

Understanding the Transition from PCOS TO PMOS: Etiology, pathogenesis and contributing factors

Sugra Begum^{#1}, Syed Obaid^{*2}, Muskan Khatoon^{#3}

[#] Pharm-D, Prathap Narender Reddy College of Pharmacy,
Hyderabad, Telangana, India

¹sharerham7865@gmail.com, ²syedobaidoppo@gmail.com, ³dr.muskankhan30@gmail.com

Abstract:

Polyendocrine Metabolic Ovarian Syndrome (PMOS), formerly known as Polycystic Ovary Syndrome (PCOS), is one of the most common endocrine and metabolic disorders affecting women of reproductive age worldwide. The previous term, Polycystic Ovary Syndrome, was considered misleading because many affected women do not develop true ovarian cysts, while the name focused primarily on ovarian morphology and fertility rather than the disorder's systemic endocrine, metabolic, cardiovascular, and psychological manifestations. The updated terminology, PMOS, reflects the complex multisystem nature of the disease and emphasizes that it is not confined to the ovaries but involves multiple endocrine organs and metabolic pathways. According to global health estimates, PMOS affects approximately 1 in 8 women of reproductive age, accounting for more than 170 million individuals worldwide. The global prevalence ranges from 5% to 15%, depending on the diagnostic criteria and study population, with the highest prevalence reported in the WHO Eastern Mediterranean Region (15.1%) and the WHO South-East Asian Region (14.3%). Despite its high prevalence, nearly 70% of affected women remain undiagnosed, leading to delayed diagnosis, disease progression, and increased risk of long-term complications. The recent proposal to adopt the term PMOS followed extensive international collaboration involving healthcare professionals, scientific societies, patient advocacy organizations, and thousands of women living with the condition, with the goal of improving disease awareness, reducing misconceptions, and promoting comprehensive patient care. PMOS is characterized by a complex interaction of genetic susceptibility, insulin resistance, hyperinsulinemia, androgen excess, hypothalamic–pituitary–ovarian axis dysfunction, chronic low-grade inflammation, oxidative stress, and environmental and lifestyle factors. Clinically, the disorder presents with menstrual irregularities, anovulation, infertility, hyperandrogenism, hirsutism, acne, obesity, and polycystic ovarian morphology in some patients. Beyond reproductive dysfunction, women with PMOS are at significantly increased risk of metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnea, endometrial hyperplasia and carcinoma, anxiety, depression, and reduced quality of life. Early recognition and multidisciplinary management are essential to prevent disease progression and improve long-term health outcomes. Lifestyle modification remains the cornerstone of therapy, while individualized pharmacological treatment should target both reproductive and metabolic abnormalities. This review discusses the evolving concept of PMOS, its epidemiology, pathophysiology, clinical manifestations, diagnostic approaches, associated comorbidities, and current management strategies. By recognizing PMOS as a multisystem endocrine and metabolic disorder, healthcare professionals can adopt a more holistic approach that promotes earlier diagnosis, personalized treatment, improved metabolic health, enhanced reproductive outcomes, and better quality of life for affected women.

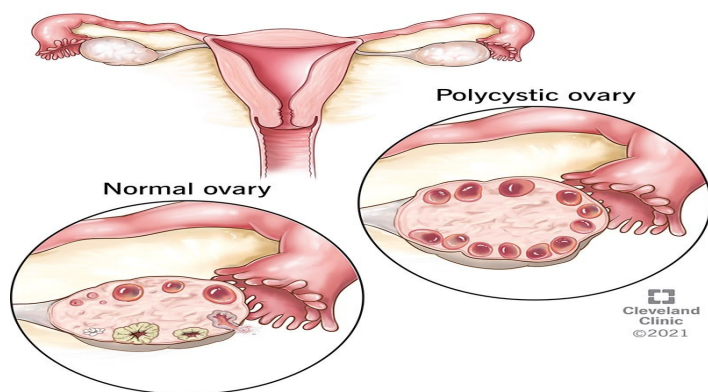
Keywords: PMOS; PCOS; Insulin Resistance; Hyperandrogenism; Metabolic Syndrome; Infertility; Obesity; Endocrine Disorder; Women's Health; Reproductive Health.

Introduction

Polyendocrine Metabolic Ovarian Syndrome (PMOS), formerly known as Polycystic Ovary Syndrome (PCOS), is one of the most common endocrine and metabolic disorders affecting women of reproductive age worldwide. It is a heterogeneous multisystem disorder characterized by reproductive dysfunction, hyperandrogenism, insulin resistance, and metabolic abnormalities that significantly affect women's physical, psychological, and reproductive health. Although traditionally regarded as a gynecological

disorder, growing scientific evidence demonstrates that PMOS is a lifelong systemic disease involving multiple endocrine organs and metabolic pathways. The condition not only impairs ovarian function but also predisposes affected women to obesity, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), infertility, pregnancy complications, anxiety, depression, and reduced quality of life. The disorder was first described by Irving F. Stein and Michael L. Leventhal in 1935 after observing a group of women presenting with amenorrhea, infertility, obesity, hirsutism, and enlarged polycystic ovaries. For decades, the

condition was referred to as Polycystic Ovary Syndrome (PCOS), with emphasis placed on ovarian morphology. However, advances in endocrinology, reproductive medicine, and metabolic research have demonstrated that ovarian cysts are neither essential for diagnosis nor the primary pathological feature of the disorder. Many women diagnosed with the condition do not have true ovarian cysts, while others with polycystic ovarian morphology remain asymptomatic



Consequently, the traditional terminology has been criticized for oversimplifying a complex endocrine–metabolic disorder and contributing to delayed diagnosis, misunderstanding, and inadequate treatment. To address these limitations, an international multidisciplinary initiative involving healthcare professionals, researchers, patient organizations, and women with lived experience proposed the term Polyendocrine Metabolic Ovarian Syndrome (PMOS). The process involved global collaboration over more than a decade, extensive scientific review, multiple international workshops, and more than 22,000 survey responses from patients and clinicians. The revised terminology recognizes that the disorder affects multiple endocrine systems and metabolic pathways rather than the ovaries alone. The change also aims to improve public awareness, reduce stigma, enhance communication between healthcare providers and patients, and encourage a more comprehensive approach to diagnosis and long-term management. PMOS represents a significant global health burden. Current estimates suggest that approximately one in eight women of reproductive age are affected, accounting for more than 170 million individuals worldwide. Despite its high prevalence, nearly 70% of women remain undiagnosed because symptoms often develop gradually, vary considerably between individuals, and are frequently mistaken for normal menstrual irregularities or isolated cosmetic concerns. Delayed diagnosis increases the likelihood of infertility, obesity, insulin

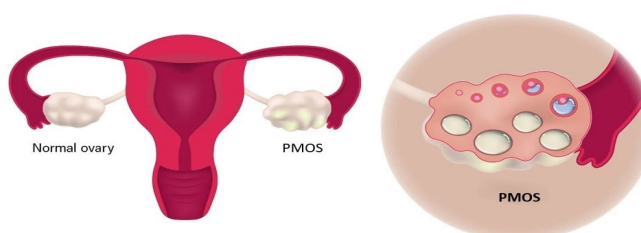
resistance, type 2 diabetes mellitus, cardiovascular disease, endometrial pathology, and psychological disorders, emphasizing the need for greater awareness among healthcare professionals and the general population. The prevalence of PMOS varies according to ethnicity, geographic region, age, and diagnostic criteria. International reports indicate prevalence rates ranging from approximately 5% to 15% among women of reproductive age. The highest prevalence has been reported in the WHO Eastern Mediterranean Region (approximately 15.1%) and the WHO South-East Asian Region (approximately 14.3%), highlighting its increasing importance as a public health concern in developing as well as developed countries. Rising obesity rates, urbanization, sedentary lifestyles, unhealthy dietary habits, environmental exposures, and genetic susceptibility are believed to contribute to the growing incidence of the disorder worldwide. Unlike traditional concepts that viewed the syndrome primarily as a reproductive disorder, PMOS is now recognized as a chronic endocrine and metabolic disease with lifelong consequences. Women affected by PMOS require continuous monitoring from adolescence through menopause because metabolic complications often become more significant with advancing age. Early diagnosis, timely intervention, lifestyle modification, and multidisciplinary management are therefore essential to reduce disease progression, improve reproductive outcomes, and minimize long-term cardiometabolic complications

Association Between Polyendocrine Metabolic Ovarian Syndrome (PMOS) and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Polyendocrine Metabolic Ovarian Syndrome (PMOS), formerly known as Polycystic Ovary Syndrome (PCOS), is one of the most common endocrine–metabolic disorders affecting women of reproductive age worldwide. It is characterized by a combination of ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology, along with significant metabolic disturbances. Increasing evidence has shifted the understanding of PMOS from an isolated reproductive disorder to a systemic metabolic condition associated with long-term complications, including insulin resistance, type 2 diabetes mellitus, cardiovascular disease, and metabolic dysfunction-associated steatotic liver disease (MASLD).

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), previously termed Non-Alcoholic Fatty Liver Disease (NAFLD), is the most prevalent chronic liver disorder worldwide and is strongly associated with metabolic

Polyendocrine metabolic ovarian syndrome (PMOS)



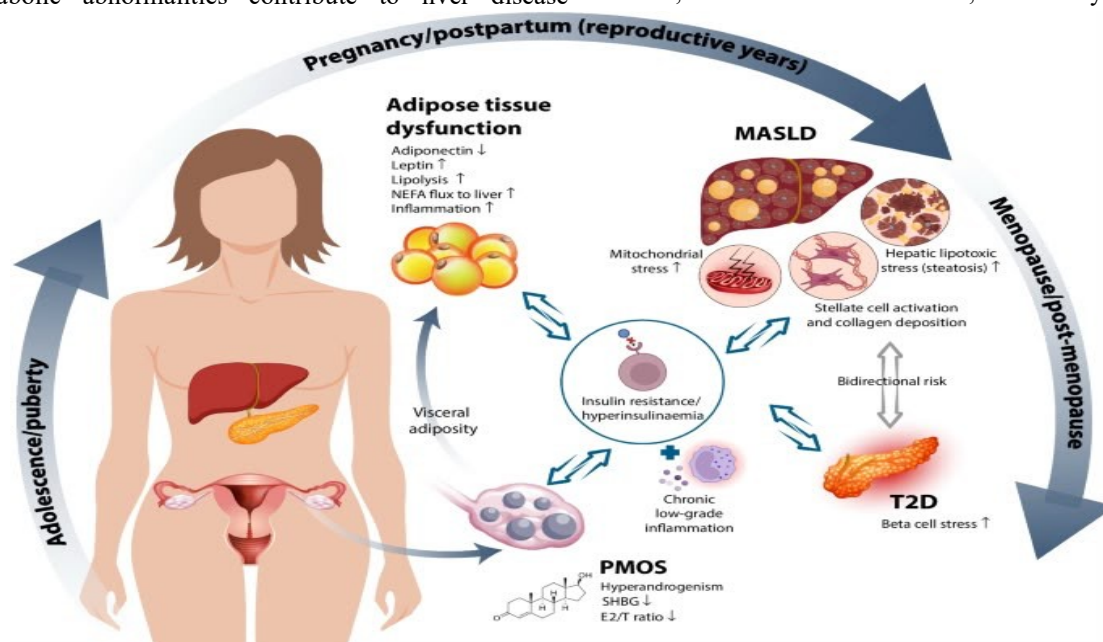
abnormalities such as insulin resistance, obesity, dyslipidemia, and type 2 diabetes. MASLD represents a spectrum ranging from simple hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. The increasing global prevalence of obesity and metabolic syndrome has contributed significantly to the rising burden of MASLD.

The relationship between PMOS and MASLD has gained increasing clinical and research attention due to the presence of shared pathogenic mechanisms. Both disorders are driven by insulin resistance, hyperinsulinemia, androgen excess, chronic low-grade inflammation, oxidative stress, and abnormal lipid metabolism. Women with PMOS have a higher prevalence of hepatic steatosis compared with women without PMOS, and this increased risk appears to occur independently of body mass index (BMI), suggesting that intrinsic hormonal and metabolic abnormalities contribute to liver disease

Understanding the association between PMOS and MASLD is essential for early identification, prevention, and comprehensive management of affected women. Routine metabolic and liver health evaluation in patients with PMOS may facilitate early intervention, reduce disease progression, and improve long-term reproductive, metabolic, and hepatic outcomes.

Etiology and Pathophysiology of Polyendocrine Metabolic Ovarian Syndrome (PMOS)

The etiology of Polyendocrine Metabolic Ovarian Syndrome (PMOS) is multifactorial and remains incompletely understood. Current evidence suggests that the disorder develops through a complex interaction between genetic susceptibility, epigenetic modifications, hormonal imbalance, insulin resistance, chronic low-grade inflammation, oxidative stress, environmental influences, and lifestyle factors. These



development.

Insulin resistance acts as a central connecting pathway between PMOS and MASLD. In PMOS, compensatory hyperinsulinemia promotes ovarian androgen production and alters hepatic lipid metabolism, leading to increased triglyceride accumulation within hepatocytes. At the same time, androgen excess enhances visceral fat deposition, inflammatory signaling, and hepatic insulin resistance, accelerating the progression of MASLD. Chronic inflammation and oxidative stress further promote hepatocellular injury and fibrosis through activation of inflammatory cytokines and mitochondrial dysfunction.

Recent research has also highlighted the role of adipose tissue dysfunction, gut microbiome alterations, epigenetic regulation, and disturbances in bile acid metabolism as potential contributors linking PMOS with MASLD. These findings emphasize that PMOS and MASLD represent interconnected metabolic disorders requiring integrated clinical assessment rather than separate disease management.

mechanisms interact throughout life, beginning before birth in genetically predisposed individuals and progressing during adolescence and adulthood. The heterogeneity of PMOS explains the wide variation in clinical presentation, severity, and long-term complications among affected women.

The etiology of Polyendocrine Metabolic Ovarian Syndrome (PMOS) is multifactorial and involves a complex interaction between genetic susceptibility, epigenetic modifications, endocrine dysregulation, insulin resistance, chronic low-grade inflammation, neuroendocrine abnormalities, environmental exposures, and lifestyle factors. Rather than a disorder confined to the ovaries, PMOS is now recognized as a systemic endocrine–metabolic disease in which reproductive and metabolic pathways continuously interact throughout life.

Genetic predisposition plays a fundamental role in PMOS, with family and twin studies demonstrating a significantly increased risk among first-degree relatives. However, genetic susceptibility alone is insufficient to explain disease development. Epigenetic mechanisms—including DNA

methylation, histone modifications, and microRNA regulation—have emerged as important contributors by altering gene expression without changing the DNA sequence. Environmental exposures during fetal development and early life, particularly endocrine-disrupting chemicals, maternal hyperandrogenism, obesity, gestational diabetes, and medications such as valproate, may induce epigenetic alterations that increase the risk of PMOS. Recent studies have demonstrated abnormal DNA methylation patterns in genes involved in insulin signaling (INSR), anti-Müllerian hormone (AMH), and its receptor (AMHR2), suggesting that epigenetic dysregulation contributes to both reproductive and metabolic abnormalities. Experimental studies further indicate that correcting abnormal DNA methylation may restore normal ovarian function, highlighting epigenetic pathways as potential therapeutic targets.

Insulin resistance represents one of the central pathogenic mechanisms of PMOS and is present in approximately 70% of affected individuals, irrespective of obesity. Reduced insulin sensitivity results in compensatory hyperinsulinemia, which amplifies ovarian androgen production through direct stimulation of ovarian theca cells and increased responsiveness to luteinizing hormone (LH). Simultaneously, hyperinsulinemia suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), increasing circulating free testosterone and worsening hyperandrogenism. Excess insulin also disrupts insulin-like growth factor-1 (IGF-1) signaling within granulosa cells, impairing follicular maturation, ovulation, and steroidogenesis. These mechanisms establish a bidirectional relationship between hyperinsulinemia and androgen excess, now considered a hallmark of PMOS pathogenesis.

Hyperandrogenism is present in more than 80% of women with PMOS and originates predominantly from excessive ovarian androgen production, although adrenal androgen secretion contributes in a subset of patients. Overexpression of steroidogenic enzymes, particularly cytochrome P450c17 (CYP17A1), increases androgen biosynthesis within ovarian theca cells. Elevated androgen concentrations stimulate premature recruitment of primordial follicles while simultaneously inhibiting dominant follicle selection, resulting in follicular arrest, chronic anovulation, and the accumulation of multiple immature follicles characteristic of polycystic ovarian morphology. Hyperandrogenism also contributes to clinical manifestations such as hirsutism, acne, androgenic alopecia, and infertility.

Neuroendocrine dysfunction involving the hypothalamic–pituitary–ovarian (HPO) axis further contributes to disease progression. Increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) preferentially stimulates luteinizing hormone secretion while relatively suppressing follicle-stimulating hormone (FSH). Elevated LH promotes ovarian androgen synthesis, whereas reduced FSH limits aromatase activity within granulosa cells, decreasing the conversion of androgens into estradiol. The resulting hormonal imbalance perpetuates chronic anovulation and disrupts normal follicular development. Excess estrone

generated through peripheral aromatization of androgens, particularly in adipose tissue, exerts persistent feedback on the hypothalamus and pituitary gland, maintaining endocrine dysfunction and increasing the risk of endometrial hyperplasia due to prolonged unopposed estrogen exposure.

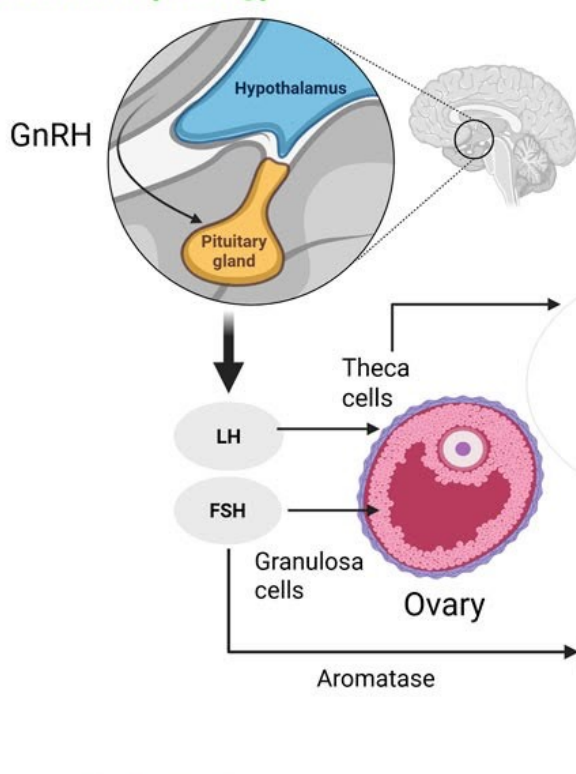
Increasing evidence also implicates chronic low-grade inflammation and oxidative stress in PMOS pathogenesis. Women with PMOS frequently exhibit elevated concentrations of inflammatory mediators, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), independent of obesity. Altered lipid metabolism and activation of inflammatory signaling pathways, including extracellular signal-regulated kinase (ERK1/2), contribute to impaired follicular development and metabolic dysfunction. Emerging evidence further suggests that abnormalities in immune regulation, angiogenesis, mitochondrial function, and oxidative stress may interact with endocrine and metabolic pathways, expanding the understanding of PMOS beyond chronic inflammation alone.

Obesity and adverse lifestyle factors significantly aggravate disease expression but are not essential for disease development. Central obesity exacerbates insulin resistance, hyperinsulinemia, inflammation, and androgen excess, creating a self-perpetuating cycle that accelerates metabolic complications. Nevertheless, many lean women develop PMOS, indicating that intrinsic endocrine and genetic abnormalities can independently initiate the disorder. Environmental factors, including sedentary behavior, unhealthy dietary patterns, chronic psychological stress, poor sleep quality, and exposure to endocrine-disrupting chemicals, further modify disease severity in genetically susceptible individuals.

A strong genetic predisposition has been demonstrated through family and twin studies, showing that women with a first-degree relative affected by PMOS have a significantly increased risk of developing the disorder. Multiple susceptibility genes involved in steroid hormone biosynthesis, insulin signaling, gonadotropin secretion, ovarian follicular development, and energy metabolism have been implicated. However, no single gene is responsible for PMOS, indicating that it is a polygenic disorder influenced by interactions between genetic and environmental factors. Epigenetic mechanisms, including DNA methylation, histone modification, and microRNA regulation, are also believed to contribute by altering gene expression without changing the DNA sequence. Maternal obesity, gestational diabetes, intrauterine androgen exposure, and adverse early-life environmental factors may further increase disease susceptibility. Overall, PMOS develops through intricate interactions among genetic, epigenetic, endocrine, metabolic, inflammatory, and environmental mechanisms. Current evidence recognizes PMOS as a heterogeneous systemic endocrine–metabolic disorder rather than an isolated ovarian disease. Understanding these interconnected pathogenic pathways is fundamental for developing personalized therapeutic strategies aimed at improving reproductive function, metabolic health, and long-term clinical outcomes.

Insulin resistance is considered one of the central mechanisms underlying PMOS and is present in a substantial proportion of affected women, including many who are not obese. Reduced insulin sensitivity results in compensatory hyperinsulinemia, which plays a pivotal role in disease progression. Elevated insulin levels stimulate ovarian theca cells to produce excess androgens while suppressing hepatic synthesis of sex hormone-binding globulin (SHBG). The resulting increase in circulating free testosterone contributes to hyperandrogenism, leading to clinical manifestations such as hirsutism, acne, androgenic alopecia, menstrual irregularities, and impaired follicular maturation. Persistent hyperinsulinemia also increases the risk of impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, and cardiovascular disease.

Normal Physiology

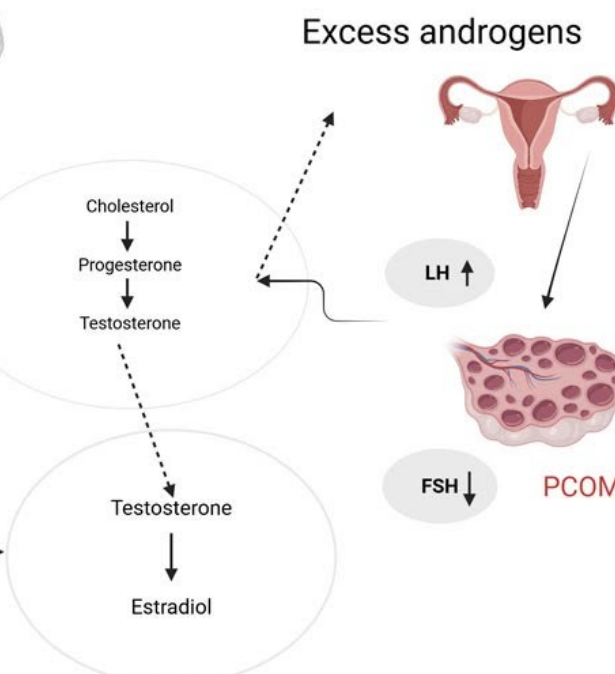


Hyperandrogenism is a defining endocrine feature of PMOS and results from excessive androgen production by the ovaries and, in some cases, the adrenal glands. Increased luteinizing hormone (LH) secretion and insulin-mediated stimulation of ovarian steroidogenesis promote excessive androgen synthesis. Elevated androgen concentrations disrupt normal follicular growth, causing arrest of follicular development, chronic anovulation, irregular menstrual cycles, and subfertility. The accumulation of multiple small immature follicles within the ovaries produces the characteristic polycystic ovarian morphology observed in many—but not all—women with PMOS. Importantly, the presence of polycystic ovarian morphology alone is insufficient for diagnosis and should be interpreted in conjunction with clinical and biochemical findings.

Alterations in the hypothalamic–pituitary–ovarian (HPO) axis further contribute to disease pathogenesis. Increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) preferentially stimulates luteinizing hormone release while relatively suppressing follicle-stimulating hormone (FSH). The elevated LH-to-FSH ratio promotes ovarian androgen production and interferes with normal follicular maturation and ovulation. Consequently, women with PMOS frequently experience oligomenorrhea, amenorrhea, chronic anovulation, infertility, and recurrent pregnancy complications.

Recent evidence also highlights the role of chronic low-grade inflammation and oxidative stress in the development of PMOS. Increased concentrations of inflammatory cytokines, including tumor necrosis factor-alpha (TNF- α), interleukin-6

PCOS Patho-Physiology



(IL-6), and C-reactive protein (CRP), contribute to insulin resistance, endothelial dysfunction, and metabolic abnormalities. Oxidative stress resulting from excessive production of reactive oxygen species further impairs ovarian function, disrupts insulin signaling pathways, and accelerates cellular damage. These inflammatory and oxidative mechanisms are believed to link reproductive dysfunction with the increased cardiometabolic risk observed in affected women.

Environmental and lifestyle factors substantially influence disease expression. Sedentary behavior, excessive caloric intake, obesity, sleep disturbances, psychosocial stress, endocrine-disrupting chemicals, and unhealthy dietary habits may exacerbate insulin resistance and hormonal imbalance in genetically susceptible individuals. Obesity, particularly central adiposity, amplifies hyperinsulinemia, chronic inflammation, and androgen excess, creating a vicious cycle

that worsens reproductive and metabolic dysfunction. Nevertheless, PMOS also occurs in women with normal body weight, emphasizing that obesity is an aggravating factor rather than the primary cause of the disorder.

The interaction between genetic, endocrine, metabolic, inflammatory, and environmental factors explains why PMOS is now recognized as a systemic endocrine–metabolic disorder rather than a condition limited to the ovaries. This comprehensive understanding has shifted clinical management toward early diagnosis, individualized treatment, long-term metabolic risk reduction, and multidisciplinary care aimed at improving reproductive, metabolic, cardiovascular, and psychological

Polyendocrine Metabolic Ovarian Syndrome (PMOS) is a complex and heterogeneous endocrine–metabolic disorder caused by the interaction of genetic, hormonal, metabolic, environmental, and molecular factors. The exact etiology remains incompletely understood; however, current evidence indicates that PMOS results from a combination of genetic predisposition, epigenetic modifications, insulin resistance, hyperandrogenism, hypothalamic–pituitary–ovarian (HPO) axis dysfunction, chronic inflammation, oxidative stress, and lifestyle-related influences. These interconnected mechanisms contribute to reproductive abnormalities, metabolic dysfunction, and increased risk of long-term systemic complications.

Genetic and Epigenetic Mechanisms

Genetic susceptibility plays an important role in PMOS development, as familial clustering and twin studies demonstrate a higher risk among first-degree relatives. Multiple genes involved in androgen synthesis, insulin signaling, gonadotropin regulation, ovarian follicular development, and metabolic pathways have been associated with disease susceptibility. However, PMOS is not caused by a single genetic abnormality, suggesting a polygenic mechanism influenced by environmental and metabolic factors.

Epigenetic alterations, including DNA methylation, histone modifications, and microRNA regulation, have emerged as important regulators of PMOS pathogenesis. These modifications can influence the expression of genes involved in insulin sensitivity, androgen production, anti-Müllerian hormone (AMH) signaling, and follicular development without altering the DNA sequence. Prenatal exposure to excess androgens, maternal metabolic abnormalities, and endocrine-disrupting chemicals may induce epigenetic changes that increase susceptibility to PMOS later in life.

Insulin Resistance and Metabolic Dysfunction

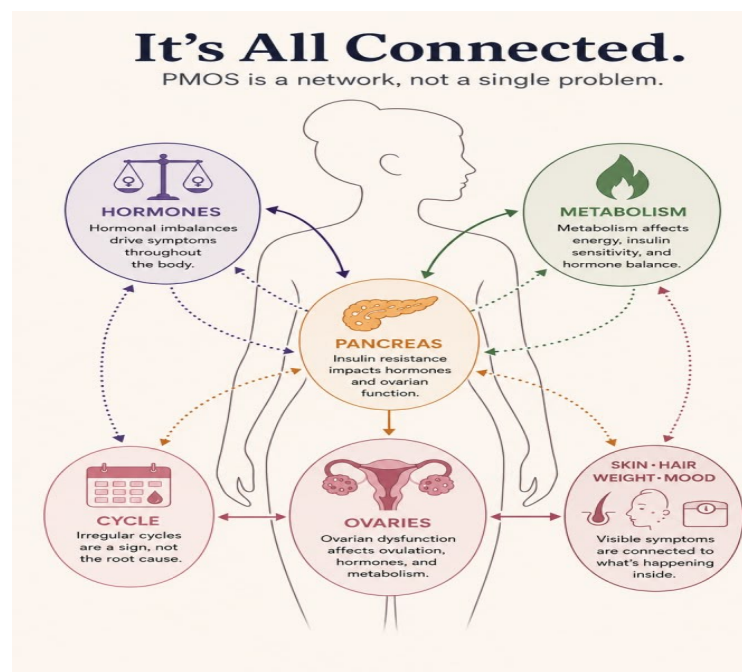
Insulin resistance is considered one of the central pathogenic mechanisms of PMOS and occurs in a significant proportion of affected women, including those without obesity. Reduced insulin sensitivity causes compensatory hyperinsulinemia, which contributes to disease progression through multiple pathways. Elevated insulin levels stimulate ovarian theca cells

to increase androgen production and reduce hepatic synthesis of sex hormone-binding globulin (SHBG), resulting in increased circulating free androgen levels.

Hyperinsulinemia also enhances luteinizing hormone (LH)-mediated ovarian steroidogenesis and disrupts insulin-like growth factor (IGF) signaling, leading to impaired follicular maturation and chronic anovulation. The interaction between insulin resistance and androgen excess creates a self-amplifying cycle that promotes both reproductive dysfunction and metabolic abnormalities, including obesity, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease.

Hyperandrogenism and Ovarian Dysfunction

Hyperandrogenism is a major pathological feature of PMOS and results from excessive androgen production, primarily by ovarian theca cells, with possible contribution from adrenal glands. Increased activity of steroidogenic enzymes, particularly CYP17A1, promotes androgen biosynthesis. Elevated androgen concentrations interfere with normal follicular development by increasing early follicular



recruitment while preventing dominant follicle selection.

This abnormal follicular process leads to follicular arrest, chronic anovulation, and polycystic ovarian morphology. Excess androgen levels are responsible for clinical manifestations such as hirsutism, acne, androgenic alopecia, menstrual irregularities, and infertility. Hyperandrogenism also worsens insulin resistance, further contributing to disease progression.

Hypothalamic–Pituitary–Ovarian Axis Dysregulation

Alterations in the hypothalamic–pituitary–ovarian axis play a key role in maintaining hormonal imbalance. Increased pulsatile secretion of gonadotropin-releasing hormone (GnRH)

promotes excessive luteinizing hormone (LH) secretion relative to follicle-stimulating hormone (FSH). Elevated LH stimulates ovarian androgen production, whereas reduced FSH activity decreases aromatase enzyme function in granulosa cells, limiting conversion of androgens into estradiol.

This hormonal imbalance disrupts normal ovulation and follicular maturation, resulting in persistent anovulation and menstrual irregularities. Increased peripheral conversion of androgens into estrone, especially in adipose tissue, may cause prolonged estrogen exposure and increase the risk of endometrial hyperplasia and carcinoma.

Inflammatory and Oxidative Pathways

Chronic low-grade inflammation and oxidative stress are increasingly recognized as important contributors to PMOS progression. Women with PMOS frequently demonstrate elevated inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α). These inflammatory mediators interfere with insulin signaling, promote endothelial dysfunction, and contribute to metabolic abnormalities.

Oxidative stress caused by excessive reactive oxygen species production can impair ovarian function, mitochondrial activity, and oocyte quality, contributing to infertility. Abnormal immune regulation and altered inflammatory pathways may further disturb follicular development and ovarian function.

Environmental and Lifestyle Influences

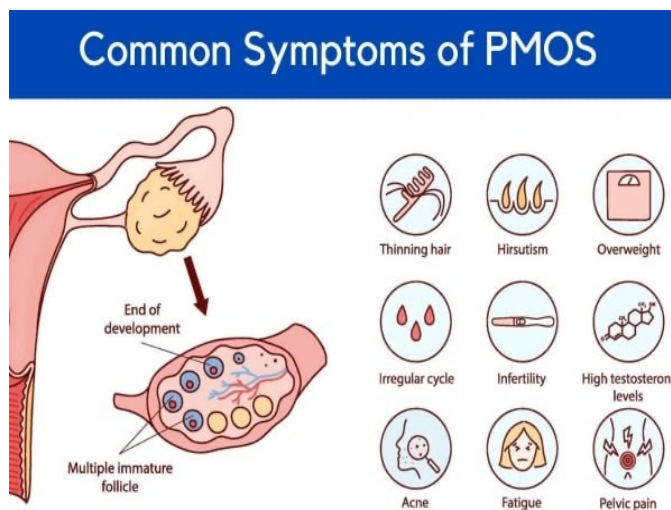
Environmental and lifestyle factors influence the severity and progression of PMOS. Obesity, sedentary behavior, unhealthy dietary patterns, psychological stress, poor sleep quality, and exposure to endocrine-disrupting chemicals can worsen insulin resistance, inflammation, and androgen excess. Central obesity particularly increases metabolic complications by enhancing insulin resistance and hormonal imbalance. However, PMOS can also occur in lean women, indicating that obesity acts as an aggravating factor rather than the sole cause.

Overall Pathogenic Mechanism

PMOS develops through a complex interaction between genetic susceptibility, hormonal dysregulation, metabolic abnormalities, and environmental influences. The core pathogenic cycle involves insulin resistance leading to hyperinsulinemia, increased ovarian androgen production, disruption of follicular development, and chronic anovulation. These mechanisms extend beyond reproductive dysfunction and contribute to metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), psychological disorders, and reduced quality of life. Understanding these

mechanisms provides the foundation for early diagnosis, targeted therapeutic strategies, and personalized management approaches aimed at improving reproductive, metabolic, and long-term health outcomes in women with PMOS

Clinical Manifestations of Polyendocrine Metabolic



Ovarian Syndrome (PMOS)

Polyendocrine Metabolic Ovarian Syndrome (PMOS) is a heterogeneous disorder with a wide spectrum of clinical manifestations that vary in severity and presentation among affected women. Symptoms commonly begin during adolescence around menarche but may also develop later during the reproductive years. The clinical presentation is influenced by the degree of hyperandrogenism, insulin resistance, metabolic dysfunction, and individual genetic susceptibility. According to current diagnostic criteria, PMOS is diagnosed when at least two of the following features are present after excluding other endocrine disorders: oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology.

Menstrual and Reproductive Manifestations

Menstrual irregularities are among the earliest and most common clinical features of PMOS. Women may experience oligomenorrhea, amenorrhea, irregular menstrual cycles, prolonged or heavy menstrual bleeding, or fewer than eight menstrual periods annually. Chronic anovulation results in reduced fertility and is a major cause of infertility among women of reproductive age. Ultrasonography frequently demonstrates enlarged ovaries containing multiple immature antral follicles arranged peripherally, although true ovarian cysts are not a characteristic feature of the disorder.

Hyperandrogenic Manifestations

Hyperandrogenism affects the majority of women with PMOS and may be evident clinically or biochemically. Clinical manifestations include hirsutism, characterized by excessive terminal hair growth on the face, chin, upper lip, chest, abdomen, back, and thighs following a male-pattern distribution. Additional features include persistent acne, oily

skin, androgenic alopecia (female-pattern scalp hair thinning), and, in severe cases, virilization. Elevated circulating androgen concentrations contribute significantly to reproductive dysfunction and cosmetic concerns, often affecting psychological well-being

Metabolic Manifestations

Metabolic abnormalities are increasingly recognized as central features of PMOS. Insulin resistance and compensatory hyperinsulinemia occur in a substantial proportion of affected women, irrespective of body mass index. Many patients experience central obesity, progressive weight gain, difficulty losing weight, impaired glucose tolerance, dyslipidemia, and metabolic syndrome. Cutaneous manifestations of insulin resistance include acanthosis nigricans, characterized by dark, velvety hyperpigmented skin over the neck, axillae, and groin, as well as multiple skin tags. These findings indicate an increased risk of developing type 2 diabetes mellitus and cardiovascular disease.

Psychological Manifestations

PMOS is frequently associated with psychological and emotional disturbances that substantially impair quality of life. Anxiety, depression, low self-esteem, body image dissatisfaction, eating disorders, sexual dysfunction, and reduced health-related quality of life are commonly reported. Cosmetic manifestations such as hirsutism, obesity, acne, infertility, and menstrual irregularities often contribute to social stigma and emotional distress, emphasizing the importance of psychological assessment and support.

Long-Term Clinical Complications

If left untreated, PMOS increases the risk of numerous long-term complications. These include metabolic syndrome, prediabetes, type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnea, and chronic kidney disease. Persistent anovulation with prolonged unopposed estrogen exposure may result in endometrial hyperplasia and endometrial carcinoma. Women with PMOS are also at increased risk of adverse pregnancy outcomes, including gestational diabetes mellitus, hypertensive disorders of pregnancy, miscarriage, preterm birth, and reduced fertility.

The clinical manifestations of PMOS evolve throughout the lifespan and often extend beyond reproductive dysfunction. Early recognition of these diverse features enables timely diagnosis, individualized treatment, and comprehensive long-term management aimed at improving reproductive, metabolic, cardiovascular, and psychological health outcomes.

•Diagnosis of Polyendocrine Metabolic Ovarian Syndrome (PMOS)

The diagnosis of Polyendocrine Metabolic Ovarian Syndrome (PMOS) is based on a comprehensive clinical, biochemical, and imaging evaluation, as there is currently no single diagnostic test that confirms the disorder. Diagnosis requires

careful assessment of reproductive, endocrine, and metabolic features while excluding other disorders that may present with similar clinical manifestations. Early diagnosis is essential for preventing long-term reproductive, metabolic, and cardiovascular complications.

The diagnosis is commonly established using the internationally accepted Rotterdam criteria, which require the presence of at least two of the following three features after excluding alternative causes:

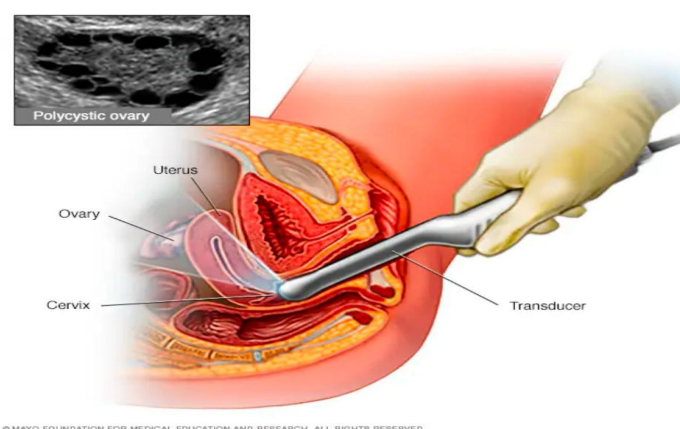
1. Oligo-ovulation or anovulation, manifested as irregular, infrequent, or absent menstrual cycles.
2. Clinical or biochemical hyperandrogenism, including hirsutism, persistent acne, androgenic alopecia, or elevated serum androgen concentrations.
3. Polycystic ovarian morphology (PCOM) on pelvic ultrasonography or elevated anti-Müllerian hormone (AMH) levels, where supported by current clinical recommendations.

Clinical Assessment

Diagnosis begins with a detailed medical history focusing on menstrual irregularities, infertility, weight changes, family history of endocrine or metabolic disorders, and symptoms of androgen excess. A comprehensive physical examination is performed to identify clinical signs of hyperandrogenism, including hirsutism, acne, seborrhea, and androgenic alopecia. Anthropometric measurements such as body mass index (BMI), waist circumference, and blood pressure are assessed to evaluate obesity and cardiometabolic risk. Cutaneous manifestations of insulin resistance, including acanthosis nigricans and skin tags, should also be examined.

Laboratory Evaluation

Biochemical investigations are performed to confirm



hyperandrogenism, assess metabolic abnormalities, and exclude disorders with similar clinical presentations. Hormonal evaluation typically includes total and free testosterone, dehydroepiandrosterone sulfate (DHEA-S), sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and anti-Müllerian hormone (AMH). Additional investigations such as thyroid-stimulating hormone (TSH), prolactin, and 17-hydroxyprogesterone are recommended to exclude thyroid

dysfunction, hyperprolactinemia, and non-classical congenital adrenal hyperplasia.

Metabolic assessment includes fasting plasma glucose, glycated hemoglobin (HbA1c), fasting insulin, oral glucose tolerance testing when indicated, and a fasting lipid profile to evaluate insulin resistance, prediabetes, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome.

Imaging Studies

Pelvic ultrasonography, preferably transvaginal ultrasonography in sexually active women, is used to assess ovarian morphology. Typical findings include enlarged ovaries containing multiple small peripheral follicles and increased ovarian volume. Recent evidence suggests that serum AMH may complement or, in selected clinical settings, reduce the need for ultrasonography because AMH reflects the increased number of small antral follicles commonly observed in PMOS.

Pelvic Examination in PMOS A pelvic examination helps assess the reproductive organs for abnormalities such as ovarian enlargement, pelvic masses, tenderness, or structural changes. Although it does not diagnosis PMOS directly, it helps exclude other gynecological conditions and supports

are interpreted along with clinical symptoms and hormonal investigations, as ovarian morphology alone is not sufficient to diagnose PMOS.

Differential Diagnosis

Before confirming PMOS, clinicians should exclude other endocrine disorders that may mimic its clinical features, including thyroid disorders, hyperprolactinemia, Cushing syndrome, androgen-secreting ovarian or adrenal tumors, non-classical congenital adrenal hyperplasia, hypothalamic amenorrhea, and primary ovarian insufficiency.

Because PMOS exhibits considerable clinical heterogeneity, diagnosis should integrate clinical findings, laboratory investigations, imaging results, and metabolic assessment rather than relying on a single investigation. A multidisciplinary approach involving gynecologists, endocrinologists, and primary care physicians facilitates early diagnosis, individualized treatment, and long-term monitoring to reduce reproductive, metabolic, and cardiovascular complications.

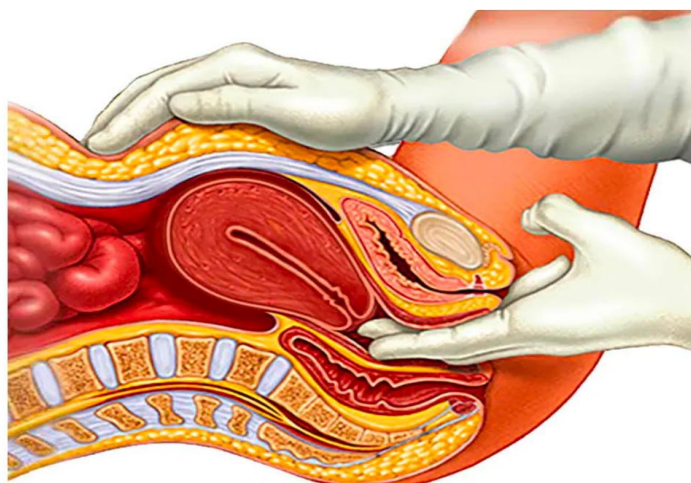
Future Perspectives of Polyendocrine Metabolic Ovarian Syndrome (PMOS)

The evolving understanding of Polyendocrine Metabolic Ovarian Syndrome (PMOS) represents a major shift from viewing the disorder as primarily an ovarian condition to recognizing it as a complex, lifelong endocrine-metabolic disease. The updated disease concept emphasizes the interaction between reproductive dysfunction, hormonal imbalance, metabolic abnormalities, cardiovascular risk, and psychological health. Future approaches are expected to focus on early identification, personalized management, multidisciplinary care, and development of targeted therapies.

Advancement in Early Diagnosis and Screening

Future diagnostic strategies for PMOS are expected to move beyond the traditional recognition of symptoms after disease manifestation and focus on early detection, particularly among adolescents and high-risk populations. Although current diagnosis relies mainly on established criteria involving ovulatory dysfunction, hyperandrogenism, and ovarian morphology, emerging biomarkers such as anti-Müllerian hormone (AMH), metabolic markers, genomic profiles, and epigenetic signatures may improve early identification and risk prediction. Earlier diagnosis may allow timely lifestyle and therapeutic interventions to prevent progression to insulin resistance, type 2 diabetes mellitus, cardiovascular disease, and other long-term complications.

Transition Toward Integrated Multidisciplinary Care



© MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH. ALL RIGHTS RESERVED.

evaluation along with hormonal tests and pelvic ultrasound.

Transvaginal Ultrasound in PMOS

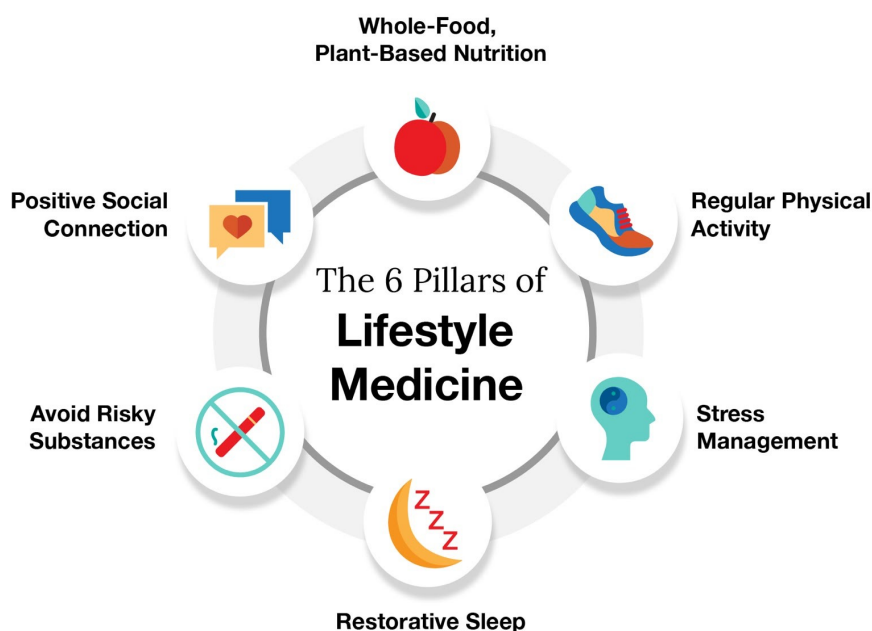
Transvaginal ultrasonography is an important imaging method used in the evaluation of PMOS. A high-frequency, wand-shaped ultrasound probe is gently inserted into the vagina to produce detailed images of the ovaries and uterus. It helps assess ovarian volume, follicular distribution, and endometrial thickness. Findings such as increased ovarian volume and multiple small antral follicles may support the diagnosis of polycystic ovarian morphology. However, ultrasound findings

The future management of PMOS will increasingly adopt a holistic, patient-centered approach rather than focusing only on menstrual irregularities and fertility problems. Comprehensive care models will include continuous monitoring of metabolic health, cardiovascular risk factors, weight management, reproductive function, dermatological symptoms, and psychological well-being. Collaboration among endocrinologists, gynecologists, nutritionists, dermatologists, fertility specialists, and mental health professionals will become essential for improving long-term

cardiovascular disease. Preventive strategies, including lifestyle modification, nutritional interventions, physical activity programs, and early metabolic screening, will play a central role in reducing disease burden.

Enhanced Research, Awareness, and Global Healthcare Policies

The expanding recognition of PMOS is expected to encourage greater investment in clinical research, patient education, and



outcomes.

Personalized Medicine and Novel Therapeutic Approaches

Advances in genomics, metabolomics, artificial intelligence, and precision medicine are expected to transform PMOS management by enabling individualized treatment strategies based on genetic, hormonal, and metabolic profiles. Future therapies may target specific pathogenic pathways involved in insulin resistance, androgen excess, inflammation, oxidative stress, and ovarian dysfunction. Research into novel pharmacological agents, metabolic therapies, microbiome-based interventions, and epigenetic modulation may provide additional treatment options beyond current approaches.

Improved Focus on Metabolic and Cardiovascular Health

As PMOS is increasingly recognized as a systemic metabolic disorder, future guidelines are expected to emphasize long-term surveillance for obesity, insulin resistance, dyslipidemia, hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), and

healthcare policies. Increased awareness among healthcare professionals and affected individuals may reduce diagnostic delays, improve access to care, and minimize the stigma associated with reproductive and metabolic symptoms. International collaboration and updated clinical guidelines will continue to refine disease classification, diagnostic approaches, and evidence-based management strategies.

Overall, the future perspective of PMOS lies in transforming care from symptom-based treatment to proactive, preventive, and personalized healthcare. A comprehensive understanding of its endocrine, metabolic, reproductive, and psychological dimensions will be essential for improving quality of life and reducing the long-term health consequences experienced by millions of women worldwide.

Conclusion

Polyendocrine Metabolic Ovarian Syndrome (PMOS), formerly recognized as Polycystic Ovary Syndrome (PCOS), is a complex, lifelong endocrine–metabolic disorder that extends beyond ovarian dysfunction. The evolving understanding of PMOS highlights its systemic nature, involving reproductive abnormalities, insulin resistance, hyperandrogenism, metabolic disturbances, inflammatory

pathways, and psychological health challenges. The condition affects millions of women worldwide and remains a significant public health concern due to its association with infertility, type 2 diabetes mellitus, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and reduced quality of life.

Advances in understanding the pathophysiology of PMOS have revealed the important roles of genetic susceptibility, epigenetic regulation, hormonal imbalance, insulin resistance, oxidative stress, and chronic low-grade inflammation in disease development and progression. Accurate diagnosis requires a comprehensive approach combining clinical assessment, biochemical evaluation, and imaging techniques while excluding other endocrine disorders with similar presentations. Early identification of affected individuals provides an opportunity for timely intervention and prevention of long-term complications.

Management of PMOS requires a multidisciplinary and patient-centered approach focusing on lifestyle modification, metabolic risk reduction, reproductive health, and psychological support. Individualized therapeutic strategies, including nutritional interventions, physical activity, pharmacological treatments, and fertility management, can significantly improve clinical outcomes. Emerging advances in precision medicine, molecular research, and biomarker discovery are expected to enhance early diagnosis and enable targeted therapies in the future.

The recognition of PMOS as a systemic endocrine–metabolic disorder represents an important step toward improving awareness, reducing diagnostic delays, and optimizing long-term healthcare. Continued research, global collaboration, and comprehensive clinical approaches are essential to reduce disease burden and improve the reproductive, metabolic, and overall health outcomes of women affected by PMOS worldwide.

REFERENCES

1. Mayo Clinic Staff. Polyendocrine metabolic ovarian syndrome (PMOS): Symptoms and causes. Mayo Clinic. 2026. Available from: <https://www.mayoclinic.org/diseases-conditions/pcos/symptoms-causes/syc-20353439>
2. Max Healthcare. Why PCOS became PMOS: Symptoms, causes, fertility and treatment. Max Healthcare. May 19, 2026. Available from: <https://www.maxhealthcare.in/blogs/why-pcos-became-pmos>
3. American Society for Reproductive Medicine (ASRM). PCOS is now PMOS: Understanding the name change. May 27, 2026. Available from: <https://www.asrm.org/news-and-events/asrm-news/latest-news/may-27-2026-pcos-is-now-pmos-understanding-the-name-change/>
4. Endocrine Society. Polyendocrine metabolic ovarian syndrome: New name to improve diagnosis and care of condition affecting 170 million women worldwide. May 12, 2026. Available from: <https://www.endocrine.org/news-and-advocacy/news-room/2026/pcos-name-change>
5. Journal of Clinical Investigation (JCI). Research article on polyendocrine metabolic ovarian syndrome (PMOS). Available from: <https://www.jci.org/articles/view/202824>
6. Mayo Clinic Staff. Polyendocrine metabolic ovarian syndrome (PMOS): Diagnosis and treatment. Mayo Clinic. 2026. Available from: <https://www.mayoclinic.org/diseases-conditions/pcos/diagnosis-treatment/drc-20353443>
7. American Society for Reproductive Medicine (ASRM). PCOS is now PMOS: Understanding the name change. May 27, 2026. Available from: <https://www.asrm.org/news-and-events/asrm-news/latest-news/may-27-2026-pcos-is-now-pmos-understanding-the-name-change/>
8. Endocrine Society. Polyendocrine metabolic ovarian syndrome: New name to improve diagnosis and care of condition affecting 170 million women worldwide. May 12, 2026. Available from: <https://www.endocrine.org/news-and-advocacy/news-room/2026/pcos-name-change>
9. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *J Clin Endocrinol Metab.* 2023;108(10):2447–2469. doi:10.1210/clinem/dgad463. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10505534/>
10. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1):19–25. Available from: <https://pubmed.ncbi.nlm.nih.gov/?term=Revised+2003+consensus+diagnostic+criteria+polycystic+ovary+syndrome>
11. Bruni V, Capozzi A, Lello S. The role of genetics, epigenetics and lifestyle in polycystic ovary syndrome development: The state of the art. *Reprod Sci.* 2022;29(3):668–679. doi:10.1007/s43032-021-00515-4. Available from: <https://pubmed.ncbi.nlm.nih.gov/33709373/>
12. Stener-Victorin E, Deng Q. Epigenetic inheritance of polycystic ovary syndrome—challenges and opportunities for treatment. *Nat Rev Endocrinol.* 2021;17:521–533. doi:10.1038/s41574-021-00517-x. Available from: <https://www.nature.com/articles/s41574-021-00517-x>
13. Chen Y, Wang G, Chen J, Dong X, Chang HM, Yuan S, et al. Genetic and epigenetic landscape for drug development in PCOS. *Endocr Rev.* 2024. doi:10.1210/endrev/bnae002. Available from: <https://doi.org/10.1210/endrev/bnae002>
14. Manzano-Nunez R, Santana-Dominguez M, Rivera-Esteban J, Sabiote C, Sena E, Bañares J, et al. Non-alcoholic fatty liver disease in patients with polycystic ovary syndrome: A systematic review, meta-analysis, and meta-regression. *J Clin Med.* 2023;12(3):856. doi:10.3390/jcm12030856. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9917911/>
15. Shengir M, Chen T, Guadagno E, Ramanakumar AV, Ghali P, Deschenes M, et al. Non-alcoholic fatty liver disease in premenopausal women with polycystic ovary syndrome: A systematic review and meta-analysis. *JGH Open.* 2021;5(4):434–445. doi:10.1002/jgh3.12512. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8035436/>
16. Mayo Clinic Staff. Polycystic ovary syndrome: Symptoms and causes. Available from:

<https://www.mayoclinic.org/diseases-conditions/pcos/symptoms-causes/syc-20353439>

17. Mayo Clinic Staff. Polycystic ovary syndrome: Diagnosis and treatment. Available from:

<https://www.mayoclinic.org/diseases-conditions/pcos/diagnosis-treatment/drc-20353443>

18. Max Healthcare. Why PCOS became PMOS: Symptoms, causes, fertility and treatment. May 19, 2026. Available from:

<https://www.maxhealthcare.in/blogs/why-pcos-became-pmos>

19. Journal of Clinical Investigation. Article associated with PMOS terminology. Available from:

<https://www.jci.org/articles/view/202824>