POLYENDOCRINE METABOLIC OVARIAN SYNDROME (PMOS): PATHOPHYSIOLOGY, DIAGNOSTIC CRITERIA, AND THERAPEUTIC STRATEGIES, A COMPREHENSIVE REVIEW

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Abstract

Background. *Polyendocrine Metabolic Ovarian Syndrome (PMOS) is an emerging clinical construct that encompasses the convergence of multiple endocrine dysregulations principally hyperandrogenism, insulin resistance, hypothyroidism, and hyperprolactinemia manifesting with ovarian dysfunction, metabolic disturbance, and reproductive impairment.*

Unlike classical Polycystic Ovary Syndrome (PCOS), PMOS integrates simultaneous or sequential dysfunction across the thyroid, adrenal, and gonadal axes, creating a complex, overlapping endocrine phenotype that challenges conventional diagnostic algorithms and single axis therapeutic protocols.

Objective. *To comprehensively review the pathophysiological mechanisms underlying PMOS, establish a proposed unified diagnostic framework, and evaluate current and emerging therapeutic strategies that address the syndrome's multiglandular nature.*

Materials and Methods. *A systematic literature review was conducted using PubMed, Scopus, and Google Scholar databases. Studies published between 2005 and 2024 addressing polyendocrine disorders intersecting with ovarian dysfunction, metabolic syndrome, and hormonal dysregulation were included. Case series, observational studies, randomized controlled trials, and review articles were analyzed. Data were synthesized narratively given the heterogeneity of study designs and patient populations.*

Results. *PMOS demonstrates a distinct hormonal signature characterized by elevated androgens, impaired insulin signaling, disrupted thyroid hormone metabolism, and hyperprolactinemic suppression of gonadotropin release. Metabolic co-morbidities including dyslipidemia, visceral adiposity, and nonalcoholic fatty liver disease are present in a significant proportion of affected patients. No universally accepted diagnostic criteria exist; however, proposed frameworks incorporating hormonal panels, ultrasound morphology, and metabolic indices show promising discriminatory validity. Therapeutic approaches targeting insulin resistance as a central pathophysiological hub yield improvements across multiple endocrine axes simultaneously.*

Conclusion. *PMOS represents a clinically significant polyendocrine entity requiring a coordinated, multidisciplinary approach to diagnosis and management. Recognition of its multi-axis nature is essential for optimizing reproductive, metabolic, and long-term cardiovascular outcomes in affected women.*

Keywords: *polyendocrine metabolic ovarian syndrome, PMOS, PCOS, insulin resistance, hyperandrogenism, hypothyroidism, hyperprolactinemia, ovarian dysfunction, metabolic syndrome, endocrine axes.*

INTRODUCTION

The female endocrine system is organized around tightly integrated axes hypothalamic pituitary ovarian (HPO), hypothalamic pituitary thyroid (HPT), and hypothalamic pituitary adrenal (HPA) that function in physiological concert to regulate reproductive cyclicity, metabolism, and homeostasis. When dysfunction emerges within one axis, it rarely exists in isolation. Cross-axis hormonal crosstalk ensures that dysregulation in one gland imposes downstream and upstream consequences upon adjacent endocrine organs. In clinical practice, however, this integrative reality has historically been underappreciated, leading to fragmented diagnostic workups and incomplete therapeutic responses.

Polycystic Ovary Syndrome (PCOS) is the most prevalent female endocrine disorder, affecting an estimated 8–13% of women of reproductive age worldwide. Its diagnostic criteria the Rotterdam, NIH, and AES criteria emphasize androgen excess, oligo ovulation, and polycystic ovarian morphology. Yet a substantial cohort of women presenting with ovarian dysfunction and metabolic disturbance does not fit neatly within these frameworks. Many exhibit concurrent thyroid pathology, adrenocortical hyperactivity, prolactin excess, and profound insulin resistance in a pattern that transcends any single-gland diagnostic label.

The concept of Polyendocrine Metabolic Ovarian Syndrome (PMOS) has emerged from clinical observations at the intersection of gynecological endocrinology, metabolic medicine, and reproductive biology. PMOS is proposed as a syndrome characterized by the simultaneous or sequential dysfunction of two or more endocrine axes most commonly the gonadal, thyroid, adrenal, and pancreatic-metabolic axes with the ovary as the central target and metabolic derangement as both a driver and a consequence of the syndrome. The clinical manifestations are heterogeneous and include anovulatory infertility, hirsutism, acne, alopecia, weight gain, fatigue, menstrual irregularity, and psychological morbidity.

At the Andijan State Medical Institute and its affiliated ASMI Clinic named after Yusuf Otabekov, clinicians encounter a significant burden of female patients presenting with complex endocrine-metabolic-reproductive complaints. The Fergana Valley region of Uzbekistan bears a notable prevalence of thyroid pathology, iodine deficiency disorders, and metabolic syndrome, which may create a regional substrate particularly conducive to polyendocrine overlap syndromes. This review was undertaken to synthesize the current evidence base for PMOS, propose a clinically applicable diagnostic framework, and evaluate therapeutic strategies relevant to both specialized centers and regional clinical practice.

MATERIALS AND METHODS

Literature Search Strategy

A systematic literature search was performed across PubMed/MEDLINE, Scopus, Google Scholar, and the Cochrane Library. Search terms included combinations of: "polycystic ovary syndrome AND thyroid dysfunction", "hyperandrogenism AND insulin resistance AND hypothyroidism", "polyendocrine syndrome AND ovarian dysfunction", "hyperprolactinemia AND PCOS", "adrenal androgen excess AND metabolic syndrome", and "multi-axis endocrine disorder AND reproductive dysfunction". The search was limited to publications from January 2005 to December 2024.

Inclusion and Exclusion Criteria

Inclusion criteria:

• Original research articles, systematic reviews, and meta-analyses addressing polyendocrine conditions intersecting with ovarian dysfunction

• Studies involving women of reproductive age (18–45 years)

• Publications in English, Russian, or Uzbek languages

• Studies reporting hormonal, metabolic, ultrasound, or clinical outcomes

Exclusion criteria:

• Case reports with fewer than 3 patients

• Studies focused exclusively on postmenopausal women

• Publications addressing single axis endocrine disorders without ovarian or metabolic component

• Abstracts without full-text availability

Data Extraction and Synthesis

Two reviewers independently screened titles, abstracts, and full texts. Data were extracted using a standardized template encompassing study design, patient population, endocrine axes involved, diagnostic criteria applied, treatment modalities assessed, and clinical outcomes reported. Narrative synthesis was employed due to the heterogeneity of study designs and outcome measures. Where quantitative data were available, descriptive statistics are presented.

RESULTS AND DISCUSSION

1. Pathophysiological Foundations of PMOS

The pathophysiology of PMOS is anchored in the principle of endocrine axis crosstalk.

Insulin resistance present in up to 70% of women with classical PCOS and an even higher proportion in PMOS functions as a central pathophysiological hub. Hyperinsulinemia stimulates ovarian theca cell androgen synthesis via upregulation of luteinizing hormone (LH) receptor sensitivity, while simultaneously suppressing hepatic sex hormone-binding globulin (SHBG) production, thereby amplifying the bioavailability of free androgens. This androgenic milieu disrupts folliculogenesis, impairs oocyte maturation, and promotes the accumulation of arrested antral follicles characteristic of polycystic ovarian morphology.

The thyroid axis intersects with ovarian function at multiple levels. Thyroid hormone receptors are expressed in granulosa cells, oocytes, and corpus luteum tissue. Hypothyroidism whether overt or subclinical reduces ovarian sensitivity to gonadotropins, impairs granulosa cell proliferation, and suppresses the midcycle LH surge essential for ovulation. Furthermore, thyroid-stimulating hormone (TSH) shares structural homology with FSH and may directly stimulate ovarian receptors, while elevated TSH in hypothyroid states promotes hyperprolactinemia through thyrotropin-releasing hormone (TRH) stimulation of prolactin-secreting pituitary lactotrophs.

Hyperprolactinemia, whether primary or secondary to hypothyroidism or dopaminergic dysregulation, exerts potent inhibitory effects on GnRH pulsatility, thereby suppressing FSH and LH secretion, impairing follicular development, and inducing anovulation. In the context of PMOS, hyperprolactinemia frequently coexists with thyroid dysfunction and insulin resistance, compounding gonadotropin suppression and deepening the severity of ovarian dysfunction.

The adrenal axis contributes to PMOS through excessive production of dehydroepiandrosterone sulfate (DHEAS) and androstenedione, which undergo peripheral

conversion to testosterone and dihydrotestosterone. Adrenocortical hyperresponsiveness mediated by insulin, cortisol excess, or primary adrenal dysregulation augments the total androgenic burden superimposed upon ovarian hyperandrogenism, creating a dual-source androgen excess that is characteristic of the PMOS phenotype.

Table 1. Endocrine Axes Involved in PMOS and Their Primary Mechanisms

Endocrine Axis	Primary Dysregulation	Ovarian Impact	Metabolic Consequence
Gonadal (HPO)	Hyperandrogenism, LH/FSH imbalance	Anovulation, follicular arrest	SHBG suppression, visceral adiposity
Thyroid (HPT)	Hypothyroidism (overt/subclinical)	Impaired folliculogenesis, anovulation	Dyslipidemia, insulin resistance
Prolactin	Hyperprolactinemia	GnRH suppression, luteal defect	Weight gain, dopaminergic disruption
Adrenal (HPA)	DHEAS/androstenedione excess	Androgen amplification	Visceral adiposity, cortisol dysregulation
Pancreatic-Metabolic	Insulin resistance, hyperinsulinemia	Theca cell androgen stimulation	Type 2 DM risk, dyslipidemia, NAFLD

2. Clinical Presentation and Phenotypic Spectrum

The clinical presentation of PMOS is heterogeneous and reflects the particular combination of endocrine axes affected in a given patient. The most common presenting complaints include menstrual irregularity (oligomenorrhea or secondary amenorrhea), anovulatory infertility, hirsutism, acne, androgenic alopecia, weight gain disproportionate to caloric intake, and fatigue. Psychological morbidity including depression, anxiety, and reduced health-related quality of life is prevalent and may be compounded by the chronic, often refractory nature of the syndrome.

Physical examination findings may include signs of androgen excess (Ferriman-Gallwey score > 8), acanthosis nigricans indicating insulin resistance, thyroid enlargement or nodularity, galactorrhea in cases of hyperprolactinemia, and central adiposity. Distinguishing PMOS from isolated PCOS requires a high index of clinical suspicion and a systematic hormonal workup that extends beyond the standard PCOS panel to encompass thyroid function, prolactin, DHEAS, fasting insulin, and adrenal androgen profiles.

3. Diagnostic Framework

No universally accepted diagnostic criteria for PMOS have been established in the peer-reviewed literature, reflecting the syndrome's relatively recent conceptualization. Based on synthesis of available evidence, the following proposed diagnostic framework is presented for clinical consideration. The framework requires fulfillment of the ovarian dysfunction criterion plus evidence of dysfunction in at least two additional endocrine axes:

• **Ovarian Dysfunction Criterion:** Oligo/anovulation AND/OR polycystic ovarian morphology on ultrasound (≥20 follicles per ovary or ovarian volume >10 mL)

• **Androgen Excess Criterion:** Biochemical hyperandrogenism (elevated total or free testosterone, elevated DHEAS) and/or clinical signs of androgen excess (hirsutism, acne, alopecia)

• **Metabolic-Insulin Criterion:** HOMA-IR > 2.5, fasting insulin > 12 mIU/L, or diagnosis of prediabetes/type 2 diabetes mellitus; dyslipidemia (elevated triglycerides, reduced HDL)

• **Thyroid Axis Criterion:** TSH > 4.0 mIU/L (subclinical hypothyroidism) or overt hypothyroidism; positive anti-TPO or anti-thyroglobulin antibodies

• **Prolactin Criterion:** Serum prolactin > 25 ng/mL on two separate measurements, excluding pituitary adenoma by MRI if levels > 100 ng/mL

• **Adrenal Criterion:** DHEAS > 350 µg/dL in the absence of non-classical congenital adrenal hyperplasia (confirmed by 17-OHP stimulation test if indicated)

Table 2. Proposed PMOS Diagnostic Panel

Investigation	Parameter	Threshold / Finding	Axis Assessed
Pelvic Ultrasound	Follicle count / ovarian volume	≥20 follicles or >10 mL	Ovarian (HPO)
Total / Free Testosterone	Serum level	Above laboratory upper limit	Gonadal / Adrenal
DHEAS	Serum level	> 350 µg/dL	Adrenal (HPA)
TSH / fT4 / fT3	Thyroid function	TSH > 4.0 mIU/L	Thyroid (HPT)
Anti-TPO / Anti-Tg Ab	Thyroid autoimmunity	Positive	Thyroid (Autoimmune)
Serum Prolactin	Pituitary lactotroph	> 25 ng/mL (×2)	Prolactin axis
Fasting Insulin / HOMA-IR	Insulin resistance	HOMA-IR > 2.5	Metabolic-Pancreatic
Lipid Profile	Metabolic panel	TG > 150, HDL < 50 mg/dL	Metabolic
LH / FSH ratio	Gonadotropin balance	> 2:1	HPO axis
17-OH Progesterone	Adrenal steroidogenesis	Baseline or stimulated	Adrenal (NCCAH exclusion)

4. Metabolic Co-morbidities

Metabolic co-morbidities represent both a consequence and an amplifier of PMOS. Non-alcoholic fatty liver disease (NAFLD) is present in approximately 30–40% of women with PCOS and is expected to be even more prevalent in PMOS given the additive hepatotoxic effects of hyperinsulinemia, androgen excess, and thyroid hormone deficiency on hepatic lipid metabolism.

Dyslipidemia characterized by elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and elevated small dense low-density lipoprotein (sdLDL) confers substantial cardiovascular risk that extends far beyond the reproductive years.

Type 2 diabetes mellitus represents the most severe metabolic sequela of uncontrolled PMOS. The convergence of insulin resistance, hyperandrogenism, and hypothyroidism creates a profoundly diabetogenic milieu. Long-term cardiovascular risk, including hypertension, atherosclerotic cardiovascular disease, and stroke, is markedly elevated in women with polyendocrine metabolic overlap, necessitating early and sustained metabolic intervention regardless of the patient's primary presenting complaint.

5. Therapeutic Strategies

The therapeutic approach to PMOS must be multimodal and address each dysregulated axis in a coordinated sequence. Because insulin resistance functions as the central pathophysiological driver in the majority of PMOS patients, insulin-sensitizing therapy constitutes the cornerstone of management. Metformin, a biguanide that reduces hepatic glucose production and enhances peripheral insulin sensitivity, has demonstrated efficacy not only in improving metabolic parameters but also in reducing ovarian androgen production, restoring menstrual cyclicity, and improving ovulatory rates in PCOS benefits that are hypothesized to extend to the broader PMOS phenotype.

Thyroid hormone replacement with levothyroxine is indicated in all patients meeting criteria for overt or subclinical hypothyroidism within the PMOS framework. Adequate thyroid hormone restoration ameliorates hyperprolactinemia secondary to elevated TRH, improves gonadotropin pulsatility, and reduces the metabolic burden of hypothyroid-associated dyslipidemia. The target TSH in women of reproductive age seeking fertility should be maintained between 1.0 and 2.5 mIU/L in accordance with current reproductive endocrinology guidelines.

Hyperprolactinemia refractory to thyroid hormone correction warrants dopamine agonist therapy with cabergoline or bromocriptine. These agents reduce prolactin secretion, restore GnRH pulsatility, and have demonstrated beneficial effects on ovulatory function and fertility outcomes. In patients with PMOS, cabergoline may be particularly advantageous given its additional weight-reducing and insulin-sensitizing properties demonstrated in recent clinical literature.

Anti-androgenic therapies including oral contraceptive pills containing cyproterone acetate or drospirenone, and spironolactone address the cutaneous and psychological manifestations of hyperandrogenism while providing cycle regulation. In patients not seeking immediate fertility, combined oral contraceptive therapy remains a valuable component of the PMOS management algorithm. For women pursuing conception, ovulation induction with letrozole (aromatase inhibitor) or clomiphene citrate, adjuncted by insulin sensitizers, represents the primary pharmacological strategy.

Table 3. Therapeutic Algorithm for PMOS by Target Axis

Target Axis	First-Line Therapy	Second-Line / Adjunct	Monitoring Parameter
Insulin Resistance	Metformin 500–2000 mg/day	Inositol, GLP-1 agonists	HOMA-IR, HbA1c, fasting glucose
Thyroid	Levothyroxine (target TSH	Selenium	TSH, fT4, anti-TPO

Target Axis	First-Line Therapy	Second-Line / Adjunct	Monitoring Parameter
(Hypothyroidism)	1–2.5)	supplementation	
Hyperprolactinemia	Cabergoline 0.5–1 mg/week	Bromocriptine	Serum prolactin, MRI if >100
Hyperandrogenism	OCP (cyproterone/drospirenone)	Spironolactone 50–100 mg	FAI, testosterone, Ferriman score
Adrenal Androgen Excess	Low-dose dexamethasone (if NCCAH)	Metformin (insulin-adrenal link)	DHEAS, 17-OHP
Anovulation / Infertility	Letrozole 2.5–5 mg (days 3–7)	Clomiphene + Metformin	Follicular tracking, LH surge
Metabolic / Lipid	Lifestyle modification + Metformin	Statins if indicated	Lipid profile, liver enzymes, BMI

6. Lifestyle Modification and Non-Pharmacological Interventions

Lifestyle modification constitutes an indispensable pillar of PMOS management and should be instituted in parallel with pharmacological therapy rather than as a sequential precondition. A structured program of aerobic exercise (150 minutes per week of moderate-intensity activity) combined with resistance training has been shown to reduce insulin resistance, lower androgen levels, decrease visceral adiposity, and improve menstrual regularity in women with PCOS. These effects are mediated through improvements in skeletal muscle glucose uptake, reduction of adipokine-driven inflammation, and enhanced hypothalamic-pituitary signaling.

Dietary interventions emphasizing a low-glycemic index, anti-inflammatory pattern rich in whole grains, legumes, lean protein, and omega-3 fatty acids are associated with improvements across the metabolic-endocrine spectrum relevant to PMOS. Nutritional iodine adequacy should be specifically assessed in regions such as Uzbekistan where iodine deficiency prevalence is documented, as iodine insufficiency may perpetuate thyroid dysfunction and amplify the PMOS phenotype. Psychological support, including cognitive behavioral therapy for body image disturbance and depression, should be incorporated into the multidisciplinary management plan.

7. Discussion

The conceptual framework of PMOS challenges the longstanding clinical convention of evaluating female endocrine disorders through single-axis lenses. The abundant evidence of bidirectional crosstalk between the HPO, HPT, HPA, and metabolic axes demands an integrative diagnostic and therapeutic paradigm. The clinical implications of missing a concurrent thyroid disorder or adrenal androgen excess in a woman presenting with apparent PCOS are substantial: incomplete treatment, persistent anovulation, failed fertility interventions, and progressive metabolic deterioration.

The regional relevance of PMOS to the Fergana Valley clinical context is notable. Uzbekistan's documented burden of iodine deficiency, evolving rates of metabolic syndrome associated with dietary transition, and relatively limited access to subspecialty endocrinological

evaluation in district-level facilities make the polyendocrine overlap syndrome a practically important diagnostic consideration for general practitioners and gynecologists at institutions such as Andijan State Medical Institute. A low threshold for comprehensive hormonal screening, combined with awareness of the PMOS phenotype, may substantially improve diagnostic yield and treatment outcomes in this population.

The limitations of this review include the absence of universally accepted diagnostic criteria for PMOS, precluding precise epidemiological estimates. The heterogeneity of existing literature on endocrine overlap syndromes and the predominant focus on PCOS as a single-axis entity limit direct data synthesis. Future prospective cohort studies employing the proposed PMOS diagnostic framework, ideally with stratification by regional iodine status and metabolic risk factors, are required to validate the clinical utility of this syndrome construct and establish evidence-based treatment algorithms.

CONCLUSION

Polyendocrine Metabolic Ovarian Syndrome (PMOS) represents a clinically meaningful and physiologically coherent entity that transcends the boundaries of classical PCOS. Its defining characteristic the convergence of dysfunction across multiple endocrine axes upon the ovarian substrate, sustained and amplified by metabolic derangement demands a diagnostic approach that is as comprehensive as the syndrome itself. The proposed diagnostic framework integrating ovarian morphology, androgen profiling, thyroid function, prolactin assessment, and insulin resistance indices provides a clinically applicable starting point for systematic evaluation.

Therapeutically, the recognition of insulin resistance as the central pathophysiological driver justifies its prioritization in the management hierarchy, with targeted interventions for thyroid, prolactin, and adrenal axis dysregulation deployed in coordinated sequence. Lifestyle modification remains foundational and exerts cross-axis benefits that pharmacological therapy alone cannot replicate.

For clinicians practicing in regional settings such as Andijan, Uzbekistan, where thyroid pathology and metabolic syndrome converge against a backdrop of evolving dietary and environmental conditions awareness of PMOS as a distinct clinical syndrome carries direct and immediate clinical value. Improved diagnostic accuracy, tailored multidisciplinary treatment, and earlier metabolic intervention in affected women hold the potential to reduce the long-term burden of infertility, type 2 diabetes, cardiovascular disease, and psychological morbidity associated with this complex endocrine syndrome. This review provides a framework for further clinical investigation and a rationale for the development of standardized PMOS diagnostic and management protocols in regional medical institutions.

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