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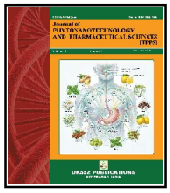

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Polyendocrine metabolic ovarian syndrome: A comprehensive review of emerging pathophysiological and clinical perspectives

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Abstract

Polyendocrine metabolic ovarian syndrome (PMOS), formerly termed polycystic ovary syndrome, is a complex, multifactorial endocrine-metabolic disorder affecting women throughout the reproductive lifespan. The emerging terminology "PMOS" better reflects the heterogeneous and multisystem nature of the disorder, extending beyond ovarian dysfunction to include metabolic, inflammatory, cardiovascular, and psychological abnormalities. Although, traditionally characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology, increasing evidence suggests that ovarian cysts are neither universally present nor central to disease pathogenesis. Instead, insulin resistance, compensatory hyperinsulinemia, obesity, dyslipidemia, chronic low-grade inflammation, oxidative stress, neuroendocrine imbalance, mitochondrial dysfunction, and gut microbiota dysbiosis are increasingly recognised as key contributors to disease progression and long-term morbidity. PMOS is associated with significant reproductive and metabolic complications, including infertility, menstrual irregularities, type 2 diabetes mellitus, metabolic syndrome, cardiovascular risk, and impaired quality of life. The disorder arises from a complex interaction among genetic susceptibility, epigenetic alterations, hypothalamic-pituitary-ovarian axis dysfunction, adipose tissue abnormalities, inflammatory mediators, and environmental factors. This review was conducted through a comprehensive literature search of PubMed, Scopus, NCBI, ScienceDirect, Embase, Google Scholar, and the Cochrane library, focusing on studies related to PCOS nomenclature, pathophysiology, and multisystem clinical manifestations. Furthermore, this review summarises recent advances in molecular mechanisms, diagnostic approaches, biomarkers, and therapeutic strategies while emphasising the scientific rationale and clinical significance of transitioning from PCOS to PMOS. The PMOS framework may facilitate improved disease recognition, holistic management, and personalised therapeutic interventions for affected women.

1. Introduction

Polyendocrine metabolic ovarian syndrome (PMOS), formerly known as polycystic ovary syndrome (PCOS), is a highly heritable, complex multisystem disorder affecting nearly one in eight women of reproductive age worldwide. It represents the most common endocrine-metabolic condition in this population and is a major cause of anovulatory infertility, obesity, and type 2 diabetes mellitus, with considerable long-term metabolic and reproductive consequences. The syndrome is characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, obesity, and chronic low-grade inflammation, reflecting its multifactorial and polygenic nature. Despite its high prevalence and significant disease burden, PMOS remains underdiagnosed and frequently recognised late in clinical practice, with affected women often receiving suboptimal or delayed care. Historically considered primarily an ovarian disorder, accumulating evidence now places PMOS as a systemic endocrine-metabolic condition involving dysregulated insulin signaling, neuroendocrine dysfunction, metabolic derangements, and increased cardiovascular risk, underscoring its complex pathophysiology and broad clinical impact (Chang and Dunaif, 2021; Teede *et al.,* 2026).

The 2026 international consensus reported in The Lancet officially endorsed the terminology PMOS instead of PCOS, emphasizing the disorder's complex systemic pathophysiology rather than isolated ovarian pathology. The new designation reflects the integration of endocrine imbalance, metabolic abnormalities, and ovarian dysfunction while correcting the inadequacies of the earlier terminology. PMOS is associated with diverse clinical manifestations, including infertility, menstrual irregularities, hirsutism, metabolic syndrome, dyslipidemia, cardiovascular complications, and mental health disturbances (Teede *et al.,* 2026). Despite continued reliance on the Rotterdam diagnostic criteria, increasing recognition of the metabolic and inflammatory dimensions of PMOS has highlighted the need for improved diagnostic and therapeutic approaches. Therefore, this review aims to comprehensively summarise current advances in the pathophysiology, endocrine-metabolic interactions, clinical manifestations, diagnosis, and emerging therapeutic strategies of PMOS, with emphasis on improving long-term reproductive and metabolic outcomes.

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2. Riview methodology

This review was conducted to study the historical evolution and proposed reclassification of PCOS into PMOS. An extensive literature search was performed using PubMed, Google Scholar, Scopus, NCBI, ScienceDirect, Embase and the Cochrane library, covering all available publications up to the present.

Search terms included "Polycystic ovary syndrome," "PCOS pathophysiology," "hyperandrogenism," "insulin resistance," "metabolic syndrome," "ovarian dysfunction," "cardiovascular risk," "PCOS and obesity," "PCOS and diabetes," and "renaming PCOS," "polyendocrine metabolic ovarian syndrome" among others.

Original research articles, systematic and narrative reviews, and major guideline or consensus documents were included, particularly those addressing PCOS nomenclature, pathophysiology, and its metabolic reproductive implications. Priority was given to studies highlighting key advances in understanding PCOS as a multisystem endocrine-metabolic disorder.

Inclusion criteria comprised peer-reviewed English publications with clinical, epidemiological, genetic, or mechanistic relevance to PCOS or its proposed alternative nomenclature. Non-human studies, non-relevant reports, and non-peer-reviewed literature were excluded. High-impact studies contributing to the evolving concept of PCOS redefinition were prioritised to ensure a robust evidence base reflecting its endocrine, metabolic, reproductive, and systemic complexity.

3. Historical perspective and evolution from PCOS to PMOS

Polycystic ovary syndrome has evolved from being considered primarily an ovarian reproductive disorder to a complex multisystem endocrine-metabolic syndrome. This evolving understanding has recently led to the adoption of the term PMOS, emphasising its systemic endocrine and metabolic involvement.

3.1 Early historical foundations

PCOS can be historically traced to observations documented in ancient Greek medicine. In historical medical texts, *Diseases of Women,* Hippocrates (460-377 BC) reported women exhibiting infrequent menstruation, infertility, a strong body habitus, and masculine features, manifestations now recognised as indicative of hyperandrogenism and ovulatory dysfunction. These early clinical accounts suggest that PCOS-like features were identified long before the disorder was formally characterised in contemporary medicine (Hanson, 1975). Earlier historical evidence also suggests that one of the first descriptions may be attributed to Vallisneri in 1721, who reported the ovaries of an infertile woman as enlarged, smooth, and resembling a pigeon's egg, indicating possible early recognition of polycystic ovarian morphology (Szydlarska *et al.,* 2017).

In 1844, the French physician Achille Chereau documented enlarged ovaries containing multiple peripheral cyst-like structures with smooth and shiny surfaces in his book on the diseases of the ovaries. His observations represented one of the earliest anatomical descriptions of polycystic ovarian morphology (Chereau, 1844). In 1879, Lawson Tait advocated surgical management through bilateral oophorectomy for cystic ovarian disease, later followed by partial ovarian resection approaches, reflecting early therapeutic attempts based on severe ovarian pathology. By 1902, von Kahlden provided one of the earliest systematic pathological reviews of these ovarian conditions, linking structural abnormalities with clinical reproductive dysfunction (Taieb *et al.,* 2024).

A major milestone occurred in 1935 when Irving F. Stein Sr. and Michael L. Leventhal reported seven women presenting with amenorrhea, hirsutism, infertility, and bilaterally enlarged polycystic ovaries. This condition became known as the "Stein-Leventhal syndrome," which later evolved into the term "Polycystic ovary syndrome". For several decades, the syndrome was viewed predominantly as a gynecological disorder centred on ovarian morphology and reproductive dysfunction (Stein and Leventhal, 1935).

3.2 Evolution of endocrine and metabolic understanding

From the 1930s onward, PCOS research focused predominantly on endocrine abnormalities, particularly hyperandrogenism, altered gonadotropin secretion, and ovarian dysfunction. By the 1950s, studies demonstrated elevated luteinizing hormone (LH) levels in women with bilateral cystic ovaries, and concomitant increases in testosterone were identified as key diagnostic markers. Yen and colleagues subsequently proposed hyperandrogenism as a central pathogenic feature, while Swanson and others emphasised polycystic ovarian morphology as a diagnostic cornerstone. In the 1980s, the concept of an altered LH: FSH ratio gained prominence as an endocrine hallmark of the syndrome (Yen *et al.,* 1970; Swanson *et al.,* 1981; Shoupe *et al.,* 1983). By the 1980s and 1990s, emerging evidence linked PCOS with insulin resistance, hyperinsulinemia, obesity, dyslipidemia, impaired glucose tolerance, and type 2 diabetes mellitus, leading to its recognition as a multisystem endocrine-metabolic disorder rather than solely a reproductive condition (Azziz, 2014; Meczekalski *et al.,* 2023). In 1985, Franks and colleagues further refined diagnostic understanding by proposing a threshold of e"12 follicles per ovary for ultrasonographic diagnosis of polycystic ovarian morphology, marking a shift toward imaging-based criteria.

3.3 Rotterdam criteria and recognition of phenotypic heterogeneity

A major paradigm shift occurred in 2003 when the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine established the Rotterdam diagnostic criteria. According to these criteria, PCOS could be diagnosed when at least two of the following were present:

- Ovulatory dysfunction.
- Clinical and/or biochemical hyperandrogenism.
- Polycystic ovarian morphology on ultrasonography or elevated Antimüllerian hormone (AMH).

The Rotterdam criteria broadened the diagnostic spectrum and highlighted the disorder's marked phenotypic heterogeneity. Importantly, many women exhibited endocrine and metabolic abnormalities despite lacking classical polycystic ovarian morphology. Consequently, increasing attention was directed toward metabolic dysfunction, insulin resistance, cardiovascular risk, chronic inflammation, oxidative stress, and psychological disturbances associated with PCOS**.** In 1990, the NIH consensus first formally defined PCOS using a combination of hyperandrogenism, oligo/anovulation, and exclusion of other etiologies, laying the foundation for modern diagnostic frameworks **(***Zawadzki et al., 1992).*

In 2006, the Androgen Excess Society emphasised hyperandrogenism as an essential diagnostic criterion, aiming to distinguish metabolically and clinically significant phenotypes from milder forms (Azziz *et al.,* 2006). Subsequent international evidence-based guidelines published in 2018 and updated in 2023 further reinforced the disorder's multisystem nature and emphasised the importance of long-term metabolic and psychological management (Chang and Dunaif, 2021; Forslund *et al.,* 2024). These evolving frameworks increasingly recognise PCOS as a spectrum disorder with distinct reproductive, metabolic, and psychological phenotypes rather than a single homogeneous condition.

3.4 Limitations and criticism of the term "PCOS"

Despite advances in understanding, the terminology "polycystic ovary syndrome" became increasingly controversial. The term was criticised for several reasons. First, many affected individuals do not exhibit polycystic ovarian morphology, while polycystic-appearing ovaries may also occur in healthy women. Second, the so-called "cysts" are not true pathological cysts but rather immature follicles arrested in development due to hormonal dysregulation and hyperandrogenism. Third, the ovarian-centric terminology obscured the central contributions of neuroendocrine dysfunction, insulin resistance, inflammation, and metabolic abnormalities to disease pathogenesis. Furthermore, the name contributed to misconceptions among both clinicians and patients, often leading to under-recognition of metabolic complications and delayed diagnosis in individuals lacking classical ovarian findings. As understanding of the syndrome expanded, researchers increasingly argued that the term PCOS inadequately represented the true multisystem nature of the condition.

3.5 Transition from PCOS to PMOS

The transition from PCOS to PMOS represents a major paradigm shift in understanding this complex multisystem disorder. Traditionally, PCOS was considered primarily a gynaecological condition characterised by menstrual irregularities, hyperandrogenism, infertility, and polycystic ovarian morphology. However, advancing evidence demonstrated that the disorder extends beyond ovarian dysfunction and involves significant endocrine, metabolic, neuroendocrine, reproductive, and psychological abnormalities.

The renaming was driven by the scientific inaccuracy of the term "polycystic ovary syndrome." The word "polycystic" incorrectly suggests pathological ovarian cysts, whereas the ovaries actually contain arrested immature follicles. Moreover, the ovarian-focused terminology failed to reflect the central roles of insulin resistance, hyperinsulinemia, androgen excess, chronic inflammation, adipokine imbalance, and metabolic dysfunction, which affect most affected individuals. The reproductive emphasis of PCOS also contributed to stigma, delayed diagnosis, fragmented care, and poor patient awareness.

To address these concerns, an international consensus initiative conducted during 2025-2026 involved more than 14,000 participants, including patients, clinicians, researchers, and advocacy organizations worldwide. Through Delphi surveys, workshops, and implementation analyses, the consensus terminology PMOS was established. "Polyendocrine" reflects the multiple endocrine disturbances underlying the disorder, "metabolic" acknowledges its cardiometabolic implications, and "ovarian" represents ovarian dysfunction without implying cyst formation (Taieb *et al.,* 2024).

A global implementation strategy, including integration into clinical guidelines, ICD disease classification systems, electronic health records, and educational resources, has been initiated with a planned three-year transition period. The updated terminology is also planned for inclusion in the 2028 International Evidence-Based Guidelines, which are utilised across 195 countries. Collectively, the transition from PCOS to PMOS signifies a paradigm shift from observing the disorder as an isolated ovarian condition to recognising it as a lifelong polyendocrine and metabolic syndrome with broad systemic implications (Teede *et al.,* 2023).

4. Pathophysiology of PMOS

The pathophysiology of PMOS is highly complex and remains incompletely understood. Current evidence suggests that the disorder arises from bidirectional interactions between metabolic dysfunction and reproductive endocrine abnormalities, superimposed on a background of genetic susceptibility, chronic low-grade inflammation, oxidative stress, and environmental influences. Central to disease progression are insulin resistance, compensatory hyperinsulinemia, androgen excess, hypothalamic-pituitary-ovarian axis dysregulation, and altered neuroendocrine signaling (Figure 1).

4.1 Insulin resistance: The central pathophysiological mechanism

Insulin resistance is considered one of the most important pathogenic mechanisms underlying PMOS and is observed in approximately 65-70% of affected individuals. In this condition, peripheral tissues such as skeletal muscle and adipose tissue exhibit reduced insulin responsiveness, leading to compensatory hyperinsulinemia. Elevated insulin concentrations play a pivotal role in amplifying ovarian androgen production and exacerbating reproductive dysfunction. Hyperinsulinemia stimulates ovarian theca cells to increase testosterone synthesis while simultaneously suppressing hepatic production of sex hormone-binding globulin (SHBG). Reduced SHBG levels increase circulating free testosterone concentrations, thereby intensifying clinical manifestations of hyperandrogenism, including hirsutism, acne, androgenic alopecia, menstrual irregularities, and anovulation. Importantly, insulin resistance is not restricted to obese individuals and may also occur in lean women with PMOS, indicating that metabolic dysfunction can develop independently of body weight (Malini and Roy, 2021; Xu and Qiao, 2022).

A vicious cycle exists between insulin resistance and androgen excess, in which hyperinsulinemia promotes androgen production, while hyperandrogenism further aggravates insulin resistance. Consequently, women with PMOS exhibit substantially increased risks of impaired glucose tolerance, prediabetes, type 2 diabetes mellitus, metabolic syndrome, and long-term cardiovascular complications. Notably, these metabolic disturbances frequently persist even after menopause (Szkodziak *et al.,* 2025; Xu and Qiao, 2022).

4.2 Hyperandrogenism and androgen excess

Hyperandrogenism represents the hallmark feature of PMOS and is primarily responsible for many of its reproductive and dermatological manifestations. Excess androgen production originates predominantly from ovarian theca cells under the influence of LH and hyperinsulinemia. Increased adrenal androgen secretion, particularly dehydroepiandrosterone sulfate (DHEA-S), may also contribute to androgen excess in certain individuals. Elevated androgen levels disrupt

normal follicular maturation and ovulation, leading to menstrual irregularities, infertility, and arrested follicular development. Clinically, hyperandrogenism manifests as hirsutism, acne, seborrhea, and androgenic alopecia due to androgen-mediated stimulation of sebaceous glands and hair follicles. The characteristic "polycystic" ovarian appearance observed on ultrasonography actually reflects the accumulation of immature antral follicles arrested in development rather than true pathological cysts (Wang *et al.,* 2023; Xu and Qiao, 2022).

4.3 Hypothalamic-pituitary ovarian axis dysregulation

Neuroendocrine abnormalities involving the hypothalamic -pituitary-ovarian axis play a critical role in PMOS pathogenesis. Increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus results in preferential elevation of LH secretion relative to follicle-stimulating hormone (FSH). The altered LH: FSH ratio promotes excessive stimulation of ovarian theca cells and enhances androgen synthesis. Relative FSH deficiency impairs granulosa cell function and follicular maturation, preventing dominant follicle selection and ovulation. Consequently, multiple immature follicles accumulate within the ovaries, leading to chronic anovulation and infertility. These endocrine disturbances contribute significantly to menstrual dysfunction and impaired reproductive competence in PMOS (Mikhael *et al.,* 2019).

4.4 Neuroendocrine and hormonal disturbances

PMOS is associated with widespread hormonal dysregulation involving insulin, androgens, gonadotropins, cortisol, and anti-Müllerian hormone. Hyperinsulinemia and elevated testosterone levels represent central endocrine abnormalities driving both metabolic and reproductive dysfunction. Increased LH secretion further amplifies ovarian androgen production, whereas relatively low or normal FSH concentrations impair follicular development. Elevated AMH levels are frequently observed due to increased numbers of small antral follicles and may further inhibit follicular recruitment and maturation. Additionally, altered hypothalamic-pituitary-adrenal axis activity and cortisol dysregulation may contribute to stress-related metabolic abnormalities and chronic inflammatory responses (Ran *et al.,* 2021).

4.5 Chronic low-grade inflammation and oxidative stress

Chronic low-grade inflammation is increasingly recognised as an important contributor to PMOS pathogenesis. Women with PMOS often exhibit elevated circulating levels of inflammatory mediators, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α). These inflammatory pathways contribute to insulin resistance, endothelial dysfunction, and cardiovascular risk. Oxidative stress further aggravates metabolic and reproductive dysfunction by impairing insulin signaling, disrupting ovarian steroidogenesis, and adversely affecting oocyte quality. Persistent inflammation and oxidative stress are thus believed to contribute to the long-term metabolic and reproductive complications associated with PMOS (Bansal *et al.,* 2025).

4.6 Genetic and epigenetic influences

PMOS demonstrates a strong genetic predisposition, supported by familial clustering and heritability studies. Multiple susceptibility genes associated with insulin signaling, androgen biosynthesis, gonadotropin action, inflammation, and energy metabolism have been implicated in disease development. Genes involved in ovarian and adrenal steroidogenesis, including CYP11A, CYP17, CYP19, and CYP21, have been associated with altered androgen biosynthesis and steroid hormone metabolism in PMOS. Variations in the androgen receptor (AR) and SHBG genes further contribute to hyperandrogenism and endocrine dysregulation. In addition, abnormalities in genes regulating gonadotropin action and follicular development, such as LH, anti-Müllerian hormone (AMH), and follicle-stimulating hormone receptor (FSHR), have been implicated in ovulatory dysfunction and infertility. Insulin-related genes, including INS, INSR, IRS-1, IRS-2, CAPN10, and obesity-associated genes such as FTO, also contribute to insulin resistance, metabolic disturbances, and increased susceptibility to PMOS. However, no single gene fully explains the syndrome, highlighting its polygenic nature (Khan *et al.,* 2019).

Epigenetic mechanisms also appear to play an important role in disease programming. Prenatal exposure to androgen excess, maternal metabolic dysfunction, and environmental factors such as diet, stress, and endocrine-disrupting chemicals may induce epigenetic modifications that predispose individuals to PMOS later in life. Experimental and clinical studies suggest that fetal androgen excess may induce persistent epigenetic alterations, including abnormal DNA methylation and CpG island modifications in genes involved in steroidogenesis, insulin signaling, and ovarian function. Altered methylation patterns in genes such as PPARG1 and NCOR1 have been associated with hyperandrogenism-induced ovarian dysfunction, supporting the concept of fetal programming and transgenerational inheritance of metabolic and reproductive abnormalities in PMOS. These epigenetic alterations may contribute to transgenerational transmission of metabolic and reproductive abnormalities (Khan *et al.,* 2019).

4.7 Metabolic-reproductive axis dysfunction in PMOS

The reproductive and metabolic systems are intricately interconnected, and PMOS represents a disruption of this physiological equilibrium. Reproductive processes, including folliculogenesis, ovulation, and pregnancy, are highly energy-dependent and require optimal metabolic homeostasis. Metabolic disturbances such as insulin resistance, obesity, and altered energy balance impair ovarian function and disrupt sex hormone regulation, thereby compromising reproductive competence. Conversely, reproductive endocrine abnormalities, particularly hyperandrogenism, further aggravate insulin resistance and metabolic dysfunction through complex neuroendocrine and metabolic pathways. This bidirectional interaction between the reproductive and metabolic axes constitutes a central mechanism in PMOS pathophysiology and contributes to the coexistence of reproductive, metabolic, inflammatory, and psychological manifestations associated with the syndrome (Teede *et al.,* 2026).

4.8 Dyslipidemia and cardiovascular risk

Women with PMOS commonly exhibit dyslipidemia characterised by elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, reduced high-density lipoprotein (HDL) cholesterol, and increased concentrations of small dense LDL particles. These abnormalities, combined with insulin resistance, obesity, chronic inflammation, and endothelial dysfunction, contribute to an increased risk of hypertension, atherosclerosis, and cardiovascular disease.

Importantly, cardiovascular risk may persist independently of obesity, emphasising that PMOS itself is an independent cardiometabolic risk factor requiring long-term monitoring and management (Kim and Choi, 2013; Teede *et al.,* 2026).

4.9 Adrenal dysfunction and ovarian abnormalities

PMOS involves dysfunction of both ovarian and adrenal endocrine pathways. Ovarian abnormalities include theca cell hyperplasia, excessive androgen synthesis, elevated AMH levels, and arrested follicular maturation. Simultaneously, adrenal dysfunction may contribute to increased production of adrenal androgens and altered cortisol metabolism. Enhanced adrenal responsiveness to adrenocorticotropic hormone (ACTH) has also been reported in subsets of affected individuals (Teede *et al.,* 2026).

4.10 Gut microbiome dysbiosis

Emerging evidence suggests that alterations in gut microbiota composition may contribute to PMOS pathogenesis. Gut microbiome dysbiosis has been associated with insulin resistance, systemic inflammation, altered energy metabolism, and abnormal steroid hormone metabolism. Although, the precise mechanisms remain under investigation, the gut microbiome is increasingly recognised as a potential contributor to the endocrine and metabolic disturbances observed in PMOS (Du *et al.,* 2026).

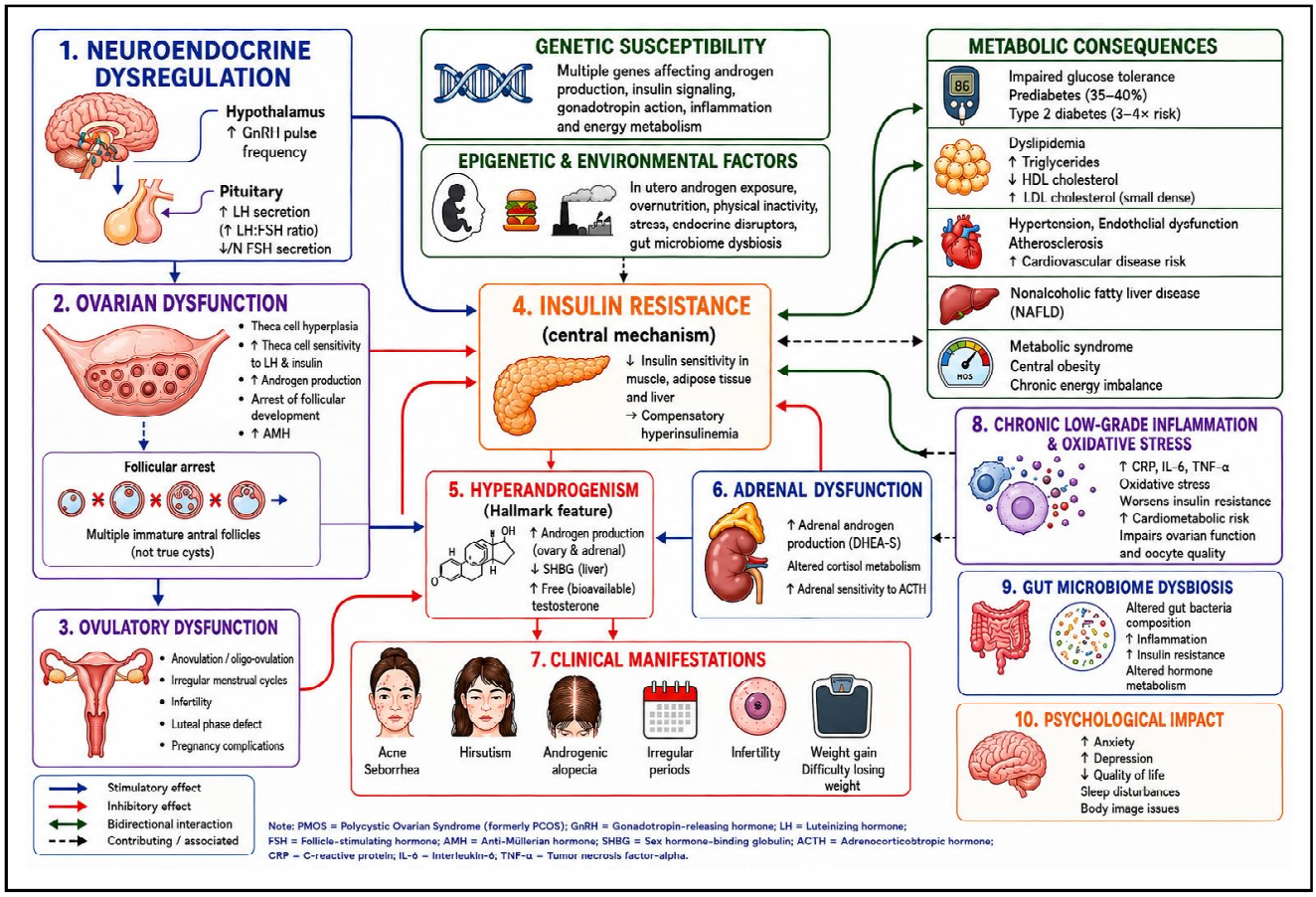

Figure 1: Schematic representation of the interconnected pathophysiological mechanisms and clinical manifestations of PMOS, highlighting the roles of insulin resistance, hyperandrogenism, neuroendocrine dysfunction, metabolic abnormalities, inflammation, and genetic/environmental factors.

4.11 Psychological disturbances

Women with PMOS commonly experience psychological disturbances, including depression, anxiety, stress, and reduced quality of life. These disorders arise from complex interactions among hormonal imbalance, insulin resistance, obesity, and genetic susceptibility. Elevated androgen levels and adverse maternal-fetal hormonal environments may also influence brain development and emotional regulation. Additionally, body image concerns, infertility, and chronic metabolic complications further contribute to emotional distress and psychiatric symptoms (Stener-Victorin *et al.,* 2024).

5. Diagnostic criteria of PMOS

Several diagnostic criteria have been established by different scientific organisations to address the multifactorial pathophysiology and marked phenotypic heterogeneity of PMOS. These diagnostic frameworks primarily incorporate hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology as the principal diagnostic features. Among them, the Rotterdam criteria are the most widely accepted owing to their broader inclusion of clinical phenotypes. The major diagnostic criteria currently used for the diagnosis of PMOS are summarised in Table 1(Huffman *et al.,* 2023).

Table 1: Diagnostic criteria for PMOS

Diagnostic criteria	Year	Required features for diagnosis	Key characteristics
NIH criteria	1990	1. Hyperandrogenism and/or hyperandrogenemia 2. Oligo/anovulation	Most stringent criteria; primarily focuses on reproductive and androgen excess abnormalities
Rotterdam criteria	2003	Presence of any two of the following: 1. Hyperandrogenism and/or hyperandrogenemia 2. Oligo/anovulation 3. Polycystic ovarian morphology (PCOM)	Most widely used criteria; recognises broader phenotypic heterogeneity
Androgen excess and PMOS Society (AE-PMOS) criteria	2006	1. Hyperandrogenism and/or hyperandrogenemia 2. Oligo/anovulation or Polycystic ovarian morphology	Emphasises androgen excess as the central pathogenic feature
NIH evidence-based workshop recommendation	2012	Endorsed Rotterdam criteria with phenotype specification	Recommended phenotypic classification for improved clinical and research stratification

6. Biomarkers associated with PMOS

Biomarkers play a crucial role in understanding the multifactorial pathophysiology of PMOS. These biomarkers reflect disturbances in endocrine, metabolic, inflammatory, oxidative and genetic pathways, thereby aiding in early diagnosis, prognosis, disease monitoring, and development of personalised therapeutic strategies. Table 2 summarises the major biomarker categories and their associated biomarkers implicated in PMOS.

Table 2: Major biomarkers associated with PMOS (Singh *et al.*, 2025; Huffman *et al.*, 2023)

Biomarker category	Biomarker	Key findings in PMOS	Clinical significance
Hormonal biomarkers	Hyperandrogenism (Testosterone, DHT, A4, DHEA-S, DHEA)	Elevated androgen levels are observed in 60-80% of women with PMOS	Diagnostic marker for androgen excess and reproductive dysfunction
	FSH: LH ratio	Increased LH: FSH ratio (>2:1) is commonly seen	Indicates HPO-axis dysregulation and chronic anovulation
	Anti-Müllerian hormone (AMH)	AMH levels are 2-4 times higher in women with PMOS	A marker of follicular dysfunction and ovarian reserve
	Sex hormone-binding globulin (SHBG)	Reduced serum SHBG levels	A marker of hyperandrogenism and insulin resistance
Hormonal/metabolic biomarkers	Insulin and insulin resistance (HOMA-IR)	Elevated fasting insulin and insulin resistance are present in 50-70% of patients	Indicates metabolic dysfunction and predicts diabetes risk
Inflammatory biomarkers	C-reactive protein (CRP)	CRP levels significantly elevated in PMOS	A marker of chronic low-grade inflammation
	Interleukin-18 (IL-18)	Increased IL-18 levels are associated with insulin resistance	Reflects inflammatory and cardiovascular risk
	Monocyte chemoattractant protein-1 (MCP-1)	Elevated MCP-1 levels in PMOS	Linked to obesity, inflammation, and atherosclerosis
	Macrophage inflammatory protein-1α (MIP-1α)	Overexpressed in PMOS patients	Indicates a chronic inflammatory state
Oxidative stress biomarkers	Malondialdehyde (MDA)	Circulating MDA increased by ~ 47% in PMOS	Reliable indicator of lipid peroxidation and oxidative stress
	Nitric oxide (NO)	Elevated NO levels in women with PMOS	Reflects oxidative stress and metabolic abnormalities

	Xanthine oxidase (XO)	Increased XO activity and an inverse correlation between NO levels and insulin resistance indices have been observed in PMOS	Associated with ROS generation and metabolic inflammation
	Superoxide dismutase (SOD)	Altered SOD activity reported	Indicates a disturbed antioxidant defense system
Metabolic biomarkers	Dyslipidemia (TG, HDL-C)	Increased triglycerides and reduced HDL-C	Predicts cardiovascular risk
	Apolipoprotein B48	Elevated ApoB48 levels in adolescent PMOS	Marker of atherogenic risk
Genetic/epigenetic biomarkers	MicroRNAs (miR-18b, miR-146a, miR-135a)	Dysregulated expression in follicular fluid	Affect steroidogenesis and menstrual abnormalities
	Long non-coding RNAs (lnc RNA SRA, CTBP1-AS)	Elevated expression in PMOS	Associated with androgen receptor activity
Anthropometric biomarkers	Body mass index (BMI)	Commonly used first-level measure of adiposity; limited accuracy for individual body fat estimation	Screening tool for obesity and metabolic risk assessment
	Waist circumference (WC)	Reflects central adiposity and visceral fat accumulation	Indicator of cardiometabolic risk
	Neck circumference	Positively correlated with BMI, waist-to-hip ratio, and insulin resistance	Marker of decreased insulin sensitivity and androgen excess
	Waist-to-hip ratio (WHR)	Associated with abdominal obesity and insulin resistance	Predictor of metabolic and cardiovascular complications
Anthropometric/ metabolic biomarkers	Visceral adipose index (VAI)	Positively correlated with bioavailable androgens, fasting glucose, TG, and HOMA-IR; negatively correlated with HDL-cholesterol	Predictor of insulin resistance and metabolic syndrome across PMOS phenotypes
	Lipid accumulation product (LAP)	Elevated in women with PMOS; correlated with insulin resistance and hyperandrogenism	Superior predictor of metabolic syndrome and insulin resistance

7. Therapeutic strategies for PMOS

The therapeutic management of PMOS requires a comprehensive and individualised approach targeting metabolic dysfunction, hyperandrogenism, reproductive abnormalities, psychological disturbances, and long-term cardiometabolic risk. Current therapeutic strategies combine lifestyle modification, pharmacological interventions, reproductive therapies, and adjunctive approaches to improve metabolic, endocrine, and reproductive outcomes.

7.1 Lifestyle modification

Lifestyle intervention remains the cornerstone of PMOS management, particularly in individuals with overweight or obesity. Modest weight reduction of approximately 5-10% significantly improves insulin resistance, ovulatory dysfunction, menstrual irregularities, hyperandrogenism, and cardiometabolic risk factors. Dietary interventions emphasising caloric restriction, balanced macronutrient intake, and reduction of refined carbohydrates are beneficial; however, no specific dietary composition has demonstrated superior efficacy. Regular physical activity, particularly at least 150 min of moderate-to-vigorous exercise weekly, improves metabolic health and body composition. Behavioural and psychological counselling further enhances adherence and quality of life (Stener-Victorin *et al.,* 2024; Kataoka *et al.,* 2017; Lim *et al.,* 2019).

7.2 Combined oral contraceptives

Combined oral contraceptives (COCs) are regarded as the first-line pharmacological treatment for women with PMOS who are not seeking conception. COCs effectively regulate menstrual cyclicity and ameliorate the clinical manifestations of hyperandrogenism, including hirsutism and acne, primarily by suppressing LH-mediated ovarian androgen synthesis and enhancing sex hormone-binding globulin production, thereby reducing circulating free androgen levels. Low-dose ethinyl estradiol formulations (20-30 μg) are generally preferred to minimise metabolic and thromboembolic adverse effects. Progestins with anti-androgenic properties, such as cyproterone acetate, may provide superior androgen suppression; however, their use is typically reserved for second-line therapy due to the increased risk of venous thromboembolism (Melin *et al.,* 2024; Teede *et al.,* 2018).

7.3 Insulin sensitisers and metabolic therapies

Metformin remains the most extensively used insulin-sensitising agent in PMOS. It reduces hepatic gluconeogenesis, improves peripheral insulin sensitivity, decreases circulating insulin and

androgen levels, and restores menstrual regularity and ovulatory function. Metformin also improves lipid profile and cardiometabolic parameters (Wang *et al.,* 2017).

Novel antidiabetic therapies are increasingly being explored in PMOS. Dipeptidyl peptidase-4 (DPP-4) inhibitors improve insulin sensitivity and glucose metabolism primarily through PI3K/AKT and GLP-1/cAMP signaling pathways, thereby enhancing insulin secretion and reducing metabolic dysfunction (Ghafari *et al.,* 2025). Similarly, sodium-glucose cotransporter-2 (SGLT-2) inhibitors reduce renal glucose reabsorption and indirectly activate AMPK signaling, leading to improved insulin sensitivity, enhanced fatty acid oxidation, reduced oxidative stress, and attenuation of inflammatory pathways such as NF-êB and mTOR signaling (Marinkovic-Radosevic *et al.,* 2021). Glucagon-like peptide-1 (GLP-1) receptor agonists, particularly liraglutide and semaglutide, have emerged as promising therapeutic agents for obesity-associated PMOS. These agents activate GLP-1 receptor-mediated cAMP/PKA signaling pathways, resulting in enhanced glucose-dependent insulin secretion, suppression of glucagon release, delayed gastric emptying, and increased satiety (Szczesnowicz *et al.,* 2023). Clinical studies have demonstrated significant improvements in body weight, insulin resistance, menstrual regularity, and hyperandrogenic manifestations. Furthermore, combination therapy with metformin appears to provide superior metabolic and reproductive benefits compared with monotherapy.

7.4 Ovulation induction and fertility management

Fertility management in PMOS should commence with preconception counselling and optimisation of metabolic and reproductive health. Lifestyle modification and weight reduction have been shown to improve ovulatory function, enhance spontaneous conception rates, and increase the efficacy of fertility treatments. Letrozole is currently regarded as the first-line pharmacological agent for ovulation induction in women with anovulatory infertility associated with PMOS. Clomiphene citrate induces ovulation by antagonising hypothalamic estrogen receptors, thereby increasing gonadotropin-releasing hormone secretion, stimulating follicle-stimulating hormone production, and promoting follicular maturation. In women who are resistant to clomiphene citrate, combination therapy with metformin may improve ovulatory and pregnancy outcomes (Palomba *et al.,* 2014; Legro and Zhang, 2014). Second-line therapeutic approaches include low-dose gonadotropin therapy, laparoscopic ovarian drilling, and assisted reproductive technologies such as *in vitro* fertilization (IVF). Contemporary IVF protocols incorporating elective single embryo transfer and freeze-all strategies have substantially reduced the risk of ovarian hyperstimulation syndrome and multiple pregnancies while improving reproductive outcomes in women with PMOS (Stener-Victorin *et al.,* 2024).

7.5 Antiandrogen therapy

Spironolactone is widely used for the management of hirsutism and acne because of its androgen receptor antagonistic effects. Other antiandrogens include Finasteride and Cyproterone acetate. These agents should be prescribed cautiously owing to potential teratogenicity and menstrual irregularities (Rothenberg *et al.,* 2018).

7.6 Bariatric surgery

Bariatric surgery is recommended in selected women with severe obesity (BMI >35 kg/m²) and refractory metabolic dysfunction. Surgical intervention produces substantial and sustained improvements in weight reduction, insulin resistance, lipid profile, androgen excess, ovulatory dysfunction, and fertility outcomes. Significant improvement or complete resolution of hirsutism has also been reported following bariatric surgery (Stener-Victorin *et al.,* 2024).

7.7 Nutraceuticals and complementary therapies

Myo-inositol and D-chiro-inositol improve insulin sensitivity, menstrual cyclicity, and ovulatory function through modulation of insulin and follicle-stimulating hormone signaling pathways. Vitamin D supplementation and omega-3 fatty acids demonstrate beneficial effects on inflammatory markers, insulin resistance, hormonal balance, and mental health (Dason *et al.,* 2024; Saidaiah *et al.,* 2024). Natural compounds such as quercetin exhibit antioxidant and anti-androgenic effects through modulation of the PI3K/Akt signaling pathway and inhibition of CYP17A1-mediated androgen synthesis. Cinnamon supplementation may improve oxidative stress and insulin sensitivity by regulating PI3K and NF-κB signaling pathways (Ghafari *et al.,* 2025).

Acupuncture has also shown potential benefits in restoring neuroendocrine balance by modulating GnRH secretion, sympathetic activity, and PI3K/AKT and MAPK signaling pathways, thereby improving ovulatory function and insulin sensitivity (Zheng *et al.,* 2021).

7.8 Psychological and long-term management

Psychological disturbances, including anxiety, depression, eating disorders, and body image dissatisfaction, are highly prevalent in PMOS. Routine psychological screening and cognitive behavioural therapy are, therefore, essential components of management. Long-term monitoring of glucose tolerance, lipid profile, blood pressure, endometrial health, and reproductive function is recommended to prevent future cardiometabolic and reproductive complications. Overall, therapeutic strategies in PMOS should emphasise individualised, multidisciplinary, and evidence-based interventions aimed at improving metabolic health, reproductive function, hormonal balance, and quality of life.

8. Conclusion

PMOS represents a complex, heterogeneous, and multisystem endocrine-metabolic disorder with profound reproductive, metabolic, cardiovascular, inflammatory, and psychological implications. The transition from the traditional term “polycystic ovary syndrome” to PMOS reflects a major conceptual advancement in understanding the disorder beyond ovarian morphology and reproductive dysfunction. Accumulating evidence demonstrates that insulin resistance, hyperandrogenism, neuroendocrine dysregulation, chronic low-grade inflammation, oxidative stress, adipose tissue dysfunction, mitochondrial abnormalities, and genetic and epigenetic factors collectively contribute to disease pathogenesis and progression. The recognition of PMOS as a systemic disorder has important clinical implications for diagnosis, risk stratification, and long-term management. Although, the Rotterdam criteria remain widely used, increasing emphasis is being placed on metabolic, inflammatory, and endocrine biomarkers to improve phenotypic characterisation and facilitate personalised therapeutic approaches. Emerging evidence regarding gut microbiome alterations, molecular signaling pathways,

and epigenetic mechanisms further expands current understanding of disease complexity and may provide future therapeutic targets. Management of PMOS requires a multidisciplinary and individualised approach integrating lifestyle intervention, metabolic therapies, hormonal regulation, fertility management, psychological support, and long-term cardiometabolic surveillance. Novel pharmacological strategies, including GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors, show promising benefits in addressing both metabolic and reproductive abnormalities. In addition, increasing recognition of psychological burden and reduced quality of life highlights the need for holistic patient-centred care.

Overall, the evolving PMOS framework provides a more scientifically accurate and clinically meaningful representation of the disorder. Future research should focus on refining diagnostic biomarkers, elucidating molecular and epigenetic mechanisms, developing targeted therapies, and implementing precision medicine approaches to improve reproductive, metabolic, and psychological outcomes in affected women.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Summaiya Banu: Contributed to literature review, drafting, reviewing and editing the manuscript and methodology. **Zeenath Banu:** Contributed to conceptualisation, literature collection and analysis, methodology, supervision, and critical revision of the review manuscript.

Consent for publication

All authors gave their full consent for publication and submission to this journal.

Conflict of interest

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