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Review

Obesity and Polycystic Ovary Syndrome: Mechanisms Linking Metabolic Disturbance to Reproductive Dysfunction—A Narrative Review

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Abstract

Objective: Polyendocrine metabolic ovarian syndrome (PMOS) is a major endocrine-metabolic disorders affecting reproductive-aged women and are closely associated with ovulatory failure, infertility, obesity, and metabolic dysfunction. Clinical evidence indicates women with coexisting PMOS and obesity tend to exhibit more severe reproductive and metabolic abnormalities. However, the biological mechanism by which obesity alters the clinical manifestations of PMOS remains incompletely understood. This review aims to synthesize the current evidence on the interactions between obesity and PMOS, with a focus on how obesity-driven metabolic disorders contribute to reproductive dysfunction. **Mechanism:** Visceral obesity promotes insulin resistance (IR) and compensatory hyperinsulinemia, which stimulates ovarian androgen synthesis while suppressing hepatic production of sex hormone-binding globulin (SHBG), thereby increasing circulating free androgen levels. Elevated androgens can further disrupt adipose tissue metabolism and exacerbate IR, reinforcing a self-perpetuating metabolic-endocrine feedback cycle. Obesity-related chronic low-grade inflammation and immune dysregulation may further disrupt insulin signaling and ovarian steroidogenesis. Additionally, heightened sympathetic nervous system activity may disrupt neuroendocrine regulation within the hypothalamic-pituitary axis. These processes are not confined to the ovaries; instead, they involve multiple organ systems, including the liver, thyroid, and adrenal glands, ultimately impairing follicle development, ovulation, and oocyte quality. **Findings in Brief:** Current evidence indicates that women with obesity-associated PMOS often exhibit more pronounced IR, elevated androgen levels, and greater ovulatory dysfunction compared to lean women with PMOS. Obesity-related metabolic stress may alter the ovarian microenvironment by promoting inflammation, oxidative stress, and extracellular matrix remodeling, thereby impairing follicle development and reproductive capacity. Neuroendocrine and metabolic dysregulation across multiple organ systems, including the liver, thyroid, and adrenal glands, may further amplify the reproductive phenotype associated with PMOS. **Conclusions:** Rather than being regarded solely as a common comorbidity, obesity should be recognized as an important metabolic modifier shaping the reproductive and metabolic characteristics of PMOS. Through interactions with endocrine, metabolic, and inflammatory pathways, obesity may exacerbate ovarian dysfunction and worsen reproductive outcomes. Conceptualizing obesity-related PMOS as a phenotypic subgroup of this syndrome characterized by metabolic amplification may inform the development of more comprehensive and individualized clinical management strategies.

Keywords: polyendocrine metabolic ovarian syndrome; obesity; insulin resistance; hyperandrogenism; reproductive dysfunction; endocrine metabolism

1. Introduction

Polyendocrine metabolic ovarian syndrome (PMOS) is a common endocrine and metabolic disorder among reproductive-aged women that remains a primary cause of anovulatory infertility [1]. PMOS is characterised by infrequent ovulation or anovulation together with hyperandrogenism, and is frequently accompanied by metabolic abnormalities, most notably insulin resistance (IR) and central obesity [2,3]. Obesity, in turn, has been demonstrated to exacerbate the symptoms of PMOS, including those affecting the reproductive and metabolic systems. Clinical observations have revealed that women with PMOS who are also obese typically exhibit more pronounced hyperandrogenism, IR, and lower ovulation rates [4]. Concurrently, they face a significantly increased risk of developing additional diseases, including infertility, miscarriage, cardiovascular diseases, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) [5,6,7].

Although the association between obesity and PMOS has been increasingly well-established, most existing reviews have considered the underlying mechanisms from relatively isolated perspectives, focusing specifically on

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IR, hyperandrogenism, inflammation, or other individual pathogenic processes [8,9]. As a result, the mechanistic links between metabolic abnormalities and reproductive dysfunction in obesity-related PMOS remain insufficiently integrated. A more coherent framework is therefore needed to explain how IR, androgen excess, chronic inflammation, oxidative stress, and related abnormalities interact to impair follicular development, ovulation, oocyte competence, and fertility. Importantly, these processes are unlikely to act exclusively within the ovaries, but rather through coordinated effects across multiple organs and regulatory systems involved in the control of reproductive and metabolic homeostasis. In this review, we therefore integrate current evidence on the mechanistic links between metabolic abnormalities and reproductive dysfunction in obesity-related PMOS, and we further examine how these pathways operate across the hypothalamus-pituitary axis, liver, thyroid, adrenal glands, and ovaries. We then discuss the potential clinical implications of these interactions and highlight future directions for research and management.

2. Methods

This narrative review was conducted to summarize current evidence on the mechanistic links between obesity-related metabolic disturbance and reproductive dysfunction in PMOS. A literature search was performed in PubMed and Web of Science up to April 2026. The search strategy combined terms related to obesity and adiposity, including "obesity", "central obesity", "overweight", "body weight", "body mass index", "adipose tissue", "visceral adiposity", and "fat", with terms related to PMOS and reproductive dysfunction, including "polyendocrine metabolic ovarian syndrome", "polycystic ovary syndrome", "polycystic ovarian morphology", "polycystic ovaries", "ovary", "ovulatory dysfunction", "oligo-ovulation", "follicular development", "menstrual irregularities", "amenorrhea", "hirsutism", "acne", "androgens", "hyperandrogenism", "testosterone", "estradiol", "gonadotropins", "luteinizing hormone", "follicle-stimulating hormone", "gonadotropin-releasing hormone", "anti-Müllerian hormone", "infertility", and "reproductive dysfunction". Additional search terms were used to capture the major mechanistic pathways and organ-level interactions discussed in this review. These included "insulin resistance", "hyperinsulinemia", "glucose metabolism", "inflammation", "chronic inflammation", "pro-inflammatory", "anti-inflammatory", "immune dysregulation", "oxidative stress", "reactive oxygen species", "interleukin-6", "interleukin-18", "TNF-α", "fatty acids", "macrophages", "adipokines", "leptin", "adiponectin", "sympathetic nervous system", "nerve", "nerve endings", "genetics", "offspring", "gut microbiota", "gut dysbiosis", "microbiota-gut-brain axis", "hypothalamus", "pituitary gland", "thyroid", "thyroid-stimulating hormone", "thyroid hormones", "liver", "adrenal glands", and "sex hormone-binding globulin". Terms related to management were also searched, including "lifestyle modification", "physical exercise", "diet", "weight loss", "insulin sensitizers", "metformin", "myo-inositol", "GLP-1 receptor agonists", "aromatase inhibitors" and "letrozole".

Titles and abstracts were screened to identify articles relevant to the scope of this review. Studies were considered eligible if they addressed at least one of the following topics: (1) the association between obesity and PMOS; (2) metabolic, endocrine, inflammatory, oxidative stress-related, neuroendocrine, genetic, gut microbiota-related, or organ-level mechanisms linking obesity to PMOS; (3) the effects of obesity-related metabolic disturbance on follicular development, ovulation, oocyte quality, infertility, or other reproductive outcomes; or (4) clinical or experimental interventions targeting obesity, insulin resistance, metabolic dysfunction, inflammation, or reproductive impairment in PMOS. No language restrictions were applied during the initial screening. Original clinical studies, animal and cell-based mechanistic studies, systematic reviews, meta-analyses, and relevant narrative reviews were considered. For epidemiological data and intervention-related evidence, systematic reviews and meta-analyses were preferentially selected when available. Mechanistic studies were included when they provided direct evidence relevant to the pathways discussed in this review.

3. Pathophysiological Mechanisms Linking Obesity and PMOS

3.1 IR: The Core Link Between PMOS and Obesity

IR is one of the most common metabolic abnormalities observed in women with PMOS and is widely considered a key factor contributing to the pathogenesis of this syndrome [10]. IR is characterised by impaired glucose uptake and utilisation, leading to compensatory hyperinsulinemia. The coexistence of obesity further exacerbates IR through adipocyte hypertrophy, visceral fat accumulation, and adipokine dysregulation. In women with PMOS accompanied by IR, adipocyte enlargement and increased waist circumference are frequently observed, reflecting underlying adipose tissue dysfunction [11]. Clinical studies consistently show that women with both PMOS and obesity tend to exhibit more severe manifestations of IR compared with women of leaner body compositions. Bannigida et al. [12], for instance, demonstrated that women with obesity and PMOS have significantly higher fasting blood glucose, serum insulin levels, and associated IR-related indices relative to lean or normal-weight women with PMOS. These findings suggest that excessive adiposity amplifies metabolic disturbances already present in PMOS.

Adiponectin, primarily secreted by adipocytes, is an insulin-sensitizing molecule critical for regulating insulin homeostasis and glucose metabolism. Metformin can both reduce blood glucose levels and restore low adiponectin levels in endometrial cells in tumor necrosis factor-α (TNF-α) induced models of obesity, optimizing the insulin re-

sponse and improving reproductive performance in women with PMOS [13]. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) can reduce hunger, promote weight loss, and alleviate IR by increasing the expression of glucose transporters in insulin-dependent tissues. They also tend to enhance fertility by either enhancing hypothalamic-pituitary suppression of luteinizing hormone (LH) surges or reducing excessively high LH levels associated with hyperinsulinemia [14,15]. Activating transcription factor 4 (ATF4) is involved in energy homeostasis and the control of glucose metabolism. Elevated ATF4 levels are an important trigger for lipid accumulation and abnormal insulin signaling in women with PMOS [16]. Dietary interventions are considered effective measures for addressing IR and obesity in women with PMOS [17]. Studies have shown that losing more than 5 kg can alter the secretion of neuroendocrine hormones from ovarian granulosa cells (GCs) and modulate IR, potentially reducing rates of miscarriage in women undergoing *in vitro* fertilization-embryo transfer procedures [18]. Overall, the available evidence suggests that IR is the core metabolic link between obesity and PMOS. The accumulation of visceral fat, abnormal secretion of adipokines, and associated hormonal dysregulation jointly exacerbate IR, thereby leading to endocrine imbalance and reproductive dysfunction. Interventions such as drug treatment, weight loss, and dietary adjustments to improve insulin sensitivity offer promising avenues for regulating metabolic balance and potentially improving reproductive health.

3.2 Hyperandrogenism: A Driver of Reproductive and Metabolic Disturbance

The most common biochemical abnormality observed in women with PMOS is the elevation of circulating testosterone and androstenedione levels. Approximately 60% of the androgens in these women originate from the ovaries, while 40% are produced by the adrenal glands [19]. Compared to healthy women, those with PMOS often exhibit excessive androgen secretion by ovarian theca cells [20]. Exposure to elevated levels of androgens can interfere with normal follicular development, leading to anovulation, making this the leading cause of infertility in women with PMOS. Accumulating evidence has established several mechanistic links through which obesity can aggravate hyperandrogenism. For one, obesity sensitizes theca cells to LH stimulation, increasing androgen production [21]. Obesity also elevates the levels of key enzymes in the androgen biosynthesis pathway enzymes involved in androgen synthesis, including cytochrome P450c17, 3β-hydroxysteroid dehydrogenase type 2, P450scc, and 17β-hydroxysteroid dehydrogenase type 5 [20]. As cytochrome P450c17 is present in both ovarian theca cells and the adrenal cortex, this leads to increased androgen secretion by both the ovaries and adrenal glands. Moreover, the concentration of circulating sex hormone-binding globulin (SHBG), which is the primary serum carrier protein for testosterone, is primarily determined by body mass index (BMI) [22,23]. Obesity suppresses hepatic SHBG synthesis, thereby increasing circulating free testosterone levels and worsening androgen excess [24]. Elevated free androgen levels lead to the disruption of folliculogenesis and the impairment of ovulation, thereby contributing to the characteristic reproductive phenotype of PMOS.

In contrast with these adverse effects, adipocyte-derived adiponectin has potential beneficial effects on hyperandrogenism in PMOS, as it can reduce androgen production, possibly through modulation of LH receptors, steroid acute regulatory proteins, cholesterol side-chain cleavage enzyme, and 17α-hydroxylase [25]. Declining adiponectin levels in obesity may therefore abrogate this protective effect and contribute to androgen excess. Lifestyle interventions may partially mitigate or even reverse these endocrine disturbances. For example, a review focused on intermittent fasting and reproductive hormones suggested that this form of dietary intervention may improve fat metabolism while reducing testosterone levels and the free androgen index, in addition to increasing SHBG concentrations. Although these findings were reported in preimenopausal women with obesity [26], their relevance to PMOS warrants further investigation. Overall, current evidence suggests that hyperandrogenism serves as a critical link between metabolic dysfunction and reproductive abnormalities in PMOS. Specifically, obesity exacerbates androgen excess by enhancing steroidogenesis, suppressing SHBG synthesis, and altering adipokine signaling, ultimately leading to ovulatory dysfunction and infertility.

3.3 Immune Dysregulation, Chronic Inflammation and Oxidative Stress: A Common Substrate for PMOS and Obesity

Disruption of immune system activity is closely associated with chronic inflammation and IR among women with PMOS [27,28,29]. As a consequence, immunological dysfunction can contribute to direct impairment while also shaping multiple pathological mechanisms underlying the development of PMOS. For example, women with PMOS who experience low progesterone levels may exhibit the overstimulation of their immune systems, leading to increased estrogen production and elevated antibody levels [30]. Consequently, some women with PMOS may also suffer from autoimmune diseases, including autoimmune thyroid disease and autoimmune liver disease. Similar inflammation-related patterns are also observed in obesity, as the adipose tissue serves as an immunologically active organ in addition to its function as a site of energy storage. In obese individuals, both innate and adaptive immune cells infiltrate adipose tissue and participate in metabolic regulation [31].

While inflammation is often regarded as a component of the immune response, the chronic inflammatory state

that characterizes PMOS underscores its association with metabolic dysfunction. Elevated concentrations of several inflammatory mediators have been reported in PMOS, including C-reactive protein, interleukin-18 (IL-18), TNF-α, interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), white blood cell counts, and macrophage inflammatory protein-1α (MIP-1α) [32,33]. Obesity may further increase circulating TNF-α and IL-6 levels, thereby negatively impacting the insulin signaling cascade. Research by Lai et al. [34] revealed that the concentrations of fatty acids, along with inflammatory factors (interleukin-8 (IL-8), IL-18, and IL-6), are significantly elevated in the follicular fluid in women with PMOS. These inflammatory factors were also reportedly positively correlated with fatty acid levels, suggesting that abnormal fatty acid metabolism induces ovarian inflammation [34]. Studies by Alenezi et al. [35] have additionally demonstrated that obesity and PMOS are associated with upregulated NLR family pyrin domain containing 3 (NLRP3) inflammasome expression in adipose tissue, contributing to inflammatory activity. However, the potential to alleviate or reverse this adipose inflammation by normalizing levels of adipokines and inflammatory factors may offer a means of improving both metabolic and reproductive outcomes in women with PMOS.

Oxidative stress may represent another important link between obesity-related metabolic dysfunction and reproductive impairment in PMOS [36]. Previous studies have suggested that oxidative stress is closely associated with insulin resistance, hyperandrogenism, chronic inflammation, and obesity in women with PMOS [37]. Excess adiposity is associated with mitochondrial dysfunction, lipid overload, and increased production of reactive oxygen species (ROS), which may further aggravate insulin signaling defects and inflammatory activation [36]. In women with PMOS, oxidative stress has been implicated in altered steroidogenesis, granulosa cell dysfunction, impaired oocyte maturation, and reduced follicular competence. Moreover, oxidative stress and inflammation are closely interconnected: ROS may activate inflammatory pathways such as the inflammasome, while inflammatory mediators may, in turn, exacerbate oxidative injury. This reciprocal amplification may contribute to the deterioration of both metabolic homeostasis and ovarian function in obesity-related PMOS.

Analyses of peripheral blood samples from women with PMOS have revealed the significant expansion of certain circulating immune cell populations, including lymphocytes, macrophages, eosinophils, and neutrophils [38]. The balance between T helper 1 (Th1) and T helper 2 (Th2) cells is closely tied to the orchestration of cellular and humoral immunity. The Th1/Th2 ratio in women with PMOS is significantly higher than in the general population, confirming that an imbalance in these immune cells is associated with obesity, particularly central obesity [39]. Macrophage infiltration of adipose tissue is an important pathway underlying obesity-induced IR [40]. Among women with PMOS, an increased number of M1 macrophages is observed in both the peripheral blood and ovarian tissues [30]. Consistent with these observations, in dehydroepiandrosterone (DHEA)-induced mouse models of PMOS, greater M1 macrophage abundance together with a drop in M2 macrophage levels has been reported, reflecting a shift from an anti-inflammatory (M2-dominant) state to a pro-inflammatory (M1-dominant) state [41]. Natural killer (NK) cell abnormalities within the endometrium have been proposed as markers for endometrial dysfunction in women with PMOS, with obesity further exacerbating this risk [42]. Immune modulation has also been advanced as a possible approach to alleviating ovarian dysfunction in PMOS. Although mesenchymal stem cell (MSC) therapy is not currently a standard treatment for PMOS, these experimental findings provide proof-of-concept that immune-inflammatory pathways may be mechanistically important and potentially modifiable. Specifically, researchers found that mesenchymal stem cell intervention in a DHEA-induced PMOS model in mice significantly downregulated TNF-α, interleukin-1 beta (IL-1β), and interferon (IFN)-γ mRNA expression in ovarian and uterine tissues, with corresponding reductions in steroid-related gene expression and androgen production. Furthermore, mesenchymal stem cell injections were found to inhibit inflammatory responses in peripheral blood and the spleen, ultimately alleviating ovarian dysfunction [41,43]. Taken together, these findings indicate that immune dysregulation, chronic inflammation and oxidative stress represent important mechanisms linking obesity and PMOS. Through coordinated effects on insulin signaling, androgen production, GCs function, and the ovarian microenvironment, these pathways may play a central role in translating metabolic stress into reproductive dysfunction.

3.4 The Sympathetic Nervous System: Neuroendocrine Disturbances in Obesity-Related PMOS

Overactivity of the sympathetic nervous system may be a contributing factor to PMOS. Research by Stener-Victorin et al. [44] indicates that women living with PMOS exhibit heightened sympathetic nerve activity in their muscle vasculature. One study further demonstrated that hyperandrogenism in PMOS-induced rats, along with an increase in mean arterial pressure, is associated with the excitation of the sympathetic nervous and renal nerves [45]. These findings support the view that sympathetic activation may participate in the neuroendocrine abnormalities of PMOS. Obesity may further intensify this process. Type 2 innate lymphoid cells (ILC2s), which participate in adipose tissue immune regulation, have been found to interact with sympathetic nerve endings. These nerve endings influence adjacent adipose mesenchymal cells through β2-adrenergic receptors, thereby regulating energy expenditure, insulin regulation, and obesity [46]. Excessive psychological stress, which can lead to anxiety and depression, also acts as a trig-

ger for PMOS and obesity, with the sympathetic nervous system playing a significant role in this process [47,48]. Collectively, the available evidence suggests that symptoms related to PMOS and obesity are partially governed by the sympathetic nervous system, with changes in sympathetic nerve activity contributing to associated pathological states.

Nerve growth factor (NGF) supports the survival and growth of neurons and is found in the ovaries [49]. Women with PMOS have been reported to exhibit reduced serum NGF levels, suggesting altered neurotrophic regulation [50]. Experimental studies, however, have shown that excessive ovarian NGF expression can also induce sympathetic excitation in mice, leading to reproductive dysfunction and metabolic abnormalities such as increased body fat and IR [51]. These findings indicate that both excessive and insufficient NGF levels exacerbate the progression of PMOS. Electroacupuncture has been identified as an effective method for regulating sympathetic nerve activity. Low-frequency electroacupuncture can reduce elevated muscle sympathetic nerve activity in women with PMOS. Further research has shown that continuous electroacupuncture treatment lowers androgen levels in the bloodstream and adipose tissue of women with PMOS, at least in part, by modulating the activity of sympathetic nerves in adipose tissue [52]. Additionally, electroacupuncture can improve ovarian morphology and ovulation in the ovaries of PMOS-induced rats [53,54]. Overall, the sympathetic nervous system appears to provide an important link between obesity, metabolic stress, and reproductive dysfunction in PMOS. Although the underlying mechanisms remain incompletely understood, existing evidence suggests that sympathetic overactivity may contribute to both endocrine imbalance and impaired ovarian function.

3.5 Genetics: Shared Susceptibility Linking Obesity and PMOS

The tendency of PMOS to affect members of the same family underscores its genetic origins, with both male and female relatives of women living with PMOS facing an increased risk of experiencing reproductive and metabolic challenges related to the condition [55]. The heritability of PMOS is estimated to be approximately 70%; however, only about 10% of the genetic loci associated with the condition have been identified to date [56]. Hyperandrogenism is a common symptom in women with PMOS, and this phenomenon plays an important role in transmitting the condition to their offspring [57]. Key traits associated with PMOS, such as polycystic ovaries, hyperandrogenism, paternal metabolic syndrome, obesity, and impaired insulin function related to type 2 diabetes, are most pronounced among immediate family members [57].

Although genes distributed on multiple chromosomes are involved in the occurrence and development of PMOS, no single gene has been clearly identified as the sole genetic determinant of this disease [58,59]. Studies have confirmed that steroid-related genes, such as cytochrome P450 family 17 subfamily A member 1 (CYP17A1), cytochrome P450 family 11 subfamily A member 1 (CYP11A1), and cytochrome P450 family 19 subfamily A member 1 (CYP19A1), are tied to genetic vulnerability to both PMOS and fertility issues [60]. Additionally, PMOS and obesity share a common genetic background. The heritability of BMI is estimated to range from 40% to 70% [61], and genome-wide association studies have reported a positive genetic relationship between PMOS and adult BMI, identifying a susceptibility region on chromosome 18 (57630483-59020751) [62]. Further research in the UK has confirmed that the *FTO* gene is associated with an increased risk of PMOS, particularly among obese individuals [63]. Although these findings suggest a genetic component linking PMOS and obesity, the clinical significance of individual genetic variants remains uncertain. Currently, genetic susceptibility is generally considered a background factor that may increase susceptibility to endocrine and metabolic disturbances rather than a direct determinant of disease severity. In women with PMOS, genetic predisposition likely interacts with obesity, IR, and hormonal imbalance to shape the final reproductive phenotype.

3.6 The Gut Microbiota: A Metabolic-Reproductive Interface

The function of the gut microbiota in PMOS and obesity is receiving increasing attention [64]. Women with PMOS have been reported to show increased intestinal abundance of several bacterial taxa, such as *Escherichia spp.*, *Bacteroides spp.*, *Comamonas kerstersii*, *Parabacteroides merdae*, and *Shigella spp.* [65]. Obesity may further modify these microbial patterns. In the PMOS models, rats fed a high-fat diet, researchers observed a decrease in the diversity of gut bacteria (α-diversity) and an increase in the concentration of *Firmicutes* [66]. In human studies, four key signature bacterial taxa (*Lachnoclostridium*, *Fusobacterium*, *Coprococcus_2*, and *Tyzzerella_4)* have been identified, suggesting that obesity may contribute to a unique gut microbiota profile [67]. In addition to metabolic dysregulation, the gut microbiota may also influence reproductive endocrine function through the microbiota-gut-brain axis. Associations between gut microbiota composition and sex hormone levels have been reported. For instance, reduced microbial diversity has been linked to higher total testosterone concentrations and increased hirsutism in women with PMOS [68]. In addition, serum LH has been positively correlated with *Bifidobacterium* abundance, while estradiol levels have been shown to be negatively associated with the abundance of *Eubacterium hallii* and *Fusicatenibacter* [67]. These findings support the possibility that gut microbial imbalance may influence both endocrine regulation and reproductive phenotypes in PM OS. There is also evidence that mod-

ulation of the gut microbiota may improve PMOS-related manifestations. Probiotic interventions, for instance, have shown promise as a means of alleviating these symptoms by positively influencing serum testosterone levels and reducing hirsutism [69]. Therefore, the gut microbiota may contribute to hyperandrogenic conditions in PMOS through both metabolic effects and neuroendocrine mechanisms. In obesity-related dysbiosis, disruption of the intestinal barrier may increase systemic exposure to bacterial endotoxins, thereby sustaining chronic inflammation and activating stress-related signaling pathways [70]. At the same time, altered production of microbial metabolites, such as short-chain fatty acids, secondary bile acids, and tryptophan-derived molecules, may influence hypothalamic neurons involved in reproductive regulation [71]. Through these inflammatory and neuroactive signals, gut dysbiosis may interfere with the hypothalamic-pituitary-gonadal (HPG) axis, particularly by disturbing gonadotropin-releasing hormone (GnRH)/LH pulsatility [72]. Because excessive LH stimulation promotes ovarian theca cell-mediated steroidogenesis, this pathway may provide a plausible explanation for how intestinal dysbiosis contributes to androgen excess in PMOS.

Despite growing interest in this field, the relationship between gut microbiota and PMOS remains incompletely defined. Heterogeneity across populations, methods, and dietary backgrounds makes it difficult to draw firm conclusions regarding the nature and magnitude of this association. Nevertheless, current evidence suggests that gut microbiota may represent an important factor linking obesity with endocrine and ovarian dysfunction in women with PMOS [64].

4. Organ-Level Pathways Linking Obesity to Reproductive Dysfunction in PMOS

The pathophysiological mechanisms described above ultimately manifest through coordinated effects on multiple organs involved in endocrine and metabolic regulation. In women with PMOS, obesity may influence reproductive function by altering neuroendocrine signaling, metabolic homeostasis, and steroid hormone production. These disturbances interact across several organ systems, including the hypothalamus-pituitary axis, metabolic organs such as the liver and thyroid, the adrenal glands, and the ovaries themselves. Together, these organ-level interactions contribute to the development and progression of reproductive dysfunction in PMOS.

4.1 Neuroendocrine Regulation: The Hypothalamus-Pituitary Axis

GnRH neurons are primarily located in the medial basal hypothalamus and preoptic area. The hypothalamus releases GnRH, a hormone that controls the pulsatile secretion of follicle-stimulating hormone (FSH) and LH from the anterior pituitary gland, thereby regulating ovarian follicular development and ovulation [73]. However, under pathological conditions, an increase in pulsatile GnRH release is observed, whereupon it binds to the gonadotropin receptors on the anterior pituitary, leading to elevated levels of LH secretion without a corresponding increase in FSH concentrations, resulting in a higher LH/FSH ratio that contributes to the pathogenesis of PMOS [74]. Silva et al. [75] found that stimulating neurons within the arcuate nucleus of the hypothalamus with gamma-aminobutyric acid (GABA) in healthy female mice increased the frequency of LH pulses, disrupted the estrous cycle, reduced the number of corpora lutea, and contributed to greater testosterone levels.

Obesity may further influence hypothalamic regulation through metabolic and inflammatory signals [76]. High-fat diets and excess adiposity have been associated with hypothalamic inflammation and gliosis, which may impair neuronal signaling and alter patterns of GnRH secretion [77]. Adipokines and metabolic hormones also participate in neuroendocrine regulation. The adipocyte-derived hormone leptin can relay information regarding energy stores to hypothalamic neurons involved in reproductive control, including GnRH and kisspeptin neurons [78]. In women with PMOS, leptin levels are often elevated, but hypothalamic responsiveness to leptin may be reduced, potentially contributing to reproductive endocrine dysregulation. Other neuropeptides involved in energy balance may also participate in hypothalamic reproductive regulation [79,80,81]. Together, these observations indicate that obesity-related metabolic disturbances may influence hypothalamic signaling and thereby contribute to the neuroendocrine abnormalities observed in PMOS.

4.2 Metabolic Organs: The Liver and Thyroid

Metabolic organs including the liver and thyroid play important roles in maintaining endocrine and metabolic homeostasis and may indirectly influence reproductive function in women with PMOS. The liver plays a central role in lipid metabolism, glucose homeostasis, and endocrine regulation. One of its most relevant functions in PMOS is the production of SHBG, which regulates the bioavailability of circulating androgens. IR, obesity, and dietary factors may reduce hepatic SHBG production, thereby increasing free androgen levels and contributing to oligo-ovulation or anovulation [82]. NAFLD is commonly found in women with PMOS [83], with central obesity and IR being considered the main factors linking these two conditions. Vajravelu et al. [84] proposed that excessive hepatic and visceral fat accumulation may contribute to the development of endocrine abnormalities in PMOS and further demonstrated that reducing hepatic fat levels in adolescent girls may lead to improvements in ovulation and hyperandrogenism.

The thyroid is an endocrine organ that not only regulates the metabolism of various substances but also plays a key role in reproductive function [85]. Several studies

have shown that thyroid-stimulating hormone (TSH) levels are elevated in women with PMOS compared to those who are healthy [86]. In the context of otherwise normal thyroid function, higher levels of TSH in women with PMOS may be related to excessive androgens [87]. Furthermore, women with PCOS appear to have a higher prevalence of subclinical hypothyroidism and autoimmune thyroid disease. Obesity itself has also been linked to an increased risk of hypothyroidism and thyroid dysfunction [88]. Inflammatory cytokines associated with obesity may influence thyroid autoimmunity, and a positive association between thyroid volume and LH levels has been reported in women with PMOS [89]. These findings suggest that metabolic and endocrine alterations in the liver and thyroid may contribute to the systemic hormonal imbalance observed in PMOS.

4.3 Steroidogenic Contributions: The Adrenal Glands

The adrenal glands represent an additional endocrine source of steroid hormones that may contribute to the hormonal abnormalities observed in PMOS. Activation of the hypothalamic–pituitary–adrenal (HPA) axis stimulates the adrenal cortex to produce glucocorticoids, mineralocorticoids, and adrenal-derived androgens. In some women with PMOS, increased adrenal androgen production contributes to the overall hyperandrogenic state [90]. Obesity may also influence adrenal endocrine activity. Elevated cortisol production has been reported both in women with PMOS and in individuals with obesity. Cortisol can promote adipocyte differentiation and fat accumulation, emphasizing the potential existence of a link between adrenal hormone activity and metabolic disturbances [91]. Metabolic conditions may also affect adrenal structure and steroidogenesis. Experimental studies have shown that high-fat diets stimulate the proliferation of progenitor cells in the adrenal cortex and increase the number of steroid-producing cells. These structural changes may lead to increased hormone secretion [92]. The contribution of adrenal androgens differs among women with PMOS. Nevertheless, adrenal endocrine activity may interact with metabolic disturbances related to obesity and participate in the hormonal imbalance characteristic of PMOS.

4.4 The Ovary: The Final Target of Reproductive Dysfunction

In addition to secreting sex hormones, the ovaries play a central role in follicular development and ovulation. Normal physiological ovulation in women follows a cyclical pattern under the control of the hypothalamic-pituitary-ovarian (HPO) axis. However, metabolic and hormonal imbalances can lead to HPO axis dysfunction in PMOS, resulting in ovarian dysfunction. Ultrasonography typically reveals a lack of dominant follicles in the ovaries of affected patients, with polycystic changes. Moreover, obesity-induced inflammation and oxidative stress can contribute to ovarian inflammation, impairing oocyte meiosis and cytoplasmic maturation, further reducing the capacity for fertilization and pre-implantation embryonic development [93]. Collagen deposition, leading to fibrosis of the ovarian stroma and the formation of a rigid barrier has been advanced as a potential mechanism underlying oocyte release disorders [94]. In animal model studies, obesity has been shown to exacerbate ovarian interstitial fibrosis in mice through a process tentatively linked to obesity-induced mitochondrial dysfunction, leading to inflammation, oxidative stress, and collagen deposition [95]. PMOS and ovarian aging share several common pathophysiological mechanisms, including altered cellular metabolic processes, changes in mechanistic target of rapamycin (mTOR) pathway signaling activity, and oxidative stress. Obesity accelerates ovarian aging in rodents, as evidenced by an increase in lipofuscin accumulation in ovarian cells and elevated levels of p21 and p16 expression, consistent with cell cycle arrest [96]. Additionally, obesity accelerates follicular development and loss by activating the mTOR pathway and inhibiting silent information regulator 1 (SIRT1), thus promoting ovarian aging [97]. Studies have found that in mice, obesity-induced reproductive dysfunction is related to its promotion of apoptosis in GCs and altered immune function [98]. Additionally, obesity causes a follicle stage-dependent increase in the expression of ataxia telangiectasia mutated protein in rat ovaries [99]. Obesity is closely related to autophagy processes. Ovarian GCs express oxidized low-density lipoprotein receptor-1, and in obese individuals oxidized low-density lipoprotein (oxLDL) levels are significantly elevated, leading to increased rates of autophagy in GCs, which may exacerbate PMOS [100]. These observations suggest that obesity-related metabolic disturbances may significantly impair ovarian function and reproductive outcomes in women with PMOS.

5. Clinical Implications for the Management of Obesity-Related PMOS

The evidence summarized above indicates that obesity is closely related to the metabolic and reproductive manifestations of PMOS. In clinical practice, women with obesity-related PMOS often exhibit more significant IR, hyperandrogenemia, and ovulatory dysfunction. These characteristics suggest that this subgroup may require a more comprehensive management strategy, with a dual focus on both reproductive and metabolic health. Weight management remains a core component of treatment [101]. Even moderate weight loss can reportedly improve metabolic parameters, menstrual regularity, and ovulatory function in women with PMOS [18]. Lifestyle intervention should thus be regarded as an important first step, especially for patients with central obesity or metabolic abnormalities. Dietary adjustments, regular exercise, and behavioral support may promote improved metabolic activity while helping to achieve better reproductive outcomes. Drug-based treatment strategies may also be effective in certain patient populations. Met-

formin has been widely used in women with PMOS who have metabolic disorders, while GLP1-RAs have gained increasing attention owing to their ability to promote weight loss and improve glucose metabolism. These treatment options may be particularly applicable to women with PMOS who are unable to achieve the desired degree of metabolic improvement through lifestyle intervention alone.

Women with obesity-related PMOS often present with more significant ovulatory dysfunction and impaired follicular development as compared to their normal-weight counterparts. For patients seeking to achieve pregnancy, improving metabolic status before initiating fertility treatment may be beneficial. In the context of ovulation induction or assisted reproductive technology use, optimizing weight and metabolic parameters may afford better reproductive outcomes. Long-term follow-up is particularly important for women with obesity-related PMOS. In addition to reproductive disorders, women with obesity-related PMOS face an increased risk of type 2 diabetes, cardiovascular disease, and NAFLD [5]. Clinical workups for these patients should thus extend beyond the reproductive system, incorporating the routine monitoring of cardiometabolic health. In conclusion, these observations highlight the importance of a comprehensive management strategy for obesity-related PMOS that focuses on simultaneously addressing obesity, metabolic dysfunction, and reproductive health.

6. Discussion

Obesity is relatively common among women with PMOS and has been found to affect the severity of metabolic and reproductive abnormalities. Clinical studies have consistently shown that women affected by both diseases often exhibit more significant IR, higher androgen levels, and more severe ovulatory dysfunction [101]. These observations suggest that obesity may promote the clinical manifestations of PMOS rather than merely coexisting with it. An important aspect of this interaction involves the relationship between visceral adiposity, IR, and excessive androgens [102,103]. Visceral adiposity is typically associated with compensatory hyperinsulinemia. Elevated insulin levels may stimulate ovarian theca cells to produce androgens and reduce the synthesis of SHBG in the liver, thereby increasing circulating free androgen levels. In turn, excessive androgens may further disrupt fat tissue metabolism and exacerbate IR [104]. Therefore, these metabolic and endocrine disorders appear to reinforce one another, precipitating a persistent pathological cycle. This interpretation is consistent with recent views that PMOS is not only a reproductive disorder but also a metabolic disease, in which insulin resistance and compensatory hyperinsulinemia, both intrinsic to PMOS and exacerbated by obesity, contribute to metabolic complications, hyperandrogenism, and reproductive dysfunction [1,10]. However, this interaction is unlikely to arise in isolation. Available evidence suggests that reproductive dysfunction in obesity-related PMOS is more plausibly explained by the interplay of multiple pathogenic pathways, with chronic inflammation, oxidative stress, neuroendocrine dysregulation, and gut dysbiosis all interacting with IR and hyperandrogenism to further amplify ovarian dysfunction and reproductive impairment [1,36,105]. This integrated perspective extends beyond previous single-pathway interpretations and provides a more coherent understanding of how obesity-driven metabolic disturbance may be linked to reproductive dysfunction in PMOS.

In addition to this interconnected metabolic-endocrine network, obesity exhibits effects that extend beyond changes in systemic metabolic markers. The evidence summarized in this review indicates that obesity-related disorders involve multiple organ systems relevant to the regulation of reproductive function [106]. Changes in HPO signaling may affect gonadotropin secretion patterns and lead to endocrine imbalance. Metabolic changes affecting organs such as the liver and thyroid may further disrupt hormone homeostasis. In some individuals, adrenal steroidogenesis may also contribute to an increase in androgen production. Ultimately, these changes converge on the ovaries, where inflammation, oxidative stress, and changes in ovarian tissue structure may damage follicle development and ovulatory function. This multi-organ perspective may help explain why women with obesity-related PMOS often present with more severe follicular dysfunction, anovulation, and impaired fertility.

From a clinical perspective, these observations suggest that obesity-related PMOS may represent a more complex metabolic manifestation of this syndrome [101]. In patients affected by both obesity and PMOS, reproductive dysfunction arises within a broader context of endocrine and metabolic abnormalities. This may partially explain why obesity in PMOS patients is associated with menstrual irregularities and infertility, as well as a greater risk of miscarriage and long-term cardiometabolic complications. Crucially, several of the mechanisms underlying this association may be modifiable. Clinical studies have shown that weight loss and improvements in insulin sensitivity are associated with better ovulatory function and reproductive outcomes [107,108]. These findings support the importance of focusing on metabolic health when managing PMOS in the clinic, particularly in those with central obesity, marked IR, hyperandrogenism, and severe ovulatory dysfunction.

At the same time, this integrated framework highlights several important directions for future research and therapeutic investigation. One priority will be to determine whether obesity-related PMOS can be further stratified based on factors beyond body weight alone, particularly according to dominant features such as IR, androgen excess, inflammatory burden, oxidative stress, or gut microbiota-related alterations [1]. Such stratification may help explain the substantial heterogeneity in reproductive and metabolic outcomes observed among affected women. Another im-

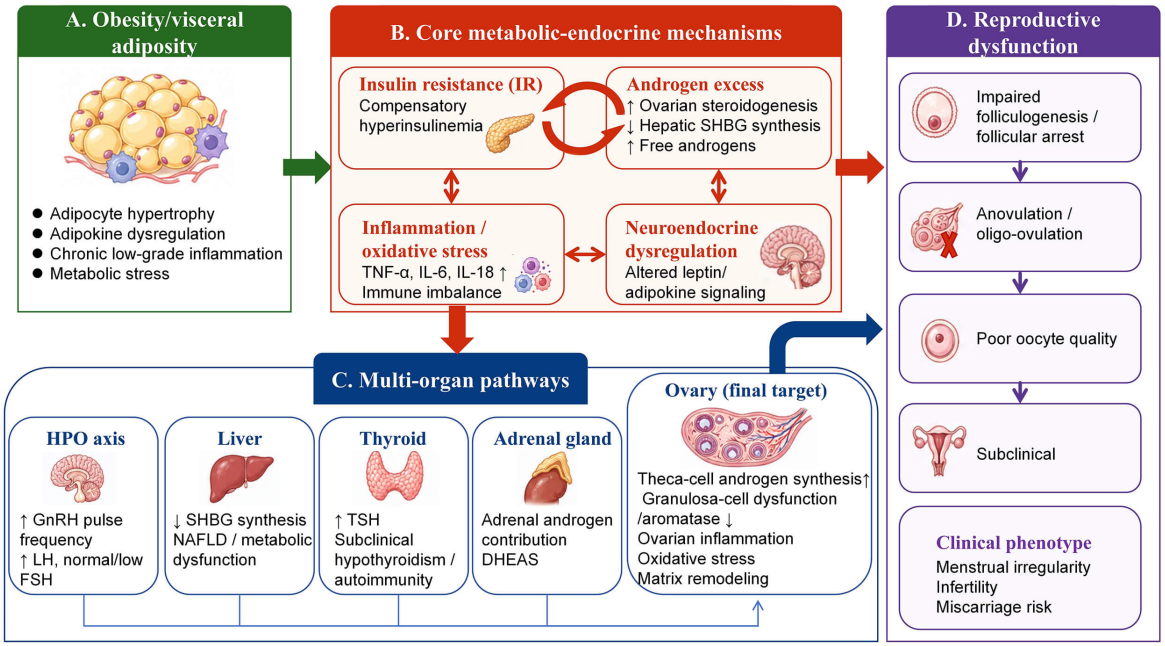


Fig. 1. Core mechanisms linking obesity-related metabolic disturbance to reproductive dysfunction in polyendocrine metabolic ovarian syndrome (PMOS). (A) Obesity/visceral adiposity as the initiating metabolic state in obesity-related PMOS. (B) Core metabolic-endocrine mechanisms linking obesity to reproductive dysfunction. (C) Multi-organ pathways through which obesity-related metabolic disturbance contributes to ovarian dysfunction. (D) Reproductive consequences of obesity-related metabolic disturbance in PMOS. Overall, the figure highlights that obesity acts not merely as a comorbidity, but as a metabolic amplifier of reproductive dysfunction in PMOS. HPO, hypothalamic-pituitary-ovarian; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; NAFLD, non-alcoholic fatty liver disease; TSH, thyroid-stimulating hormone; TNF-α, tumor necrosis factor-α; IL-18, interleukin-18; IL-6, interleukin-6; DHEAS, dehydroepiandrosterone sulfate.

portant direction for further study will be the clarification of how these interacting mechanisms are temporally and functionally organized, particularly with respect to which pathways act as key drivers and which primarily serve to amplify disease progression. Greater attention should also be paid to multi-organ communication, particularly the interactions that take place between the hypothalamic-pituitary axis, liver, thyroid, adrenal glands, and ovaries, in order to better understand how systemic metabolic stress is translated into ovarian dysfunction [106].

From a therapeutic perspective, future studies should further evaluate whether prioritizing metabolic optimization before or alongside fertility-directed treatment can lead to improvements in both reproductive outcomes and long-term metabolic health in women with obesity-related PMOS [10,107]. There is also a clear need to clarify whether interventions targeting not only insulin sensitivity and body weight, but also inflammatory status, oxidative stress, or gut microbiota-related dysregulation, may provide additional benefit in selected patients [7,36]. Overall, viewing obesity-related PMOS within an integrated multi-mechanism and multi-organ framework may help move the field beyond isolated pathway-based interpretations and support more precise, phenotype-oriented management strategies (Fig. 1).

Limitations

While the current evidence is compelling, it is subject to certain limitations. First, the diagnostic criteria for PMOS vary across studies, and the definitions of obesity, particularly central obesity, are not fully consistent. This heterogeneity may have some bearing on the comparability of findings while limiting the generalizability of the associated conclusions. Second, there have been relatively few longitudinal and interventional studies in this space. As much of the available evidence is derived from cross-sectional or observational studies, it remains difficult to establish causal relationships between obesity and specific reproductive or metabolic features of PMOS. Third, some mechanistic insights discussed in this review are based on experimental models, including animals and *in vitro* studies. Although these studies provide valuable information, their findings may not fully reflect the complexity of human disease. Finally, a high degree of variability was evident across studies with respect to factors such as ethnicity, lifestyle, and dietary patterns, potentially influencing both metabolic status and reproductive phenotypes. These variables were not consistently addressed in the included studies.

7. Conclusions

Rather than simply representing a common accompanying symptom of PMOS, obesity also plays a role as a positive driver of its attendant reproductive and metabolic manifestations. By exacerbating IR, hyperandrogenemia, inflammatory responses, neuroendocrine disorders, and organ dysfunction, obesity may lead to the deterioration of reproductive phenotypes and contribute to greater long-term metabolic risks. This review supports the perspective that obesity-related PMOS may be more effectively conceptualized as a distinct subtype of this disease defined by metabolic amplification, rather than as a subgroup of patients solely defined by differences in body weight. A more clearly defined integrative multi-mechanism and multi-organ framework may help refine risk stratification and support the formulation of comprehensive treatment strategies that combine weight control, metabolic optimization, and reproductive health care to more effectively manage PMOS.

Abbreviations

PMOS, polyendocrine metabolic ovarian syndrome; IR, insulin resistance; TNF-α, tumor necrosis factor-α; GLP1-RAs, glucagon-like peptide-1 receptor agonists; LH, luteinizing hormone; ATF4, activating transcription factor 4; GCs, granulosa cells; BMI, body mass index; IL-18, interleukin-18; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; IL-8, interleukin-8; NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species; Th1, T helper 1; Th2, T helper 2; DHEA, dehydroepiandrosterone; NK, natural killer; MSC, mesenchymal stem cell; IL-1β, interleukin-1β; IFN, interferon; ILC2s, type 2 innate lymphoid cells; NGF, nerve growth factor; CYP17A1, cytochrome P450 family 17 subfamily A member 1; CYP11A1, cytochrome P450 family 11 subfamily A member 1; CYP19A1, cytochrome P450 family 19 subfamily A member 1; HPG, hypothalamic-pituitary-gonadal; SHBG, sex hormone-binding globulin; HPA, hypothalamic-pituitary-adrenal; HPO, hypothalamic-pituitary-ovarian; GABA, gamma-aminobutyric acid; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; NAFLD, non-alcoholic fatty liver disease; mTOR, mechanistic target of rapamycin; SIRT1, silent information regulator factor 1; oxLDL, oxidized low-density lipoprotein.

Author Contributions

RNL, HWG and TTL designed the research study. TTL, SZL, JHP and YY conducted the literature search and contributed to evidence screening and narrative synthesis. RNL, TTL and SZL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT-5.2 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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