapeutic targeting.

9.3 Emerging Therapeutic Frontiers

Novel research directions include:

- **Gene editing (CRISPR-Cas9)** to modulate androgen biosynthesis genes.
- **Artificial intelligence (AI)-driven diagnostics** utilizing ovarian imaging and hormonal profiling.
- **Gut microbiome modulation** through probiotics and synbiotics to reduce systemic inflammation and IR.
- **Stem-cell therapy** for ovarian regeneration and hormonal rebalancing [18,21].

10. Conclusion

Polycystic Ovary Syndrome is a complex, systemic, and long-term condition affecting reproductive, metabolic, and mental health. Current research highlights the need for timely diagnosis, tailored treatment, and a comprehensive, multidisciplinary approach to care. Integration of genomic, hormonal, and lifestyle data will pave the way toward **precision endocrinology** in PCOS care. Ultimately, addressing PCOS requires not only pharmacological innovation but also **public health strategies** promoting awareness, early screening, and lifestyle reform.

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