

POLYENDOCRINE METABOLIC OVARIAN SYNDROME: REFRAMING POLYCYSTIC OVARY SYNDROME AS A MULTISYSTEM DISORDER

Sunil Kumar Verma¹, Meno Shubhranshu Deep²
Konthoujam Ushakiran Devi³ Dr Sunaina Nishad⁴
Meral Rai⁵ Mrs. Vertika Solomon⁶ Ramendra Singh
Hada⁷

1. Professor , Heritage Centre for Nursing Excellence, Uttar Pradesh
2. Professor cum Principal , Heritage Centre for Nursing Excellence, Uttar Pradesh
3. Professor, Heritage Centre for Nursing Excellence, Uttar Pradesh
4. Professor, Madhuban College of Nursing, Madhya Pradesh
5. Professor, Sri Sathya Sai Sanjeevani Institute of Nursing & Allied Healthcare Sciences, Chhattisgarh
6. Professor Shri Balaji Institute of Nursing, Chhattisgarh
7. Professor, School of Nursing, Sri Satya Sai University of Technology and Medical Sciences, Madhya Pradesh

Corresponding Author: Sunil Kumar Verma¹ / Email: sunilvrm77@gmail.com

Abstract

Background: Polycystic Ovary Syndrome (PCOS) is traditionally classified as a localized gynecological disorder. However, accumulating clinical and molecular evidence demonstrates that it is a complex, systemic endocrine-metabolic condition. The current nomenclature—focused entirely on ovarian morphology—creates significant diagnostic bias and clinical fragmentation.

Objective: This manuscript presents a clinical rationale for reframing PCOS as **Polyendocrine Metabolic Ovarian Syndrome (PMOS)** to better reflect its multi-organ pathogenesis and drive comprehensive, cross-disciplinary management.

Methods: A narrative review of current literature regarding insulin resistance, neuroendocrine disruption, and metabolic sequelae in patients diagnosed with PCOS under the Rotterdam criteria was conducted

Results: The primary drivers of this condition extend far beyond the ovaries, involving hypothalamic-pituitary-adrenal (HPA) axis acceleration, profound peripheral insulin resistance, hepatic metabolic alterations, and chronic low-grade tissue inflammation. Ovarian cysts are a variable, secondary feature of this broader metabolic cascade rather than a mandatory root cause.

Conclusion: Transitioning to the diagnostic framework of PMOS de-emphasizes pure ovarian morphology. This shift is critical to optimizing early cardiovascular, metabolic, and hepatic intervention, ultimately improving long-term patient outcomes.

Keywords: PCOS, PMOS, insulin resistance, reproductive endocrinology, Metabolic

Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that affects women during their reproductive years and beyond, into later stages of life. PCOS occurs when inappropriate hormonal signalling leads to higher than normal androgen levels and other hormonal

imbalances (WHO, 2026). It affects approximately 6–20% of women of reproductive age and remains a leading cause of infertility. Traditionally viewed as an ovarian disorder, PCOS is now increasingly recognized as a systemic condition involving multiple endocrine and metabolic pathways. It is a complex hormonal and metabolic disorder affecting roughly 1 in 8 women. It affects multiple body systems and is characterized by elevated androgens, insulin resistance, and reproductive dysfunction.

The term **Polyendocrine Metabolic Ovarian Syndrome (PMOS)** reflect this broader understanding, integrating reproductive, metabolic, and endocrine dysfunction into a unified framework. This reconceptualization aligns with emerging evidence highlighting the interconnected roles of insulin resistance, neuroendocrine dysregulation, and chronic inflammation.

More than 50 patient and professional organizations, including the Endocrine Society, took part in the process to develop the new name.

Professor Helena Teede, Director of Monash University's **Monash Centre for Health Research & Implementation** and an endocrinologist at Monash Health, led the name change process after spending decades researching the condition and seeing the patient impacts firsthand. According to **Professor Teede**, there is no increase in abnormal cysts on the ovary and the diverse features of the condition were often unappreciated leading to delayed diagnosis, limited awareness and inadequate care to those affected by this neglected condition.

Rationale for the PMOS Concept

The conventional term PCOS inadequately captures the full spectrum of systemic involvement. The change updates outdated terminology that historically reduced a serious, multisystem disease to an issue localized solely to ovarian cysts. The proposed term PMOS is based on:

- **Polyendocrine involvement:** Dysregulation of ovarian, pancreatic, adrenal, and hypothalamic–pituitary axes
- **Metabolic dysfunction:** Insulin resistance, obesity, dyslipidemia
- **Ovarian pathology:** Follicular arrest and anovulation

This broader terminology emphasizes that ovarian manifestations are one component of a multisystem disorder, not the sole defining feature.

Pathophysiological Framework of PMOS Insulin

Resistance and Hyperinsulinemia

Impaired cellular response to insulin forces the pancreas to produce excess insulin which stimulate the ovaries to:

- Increased ovarian androgen production
- Reduced sex hormone-binding globulin (SHBG)
- Exacerbation of hyperandrogenism

Hyperandrogenism

Excess androgen production disrupts normal follicle maturation in the ovaries, leading to: anovulation and halting regular menstruation. It also causes physical symptoms like

- Hirsutism
- Acne

POLYENDOCRINE METABOLIC OVARIAN SYNDROME: REFRAMING POLYCYSTIC OVARY SYNDROME AS A MULTISYSTEM DISORDER

- Follicular maturation arrest

Hypothalamic–Pituitary–Ovarian Axis Dysfunction

Altered GnRH (gonadotrophin-releasing hormone) pulsatility leads to disproportionately

- High LH (leutenising hormone) secretion to FSH(follicular stimulating hormone) ratio.
- Impaired folliculogenesis
- Chronic anovulation

Adipose Tissue Dysfunction

In Polyendocrine Metabolic Ovarian Syndrome, adipose tissue ceases to function as a healthy endocrine organ and it:

- Releases adipokines (leptin, adiponectin)
- Promotes inflammation
- Worsens insulin resistance

Chronic Inflammation and Oxidative Stress

- Low-grade inflammation contributes to metabolic and reproductive abnormalities
- Increased oxidative stress damages ovarian function

Gut–Endocrine Axis

In Polyendocrine Metabolic Ovarian Syndrome, the gut–endocrine axis is frequently broken down, contributing heavily to the disease's progression:

- Gut microbiota imbalance which degrades the gut lining, also known as ‘leakygut’.
- Lipopolysaccharides (LPS)—toxic cell walls from bad bacteria—leak through the damaged gut lining into the bloodstream triggers chronic inflammation and oxidative stress.
- Altered metabolic signalling - the inflamed gut fails to secrete normal amounts of GLP-1(Glucagon-Like Peptide-1) and PYY (Peptide YY) after a meal, which makes an individual feeling chronically hungry or unsatisfied, driving the weight gain that worsens **adipose tissue dysfunction**.
- Escalating Insulin Resistance: The resulting drop in GLP-1 secretion reduces the body's natural insulin efficiency, driving up blood glucose and trapping the body in a metabolic loop

Multisystem Clinical Manifestations

Organ System	Pathophysiological Mechanism	Clinical & Long-Term Phenotype
Metabolic & Endothelial	• Post-receptor insulin signaling defects; • Advanced glycation end-products	• Acanthosis nigricans, • Visceral adiposity, • Impaired glucose tolerance, • Type 2 Diabetes Mellitus
Reproductive & Axis	• Altered LH:FSH ratio; • Arrested folliculogenesis; • Excessive intraovarian hyperandrogenism	• Anovulatory infertility, • Oligomenorrhea, • Hirsutism, • Severe acne, • Increased risk of endometrial hyperplasia/ carcinoma
Cardiovascular	• Endothelial dysfunction; • asymmetric dimethylarginine accumulation; • premature vascular remodeling	• Early-onset of hypertension, • Atherogenic dyslipidemia, • Accelerated coronary artery disease

Hepatic & Respiratory	• Visceral lipotoxicity; • Altered adipokine profiles; • Upper airway fat deposition	• Metabolic Dysfunction-Associated Steatohepatitis (MASH), • Severe Obstructive Sleep Apnea (OSA)
Neuropsychiatric	• Hyperandrogenemia altering neurosteroid synthesis; • Chronic metabolic stress burdens	• Generalized Anxiety Disorder, Major Depressive Disorder, • Impaired quality-of-life indices

Diagnostic Considerations

While PMOS is a conceptual model, diagnosis should still follow established **PCOS criteria (Rotterdam 2003)**:

- Oligo/anovulation
- Hyperandrogenism
- Polycystic ovarian morphology

The PMOS framework encourages **expanded evaluation**, including:

- Metabolic screening
- Cardiovascular risk assessment
- Psychological evaluation

Complications

Long-term health risks and complications of PMOS fall into several key areas:

1. Metabolic & Cardiovascular Risks
 - Insulin resistance and Diabetes
 - Heart Disease
 - Fatty Liver
2. Reproductive and Pregnancy Complications
 - Infertility
 - Endometrial cancer: Irregular periods cause the uterine lining to thicken over time, increasing the risk of uterine or endometrial cancer.
 - Pregnancy hazards: If conception occurs, PMOS heightens the risk of gestational diabetes, preeclampsia, miscarriage and premature birth.
3. Physical appearance and systemic issues
 - Hirsutism and acne
 - Obesity
 - Sleep apnea
4. Mental Health
 - Anxiety
 - Depression
 - Low self-esteem

Management Approach in PMOS Framework

1. Lifestyle Modifications (First-Line)
 - Weight management: losing as little as 5% of body weight can improve menstrual regularity, lower androgen levels and restore ovulation.
 - Physical activity: Regular physical exercise improves how the body processes insulin and lowers blood sugar.
 - Dietary modification: Adopting a low-glycemic, high-fibre and anti-inflammatory diet (whole grains, lean proteins, healthy fats), and minimize refined carbohydrates and sugars to manage insulin resistance.

POLYENDOCRINE METABOLIC OVARIAN
SYNDROME: REFRAMING POLYCYSTIC
OVARY SYNDROME AS A MULTISYSTEM DISORDER

2. Pharmacological Management (As per directed by Gynaecologists)
 - Combined oral contraceptives (menstrual regulation)
 - Metformin (insulin sensitization)
 - Anti-androgens (symptom control)
3. Reproductive Management
 - Ovulation induction (letrozole, clomiphene)
 - Assisted reproductive techniques
4. Symptom-based treatment
 - Hyperandrogenism: In addition to contraceptives, anti-androgen medications or cosmetic treatments like laser and electrolysis are used to treat hirsutism and scalp hair loss.
5. Long-term health monitoring
 - Metabolic screening: Consistent screening for type 2 diabetes, high cholesterol and cardiovascular risk factors is vital.
 - Mental Health: Psychological support and addressing conditions like anxiety or depression are core components of care.

Future Directions

The future of managing Polyendocrine Metabolic Ovarian Syndrome (PMOS) is shifting away from short-term symptom control and moving toward disease modification, precision medicine, and holistic, lifelong health tracking. Driven by the landmark global initiative to officially rename the condition from PCOS to PMOS, future clinical directions focus heavily on targeting the systemic endocrine and metabolic pathways rather than just gynecological symptoms. Future therapeutic directions and emerging clinical trends encompass several key areas:

1. Phenotype-Targeted Precision Medicine
 - Genetic & Metabolomic Profiling: Emerging research targets specific individual genetic and endocrine profiles to match patients with tailored therapies instead of utilizing a “one-size-fits-all” approach.
 - Phenotypic subtyping: Categorising individuals with the same overarching disease into distinct subgroups based on their observable traits, physical symptoms, and laboratory markers (their phenotype), rather than treating them all as if they have the exact same condition.
2. Next generation metabolic and second line therapies
 - Advanced weight and metabolic management: Integrate clinical precision, cellular reprogramming, and modern pharmacotherapy to address obesity and metabolic dysfunction at their core.
 - Metabolic reprogramming: Altering cellular energy pathways to reverse the deep genetic and hormonal adaptations that lock the body into a state of chronic fat storage, low energy expenditure, and severe insulin resistance.
3. Gut microbiome and regenerative therapies
 - Microbiome interventions: Targeted prebiotic, probiotic, and dietary therapies designed to repair gut dysbiosis are being studied for their direct impact on improving peripheral insulin sensitivity and lowering circulating testosterone levels.
 - Mesenchymal Stem Cell (MSC) Therapy: Early-stage clinical studies are exploring the regenerative capabilities of MSCs to potentially restore damaged ovarian tissue and fundamentally normalize disrupted ovarian function.
4. Advanced Digital Health and Artificial Intelligence (AI)
 - AI- Guided Diagnostics: Machine learning models are being deployed to predict

- long-term metabolic risks (such as type 2 diabetes or cardiovascular events) decades before symptoms worsen, prompting aggressive early interventions.
 - **Wearable Self-Monitoring Tools:** Continuous glucose monitors (CGMs) and smart biometric rings are expected to become standard care elements to track a patient's real-time metabolic and ovulatory responses to specific lifestyle changes.
5. Global policies and guidelines integration
- **The 2028 International Guideline Update:** A co-designed global transition strategy is underway to fully align clinical health systems, education campaigns, and diagnostic coding with the PMOS paradigm. This shift moves the focus from treating infertility on demand to protecting cardiometabolic, liver, and brain health over a patient's entire lifespan.

Discussion

The paradigm shift from Polycystic Ovary Syndrome (PCOS) to Polyendocrine Metabolic Ovarian Syndrome (PMOS) addresses long-standing clinical limitations. Historically, the condition was treated as a localized gynecological problem. This narrow view led to delayed diagnoses, fragmented healthcare, and an overemphasis on "ovarian cysts"—which are actually harmless follicles and not pathologically present in all patients.

The updated consensus nomenclature, published in *The Lancet*, redefines PMOS as a systemic, lifelong endocrinopathy. By emphasizing its polyendocrine and metabolic foundations, the medical community acknowledges that core dysfunctions (such as tissue-level insulin resistance and chronic inflammation) extend far beyond reproductive health.

Conclusion

The designation "Polycystic Ovary Syndrome" is a clinical anachronism that hinders optimal patient care. Reframing this condition as **Polyendocrine Metabolic Ovarian Syndrome (PMOS)** aligns medical nomenclature with modern molecular and clinical reality. By acknowledging the condition as a systemic, multi-organ metabolic disorder, the medical community can dismantle fragmented care models, implement proactive screening, and design targeted therapies that address the root pathophysiological drivers of this lifelong syndrome.

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POLYENDOCRINE METABOLIC OVARIAN
SYNDROME: REFRAMING POLYCYSTIC
OVARY SYNDROME AS A MULTISYSTEM DISORDER

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