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Endocrine and metabolic dysfunction in polyendocrine metabolic ovarian syndrome: An overview

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Abstract
Polyendocrine Metabolic Ovarian Syndrome (PMOS) is an emerging concept that expands the understanding of conventional Polycystic Ovary Syndrome (PCOS) by emphasizing its multisystem endocrine and metabolic nature. Rather than being confined to ovarian dysfunction alone, PMOS involves complex interactions among the hypothalamic–pituitary–ovarian (HPO) axis, insulin signaling pathways, adrenal glands, thyroid function, pancreatic endocrine activity, adipose tissue, and inflammatory mediators. These interconnected abnormalities result in reproductive dysfunction, metabolic disturbances, cardiovascular complications, and long-term endocrine disorders. Hyperandrogenism, insulin resistance, obesity, chronic low-grade inflammation, dyslipidemia, oxidative stress, and altered adipokine secretion are central features contributing to disease progression. Emerging evidence also highlights the role of gut microbiota, mitochondrial dysfunction, and epigenetic modifications in disease pathogenesis. Understanding PMOS as a systemic endocrine-metabolic disorder facilitates earlier diagnosis, individualized therapeutic interventions, and improved long-term outcomes. This review summarizes the endocrine abnormalities, metabolic dysfunctions, underlying molecular mechanisms, associated complications, and current therapeutic approaches in PMOS.

Keywords: Polyendocrine metabolic ovarian syndrome, pcos, insulin resistance, hyperandrogenism, endocrine dysfunction, metabolic syndrome, obesity, inflammation

Introduction

Polyendocrine Metabolic Ovarian Syndrome (PMOS) represents an evolving paradigm that recognizes ovarian dysfunction as only one manifestation of a broader systemic endocrine disorder (Kordowitzki and Teede, 2026) [44, 82]. Traditionally, Polycystic Ovary Syndrome (PCOS) has been characterized by hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology (Azziz, 2018) [2]. However, accumulating evidence demonstrates that the syndrome involves multiple endocrine organs and metabolic pathways beyond the ovaries (Livadas and Diamanti-Kandarakis, 2013) [52].

PMOS encompasses disturbances involving the hypothalamic-pituitary axis, pancreas, thyroid gland, adrenal cortex, adipose tissue, liver, gastrointestinal tract, and immune system. These abnormalities interact through hormonal, inflammatory, neural, and metabolic pathways, creating a self-perpetuating cycle of endocrine dysfunction (Senthilkumar *et al*., 2025; Ortega *et al*., 2022) [56, 74].

The syndrome affects approximately 8–20% of reproductive-aged women depending on diagnostic criteria and represents one of the leading causes of infertility, metabolic syndrome, and type 2 diabetes among young women (Thong *et al*, 2020) [86]. Beyond reproductive health, PMOS significantly increases lifetime risks of cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, endometrial carcinoma, and psychological disorders (Tewari *et al*., 2026a) [83].

Endocrine Basis of Polyendocrine Metabolic Ovarian Syndrome (PMOS)

PMOS is fundamentally a disorder of endocrine communication where multiple hormone-producing organs lose coordinated regulation. Instead of isolated ovarian pathology, endocrine abnormalities involve several hormonal axes that collectively contribute to disease progression (Dunlap, 2026) [20].

1. Hypothalamic–Pituitary–Ovarian (HPO) Axis

The hypothalamic–pituitary–ovarian (HPO) axis plays a central role in regulating female reproductive function and is profoundly disrupted in Polyendocrine Metabolic Ovarian Syndrome (PMOS) (Zhao *et al*., 2026) [95]. Normally, the hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner, stimulating the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Zikopoulos *et al*., 2026) [98]. In PMOS, increased GnRH pulse frequency results in excessive LH secretion relative to FSH, leading to enhanced ovarian androgen production by theca cells and impaired follicular maturation (Chan *et al*., 2026; Tewari *et al*., 2026a) [11, 83]. Consequently, ovulation is disrupted, resulting in menstrual irregularities, anovulation, infertility, and the development of multiple immature ovarian follicles. Persistent hyperandrogenism further exacerbates reproductive dysfunction, making HPO axis dysregulation the cornerstone endocrine abnormality in PMOS (Sharma *et al*., 2026) [75].

2. Hypothalamic–Pituitary–Adrenal (HPA) Axis

The hypothalamic–pituitary–adrenal (HPA) axis regulates the body's response to stress through coordinated secretion of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol (Lindholm, 2026) [51]. In PMOS, chronic psychological

stress, metabolic disturbances, and inflammation may alter HPA axis activity, leading to dysregulated cortisol secretion and increased adrenal androgen production, particularly dehydroepiandrosterone sulfate (DHEAS). Elevated adrenal androgens contribute to hyperandrogenism, worsening symptoms such as hirsutism, acne, and ovulatory dysfunction. Furthermore, prolonged cortisol imbalance promotes insulin resistance, visceral obesity, chronic inflammation, and metabolic syndrome, highlighting the significant contribution of adrenal endocrine dysfunction to the systemic manifestations of PMOS (Silva *et al*., 2026) [76].

3. Pancreatic Endocrine System

The pancreatic endocrine system is critically involved in glucose homeostasis through the secretion of insulin and glucagon by the islets of Langerhans. Insulin resistance is one of the defining metabolic abnormalities of PMOS, resulting in compensatory hyperinsulinemia (Pal and Anoop, 2026) [58]. Elevated circulating insulin not only attempts to maintain normal blood glucose levels but also directly stimulates ovarian theca cells to produce excessive androgens while suppressing hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing free testosterone concentrations (Laurent *et al*., 2026) [46]. Over time, chronic insulin demand may impair pancreatic β-cell function, increasing the risk of impaired glucose tolerance, prediabetes, and type 2 diabetes mellitus. Thus, pancreatic endocrine dysfunction represents a major driver of both reproductive and metabolic abnormalities in PMOS (Teede *et al*., 2026) [82].

4. Thyroid Gland

The thyroid gland regulates basal metabolic rate, energy expenditure, lipid metabolism, and reproductive health through the secretion of thyroxine (T4) and triiodothyronine (T3). Women with PMOS frequently exhibit thyroid dysfunction, particularly subclinical hypothyroidism and autoimmune thyroid disorders such as Hashimoto's thyroiditis (Palomba *et al*., 2023) [59]. Reduced thyroid hormone activity contributes to weight gain, dyslipidemia, insulin resistance, menstrual irregularities, and decreased fertility, thereby compounding the endocrine and metabolic disturbances associated with PMOS. Additionally, elevated thyroid-stimulating hormone (TSH) levels may influence ovarian function and worsen reproductive outcomes. Routine assessment of thyroid function is therefore considered an important component of comprehensive PMOS evaluation.

5. Adipose Tissue Endocrine Function

Adipose tissue functions as an active endocrine organ that secretes numerous bioactive molecules collectively known as adipokines, including leptin, adiponectin, resistin, visfatin, and chemerin. In PMOS, increased visceral adiposity alters adipokine secretion, characterized by reduced adiponectin and elevated leptin and pro-inflammatory cytokines (Bril *et al*., 2023) [9]. These hormonal changes impair insulin sensitivity, promote chronic low-grade inflammation, increase oxidative stress, and stimulate ovarian androgen production. Excess adipose tissue also releases free fatty acids that contribute to hepatic insulin resistance and dyslipidemia. Consequently, adipose tissue dysfunction serves as a critical link between obesity, endocrine abnormalities, and metabolic complications in PMOS.

6. Gastrointestinal Hormone System

The gastrointestinal tract acts as an endocrine organ by producing hormones that regulate appetite, glucose metabolism, insulin secretion, and energy balance. Hormones such as glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), ghrelin, peptide YY (PYY), and cholecystokinin (CCK) play important roles in maintaining metabolic homeostasis. In PMOS, altered secretion and responsiveness of these gastrointestinal hormones contribute to impaired satiety, increased appetite, insulin resistance, and abnormal glucose metabolism (Wu *et al*., 2026). Emerging evidence also suggests that gut microbiota dysbiosis influences gastrointestinal hormone production, promotes systemic inflammation, and exacerbates endocrine dysfunction. These findings have led to increasing interest in incretin-based therapies, including GLP-1 receptor agonists, for improving both metabolic and reproductive outcomes in women with PMOS.

7. Hepatic Endocrine Signaling

The liver is an essential endocrine and metabolic organ that regulates glucose metabolism, lipid homeostasis, insulin clearance, and hormone transport. In PMOS, hepatic insulin resistance reduces the production of sex hormone-binding globulin (SHBG), resulting in increased circulating free and biologically active testosterone, which aggravates hyperandrogenism (Yan *et al*., 2026). The liver also contributes to abnormal lipid metabolism, increased very-low-density lipoprotein (VLDL) production, and the development of non-alcoholic fatty liver disease (NAFLD), a common metabolic complication associated with PMOS (Yu *et al*., 2026). Furthermore, impaired hepatic insulin clearance sustains hyperinsulinemia, reinforcing the cycle of insulin resistance and androgen excess. Therefore, hepatic endocrine signaling plays a pivotal role in integrating metabolic and hormonal disturbances throughout the progression of PMOS (Stener-Victorin *et al*., 2026) [77].

8. Integrated Endocrine Crosstalk in PMOS

The endocrine abnormalities observed in PMOS do not occur independently but arise from continuous interactions among the hypothalamic–pituitary–ovarian axis, hypothalamic–pituitary–adrenal axis, pancreas, thyroid gland, adipose tissue, gastrointestinal tract, and liver (Piorkowska *et al*., 2026) [63]. These organs communicate through complex hormonal feedback mechanisms involving insulin, gonadotropins, cortisol, thyroid hormones, adipokines, incretin hormones, and inflammatory mediators. Dysregulation in one endocrine system amplifies dysfunction in others, creating a self-perpetuating cycle of hyperandrogenism, insulin resistance, chronic inflammation, oxidative stress, and reproductive impairment. This intricate endocrine crosstalk underscores why PMOS is increasingly recognized as a multisystem endocrine-metabolic disorder rather than merely a condition of ovarian dysfunction, emphasizing the need for multidisciplinary and personalized therapeutic approaches (Xu and He, 2026).

Table 1: Major Endocrine Abnormalities in Polyendocrine Metabolic Ovarian Syndrome (PMOS) (Chan *et al*., 2026; Tewari *et al*., 2026a; Sharma *et al*., 2026) [11, 75, 83]

Endocrine Organ/System	Major Hormonal Alteration	Pathophysiological Consequences	Clinical Manifestations
Hypothalamus	Increased GnRH pulse frequency	Increased LH secretion, decreased FSH stimulation	Chronic anovulation, menstrual irregularities
Pituitary Gland	Elevated LH:FSH ratio	Excess ovarian androgen synthesis	Hyperandrogenism, infertility
Ovary	Increased testosterone, androstenedione, AMH; reduced progesterone	Follicular arrest, impaired ovulation	Polycystic ovaries, infertility
Pancreas	Hyperinsulinemia	Ovarian androgen stimulation, reduced SHBG	Insulin resistance, hyperandrogenism
Thyroid	Elevated TSH, subclinical hypothyroidism	Reduced metabolic rate, impaired ovulation	Weight gain, menstrual disturbances
Adrenal Gland	Elevated DHEAS, cortisol dysregulation	Adrenal hyperandrogenism	Acne, hirsutism, androgen excess
Adipose Tissue	↓ Adiponectin; ↑ Leptin, Resistin, Visfatin, Chemerin	Chronic inflammation and insulin resistance	Obesity, metabolic syndrome
Liver	Reduced SHBG, hepatic insulin resistance	Increased free testosterone	Dyslipidemia, NAFLD
Gastrointestinal Tract	Altered GLP-1, GIP, Ghrelin, PYY	Appetite dysregulation and impaired glucose metabolism	Obesity, diabetes risk

Hypothalamic–Pituitary–Ovarian (HPO) Axis Dysfunction

Disruption of the HPO axis is the hallmark endocrine abnormality in PMOS.

1. Altered GnRH Pulsatility

Disruption of the hypothalamic–pituitary–ovarian (HPO) axis is the hallmark endocrine abnormality underlying the pathophysiology of Polyendocrine Metabolic Ovarian Syndrome (PMOS). Under normal physiological conditions, the hypothalamus releases gonadotropin-releasing hormone (GnRH) in a tightly regulated pulsatile manner, stimulating the anterior pituitary gland to secrete balanced amounts of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which together regulate follicular development, ovulation, and ovarian steroidogenesis (Ben *et al*., 2026). In women with PMOS, the frequency of GnRH pulsatility is accelerated, leading to preferential secretion of LH over FSH and an elevated LH:FSH ratio (Xu *et al*., 2026). Excess LH overstimulates ovarian theca cells, resulting in increased synthesis of androgens such as testosterone and androstenedione, while relatively lower FSH levels impair granulosa cell function and reduce aromatase activity, limiting the conversion of androgens to estrogens. This hormonal imbalance arrests normal follicular maturation, prevents the selection of a dominant follicle, and ultimately inhibits ovulation. Consequently, multiple immature follicles accumulate within the ovaries, producing the characteristic polycystic ovarian morphology observed in many women with PMOS. Persistent anovulation leads to irregular menstrual cycles, oligomenorrhea or amenorrhea, infertility, and prolonged unopposed estrogen exposure, which may increase the risk of endometrial hyperplasia. Furthermore, hyperinsulinemia and elevated anti-Müllerian hormone (AMH) levels commonly associated with PMOS further amplify HPO axis dysfunction by enhancing ovarian androgen production and suppressing normal follicular responsiveness to FSH, thereby creating a self-perpetuating cycle of endocrine imbalance and reproductive dysfunction. Understanding the central role of HPO axis dysregulation is essential for developing targeted therapeutic strategies aimed at restoring ovulation, improving fertility, and correcting hormonal disturbances in women with PMOS (Dutta and Sengupta, 2026) [21, 73].

2. Elevated LH:FSH Ratio

An elevated luteinizing hormone to follicle-stimulating hormone (LH:FSH) ratio is a common endocrine characteristic observed in many women with Polyendocrine Metabolic Ovarian Syndrome (PMOS), although it is not considered a universal diagnostic feature because normal ratios may also be present in some individuals (Graef and LeMieux, 2026) [34]. Typically, the LH:FSH ratio exceeds 2:1 or 3:1 as a consequence of increased gonadotropin-releasing hormone (GnRH) pulse frequency, which preferentially stimulates LH secretion by the anterior pituitary gland. Elevated LH concentrations excessively activate ovarian theca cells, leading to increased synthesis of androgens such as testosterone and androstenedione. Simultaneously, the relative deficiency of FSH impairs granulosa cell proliferation and function, reducing aromatase enzyme activity that is responsible for converting androgens into estrogens. This imbalance results in the accumulation of intraovarian androgens, disruption of normal follicular development, and inhibition of dominant follicle selection, ultimately preventing ovulation (Ezz and Balboula, 2026) [24]. The persistence of elevated LH levels therefore contributes to chronic anovulation, menstrual irregularities, infertility, and hyperandrogenic manifestations such as hirsutism, acne, and androgenic alopecia. Moreover, hyperinsulinemia commonly associated with PMOS amplifies LH-mediated androgen production, creating a vicious cycle in which endocrine and metabolic disturbances reinforce one another. Although the LH:FSH ratio alone lacks sufficient sensitivity and specificity for diagnosing PMOS, it remains an important biochemical marker that reflects dysfunction of the hypothalamic–pituitary–ovarian axis and provides valuable insight into the underlying pathophysiology of the syndrome (Wani, 2026) [88].

Ovarian Endocrine Dysfunction

1. Ovary as Both a Target and Amplifier of Endocrine Dysfunction

In Polyendocrine Metabolic Ovarian Syndrome (PMOS), the ovary functions not only as a target organ affected by systemic endocrine disturbances but also as an active amplifier of hormonal imbalance. Under normal physiological conditions, ovarian function is tightly

regulated by coordinated interactions between the hypothalamic–pituitary–ovarian (HPO) axis, insulin signaling, and local ovarian growth factors (Chebbi *et al*., 2026). However, in PMOS, chronic hyperinsulinemia, elevated luteinizing hormone (LH), inflammatory mediators, and altered metabolic signaling disrupt this finely balanced endocrine network. These abnormalities stimulate excessive androgen production, impair follicular maturation, and interfere with ovulation, while the dysfunctional ovary further contributes to systemic hyperandrogenism by continuously secreting excess steroid hormones. This reciprocal interaction creates a self-perpetuating cycle in which ovarian dysfunction both results from and exacerbates endocrine and metabolic abnormalities, establishing the ovary as a central endocrine organ in the pathogenesis of PMOS (Khatun *et al*., 2026) [43].

2. Increased Testosterone

One of the most prominent hormonal abnormalities in PMOS is the excessive production of testosterone by ovarian theca cells. Elevated LH levels and hyperinsulinemia synergistically stimulate steroidogenic enzymes, including cytochrome P450c17 (CYP17A1), leading to increased ovarian testosterone synthesis (Jozkowiak *et al*., 2022) [41]. In addition, insulin suppresses hepatic production of sex hormone-binding globulin (SHBG), resulting in higher circulating levels of biologically active free testosterone. Excess testosterone disrupts normal follicular growth, inhibits ovulation, and contributes to the clinical manifestations of hyperandrogenism, including hirsutism, acne, seborrhea, androgenic alopecia, and infertility. Elevated testosterone also worsens insulin resistance and visceral fat accumulation, thereby linking reproductive dysfunction with metabolic abnormalities and contributing to the progressive nature of PMOS (Tewari *et al*., 2026c) [85].

3. Elevated Androstenedione

Androstenedione is another major androgen that is significantly elevated in women with PMOS and serves as an important precursor for testosterone and estrogen synthesis. It is primarily produced by ovarian theca cells under the influence of LH, although the adrenal glands also contribute to its circulating levels. Increased androstenedione reflects heightened ovarian steroidogenic activity and contributes to the hyperandrogenic environment characteristic of PMOS (Saito *et al*., 2016) [70]. Excess androstenedione interferes with normal follicular development by altering granulosa cell function and reducing estrogen synthesis, thereby promoting follicular arrest and chronic anovulation (Liao *et al*., 2022) [48]. Clinically, elevated androstenedione is associated with menstrual irregularities, infertility, acne, and hirsutism, and its measurement may provide valuable information when evaluating androgen excess in women with suspected PMOS (Goodman *et al*., 2015) [33].

4. Increased Anti-Müllerian Hormone (AMH)

Anti-Müllerian hormone (AMH), produced by granulosa cells of preantral and small antral follicles, is markedly elevated in many women with PMOS due to the increased number of immature follicles present within the ovaries. While AMH normally regulates follicular recruitment and prevents premature depletion of the ovarian reserve, persistently elevated levels inhibit the sensitivity of developing follicles to follicle-stimulating hormone (FSH), thereby suppressing dominant follicle selection and ovulation (Cedars, 2022) [10]. High AMH concentrations also influence hypothalamic GnRH neurons, potentially contributing to increased LH secretion and further aggravating ovarian androgen production. Consequently, elevated AMH is not only considered a useful biomarker for ovarian dysfunction but also an active participant in the pathogenesis of chronic anovulation and follicular arrest in PMOS (Garg and Tal, 2016) [31].

5. Reduced Progesterone

Reduced progesterone secretion is a direct consequence of chronic anovulation in PMOS. Under normal menstrual physiology, ovulation leads to the formation of the corpus luteum, which secretes progesterone during the luteal phase to prepare the endometrium for implantation and regulate menstrual cyclicity. In PMOS, failure of ovulation prevents corpus luteum formation, resulting in persistently low progesterone levels. Progesterone deficiency removes its inhibitory feedback on the hypothalamus, allowing continued rapid pulsatile GnRH secretion and sustained elevation of LH levels, thereby perpetuating hyperandrogenism. Additionally, prolonged progesterone deficiency contributes to irregular menstruation, infertility, endometrial hyperplasia, and an increased long-term risk of endometrial carcinoma due to continuous unopposed estrogen stimulation (Teede *et al*., 2026) [82].

6. Persistent Estrogen Exposure

Despite impaired ovulation, women with PMOS are often exposed to persistently elevated or relatively stable estrogen levels, primarily due to continuous peripheral aromatization of androgens into estrone within adipose tissue rather than cyclic ovarian estradiol production (Sánchez-García *et al*., 2025) [72]. Unlike the normal menstrual cycle, where estrogen levels fluctuate in coordination with progesterone, PMOS is characterized by prolonged estrogen exposure without adequate progesterone opposition. This hormonal imbalance disrupts the normal feedback regulation of the hypothalamic–pituitary axis, contributes to abnormal uterine bleeding, and increases the risk of endometrial hyperplasia and endometrial carcinoma (Horne and Martin, 2025) [36]. Persistent estrogen exposure also influences gonadotropin secretion, further impairing follicular development and reinforcing the endocrine abnormalities associated with PMOS.

7. Theca Cell Hypersensitivity to LH and Insulin

Theca cell hypersensitivity is a fundamental mechanism underlying ovarian endocrine dysfunction in PMOS. Ovarian theca cells become excessively responsive to both luteinizing hormone (LH) and circulating insulin due to enhanced expression of steroidogenic enzymes and abnormalities in intracellular signaling pathways. Hyperinsulinemia acts synergistically with LH to stimulate androgen biosynthesis by increasing the activity of CYP17A1 and other enzymes involved in steroidogenesis (Iqbal and Fatima, 2026) [38]. As a result, ovarian androgen production continues even in the presence of relatively normal LH concentrations in some women. This excessive androgen synthesis contributes to follicular arrest, impairs ovulation, and amplifies systemic hyperandrogenism,

thereby establishing a strong link between metabolic dysfunction and ovarian endocrine abnormalities (Jozkowiak *et al*., 2022) [41].

8. Granulosa Cell Dysfunction and Impaired Estrogen Conversion

Granulosa Cell Dysfunction and Impaired Estrogen Conversion: Granulosa cells are essential for supporting follicular maturation and converting androgens into estrogens through the aromatase enzyme (CYP19A1) under the stimulation of follicle-stimulating hormone (FSH). In Polyendocrine Metabolic Ovarian Syndrome (PMOS), reduced FSH activity, excessive androgen exposure, insulin resistance, and chronic inflammatory mediators impair granulosa cell proliferation, differentiation, and steroidogenic function, resulting in diminished aromatase activity and reduced estradiol synthesis (Franks, 1995; Dumesic *et al*., 2015) [18, 28]. Consequently, the conversion of testosterone and androstenedione into estradiol is limited, leading to the accumulation of intraovarian androgens and further disruption of follicular development (Azziz *et al*., 2016) [3]. Dysfunctional granulosa cells also exhibit altered secretion of growth factors and increased production of anti-Müllerian hormone (AMH), which suppresses follicular sensitivity to FSH, promotes follicular arrest, and impairs oocyte maturation (Dewailly *et al*., 2014) [16]. Collectively, impaired granulosa cell function plays a pivotal role in maintaining the endocrine imbalance, chronic anovulation, and reproductive dysfunction that characterize PMOS.

9. Role of Elevated AMH in Follicular Arrest and Anovulation

Role of Elevated AMH in Follicular Arrest and Anovulation: Persistently elevated anti-Müllerian hormone (AMH) further aggravates ovarian dysfunction by directly inhibiting follicular maturation and ovulation. High AMH concentrations reduce follicular responsiveness to follicle-stimulating hormone (FSH), preventing the selection of a dominant follicle and maintaining numerous follicles in an immature developmental stage (Pellatt *et al*., 2007; Pellatt *et al*., 2010) [61, 62]. Experimental and clinical studies have also demonstrated that elevated AMH may directly influence hypothalamic gonadotropin-releasing hormone (GnRH) neurons, increasing GnRH neuronal activity and subsequently enhancing luteinizing hormone (LH) secretion and ovarian androgen production (Cimino *et al*., 2016) [13]. This establishes a vicious cycle in which excessive AMH, hyperandrogenism, and impaired follicular development continuously reinforce one another, perpetuating ovarian dysfunction. Consequently, elevated AMH is increasingly recognized not only as a reliable biomarker of ovarian reserve and polycystic ovarian morphology but also as an active pathogenic mediator contributing to chronic anovulation, infertility, and the endocrine abnormalities characteristic of Polyendocrine Metabolic Ovarian Syndrome (PMOS) (Lie Fong *et al*., 2012; Iliodromiti *et al*., 2013) [37, 49].

Hyperandrogenism

Hyperandrogenism is the central endocrine disturbance responsible for many clinical manifestations.
Major circulating androgens include:

1. Hyperandrogenism

Hyperandrogenism is the central endocrine disturbance in Polyendocrine Metabolic Ovarian Syndrome (PMOS) and is responsible for many of its reproductive, metabolic, and clinical manifestations. It results from excessive production of androgens by the ovarian theca cells and, in some women, by the adrenal cortex, driven by increased luteinizing hormone (LH) secretion, hyperinsulinemia, and abnormalities in steroidogenic enzyme activity. Insulin further amplifies androgen excess by directly stimulating ovarian androgen synthesis and suppressing hepatic production of sex hormone-binding globulin (SHBG), thereby increasing the concentration of biologically active free androgens. Persistent hyperandrogenism disrupts normal follicular development, inhibits ovulation, and contributes to chronic anovulation, menstrual irregularities, infertility, hirsutism, acne, seborrhea, and androgenic alopecia. Beyond its reproductive effects, androgen excess is closely associated with insulin resistance, visceral adiposity, dyslipidemia, chronic low-grade inflammation, and an increased risk of metabolic syndrome and cardiovascular disease. Thus, hyperandrogenism represents a critical pathogenic link connecting endocrine dysfunction with the metabolic abnormalities characteristic of PMOS (Sengupta and Dutta, 2026) [21, 73].

Table 2: Hormones Altered in Polyendocrine Metabolic Ovarian Syndrome (PMOS) and Their Clinical Significance (engupta and Dutta, 2026; Teede *et al*., 2026; Chan *et al*., 2026; Kordowitzki and Teede, 2026) [11, 21, 44, 82]

Hormone	Primary Source	Alteration in PMOS	Physiological Role	Clinical Significance
GnRH	Hypothalamus	↑ Pulsatility	Regulates LH and FSH secretion	Increased LH secretion and ovarian androgen production
LH	Anterior pituitary	↑ Increased	Stimulates ovarian theca cells	Hyperandrogenism, follicular arrest
FSH	Anterior pituitary	↓ Relative reduction	Follicular maturation and estrogen synthesis	Chronic anovulation and infertility
Testosterone	Ovary, adrenal gland	↑ Increased	Female androgen production	Hirsutism, acne, alopecia, infertility
Androstenedione	Ovary, adrenal gland	↑ Increased	Testosterone precursor	Hyperandrogenism and ovarian dysfunction
DHEAS	Adrenal cortex	↑ Increased	Adrenal androgen precursor	Indicates adrenal hyperandrogenism
Anti-Müllerian Hormone (AMH)	Granulosa cells	↑ Increased	Regulates follicular recruitment	Follicular arrest, anovulation
Progesterone	Corpus luteum	↓ Decreased	Endometrial preparation	Menstrual irregularities, infertility
Estrone	Adipose tissue	↑ Persistent	Peripheral estrogen production	Endometrial hyperplasia risk
Insulin	Pancreatic β-cells	↑ Hyperinsulinemia	Glucose homeostasis	Insulin resistance, androgen excess
Cortisol	Adrenal cortex	Altered	Stress response	Visceral obesity, metabolic dysfunction

TSH	Pituitary gland	↑ Mild elevation	Thyroid regulation	Hypothyroidism, dyslipidemia
T3/T4	Thyroid gland	↓ in hypothyroidism	Basal metabolism	Weight gain, infertility
Adiponectin	Adipose tissue	↓ Reduced	Insulin sensitization	Insulin resistance
Leptin	Adipose tissue	↑ Increased	Appetite regulation	Leptin resistance, obesity
Resistin	Adipose tissue	↑ Increased	Glucose metabolism	Inflammation and insulin resistance
Visfatin	Adipose tissue	↑ Increased	Insulin-mimetic activity	Ovarian steroidogenesis
Chemerin	Adipose tissue	↑ Increased	Adipogenesis	Chronic inflammation
GLP-1	Intestinal L-cells	↓ Reduced activity	Insulin secretion and satiety	Obesity and impaired glucose regulation
GIP	Intestinal K-cells	Altered	Insulin secretion	Glucose intolerance
Ghrelin	Stomach	Altered	Appetite regulation	Increased food intake

2. Testosterone

Testosterone is the principal circulating androgen responsible for the clinical features of hyperandrogenism in women with PMOS (Stener-Victorin *et al*., 2026) [77]. It is produced primarily by ovarian theca cells, with smaller contributions from the adrenal glands and peripheral conversion of androgen precursors. In PMOS, elevated LH levels and hyperinsulinemia stimulate excessive ovarian testosterone synthesis, while decreased hepatic production of sex hormone-binding globulin (SHBG) increases circulating free testosterone concentrations. Elevated testosterone directly interferes with normal follicular growth and ovulation and is strongly associated with clinical manifestations such as hirsutism, acne, androgenic alopecia, seborrhea, and menstrual disturbances. High testosterone levels also promote insulin resistance, central obesity, and adverse lipid profiles, reinforcing the bidirectional relationship between endocrine and metabolic dysfunction in PMOS.

3. Androstenedione

Androstenedione is an important androgen precursor synthesized predominantly by ovarian theca cells and, to a lesser extent, by the adrenal cortex. It serves as a key biochemical intermediate in the biosynthesis of testosterone and estrogens and is frequently elevated in women with Polyendocrine Metabolic Ovarian Syndrome (PMOS) as a consequence of enhanced ovarian steroidogenesis and increased theca cell activity (Rosenfield & Ehrmann, 2016; Azziz *et al*., 2016) [3, 68]. Elevated circulating androstenedione reflects excessive luteinizing hormone (LH)-mediated stimulation of the ovaries and contributes significantly to the hyperandrogenic state by acting as a precursor for peripheral testosterone production. Increased androstenedione concentrations disrupt normal follicular maturation, impair granulosa cell function, and promote follicular arrest, ultimately contributing to chronic anovulation, menstrual irregularities, and infertility (Dumesic *et al*., 2015; Escobar-Morreale, 2018) [18, 22]. Furthermore, measurement of serum androstenedione has been shown to improve the biochemical assessment of hyperandrogenism and may identify women with androgen excess even when total testosterone concentrations remain within the normal reference range, thereby enhancing the diagnostic evaluation of PMOS and related hyperandrogenic disorders (Rosenfield & Ehrmann, 2016; Teede *et al*., 2023) [68, 81].

4. Dehydroepiandrosterone Sulfate (DHEAS)

Dehydroepiandrosterone sulfate (DHEAS) is a sulfated androgen produced almost exclusively by the adrenal cortex and serves as an important marker of adrenal androgen secretion. Approximately 20–30% of women with PMOS exhibit elevated DHEAS concentrations, indicating a significant adrenal contribution to hyperandrogenism. Increased DHEAS production is often associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, enhanced adrenocorticotropic hormone (ACTH) responsiveness, or altered adrenal steroidogenic enzyme activity. Although DHEAS possesses relatively weak intrinsic androgenic activity, it can be converted into more potent androgens such as testosterone and dihydrotestosterone (DHT) in peripheral tissues, thereby contributing to hirsutism, acne, and other hyperandrogenic manifestations. Assessment of DHEAS is clinically valuable for distinguishing adrenal from ovarian sources of androgen excess and for identifying women with predominant adrenal hyperandrogenism within the PMOS spectrum (Fedotcheva and Shimanovsky, 2026) [27].

Clinical consequences include

The excessive androgen production characteristic of Polyendocrine Metabolic Ovarian Syndrome (PMOS) has widespread clinical consequences that affect reproductive, dermatological, metabolic, and psychological health. Elevated circulating androgens stimulate terminal hair growth in androgen-sensitive areas, resulting in hirsutism, while increased sebum production and follicular hyperkeratinization contribute to acne and seborrhea (Azziz *et al*., 2016; Rosenfield & Ehrmann, 2016) [3]. Prolonged androgen excess also causes androgenic alopecia, characterized by progressive thinning of scalp hair, particularly over the frontal and vertex regions (Escobar-Morreale, 2018) [22]. Within the ovaries, hyperandrogenism disrupts normal follicular development, inhibits dominant follicle selection, and impairs ovulation, leading to ovulatory dysfunction, chronic anovulation, irregular menstrual cycles, and infertility, making it one of the leading causes of anovulatory infertility in women of reproductive age (Goodarzi *et al*., 2011; Teede *et al*., 2023) [32, 81]. Beyond these reproductive manifestations, hyperandrogenism significantly aggravates insulin resistance by interfering with insulin signaling pathways in skeletal muscle, adipose tissue, and the liver, while hyperinsulinemia further stimulates ovarian androgen production and suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing circulating free testosterone (Dunaif, 1997; Diamanti-Kandarakis & Dunaif, 2012) [17, 19]. This reciprocal interaction establishes a self-perpetuating endocrine–metabolic vicious cycle in which androgen excess and insulin resistance continuously reinforce one another, promoting obesity, dyslipidemia, chronic low-grade inflammation, metabolic syndrome, and increasing the long-term risk of type 2 diabetes mellitus and cardiovascular disease (Escobar-Morreale, 2018; Teede *et al*., 2023) [81].

Consequently, effective management of hyperandrogenism is essential not only for improving cosmetic and reproductive outcomes but also for reducing the broader metabolic complications associated with PMOS.

Insulin Resistance: The Central Metabolic Defect

Insulin resistance is considered the central metabolic defect in Polyendocrine Metabolic Ovarian Syndrome (PMOS) and is present in approximately 50–80% of affected women, irrespective of obesity, although its severity is generally greater in overweight and obese individuals (Tewari *et al*., 2026b) [84]. It represents a state in which peripheral tissues, including skeletal muscle, adipose tissue, and the liver, exhibit a diminished biological response to normal circulating concentrations of insulin, thereby impairing glucose uptake and utilization. The pathogenesis of insulin resistance in PMOS is multifactorial and involves defects at several stages of the insulin signaling cascade, including impaired insulin receptor signaling, abnormal serine phosphorylation of insulin receptor substrate-1 (IRS-1), reduced phosphatidylinositol-3 kinase (PI3K) activation, defective translocation of glucose transporter type 4 (GLUT4) to the cell membrane, and decreased glucose uptake by skeletal muscle, which is the primary site of insulin-mediated glucose disposal. These molecular abnormalities are further aggravated by chronic low-grade inflammation, oxidative stress, visceral adiposity, mitochondrial dysfunction, and genetic susceptibility, resulting in persistent hyperglycemia and reduced metabolic efficiency. To compensate for diminished peripheral insulin sensitivity, pancreatic β-cells increase insulin secretion, leading to compensatory hyperinsulinemia. Beyond its metabolic role, excess insulin exerts significant endocrine effects by acting synergistically with luteinizing hormone (LH) to stimulate ovarian theca cells, thereby enhancing androgen synthesis through increased steroidogenic enzyme activity. Simultaneously, hyperinsulinemia suppresses hepatic production of sex hormone-binding globulin (SHBG), increasing circulating levels of biologically active free testosterone and exacerbating hyperandrogenism. Elevated insulin levels also promote adipogenesis, particularly within visceral adipose tissue, leading to further weight gain, central obesity, dyslipidemia, and metabolic syndrome. This reciprocal relationship establishes a vicious endocrine–metabolic cycle in which insulin resistance promotes hyperandrogenism, while androgen excess further impairs insulin signaling and worsens metabolic dysfunction. Consequently, insulin functions not only as a key regulator of glucose and lipid metabolism but also as an ovarian co-gonadotropin, amplifying ovarian steroidogenesis and playing a pivotal role in the pathogenesis of PMOS. Recognition of insulin resistance as the core metabolic abnormality underscores the importance of therapeutic strategies aimed at improving insulin sensitivity through lifestyle modification, dietary intervention, regular physical activity, weight reduction, and the use of insulin-sensitizing agents such as metformin, myo-inositol, D-chiro-inositol, and glucagon-like peptide-1 (GLP-1) receptor agonists to improve both metabolic and reproductive outcomes (Teede *et al*., 2026) [82].

Pancreatic Endocrine Dysfunction

Persistent insulin resistance eventually overloads pancreatic β-cells.

Progression typically follows:

Normal insulin sensitivity

↓

Compensatory hyperinsulinemia

↓

β-cell dysfunction

↓

Impaired glucose tolerance

↓

Prediabetes

↓

Type 2 diabetes mellitus

β-cell exhaustion represents one of the major long-term metabolic consequences of PMOS (Khatun *et al*., 2026) [43].

Adipose Tissue Dysfunction

Adipose tissue is no longer regarded as a passive energy storage depot but is recognized as a highly active endocrine organ that secretes numerous biologically active hormones and cytokines, collectively known as adipokines, which regulate metabolic, endocrine, inflammatory, and reproductive functions (Kershaw & Flier, 2004; Fasshauer & Blüher, 2015) [7, 25, 42]. In Polyendocrine Metabolic Ovarian Syndrome (PMOS), particularly in women with central obesity and visceral adiposity, adipose tissue undergoes significant endocrine dysfunction characterized by an altered adipokine profile. The most notable changes include decreased secretion of adiponectin and increased circulating levels of leptin, resistin, visfatin, and chemerin (Escobar-Morreale & Luque-Ramírez, 2017; Blüher, 2019) [6, 23]. Adiponectin is an insulin-sensitizing and anti-inflammatory adipokine that enhances glucose uptake, promotes fatty acid oxidation, improves hepatic insulin sensitivity, and suppresses inflammatory signaling pathways. Therefore, reduced adiponectin levels contribute substantially to insulin resistance, hyperinsulinemia, and metabolic syndrome in women with PMOS (Yamauchi *et al*., 2001; Blüher, 2019) [6, 92]. Conversely, elevated leptin concentrations, often associated with leptin resistance, impair appetite regulation, energy expenditure, and reproductive hormone secretion while promoting chronic inflammation (Friedman, 2019) [29]. Increased resistin interferes with insulin receptor signaling and enhances inflammatory cytokine production, whereas visfatin influences glucose metabolism and may stimulate ovarian steroidogenesis by enhancing androgen production (Steppan *et al*., 2001; Escobar-Morreale & Luque-Ramírez, 2017) [23, 79]. Chemerin, another pro-inflammatory adipokine, has been implicated in adipocyte differentiation, immune cell recruitment, insulin resistance, and impaired follicular development (Bozaoglu *et al*., 2007) [8]. Collectively, these

adipokines regulate several key physiological processes, including insulin sensitivity, inflammatory responses, appetite and energy homeostasis, ovarian steroidogenesis, and lipid metabolism, thereby establishing a critical link between obesity, endocrine dysfunction, and metabolic disturbances in PMOS. Furthermore, the altered adipokine milieu promotes oxidative stress, endothelial dysfunction, dyslipidemia, and chronic low-grade inflammation, all of which exacerbate reproductive abnormalities and increase the long-term risk of type 2 diabetes mellitus and cardiovascular disease (Diamanti-Kandarakis & Dunaif, 2012; Escobar-Morreale, 2018) [17, 22]. Consequently, adipose tissue dysfunction represents a central pathogenic mechanism in PMOS, and therapeutic strategies aimed at reducing visceral adiposity through lifestyle modification, weight management, regular physical activity, insulin-sensitizing agents, and dietary interventions can improve adipokine balance, enhance insulin sensitivity, restore endocrine homeostasis, and improve both metabolic and reproductive outcomes in affected women.

Thyroid Dysfunction

Thyroid dysfunction is a common endocrine abnormality associated with Polyendocrine Metabolic Ovarian Syndrome (PMOS), although it is not present in all affected women. Numerous clinical studies have reported a higher prevalence of thyroid disorders in women with PMOS compared with the general population, suggesting a close interaction between thyroid hormones and reproductive-metabolic homeostasis (Janssen *et al*., 2004; Romitti *et al*., 2018) [40, 67]. The most frequently observed thyroid abnormalities include subclinical hypothyroidism, Hashimoto thyroiditis, elevated thyroid-stimulating hormone (TSH) levels, and thyroid autoimmunity, often characterized by increased concentrations of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies (Ott *et al*., 2010; Poppe & Velkeniers, 2004) [57, 64]. Thyroid hormones are essential for regulating basal metabolic rate, glucose and lipid metabolism, ovarian function, follicular development, and menstrual cyclicity. Consequently, hypothyroidism can significantly aggravate the endocrine and metabolic disturbances of PMOS by promoting weight gain, increasing insulin resistance, worsening dyslipidemia, impairing ovulation, and contributing to infertility and menstrual irregularities such as oligomenorrhea, amenorrhea, and abnormal uterine bleeding (Krassas *et al*., 2010; Unuane *et al*., 2011) [45, 87]. Elevated TSH concentrations may also directly influence ovarian steroidogenesis and reduce hepatic production of sex hormone-binding globulin (SHBG), thereby increasing circulating free androgen levels and exacerbating hyperandrogenic manifestations (Diamanti-Kandarakis & Dunaif, 2012) [17]. Furthermore, autoimmune thyroid disease is associated with chronic inflammation and immune dysregulation, factors that may further impair reproductive function and increase the risk of miscarriage and adverse pregnancy outcomes (Poppe & Velkeniers, 2004) [64]. Because several clinical features of hypothyroidism—including obesity, fatigue, menstrual disturbances, infertility, and metabolic abnormalities—overlap considerably with those of PMOS, thyroid dysfunction may remain underdiagnosed if not specifically investigated. Therefore, routine evaluation of thyroid function, including measurement of serum TSH, free thyroxine (FT4), and thyroid autoantibodies when clinically indicated, is recommended as part of the comprehensive assessment of women with PMOS (Teede *et al*., 2023) [81]. Early diagnosis and appropriate management of thyroid disorders through thyroid hormone replacement therapy, nutritional optimization, and regular endocrine monitoring can improve metabolic control, restore menstrual regularity, enhance fertility outcomes, and reduce the overall endocrine burden associated with PMOS.

Adrenal Dysfunction

Adrenal dysfunction is an important endocrine component of Polyendocrine Metabolic Ovarian Syndrome (PMOS) and contributes to the heterogeneity of its clinical presentation. Approximately 20–30% of women with PMOS exhibit adrenal hyperandrogenism, characterized by excessive secretion of adrenal androgens, particularly dehydroepiandrosterone sulfate (DHEAS) and androstenedione, from the zona reticularis of the adrenal cortex. Although ovarian androgen excess remains the predominant source of hyperandrogenism in most patients, increased adrenal androgen production significantly contributes to the overall androgen burden in a substantial subset of women. The exact mechanisms underlying adrenal dysfunction are multifactorial and involve chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis, enhanced sensitivity of the adrenal cortex to adrenocorticotropic hormone (ACTH), and alterations in adrenal steroidogenic enzyme activity, particularly cytochrome P450 17A1 (CYP17A1). Chronic psychological stress, obesity, insulin resistance, systemic inflammation, and oxidative stress further stimulate HPA axis activity, resulting in increased ACTH secretion and enhanced adrenal androgen synthesis. Elevated DHEAS and androstenedione are subsequently converted into more potent androgens, including testosterone and dihydrotestosterone (DHT), contributing to clinical manifestations such as hirsutism, acne, seborrhea, androgenic alopecia, menstrual irregularities, and infertility. In addition to androgen excess, stress-induced abnormalities in cortisol secretion—including hypercortisolism, altered diurnal cortisol rhythms, or impaired cortisol metabolism—can further aggravate insulin resistance, visceral fat accumulation, dyslipidemia, hypertension, and chronic low-grade inflammation, thereby worsening the metabolic profile of women with PMOS. Persistent HPA axis activation also influences appetite regulation, energy expenditure, glucose homeostasis, and immune function, creating a complex interaction between stress physiology and endocrine-metabolic dysfunction. Therefore, evaluation of adrenal androgen levels, particularly DHEAS, is valuable in distinguishing adrenal from ovarian sources of hyperandrogenism and identifying women with predominant adrenal involvement. Management strategies that reduce chronic stress, improve insulin sensitivity, optimize lifestyle factors, and restore endocrine balance may help attenuate adrenal hyperactivity and improve both metabolic and reproductive outcomes in women with PMOS (Sharma *et al*., 2026) [75].

Metabolic Syndrome in PMOS

Polyendocrine Metabolic Ovarian Syndrome (PMOS) is strongly associated with the development of metabolic syndrome, a cluster of interrelated metabolic abnormalities that substantially increases the risk of type 2 diabetes mellitus, cardiovascular disease, and premature mortality. The coexistence of insulin resistance, hyperandrogenism,

visceral adiposity, chronic low-grade inflammation, and oxidative stress creates a favorable environment for the early onset of metabolic syndrome in affected women. According to internationally accepted diagnostic criteria, the major components of metabolic syndrome include abdominal obesity, hypertension, hyperglycemia, elevated triglyceride levels, and reduced high-density lipoprotein (HDL) cholesterol concentrations. Central or abdominal obesity, characterized by excessive visceral fat accumulation, promotes insulin resistance through increased release of free fatty acids and pro-inflammatory adipokines. Persistent hyperinsulinemia impairs glucose metabolism, resulting in elevated fasting blood glucose and an increased risk of impaired glucose tolerance and type 2 diabetes (Sharma *et al*., 2026) [75]. Dyslipidemia, characterized by elevated triglycerides and decreased HDL cholesterol, further contributes to endothelial dysfunction and accelerated atherosclerosis, while hypertension develops as a consequence of endothelial injury, sympathetic nervous system activation, sodium retention, and vascular inflammation (Krassas *et al*., 2010) [45]. Compared with healthy women of similar age, women with PMOS develop these metabolic abnormalities at a significantly younger age, even during adolescence or early adulthood, highlighting the syndrome as an early-life cardiometabolic disorder rather than solely a reproductive condition. The prevalence and severity of metabolic syndrome are particularly high among women with obesity, although lean individuals with PMOS may also exhibit significant metabolic dysfunction due to intrinsic insulin resistance. Early identification and comprehensive management of metabolic syndrome through lifestyle modification, weight reduction, dietary interventions, regular physical activity, insulin-sensitizing agents, and control of cardiovascular risk factors are essential to reduce long-term complications and improve overall health outcomes in women with PMOS (Biskup *et al*., 2026) [5].

Dyslipidemia

Dyslipidemia is one of the most common metabolic abnormalities observed in Polyendocrine Metabolic Ovarian Syndrome (PMOS) and represents a major contributor to the increased risk of cardiovascular disease associated with the disorder. The characteristic lipid profile in women with PMOS includes elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, elevated very-low-density lipoprotein (VLDL) concentrations, and reduced high-density lipoprotein (HDL) cholesterol levels (Sharma *et al*., 2026) [75]. These lipid abnormalities are primarily driven by insulin resistance, hyperinsulinemia, and visceral adiposity, which profoundly alter hepatic lipid metabolism. Impaired insulin signaling enhances the release of free fatty acids from adipose tissue to the liver, stimulating hepatic triglyceride synthesis and excessive production of VLDL particles. Increased VLDL secretion subsequently promotes the formation of small, dense LDL particles, which are highly atherogenic due to their increased susceptibility to oxidation and greater ability to penetrate the arterial wall. Simultaneously, accelerated catabolism and reduced synthesis of HDL cholesterol diminish reverse cholesterol transport, thereby reducing the body's capacity to remove excess cholesterol from peripheral tissues. Hyperandrogenism further aggravates dyslipidemia by influencing hepatic lipoprotein metabolism and promoting central fat accumulation. Chronic low-grade inflammation and oxidative stress also contribute to lipid oxidation, endothelial dysfunction, and the initiation of atherosclerotic plaque formation. Consequently, women with PMOS are at a significantly higher risk of developing premature atherosclerosis, coronary artery disease, hypertension, cerebrovascular disease, and other cardiovascular complications compared with healthy women. Because dyslipidemia often develops early in the course of PMOS—even among young and non-obese women—routine assessment of lipid profiles should be an integral component of clinical evaluation. Early intervention through lifestyle modification, weight management, regular physical activity, dietary improvement, insulin-sensitizing therapy, and, when indicated, lipid-lowering medications is essential to improve lipid metabolism and reduce long-term cardiovascular risk in women with PMOS (Riaz, 2026) [65].

Obesity and Visceral Fat Accumulation

Obesity, particularly central or visceral obesity, is one of the most prevalent metabolic features of Polyendocrine Metabolic Ovarian Syndrome (PMOS) and plays a pivotal role in the development and progression of endocrine and metabolic dysfunction. Although a significant proportion of women with PMOS have a normal body mass index (BMI), often referred to as lean PMOS, approximately 50–70% of affected individuals are overweight or obese, with excessive accumulation of visceral adipose tissue (Lim *et al*., 2012; Teede *et al*., 2023) [50, 81]. Unlike subcutaneous fat, visceral fat is highly metabolically active and functions as an endocrine organ that secretes numerous bioactive substances, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) (Kershaw & Flier, 2004; Blüher, 2019) [6, 42]. These inflammatory mediators impair insulin signaling pathways, leading to insulin resistance and compensatory hyperinsulinemia, which further stimulate ovarian androgen production and exacerbate hyperandrogenism (Diamanti-Kandarakis & Dunaif, 2012) [17]. In addition, increased visceral fat releases large amounts of free fatty acids (FFAs) into the portal circulation, promoting hepatic insulin resistance, increased gluconeogenesis, dyslipidemia, and excessive triglyceride synthesis (Samuel & Shulman, 2016) [71]. Visceral adiposity also enhances the generation of reactive oxygen species (ROS), resulting in oxidative stress, mitochondrial dysfunction, endothelial injury, and chronic low-grade inflammation that contribute to the progression of metabolic syndrome and cardiovascular disease (Furukawa *et al*., 2004; Blüher, 2019) [6, 30]. Furthermore, adipose tissue expresses steroidogenic enzymes capable of converting steroid precursors into active sex hormones, thereby influencing androgen metabolism and perpetuating the endocrine disturbances characteristic of PMOS (Escobar-Morreale, 2018) [22]. Compared with generalized obesity, central obesity is considerably more metabolically harmful because it is more strongly associated with insulin resistance, dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus, and cardiovascular complications (Després, 2012; Teede *et al*., 2023) [15, 81]. Therefore, assessment of waist circumference, waist-to-hip ratio, and visceral fat distribution is often more informative than BMI alone when evaluating metabolic risk

in women with PMOS. Effective management through calorie-controlled nutrition, regular aerobic and resistance exercise, weight reduction, behavioral modification, and insulin-sensitizing therapies remains essential for improving endocrine balance, restoring reproductive function, and reducing long-term cardiometabolic complications in women with PMOS (Moran *et al*., 2011; Teede *et al*., 2023) [54, 81].

Chronic Low-Grade Inflammation

Chronic low-grade inflammation is increasingly recognized as a fundamental pathological feature of Polyendocrine Metabolic Ovarian Syndrome (PMOS), linking endocrine dysfunction with metabolic abnormalities and long-term cardiovascular complications. Unlike acute inflammation, which is a protective immune response, PMOS is characterized by persistent, subclinical systemic inflammation driven primarily by visceral adiposity, insulin resistance, oxidative stress, and endocrine imbalance. Women with PMOS exhibit significantly elevated circulating levels of pro-inflammatory cytokines and inflammatory biomarkers, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), C-reactive protein (CRP), and monocyte chemoattractant protein-1 (MCP-1). TNF-α and IL-6 interfere with insulin receptor signaling by promoting serine phosphorylation of insulin receptor substrate (IRS) proteins, thereby reducing insulin sensitivity in skeletal muscle, adipose tissue, and the liver. IL-1β contributes to pancreatic β-cell dysfunction, impairs glucose homeostasis, and further aggravates insulin resistance, while elevated CRP reflects systemic inflammatory activity and is associated with endothelial dysfunction and an increased risk of cardiovascular disease. MCP-1 facilitates the recruitment of macrophages into adipose tissue, amplifying local inflammation and promoting the release of additional cytokines that perpetuate metabolic dysfunction. These inflammatory mediators also stimulate ovarian theca cells either directly or indirectly through activation of intracellular signaling pathways such as nuclear factor-kappa B (NF-κB), leading to enhanced androgen synthesis and worsening hyperandrogenism. Consequently, inflammation not only impairs insulin signaling but also reinforces ovarian steroidogenesis, creating a self-perpetuating cycle in which insulin resistance, hyperandrogenism, obesity, oxidative stress, and chronic inflammation continuously exacerbate one another. Persistent inflammatory activity further contributes to dyslipidemia, endothelial dysfunction, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, and accelerated atherosclerosis, substantially increasing the long-term risk of type 2 diabetes mellitus and cardiovascular disease. Therefore, targeting chronic inflammation through lifestyle modification, weight reduction, anti-inflammatory dietary patterns, regular physical activity, insulin-sensitizing therapies, antioxidants, and emerging immunometabolic interventions may play an important role in the comprehensive management of PMOS and its associated metabolic complications.

Oxidative Stress

Oxidative stress is a key pathogenic mechanism in Polyendocrine Metabolic Ovarian Syndrome (PMOS) and plays a critical role in linking endocrine dysfunction with reproductive and metabolic complications. It occurs when the production of reactive oxygen species (ROS) exceeds the body's antioxidant defense capacity, resulting in cellular and molecular damage. In PMOS, chronic hyperandrogenism, insulin resistance, obesity, mitochondrial dysfunction, and persistent low-grade inflammation contribute to excessive ROS generation, while antioxidant defenses are simultaneously weakened. Elevated ROS damages cellular lipids, proteins, and DNA, leading to mitochondrial dysfunction, impaired energy metabolism, and apoptosis in ovarian cells. Within the ovary, oxidative stress adversely affects follicular development by reducing oocyte quality, compromising meiotic competence, and decreasing fertilization and implantation potential, thereby contributing to infertility and poor reproductive outcomes. Excessive ROS also induces endothelial dysfunction by reducing nitric oxide bioavailability, promoting vascular inflammation, and accelerating atherosclerotic changes, which increase the risk of hypertension and cardiovascular disease. Furthermore, oxidative stress interferes with insulin receptor signaling pathways, exacerbating insulin resistance and hyperinsulinemia, which in turn stimulate further ovarian androgen production and perpetuate the endocrine-metabolic cycle characteristic of PMOS. Persistent oxidative injury also accelerates ovarian aging by promoting granulosa cell apoptosis, follicular atresia, diminished ovarian reserve, and impaired steroidogenesis, potentially leading to earlier reproductive senescence. Several endogenous antioxidant enzymes that normally neutralize reactive oxygen species are found to be significantly reduced in women with PMOS, including superoxide dismutase (SOD), which converts superoxide radicals into hydrogen peroxide; glutathione peroxidase (GPx), which detoxifies hydrogen peroxide and lipid hydroperoxides using reduced glutathione; and catalase, which further converts hydrogen peroxide into water and oxygen, thereby preventing oxidative cellular damage. Depletion of these antioxidant defense systems further amplifies oxidative stress and cellular injury. Consequently, oxidative stress has emerged as an important therapeutic target in PMOS, and interventions such as weight reduction, regular physical activity, antioxidant-rich diets, and supplementation with compounds including vitamin C, vitamin E, coenzyme Q10, N-acetylcysteine, alpha-lipoic acid, melatonin, selenium, and polyphenols have demonstrated potential benefits in improving antioxidant status, insulin sensitivity, ovarian function, and overall reproductive and metabolic health in affected women.

Gut Microbiota Dysbiosis

Gut microbiota dysbiosis has emerged as an important contributor to the pathogenesis of Polyendocrine Metabolic Ovarian Syndrome (PMOS), highlighting the significant role of the gut–endocrine–metabolic axis in disease development and progression (Sharma *et al*., 2026) [75]. The human gastrointestinal tract harbors trillions of microorganisms that regulate nutrient metabolism, immune function, hormone production, and energy homeostasis (Colella *et al*., 2023) [14]. Recent studies have demonstrated that women with PMOS exhibit significant alterations in gut microbial composition compared with healthy individuals, characterized by reduced microbial diversity, decreased abundance of beneficial bacteria, increased intestinal permeability, and metabolic endotoxemia (Zhu *et al*., 2025) [97]. The loss of beneficial commensal bacteria, including those that produce short-chain fatty acids (SCFAs) such as

butyrate, weakens the intestinal barrier and disrupts immune regulation, allowing bacterial components—particularly lipopolysaccharides (LPS) from Gram-negative bacteria—to enter the systemic circulation through a "leaky gut." Circulating LPS activates Toll-like receptor 4 (TLR4) and nuclear factor-kappa B (NF-κB) signaling pathways, stimulating the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). This chronic inflammatory response impairs insulin receptor signaling, aggravates insulin resistance, and contributes to compensatory hyperinsulinemia, which subsequently enhances ovarian androgen synthesis and suppresses hepatic production of sex hormone-binding globulin (SHBG) (Su *et al*., 2025). Dysbiosis also influences bile acid metabolism, incretin hormone secretion, lipid metabolism, and estrogen recycling through microbial enzymes such as β-glucuronidase, further disrupting endocrine homeostasis. Additionally, reduced production of beneficial microbial metabolites, particularly short-chain fatty acids, adversely affects glucose regulation, appetite control, intestinal integrity, and immune balance. These alterations establish a vicious cycle in which gut dysbiosis, systemic inflammation, hyperandrogenism, insulin resistance, obesity, and oxidative stress continuously reinforce one another, accelerating the progression of PMOS. Increasing evidence suggests that therapeutic strategies aimed at restoring gut microbial balance—including diets rich in dietary fibre and polyphenols, probiotics, prebiotics, synbiotics, fermented foods, and regular physical activity—may improve microbial diversity, reduce intestinal permeability and endotoxemia, decrease systemic inflammation, enhance insulin sensitivity, and support both metabolic and reproductive health in women with PMOS.

Molecular Mechanisms

The pathogenesis of Polyendocrine Metabolic Ovarian Syndrome (PMOS) is driven by a complex network of intracellular signaling pathways that regulate endocrine function, glucose metabolism, inflammation, oxidative stress, cellular proliferation, and ovarian steroidogenesis. Multiple molecular pathways interact to promote insulin resistance, hyperandrogenism, chronic inflammation, and impaired follicular development, thereby contributing to disease progression. Among the most important signaling cascades is the phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt) pathway, which plays a central role in insulin-mediated glucose uptake, glycogen synthesis, and cellular metabolism. In PMOS, impaired PI3K/Akt signaling disrupts insulin receptor function, reduces glucose transporter type 4 (GLUT4) translocation, and contributes significantly to insulin resistance and compensatory hyperinsulinemia. The AMP-activated protein kinase (AMPK) pathway, a critical cellular energy sensor, normally enhances glucose uptake, fatty acid oxidation, and mitochondrial biogenesis while suppressing hepatic gluconeogenesis and lipogenesis. Reduced AMPK activity in PMOS promotes obesity, lipid accumulation, oxidative stress, and impaired insulin sensitivity. Conversely, excessive activation of the mammalian target of rapamycin (mTOR) pathway stimulates cellular growth, protein synthesis, and ovarian steroidogenesis, contributing to abnormal follicular development, increased androgen production, and metabolic dysfunction. Chronic low-grade inflammation in PMOS is largely mediated through activation of the nuclear factor-kappa B (NF-κB) signaling pathway, which induces the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), thereby impairing insulin signaling and amplifying ovarian androgen synthesis. The mitogen-activated protein kinase (MAPK) signaling pathway also contributes to ovarian dysfunction by regulating cell proliferation, apoptosis, inflammatory responses, and steroidogenic enzyme expression, while abnormalities in this pathway may impair follicular maturation and ovulation (He *et al*., 2026). Additionally, Forkhead box O (FOXO) transcription factors regulate oxidative stress responses, apoptosis, glucose metabolism, and granulosa cell survival. Dysregulation of FOXO proteins contributes to impaired follicular development, accelerated ovarian aging, and defective insulin signaling in women with PMOS. Beyond these intracellular signaling pathways, epigenetic mechanisms have emerged as important determinants of disease susceptibility and progression. Alterations in DNA methylation, histone modifications, and microRNA (miRNA) dysregulation influence the expression of genes involved in insulin signaling, androgen biosynthesis, inflammation, adipogenesis, and folliculogenesis without altering the underlying DNA sequence. Environmental factors such as maternal nutrition, obesity, endocrine-disrupting chemicals, and chronic inflammation may induce these epigenetic changes, potentially increasing the risk of developing PMOS across generations. A deeper understanding of these molecular and epigenetic mechanisms has opened new avenues for precision medicine and targeted therapies, offering opportunities to develop novel interventions aimed at restoring normal signaling pathways, improving insulin sensitivity, reducing inflammation, correcting endocrine dysfunction, and enhancing reproductive and metabolic outcomes in women with PMOS (Patel *et al*., 2026) [60].

Table 3: Major Molecular Signaling Pathways Involved in PMOS (Roberts *et al*., 2020; Stener-Victorin *et al*., 2026; Zhou *et al*., 2026) [66, 77, 96]

Molecular Pathway	Major Function	Dysregulation in PMOS	Clinical Consequence	Therapeutic Target
PI3K/Akt	Insulin signaling	↓ Activity	Insulin resistance	Metformin, Inositols
AMPK	Energy metabolism	↓ Activity	Obesity, dyslipidemia	Exercise, Metformin
mTOR	Cell growth and steroidogenesis	↑ Activation	Hyperandrogenism	mTOR inhibitors (experimental)
NF-κB	Inflammatory signaling	↑ Activation	Chronic inflammation	Curcumin, Omega-3
MAPK	Cell proliferation	Dysregulated	Follicular arrest	Experimental target
FOXO	Oxidative stress regulation	Altered	Granulosa cell apoptosis	Antioxidants
TLR4/NF-κB	Endotoxin-mediated inflammation	↑ Activation	Gut-derived inflammation	Probiotics, Synbiotics
IRS-1/PI3K	Insulin receptor signaling	Serine phosphorylation	Hyperinsulinemia	Metformin
GLUT4	Glucose transport	↓ Translocation	Reduced glucose uptake	Exercise
CYP17A1	Steroidogenesis	↑ Expression	Excess androgen production	Anti-androgens

CYP19A1 (Aromatase)	Estrogen synthesis	↓ Activity	Reduced estradiol	FSH stimulation
Oxidative Stress Pathway	ROS metabolism	↑ ROS generation	Cellular injury	NAC, CoQ10

Table 4: Major Metabolic Abnormalities and Long-Term Complications of PMOS (Tewari *et al*., 2026a; Stener-Victorin *et al*., 2026; Kordowitzki and Teede, 2026) [44, 77, 82, 83]

Metabolic Dysfunction	Underlying Mechanism	Major Biomarkers	Clinical Consequences
Insulin resistance	Impaired PI3K/Akt signaling	Hyperinsulinemia, HOMA-IR	Type 2 diabetes mellitus
Hyperandrogenism	Ovarian and adrenal androgen excess	Testosterone, Androstenedione, DHEAS	Hirsutism, acne, infertility
Obesity	Visceral adipose tissue accumulation	BMI, Waist circumference	Metabolic syndrome
Dyslipidemia	Hepatic lipid metabolism abnormalities	↑TG, ↑LDL, ↓HDL	Atherosclerosis
Chronic inflammation	Increased TNF-α, IL-6, CRP	CRP, IL-6, TNF-α	Endothelial dysfunction
Oxidative stress	Excess ROS production	MDA↑, SOD↓, GPx↓	Cellular damage
Gut microbiota dysbiosis	Reduced SCFA-producing bacteria	LPS, microbial diversity	Leaky gut, inflammation
Thyroid dysfunction	Hypothyroidism, autoimmune thyroid disease	TSH, FT4, Anti-TPO	Infertility, obesity
Metabolic syndrome	Combined endocrine-metabolic dysfunction	Blood pressure, glucose, lipids	Cardiovascular disease

Therapeutic Approaches

The management of Polyendocrine Metabolic Ovarian Syndrome (PMOS) requires a comprehensive endocrine–metabolic approach that simultaneously addresses reproductive dysfunction, insulin resistance, obesity, chronic inflammation, and hyperandrogenism. Lifestyle modification remains the cornerstone of treatment and includes calorie restriction, adherence to a Mediterranean dietary pattern, consumption of low-glycemic index foods, regular aerobic exercise, resistance training, and sustained weight reduction, all of which improve insulin sensitivity, restore ovulatory function, reduce androgen excess, and lower cardiovascular risk (Teede *et al*., 2023; Moran *et al*., 2011) [54, 81]. Among pharmacological interventions, insulin sensitizers such as metformin remain first-line therapy for improving insulin resistance and glucose metabolism, while myo-inositol and D-chiro-inositol have demonstrated beneficial effects on insulin signaling, menstrual regularity, and ovulation. More recently, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists, including tirzepatide, have shown promising results in selected patients by promoting substantial weight loss, improving glycemic control, reducing visceral adiposity, and ameliorating metabolic dysfunction (American Diabetes Association Professional ssPractice Committee, 2025; Rubino *et al*., 2022)[1, 69]. Hormonal therapy remains essential for women not seeking immediate pregnancy and includes combined oral contraceptives to regulate menstrual cycles and suppress ovarian androgen production, anti-androgens such as spironolactone for the treatment of hirsutism and acne, ovulation induction agents including letrozole and clomiphene citrate for infertility management, and progesterone therapy to protect against endometrial hyperplasia in women with chronic anovulation (Teede *et al*., 2023; Legro *et al*., 2013) [81]. In addition, growing evidence supports the use of several nutraceuticals, including omega-3 fatty acids, vitamin D, chromium, magnesium, N-acetyl cysteine (NAC), curcumin, coenzyme Q10, probiotics, and synbiotics, which have demonstrated beneficial effects on insulin sensitivity, oxidative stress, inflammatory pathways, lipid metabolism, gut microbiota composition, and reproductive outcomes (Jamilian *et al*., 2018; Moini Jazani *et al*., 2019; Ojo *et al*., 2019) [39, 53, 55]. Collectively, an individualized multimodal therapeutic strategy integrating lifestyle interventions, pharmacotherapy, hormonal regulation, and targeted nutritional supplementation offers the greatest potential for restoring endocrine homeostasis, improving fertility, reducing metabolic complications, and enhancing the long-term health and quality of life of women with PMOS.

Table 5: Biomarkers for Diagnosis and Monitoring of PMOS (Jamilian *et al*., 2018; Moini Jazani *et al*., 2019; Ojo *et al*., 2019) [39, 53, 55]

Biomarker Category	Biomarker	Clinical Importance
Hormonal	LH	Hyperandrogenism
	FSH	Ovarian reserve and ovulation
	LH:FSH Ratio	HPO axis dysfunction
	Total Testosterone	Hyperandrogenism
	Free Testosterone	Biologically active androgen
	Androstenedione	Ovarian androgen excess
	DHEAS	Adrenal androgen excess
	AMH	Ovarian reserve and follicular arrest
	Progesterone	Ovulation assessment
	SHBG	Free androgen index
	TSH, FT4	Thyroid dysfunction
Metabolic	Fasting glucose	Diabetes screening
	HbA1c	Long-term glycemic control
	Fasting insulin	Hyperinsulinemia
	HOMA-IR	Insulin resistance
	Lipid profile	Cardiovascular risk
	BMI	General obesity
	Waist circumference	Visceral obesity

Inflammatory	CRP	Systemic inflammation
	TNF-α	Inflammatory activity
	IL-6	Chronic inflammation
	MCP-1	Macrophage recruitment
Oxidative Stress	MDA	Lipid peroxidation
	SOD	Antioxidant defense
	Catalase	Oxidative stress
	GPx	Antioxidant capacity
Imaging	Ultrasound	Polycystic ovarian morphology
	Ovarian volume	Follicular enlargement
	Antral follicle count	Ovarian reserve

Table 6: Integrated Therapeutic Strategies for PMOS (Khatun *et al*., 2026; Tewari *et al*., 2026c; Sharma *et al*., 2026) [43, 75, 85]

Therapeutic Category	Intervention	Primary Target	Expected Clinical Benefit
Lifestyle Modification	Calorie restriction	Obesity	Weight reduction
	Mediterranean diet	Insulin resistance	Improved metabolic profile
	Low-glycemic index diet	Hyperglycemia	Better glycemic control
	Aerobic exercise	Insulin sensitivity	Reduced cardiovascular risk
	Resistance training	Muscle glucose uptake	Improved insulin action
Insulin Sensitizers	Metformin	Insulin resistance	Improved ovulation
	Myo-inositol	Insulin signaling	Menstrual regularity
	D-chiro-inositol	Hyperinsulinemia	Improved fertility
	GLP-1 receptor agonists	Obesity	Weight loss
	Dual GIP/GLP-1 agonists	Severe obesity	Enhanced metabolic control
Hormonal Therapy	Combined oral contraceptives	Hyperandrogenism	Cycle regulation
	Anti-androgens	Hirsutism, acne	Reduced androgenic symptoms
	Letrozole/Clomiphene	Anovulation	Ovulation induction
	Progesterone	Endometrial protection	Prevention of hyperplasia
Nutraceuticals	Omega-3 fatty acids	Inflammation	Reduced triglycerides
	Vitamin D	Endocrine function	Improved insulin sensitivity
	Chromium	Glucose metabolism	Better glycemic control
	Magnesium	Insulin signaling	Improved metabolic function
	N-acetyl cysteine	Oxidative stress	Enhanced ovulation
	Curcumin	Inflammation	Antioxidant effects
	Coenzyme Q10	Mitochondrial dysfunction	Improved oocyte quality
	Probiotics/Synbiotics	Gut dysbiosis	Improved microbiota and metabolism

Future Perspectives

Future research increasingly supports precision medicine approaches for PMOS. Multi-omics technologies, including genomics, transcriptomics, proteomics, metabolomics, and microbiome profiling, are expected tos improve patient stratification and enable personalized therapies. Artificial intelligence and machine learning may facilitate earlier diagnosis by integrating hormonal, metabolic, imaging, and genetic data. Novel therapeutic targets, such as selective androgen receptor modulators, anti-inflammatory agents, gut microbiota modulation, mitochondrial therapies, and incretin-based medications, hold promise for improving both reproductive and metabolic outcomes. A multidisciplinary approach involving endocrinologists, gynecologists, nutritionists, psychologists, and exercise specialists will remain essential for comprehensive patient care.

Conclusion

Polyendocrine Metabolic Ovarian Syndrome represents a complex multisystem endocrine and metabolic disorder that extends far beyond ovarian dysfunction. The syndrome is characterized by intricate interactions among the hypothalamic–pituitary–ovarian axis, pancreatic insulin signaling, adrenal androgen production, thyroid function, adipose tissue endocrine activity, chronic inflammation, oxidative stress, and gut microbiota alterations. Insulin resistance and hyperandrogenism form the core pathogenic mechanisms, driving reproductive abnormalities, metabolic syndrome, cardiovascular risk, and long-term endocrine complications. Recognizing PMOS as a systemic disorder rather than an isolated gynecological condition underscores the importance of early diagnosis, comprehensive metabolic screening, and individualized multidisciplinary management. Advances in molecular biology, precision medicine, and targeted therapeutics are expected to transform future strategies for prevention and treatment, ultimately improving reproductive health, metabolic control, and quality of life in affected women.

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