Recent advances in polyendocrine metabolic ovarian syndrome and obesity: a comprehensive review

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Purpose of review
This review evaluates recent advances in polyendocrine metabolic ovarian syndrome (PMOS), emphasizing its complex association with obesity and the ongoing transition toward precision medicine. The synthesis of current evidence addresses pathophysiology, emerging biomarkers, and multiomics approaches, highlighting their potential to enhance diagnosis, risk stratification, and individualized management.

Recent findings
PMOS is a multifactorial disorder involving insulin resistance, hyperandrogenism, genetic predisposition, gut dysbiosis, and environmental factors. Obesity intensifies metabolic and reproductive dysfunction through mechanisms including chronic inflammation, adipose tissue dysfunction, and altered gut–ovary signalling. Traditional phenotype-based classifications do not adequately capture this biological heterogeneity. Multiomics approaches that integrate genomics, transcriptomics, proteomics, metabolomics, and microbiome data have identified distinct molecular subtypes, including insulin-resistant, steroidogenic, inflammatory, and neuroendocrine clusters. Novel biomarkers, including anti-Müllerian hormone, free androgen index, and specific metabolomic and lipidomic signatures, have the potential to improve diagnostic accuracy and phenotyping.

Summary
The integration of multiomics represents a pivotal advancement toward patient-centred care in PMOS by enabling early risk prediction and mechanism-based therapies. While current evidence remains largely exploratory, these developments support a shift from uniform treatment strategies to precision endocrinology, with the potential to substantially improve long-term metabolic and reproductive outcomes.

Keywords
diagnostic techniques, obesity, polycystic ovarian syndrome, precision medicine, therapeutics

INTRODUCTION

Polyendocrine metabolic ovarian syndrome (PMOS), also known as polycystic ovarian syndrome (PCOS), is characterized by irregular menstrual cycles, abnormal ovulation, hirsutism, and infertility due to higher androgen levels. Further, it also predisposes women to metabolic complications, including type 2 diabetes mellitus (T2D), gestational diabetes, dyslipidaemia, hypertension, cardiovascular disease and metabolic dysfunction-associated steatotic liver disease (MASLD) [1▪▪].

Although studies have demonstrated a positive association between obesity and PMOS, the evidence has not been sufficient to establish causality [2,3]. The risk of metabolic complications is higher in women with PMOS and obesity compared to those without obesity [4,5]. The central role of insulin resistance in PMOS pathophysiology, along with the beneficial effects of weight reduction on PMOS symptoms and comorbidities, suggests that adipose tissue dysgenesis may contribute to the link between PMOS and obesity [6▪,7▪▪].

PMOS was initially regarded as a disease driven primarily by obesity or ovarian dysfunction. However, the identification of insulin resistance and, more recently, discoveries related to the gut microbiome and genetics, have led to a paradigm shift in

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Curr Opin Endocrinol Diabetes Obes 2026, 33:257–268
DOI:10.1097/MED.0000000000000985

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KEY POINTS

- Polyendocrine metabolic ovarian syndrome (PMOS) is a multifactorial disorder that intertwines with obesity, leading to increased metabolic and reproductive dysfunction through mechanisms such as insulin resistance and chronic inflammation.
- Recent advancements in multiomics, which include integrating genomics, transcriptomics, proteomics, and metabolomics, have helped identify distinct molecular subtypes of PMOS that go beyond traditional phenotype classifications, allowing for improved risk stratification and individualized management.
- New biomarkers such as anti-Müllerian hormone, free androgen index, and specific metabolomic and lipidomic signatures enhance diagnostic accuracy and help in better phenotyping of the disorder, facilitating more precise treatment strategies.
- The integration of multiomics and novel biomarkers suggests a significant transition from uniform treatment approaches to more personalized endocrinology, potentially improving long-term metabolic and reproductive outcomes for individuals with PMOS.
- Despite the high prevalence of PMOS, its complex aetiology and diagnostic challenges underscore the necessity for developing optimal, individualized treatment modalities that account for the diverse factors influencing the condition.

understanding its pathogenesis and aetiology [8]. Factors such as gene variants, chronic low-grade inflammation, and gut dysbiosis indicate that the pathogenesis of PMOS is closely intertwined with obesity [9▪].

Despite the high prevalence of PMOS, its complex diagnostic criteria and multifactorial pathogenesis have hindered the development of optimal, individualized treatment modalities. As a result, PMOS remains one of the most extensively studied endocrine disorders. This review examines recent developments in PMOS and evaluates the interrelationship between PMOS and obesity across various stages of the disorder.

LITERATURE SEARCH STRATEGY

A comprehensive literature search was conducted in PubMed over an 18-month period (September 2024 to March 2026). Relevant keywords, both individually and in combination, included "polycystic ovary syndrome (PCOS)", "obesity", "pathophysiology", "genetics", "epigenetics", "microbiome", "omics", "diagnosis", "biomarkers", "treatment", "management", "recent advances", and "emerging therapies". Additional search terms related to omics approaches, such as "genomics", "transcriptomics", "proteomics", and "metabolomics", were also utilized. The search strategy used is provided in the Supplementary File S1, https://links.lww.com/COE/A44.

Only peer-reviewed, full-text articles published in English and involving human subjects were included. Additionally, select relevant animal model studies were considered. As this is a narrative review, studies were chosen based on relevance, scientific contribution, and recency, rather than predefined systematic criteria. The findings are organized into thematic sections and subsections to provide a structured overview of current evidence on PMOS and obesity.

TERMINOLOGY CHANGE FROM "polycystic ovarian syndrome" TO "polyendocrine metabolic ovarian syndrome"

There has been renewed interest in renaming PCOS, as the current term is considered misleading. The designation "polycystic ovary syndrome" places undue emphasis on ovarian morphology, although these features are neither consistently present nor unique to the disorder. Furthermore, this terminology frames PCOS primarily as a gynaecological condition, thereby minimizing its significant endocrine and metabolic components. Such mischaracterization may contribute to delayed diagnosis, fragmented care, and increased stigma.

Following over a decade of international consultation among clinicians, researchers, and patient advocates, a global consensus process formally adopted the term *"polyendocrine metabolic ovarian syndrome"* in 2026 [10▪▪]. This change aims to more accurately reflect the underlying pathophysiology, reduce stigma, and enhance research efforts. "PMOS" is used throughout for consistency *even though cited primary studies used PCOS*.

DISEASE PATHOPHYSIOLOGY

Despite extensive research, the pathogenesis of PMOS remains incompletely understood. Insulin resistance (IR) plays a central role, with selective resistance in the liver, adipose tissue, and skeletal muscle, leading to increased gluconeogenesis, enhanced lipolysis, and reduced glucose uptake, respectively, which results in impaired glucose tolerance. In contrast, insulin sensitivity is preserved in the ovaries and adrenals. Hyperinsulinemia stimulates ovarian androgen production and reduces hepatic sex hormone–binding globulin (SHBG), thereby increasing free androgens. Hyperandrogenaemia further contributes to dyslipidaemia, particularly through increased HDL catabolism. A bidirectional

relationship between IR and weight gain perpetuates a self-reinforcing cycle [11]. Additional factors contributing to the pathogenesis and currently under investigation are discussed below. Figure 1 illustrates the pathogenesis of PMOS.

Obesity as a driver of polyendocrine metabolic ovarian syndrome

Obesity is independently associated with insulin resistance, chronic inflammation, and gut dysbiosis, which collectively link PMOS and obesity and underscore the role of obesity as a driving force in PMOS pathophysiology. Consequently, obesity may exacerbate both the clinical features (such as hyperandrogenism) and comorbidities (including T2D, MASLD, and dyslipidaemia) associated with PMOS [6▪,11].

Genetics

Numerous gene variants have been implicated in PMOS, including those involved in ovarian and adrenal steroidogenesis, gonadotropin activity, steroid hormone action, and insulin secretion and action. Table 1 lists these genes, their functions, and their roles in PMOS [12,13▪▪,14–19]. Genes involved in insulin signalling pathways represent a common link between obesity and PMOS.

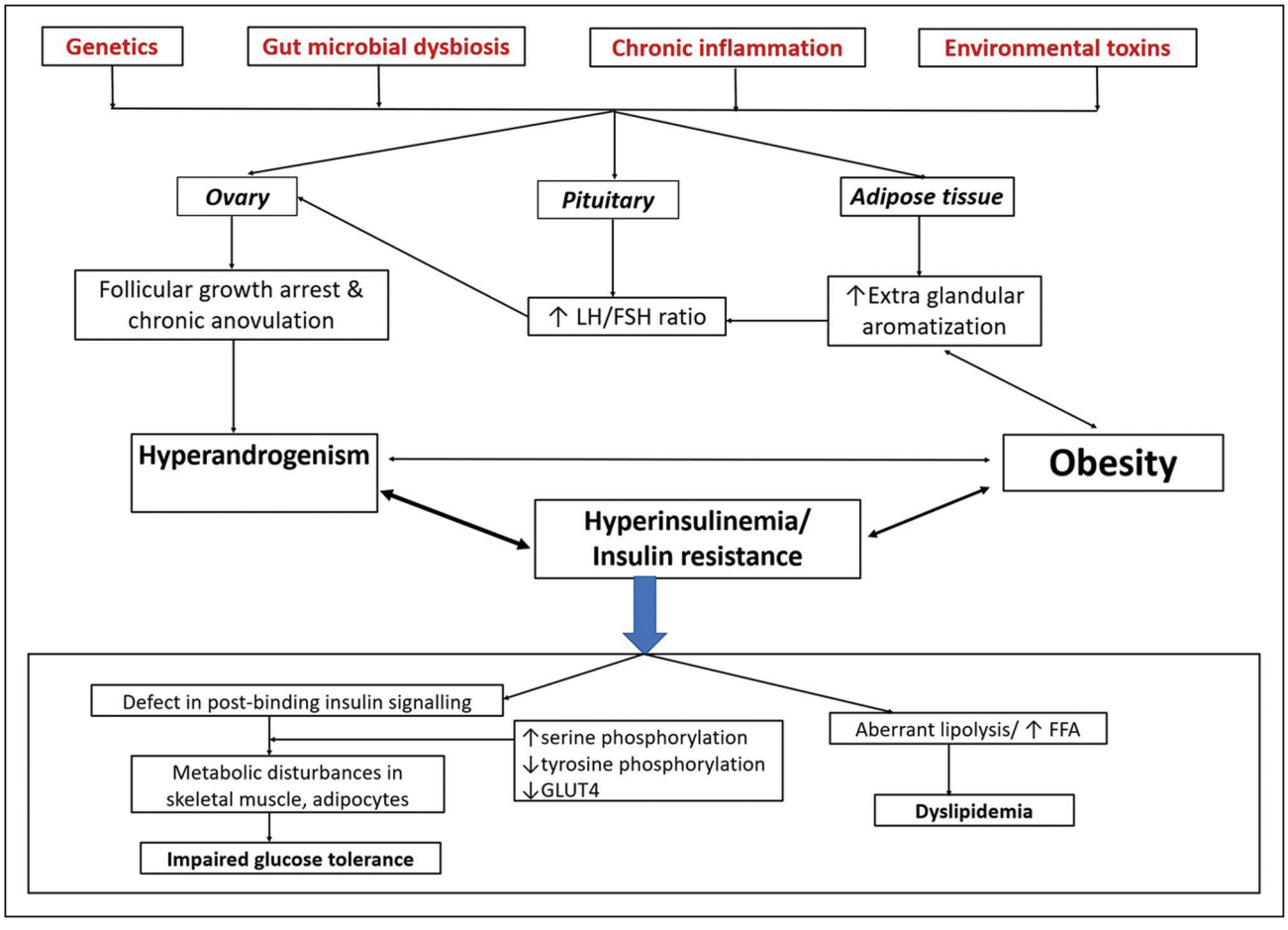

FIGURE 1. Proposed pathophysiology linking polyendocrine metabolic ovarian syndrome and obesity. Upstream contributing factors – genetic susceptibility, gut microbial dysbiosis, chronic low-grade inflammation, and environmental toxins – act on three principal target tissues: the ovary, the pituitary, and adipose tissue. Ovarian involvement produces follicular growth arrest and chronic anovulation; altered pituitary gonadotropin secretion (increased LH relative to FSH) and increased extraglandular aromatization in adipose tissue further disturb the hormonal milieu, together driving hyperandrogenism. Hyperandrogenism, obesity, and hyperinsulinaemia/insulin resistance are mutually reinforcing. Insulin resistance, in turn, gives rise to the downstream metabolic consequences shown in the lower panel: a defect in postbinding insulin signalling (increased serine and reduced tyrosine phosphorylation with reduced GLUT4 expression), producing metabolic disturbances in skeletal muscle and adipocytes and impaired glucose tolerance, and aberrant lipolysis with increased free fatty acids leading to dyslipidaemia. FFA, free fatty acids; FSH, follicle-stimulating hormone; GLUT, glucose transporter type 4; LH, luteinizing hormone.

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Table 1. List of various gene variants associated with PMOS, their function and role in PMOS

Genes	Function	Role in PMOS	Population/ethnicity studied
Genes related to androgen synthesis			
CYP11A1 *CYP17A1* *CYP19A1*	Crucial role in androgen biosynthesis	Genetic polymorphisms are associated with increased PMOS risk	Asian, European, White, Middle Eastern, North African
DENND1A[*]	Regulates androgen biosynthesis	Variant leads to overexpression of DENND1A in ovarian theca cells	White, Asian, European
SRD5A1	Codes for SD5A1 enzyme that converts testosterone to dihydrotestosterone (active form)	SRD5A1 are expressed in hair follicles and SNP in the *SRD5A1* gene is associated with hirsutism	White, European
Genes related to gonadotropin pathway			
FSHβ *FSHR*[*]	Development and maturation of ovarian follicles	Gene variants inhibit follicular maturation and have been associated with dyslipidaemia in women with PMOS	Asian, Middle Eastern, European
LHβ *LHCGR*[*]	Regulation of ovarian function	*LH* and *LHR* gene polymorphisms have been associated with PMOS and increased fasting blood glucose	Asian, Middle Eastern, European
Genes related to androgen action			
AR	*AR* gene encodes androgen receptor that binds androgens	Polymorphism in *AR* gene leads to enhancement of AR signalling, leading to exaggerated androgen effects in target tissues. Shorter repeats associated with increased severity	Asian, European
SHBG	*SHBG* gene codes for SHBG protein produced from the liver that binds to sex hormones and regulates the level of free hormones	Gene variant in PMOS has been noted to be associated with reduced SHBG	Asian, European, Hispanic, North African
Genes related to folliculogenesis *AMH* *AMHR*	*AMH* gene encodes a glycoprotein that modulates folliculogenesis and ovarian reserve and AMH acts on *AMHR*	Variant have been associated with reduced AMH-mediated signalling and dyslipidaemia in women with PMOS	Asian, White, Middle Eastern
Genes related to insulin signalling pathway			
INS[*] *INSR*[*]	Important role in insulin signalling pathway	Variants of *INSR* gene are associated with PMOS especially in lean women	Asian, White, European, Middle Eastern
CAPN10	Codes for CAPN-10 protein that has a role in insulin stimulated glucose uptake	Inconsistent association between *CAPN10* gene variants and PMOS with positive association among Asian ethnicity and mixed ethnicities in few studies	Asian, White, European, Middle Eastern
FTO[$]	Plays regulatory role in energy metabolism	Variants in *FTO* gene were associated with increased susceptibility to PMOS	Asian, European, Middle Eastern, North African
THADA[*]	Linked to energy metabolism, β-cell function, affecting insulin secretion and glucose homeostasis	Gene polymorphisms associated with PMOS and dyslipidaemia (metabolic syndrome)	Asian, European
RAB5B[*]	*RAB5B* plays crucial role in insulin-mediated glucose uptake	SNPs were significantly associated with PMOS risk only in subjects with higher BMI ($\geq$23.8 kg/m^2)	Asian (Indian, Chinese)

Table 1 (*Continued*)

Genes	Function	Role in PMOS	Population/ethnicity studied
Other genes			
TOX3	*TOX3* gene encodes a calcium-dependent neuronal transcription factor and is involved in protecting neuronal cells from cell death	*TOX3* gene polymorphism and abnormal methylation has been associated with PMOS. In knockout mice model, *TOX3* knock-out has been associated with obesity and hence has been thought to associated with PMOS through metabolic disorder-related pathway	Asian, European, middle Eastern
YAP1	*YAP1* gene codes for YAP1 protein plays a key role in the Hippo signalling network that governs cellular and organismal metabolism	Gene polymorphisms were associated with increased PMOS risk	Asian, European
HMGA2	HMGA2 is highly expressed during embryonic, implying that it might play a role in controlling cell proliferation. It has been associated with adult stature and type 2 diabetes	Gene polymorphisms have been associated with PMOS	Asian (Han Chinese)
IL-6	*IL-6* gene codes for IL-6 cytokine which has both pro-inflammatory and anti-inflammatory actions	Polymorphisms have been associated with risk of PMOS	Asian, European

AMH, antimullerian hormone; AMHR, antimullerian hormone receptor; AR, androgen receptor; CAPN10, calpain 10; DENND1A, differentially expressed in normal and neoplastic development 1A; FSH, follicle stimulating hormone; FSHR, follicle stimulating hormone receptor; FTO, fat and obesity associated gene; HMGA2, high-mobility group AT-hook 2; IL-6, interleukin 6; INS, insulin; INSR, insulin receptor; LH, luteinizing hormone; LHCGR, luteinizing hormone/ chorionic gonadotropin; RAB5B, Ras-related protein Rab-5b; SHBG, sex hormone binding globulin; SNPs, single nucleotide polymorphisms; SRD5A1, steroid 5-α reductase 1; THADA, thyroid adenoma-associated; TOX3, TOX high mobility group box family member 3; YAP1, Yes-associated protein 1.
*PMOS specific genes with obesity interaction.
$Gene variants common between obesity and PMOS.

Gut microbiota

Recent studies have identified the gut microbiome and its metabolites as critical regulators of PMOS pathogenesis. In healthy individuals, the gut microbiota and ovary communicate bidirectionally through integrated metabolic, immunologic, and neuroendocrine pathways, collectively referred to as the gut–ovary axis [20▪]. Disruption of the intestinal barrier alters the microbiota, allowing the entry of bacterial components and initiating immune dysregulation and metabolic disturbances. Gut microbial dysbiosis is associated with altered production of short-chain fatty acids and elevated branched-chain amino acids, which contribute to metabolic dysfunction and hormonal imbalance, ultimately leading to hyperandrogenism [21]. Additionally, intestinal barrier dysfunction promotes chronic inflammatory signalling, insulin resistance, adipose tissue dysfunction, and disruption of the hypothalamic–pituitary–ovarian axis. Collectively, these mechanisms contribute to the onset and progression of PMOS [20▪,21,22▪▪].

Chronic inflammation

The chronic inflammation hypothesis, which posits that immune cell imbalance and dysregulation of inflammatory factors play a pivotal role in PMOS pathogenesis by resulting in systemic low-grade chronic inflammation [23], has recently been challenged. While studies have demonstrated elevated C-reactive protein (CRP) levels, other key inflammatory markers, such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ (IFN-γ), have shown inconsistent elevation in patients with PMOS.

Emerging evidence from human and animal studies indicates that immune responses in PMOS are heterogeneous and vary across tissues, including the hypothalamus, pituitary, ovaries, endometrium, and adipose tissue. These findings suggest that PMOS involves discrete, tissue-specific immune interactions with endocrine cells that contribute to disease pathophysiology. However, most of this research has been conducted in hyperandrogenic animal models, which replicate the hormonal environment of PMOS but do not fully capture the genetic and epigenetic factors contributing to its pathogenesis [24], thus mandating more evidence from human studies.

Environmental toxins

Environmental pollutants may contribute to PMOS. Research from Taiwan [25] and Korea [26] shows that

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exposure to pollutants such as nitrogen dioxide and particulate matter is linked to a higher risk of PMOS, with risk increasing with exposure concentration and duration [26].

While smoking is not a clearly established risk factor for PMOS, some studies suggest a connection. For example, Zhang *et al.* found that women with PMOS and oligo-anovulation had greater smoke exposure than a control group (37.7% vs. 12.1%, $P < 0.01$) [27].

Additionally, studies on endocrine-disrupting chemicals (EDCs) such as parabens and bisphenol A report mixed associations with PMOS [28▪].

DISEASE DIAGNOSIS

The Rotterdam criteria are the most common diagnostic tools for PMOS, endorsed by the recent PMOS guidelines [29], requiring at least two of the following: clinical or biochemical hyperandrogenism (HA), anovulation/ovulatory dysfunction (OD), and polycystic ovary morphology (PCOM) via ultrasound. However, PCOM assessment can be subjective, and biochemical hyperandrogenism tests, such as testosterone measurement, have moderate sensitivity (~70–75%) [30].

AMH levels are significantly elevated in adult women with PMOS compared to controls [31] and the recent PMOS guidelines [29] recommended AMH as a biomarker in adults instead of PCOM in ultrasound when either anovulation or hyperandrogenism is present. Although AMH declines with age [32], levels remain comparable across age groups in women with PMOS [33]. A recent meta-analysis found that AMH alone is not an ideal diagnostic tool for PCOM in adults and is a nonspecific marker in adolescents [34▪]. Therefore, the diagnostic utility of AMH in PMOS requires further investigation, including the establishment of phenotype [35] and ethnicity-specific cut-off and its utility in diagnosis in adolescents and young adults, where transvaginal ultrasound is not feasible.

Measurement of 11-oxyandrogens is particularly valuable in diagnosing and managing PMOS, as affected women may present with clinical symptoms of androgen excess despite normal levels of traditional androgens. In contrast, 11-oxyandrogens are frequently elevated in PMOS and provide a more accurate reflection of the underlying hyperandrogenic state. Specifically, 11-ketoandrostenedione (11-KA4) has emerged as a highly discriminatory biomarker for PMOS [36,37].

To address the operator-dependent subjectivity in measuring polycystic ovary morphology (PCOM), shear wave elastography (SWE) has been investigated in women with PMOS to assess ovarian stromal thickness [38]. The meta-analysis by Ruan *et al.* reported that women with PMOS had significantly higher shear wave elasticity [SMD 1.86 kilopascal (95% CI: 1.27–2.44)] and ovarian strain ratio [SMD 2.07 kilopascal (95% CI: 1.79–2.34)] compared to control [39▪].

POLYENDOCRINE METABOLIC OVARIAN SYNDROME PHENOTYPES

The phenotypic classification of PMOS includes four categories based on diagnostic criteria: A (HA+OD +PCOM), B (HA+OD), C (HA+PCOM), and D (OD +PCOM). Phenotypes A and B, known as NIH phenotypes, are linked to more metabolic complications [40], while C and D are classified as non-NIH. A meta-analysis of genome-wide studies found similar genetic architectures in women diagnosed by both NIH and Rotterdam criteria [41], suggesting that phenotype classification may not differentiate biologically distinct subgroups for targeted therapy.

Clustering analyses using various clinical and biochemical parameters have identified three distinct phenotypes across diverse populations: a metabolic cluster (higher BMI, BP, insulin, lipids, glucose; lower SHBG and LH), a reproductive cluster (higher LH, androstenedione, DHEAS, and SHBG; lower insulin, BMI, and BP), and an intermediate cluster [42,43▪,44]. Among PMOS women undergoing in vitro fertilization (IVF), those in the reproductive cluster demonstrated better reproductive outcomes compared to the metabolic cluster (greater clinical pregnancy rate OR 3.37, 95% CI 1.77–6.44), highlighting the need for individualized care during assisted reproductive techniques [44]. Identifying these mechanistically distinct subtypes may enhance precision medicine strategies for PMOS treatment and prevention.

COMPLICATIONS

Women with PMOS are at increased risk for cardiometabolic disorders and metabolic syndrome (MetS) [45]. Insulin resistance and hyperandrogenism synergistically amplify the risk of cardiovascular disease [46]. The prevalence of gestational diabetes is also higher in women with PMOS, and a study involving 622 women identified age, BMI, blood pressure, triglycerides, testosterone, and LH as independent predictors of gestational diabetes [47▪]. Women with PMOS and pregestational diabetes are at increased risk of pregnancy complications, including pregnancy-induced hypertension (aOR 1.55; 95% CI 1.25–1.92), preeclampsia [adjusted odds ratio (aOR) 1.45; 95% CI 1.04–2.02], and preterm delivery (aOR 1.40; 95% CI 1.09–1.80) [46]. PMOS also increases

the risk of endometrial cancer in premenopausal women compared to those without PMOS (OR 5.14; 95% CI 3.22–8.21) [48]; [hazard ratio (HR) = 5.82; 95% CI, 3.64–9.30] [49]. Obesity independently increases the risk of each of the above complications and thus placing women with PMOS and obesity at a heightened risk of complications compared to women with lean PMOS [50▪].

TREATMENT

Management of PMOS has traditionally focused on lifestyle changes, hormonal contraceptives, antiandrogens, and metformin [51]. However, modern treatments are becoming more individualized and mechanism-based [52,53], with a strong emphasis on weight loss interventions. Table 2 highlights various treatment options, their mechanisms, and recent evidence supporting them [54–58,59▪,60–64,65▪,66].

Lifestyle management

Lifestyle modification is key in managing PMOS, with weight reduction being more impactful than specific diets [67▪]. The ketogenic diet shows benefits but raises sustainability concerns [68]. Time-restricted eating is a good alternative [69,70]. Regular

Table 2. Mechanisms of action of hypothesized and established pharmacological, lifestyle, surgical and adjunctive interventions in PMOS, illustrating a major study for each

Intervention	Mechanism of action	Evidence
Interventions primarily targeting weight loss		
Lifestyle modification (diet, exercise)	Energy deficit and improved body composition decrease insulin resistance and hyperinsulinemia, which in turn decrease ovarian and adrenal androgen production and restore ovulation; exercise independently improves insulin sensitivity and reduces inflammation and oxidative stress.	Dietary interventions such as foods with low glycaemic index scores, caloric restrictions, high-fibre, omega-3 fatty acid-rich diets, ketogenic diets, Mediterranean diets, antioxidant-rich foods, and anti-inflammatory diets improve insulin sensitivity and hormonal balance in women with PMOS. Physical activity, like aerobic and resistance exercise, enhances insulin sensitivity, helps with weight loss, and improves metabolic and reproductive outcomes in women with PMOS [54▪]
GLP-1 receptor agonists (liraglutide, semaglutide)	Stimulate GLP-1 receptors to increase glucose-dependent insulin secretion, inhibit glucagon, delay gastric emptying, and decrease appetite via central mechanisms. Weight loss and improved insulin sensitivity lead to decreased androgen levels and normalization of menstrual cycles.	A meta-analysis of 11 RCTs demonstrated a reduction in BMI of –1.38 kg/m^2 (95% CI –2.39 to –0.38)(55). In 330 women in 7 RCTs, liraglutide increased menstrual frequency (Hedges' g = 1.76), decreased BMI and HOMA-IR (both g = –0.52), and improved androgen and SHBG profiles [55].
Dual GIP-GLP-1 receptor agonist (Tirzepatide)	Tirzepatide is a dual GIP and GLP-1 receptor agonist that enhances glucose-dependent insulin secretion, suppresses glucagon release, slows gastric emptying, and reduces appetite. These effects increase satiety and reduce food intake, leading to substantial weight loss and improved glycaemic control.	A retrospective study that included 4241 women with self-reported PMOS, 40 women with PMOS who took Tirzepatide for 10 months lost 19.4% of body weight vs. 18.7% in women without PCOS (n = 397), with no significant difference. 57.7% of women with PCOS achieved ≥20% weight loss [56].
Bariatric/metabolic surgery	Restrictive and/or malabsorptive procedures lead to marked, durable weight loss, with neurohormonal changes that improve insulin resistance, androgen levels, and menstrual and ovulatory function.	A meta-analysis studied the efficacy of bariatric surgery on obesity complicated by PMOS. It included nine studies and found that after weight loss surgery, there was decrease in menstrual irregularity (RD = -0.83), free testosterone levels (MD = -22.70, 95% CI: –36.07~–9.34), hypertrichosis (RR = 0.63, 95% CI: 0.45–0.88), and the ovarian volume (MD = -3.09, 95%CI: –5.76~–0.42) [57]
Interventions primarily targeting insulin signalling pathway		
Inositols (myo-inositol, D-chiro-inositol)	Myo-inositol, which acts as a second messenger in the insulin signalling pathway, enhances GLUT4-mediated glucose uptake and insulin sensitivity, while D-chiro-inositol affects androgen synthesis. Net effect: less insulin resistance, less LH and androgens, more SHBG, better ovulation.	Meta-analysis of 30 trials (n = 2230) found that myo-inositol improved insulin-resistance markers (HOMA-IR and fasting insulin) and that D-chiro-inositol may promote ovulation, with fewer gastrointestinal adverse events than metformin, but metformin had benefits for waist–hip ratio and hirsutism [58]

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Table 2 (*Continued*)

Intervention	Mechanism of action	Evidence
Metformin	Activation of AMP-activated protein kinase results in inhibition of hepatic gluconeogenesis and increased peripheral insulin sensitivity. Thus biguanide decreases insulin-mediated androgen production from the ovary and may have a direct effect on ovarian steroidogenesis.	The RCT (COMET-PCOS) in adults with PMOS ($n=240$) comparing the change in prevalence of MetS after treatment with Metformin alone, COCP alone or both found no added benefit with Metformin [59▪]. However, a retrospective study ($n=133$) found that low-dose metformin (1000 mg/day), in addition of COCP, had added metabolic benefits (decrease in fasting insulin, fasting glucose and BMI) in adolescents during treatment and during post therapy follow-up(58,59)
SGLT2 inhibitors (empagliflozin)	Inhibits renal sodium-glucose cotransporter-2, leading to glycosuria; this results in weight loss, an improved glycaemic profile, and increased insulin sensitivity, indirectly reducing androgen excess.	An RCT ($n=80$) done to determine the safety and efficacy of empagliflozin in women with PMOS compared to metformin found that empagliflozin may offer greater metabolic benefits than metformin in overweight women with PMOS and prediabetes, making the SGLT2i an alternative or add-on therapy [60].
Interventions targeting the PMOS symptoms		
Combined oral contraceptive pills (COCP)	Works by suppressing the androgen production, which ameliorates skin androgenic symptoms and menstrual dysfunction	A meta-analysis comparing between different COCPs found that combined regimens containing an antiandrogen (Ethinyl oestradiol/Cyproterone acetate) may be better compared with conventional COCPs in reducing hyperandrogenism. However, in view of increased risk of venous thromboembolism, COCPs is still recommended as the first line agent [61].
Antiandrogens (spironolactone)	Competitively blocks the androgen receptor, reducing clinical hyperandrogenism (hirsutism, acne).	A systematic review and meta-analysis (13 studies, $n=961$) that investigated the efficacy and safety of antiandrogens in the management of hormonal and clinical features of PMOS found that there were no differences in hirsutism when antiandrogens + metformin + lifestyle were compared with either antiandrogens + lifestyle or metformin + lifestyle. Hence, limiting its use preferential to COCPs to treat hyperandrogenism in PMOS [62] [63].
Psychotherapy		
Psychological therapy (mindfulness-based art therapy)	Mindfulness combined with creative expression addresses the psychological burden of PMOS, resulting in better body image, distress, and quality of life	A RCT in adult women with PMOS ($n=66$) evaluating the effect of MBAT on body image alteration found that in women randomized to MBAT had greater body image scores (adjusted mean difference from baseline of 29.22 [95% CI 19.54, 38.90], $P<0.05$) and at the one-month follow-up (AMD of 34.77 [95% CI 24.75, 44.80], $P<0.05$) compared to the nonintervention group [64].

AMP, adenosine monophosphate; BMI, body mass index; COCP, combined oral contraceptive pill; DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLUT4, glucose transporter type 4; HOMA-IR, Homeostatic model assessment of insulin resistance; LH, luteinizing hormone; LPS, lipopolysaccharide; MBAT, mindfulness-based art therapy; MD, mean difference; MetS, metabolic syndrome; RCT, randomized controlled trial; RD. relative difference; RR, risk ratio; SGLT2, sodium-glucose cotransporter-2; SHBG, sex hormone-binding globulin; VTE, Venous thromoembolism.

exercise improves hormonal and metabolic health [71], even in those without excess weight [72].

Pharmacological management

Pharmacologic treatment of PMOS has shifted towards agents that specifically target underlying insulin resistance and metabolic dysfunction [73].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent the most extensively studied new pharmacological class for PMOS management [65▪,74,75▪]. Combination therapy with metformin and GLP-1 RAs has demonstrated greater efficacy than metformin alone [76,77]. Semaglutide has been shown to improve BMI and lipid profiles, providing metabolic benefits in obese women [78]. Evidence for dual Glucose-dependent insulinotropic polypeptide (GIP) – GLP-1 RA (Tirzepatide) in women with PMOS remains limited. In a retrospective study of women with overweight/obesity, tirzepatide was associated

with substantial weight loss in those with PMOS, with outcomes comparable to women without PMOS [56,79]. Due to insufficient safety data during pregnancy, discontinuation of these agents prior to conception is recommended [80] (Table 2).

Inositol supplementation, specifically myo-inositol (MI) and D-chiro-inositol (DCI) in a physiological ratio of approximately 40 : 1, has been shown to improve menstrual regularity, metabolic parameters, and fertility outcomes in women with PMOS [58,81].

Adjunctive therapies

Several nutraceutical, dietary, and complementary therapies have been investigated as adjunctive treatments in PMOS, including vitamin D, curcumin, probiotics and synbiotics [82,83]. However, given the limited and heterogeneous evidence supporting these approaches, a detailed discussion of these therapies is beyond the scope of the present review.

Bariatric surgery

For women with severe obesity (BMI $\geq$30 kg/m^2) and infertility unresponsive to lifestyle changes, bariatric surgery (like laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass) is recommended [84]. Endoscopic intragastric balloons offer a temporary option, but further research is needed to provide better reproductive outcome data.

PRECISION MEDICINE IN POLYENDOCRINE METABOLIC OVARIAN SYNDROME

Person-centred care

Studies investigating lifestyle management for PMOS have demonstrated high dropout rates [85,86], highlighting the limitations of traditional, prescriptive management strategies. These findings underscore the need for a shift toward person-centred care [29,87], which acknowledges the heterogeneity of PMOS, the chronic and relapsing nature of weight and metabolic dysfunction, and the psychosocial burden associated with the condition. Importantly, stigma, unrealistic expectations, and lack of individualization are key contributors to poor adherence and disengagement from care. The prevailing approach emphasizes person-centred, evidence-based obesity care, structured around four key pillars: Bias-Free Care, Autonomy, Education, and Access to Care. Bias-Free Care aims to treat all patients with compassion and respect, seeking to eliminate obesity-related stereotypes and stigma. The principle of Autonomy prioritizes patient voice and choice in all obesity care decisions. The Education pillar ensures that current knowledge regarding the disease and available treatments is accurately communicated to patients and their families. Access to Care advocates for equitable access to all treatment options for every patient group [88▪]. Although this framework was primarily developed for patients with obesity, it may also be applicable to the management of women with PMOS where obesity drives the disease process and weight reduction has been found to be beneficial even in women without excess adiposity [72,89].

Emerging biomarkers

Multiomics approaches are transforming the understanding of PMOS by moving beyond traditional phenotype-based diagnostic frameworks toward biologically defined endotypes that more accurately reflect disease heterogeneity. The integration of genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiome data enables the identification of distinct molecular clusters underlying similar clinical presentations [90▪,91]. These multiomics signatures have revealed subgroups characterized by predominant insulin resistance [92,93], ovarian steroidogenic dysregulation [94], inflammatory activation [95,96▪▪], or neuroendocrine imbalance, each associated with different clinical trajectories and therapeutic responses. This stratification supports patient-centred care by enabling more precise risk prediction for metabolic complications, individualized ovulation induction [97] and metabolic therapies, and earlier identification of individuals at risk for adverse outcomes such as type 2 diabetes or gestational diabetes [96▪▪].

A few examples of novel biomarkers include the following: A review of 75 systematic reviews identified 22 key biomarkers, with anti-Müllerian hormone (cut-off 4.8 ng/mL; diagnostic odds ratio (DOR) 24) and free androgen index (DOR 14.08) showing the highest accuracy for phenotyping [98]. Advances in omics technologies have revealed metabolites linked to disrupted methyl-group metabolism (AUCs up to 0.96) [99] and identified potential lipid candidates using machine learning: phosphatidylinositol PI (18 : 0/20 : 3) and phosphatidylethanolamine PE (18 : 1p/22 : 6) with a test-set AUC of 0.815 [100].

Although current evidence remains primarily exploratory and requires validation in larger longitudinal cohorts, multiomics integration represents a critical step toward precision endocrinology in PMOS, with the potential to replace uniform treatment paradigms with mechanism-based, individualized management strategies.

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Targeted therapeutics

Therapeutic strategies are shifting from symptomatic management, such as combined oral contraceptives and metformin that primarily mask rather than alter disease progression, toward agents that disrupt the insulin resistance–hyperandrogenism (IR–HA) loop at specific molecular targets [4]. This approach encompasses metabolic regulators (GLP-1 receptor agonists, SGLT2 inhibitors, brown adipose tissue activators via the BAT-ovarian axis), neuroendocrine modulators (NK3R antagonists, kisspeptin agents), and androgen-synthesis inhibitors (artemisinins acting through LONP1-mediated CYP11A1 degradation). Additionally, natural products including berberine, curcumin, and resveratrol function as multitarget network pharmacology agents that contribute to restoring systemic homeostasis [101▪].

Significant translational gaps persist. Most biomarker evidence is derived from single-centre, observational case-control studies lacking external validation [98,100]. Furthermore, novel therapeutics require comprehensive safety data and biomarker-driven, phenotype-stratified clinical trials [101▪].

CONCLUSION

Recent research highlights the complex nature of PMOS, revealing that factors like genetic predisposition and gut dysbiosis make obesity a critical component of the syndrome's development. Ongoing studies emphasize the need for personalized treatment approaches that consider each patient's unique characteristics. As knowledge grows, new therapeutic strategies informed by genetics and microbiome research may improve management for those affected by PMOS and its metabolic challenges. Continued research is vital for understanding the link between PMOS and obesity in women's health.

Acknowledgements

None.

Use of artificial intelligence: The authors used Rayyan for literature screening and study selection. Grammarly was utilised to assist with language editing and improvement of grammar and readability. No artificial intelligence tools were used for data interpretation, or generation of scientific content. All content has been reviewed and approved by the authors.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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