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LEAN PCOS AS A DISTINCT PHENOTYPE: METABOLIC DYSFUNCTION, DIAGNOSTIC IMPLICATIONS, AND THE EMERGING ROLE OF GLP-1–BASED THERAPIES

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) affects 5–26% of reproductive-age women, yet current diagnostic frameworks insufficiently distinguish metabolically distinct phenotypes, particularly lean PCOS (BMI ≤25 kg/m²).
Objective: This narrative review evaluates lean PCOS as a distinct pathophysiological entity and discusses its neuroendocrine and metabolic features, diagnostic challenges, and weight-stratified classification approaches.
Methods: A literature search of PubMed, Google Scholar, and clinical guidelines (2015–2026) was conducted, including meta-analyses and comparative studies of lean and obese PCOS phenotypes.
Results: Lean PCOS is characterized by neuroendocrine predominance (elevated LH/FSH ratio, adrenal androgen excess), intrinsic insulin resistance independent of BMI, and altered adipokine signaling reflecting adipose tissue dysfunction. Despite relatively favorable cardiometabolic profiles, patients exhibit subclinical hepatic and vascular risk. Genetic studies confirm distinct metabolic and insulin-signaling pathway involvement.
Conclusions: Lean PCOS represents a biologically distinct phenotype requiring weight-stratified diagnostic strategies and phenotype-specific therapeutic approaches, including investigation of incretin-based therapies.

KEYWORDS

Lean PCOS, Polycystic Ovary Syndrome, Metabolic Dysfunction, Endocrine Phenotypes, Incretin Therapy

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1. Introduction

Polycystic Ovary Syndrome (PCOS) is recognized as the most common endocrine disorder among women of reproductive age worldwide, with prevalence rates ranging from 5% to 26%, depending on diagnostic criteria and ethnic variations [1]. Clinically, the Rotterdam criteria are primarily used for diagnosis, requiring the presence of two out of three conditions: chronic ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound, after ruling out other similar conditions. [2]. This classification results in four phenotypic variations (A, B, C, D) that reflect significant clinical diversity.

In May 2026, after a landmark 14-year global consensus process involving 56 leading organizations and over 14,360 participants from all world regions, the condition was officially renamed **Polyendocrine Metabolic Ovarian Syndrome (PMOS)** [3]. The new name was chosen to reflect the multisystem pathophysiology of the disorder — "polyendocrine" capturing the hormonal dysregulation, "metabolic" acknowledging the inherent cardiometabolic risk, and "ovarian" recognizing the reproductive component without implying pathological cysts [3]. This change was preceded by an international survey documenting strong support from both patients and health professionals for a more accurate name [4] and has been accompanied by expert commentary on implementation strategies [5-7].

Although often linked to excess body weight, a significant number of patients have a normal Body Mass Index (BMI ≤ 25 kg/m²), classified as "lean PCOS." [1]. The existence of this non-obese group complicates both diagnosis and treatment strategies, raising important questions about whether lean PCOS is a distinct pathophysiological condition driven by unique mechanisms or merely a less severe form of the traditional syndrome [8]. This narrative review consolidates current research to characterize lean PCOS as a separate pathophysiological entity, highlighting its distinctive neuroendocrine and metabolic features, and suggests a diagnostic framework that considers weight and adiposity status for more accurate risk evaluation and management.

2. Analysis of Lean PCOS as a Phenotype

2.1. The Primacy of Body Weight over Rotterdam Phenotype Classification

The Rotterdam system, while capturing ovulatory and androgenic variance, inadequately stratifies metabolic risk profiles [2,8]. Evidence demonstrates that body weight status outweighs specific Rotterdam phenotype in determining metabolic health [8,9]. Obese patients across phenotypes A, B, and C uniformly exhibit adverse metabolic signatures including hyperinsulinemia, severe insulin resistance, and dyslipidemia [8,9]. In contrast, lean PCOS patients within phenotypes A, B, and C typically maintain normal insulin concentrations, normal lipid panels, and lack clinically significant insulin resistance [1,8,9]. This metabolic divergence suggests that mechanisms perpetuating chronic anovulation are not exclusively metabolic [1,10]. Consequently, classification models dividing each Rotterdam phenotype into obese (ob) and lean (l) sub-phenotypes (e.g., A-ob, A-l) have been proposed to align risk stratification with therapeutic planning [1]. In Mediterranean cohorts, lean phenotypes (A-l, C-l) represent the most prevalent presentations [1].

2.2. Metabolic Features: Insulin Resistance, Adiposity, and Subclinical Risk

While obesity amplifies metabolic dysfunction in PCOS, the presence of metabolic derangement in lean individuals supports intrinsic, weight-independent pathogenic mechanisms [8].

- **Insulin Resistance:** IR occurs frequently in lean PCOS, suggesting a primary defect. Altered pancreatic beta-cell function, insulin secretion dynamics, and hepatic insulin clearance are hypothesized as weight-independent pathological components [8,11]. Severity differs significantly: lean PCOS patients demonstrate markedly lower HOMA-IR values than obese patients indicating better insulin sensitivity [1]. The recognition of lean PCOS as a distinct metabolic phenotype has sparked interest in insulin-sensitizing therapies that target pathways beyond weight reduction. GLP-1 receptor agonists (GLP-1 RAs) such as liraglutide and semaglutide are under active investigation, with preliminary evidence suggesting benefits that extend beyond weight loss [12]. However, most trials have recruited predominantly overweight or obese participants, whereas up to 50% of PCOS women present with a lean phenotype [12,13]. This selection bias limits the applicability of current evidence to lean PCOS and underscores the critical need for phenotype-stratified trials [13-16].
- **Adolescent Manifestation:** In adolescent lean PCOS (BMI < 85th percentile), metabolic dysfunction is clearly evident, with significantly higher fasting insulin and HOMA-IR compared to BMI-matched controls [17]. The incretin axis may play an early role in this metabolic dysregulation, as altered GLP-1 and DPP-4 profiles have been reported in PCOS and linked to insulin resistance independently of adiposity [12,14]. Notably, no full-text trials of GLP-1 RA monotherapy in adolescents with PCOS exist to date [13], representing a critical gap given that metabolic dysfunction in this group is intrinsic rather than obesity-driven and may require distinct therapeutic strategies [13,17].
- **Adipose Tissue Dysfunction:** Despite normal BMI, lean PCOS women carry metabolic risk through increased visceral adiposity and adipose tissue dysfunction [8]. Lean PCOS adolescents show an adverse adiponectin-to-leptin ratio, signaling cardiometabolic risk and adipose inflammation similar to obese patterns [17]. GLP-1 receptors are expressed on adipocytes, and GLP-1 RAs have been shown to modulate adipose tissue function by reducing inflammation, improving adipokine profiles, and promoting favorable fat distribution [12,14]. These adipose-specific effects may be particularly relevant in lean PCOS, where adipocyte dysfunction persists despite normal BMI [8,17].
- **Skeletal muscle and lean mass:** Beyond adipose distribution, body composition data indicate that women with classic hyperandrogenic PCOS (phenotypes A and B) often have a higher appendicular lean mass index (ALMI) than BMI-matched controls, likely reflecting anabolic effects of hyperinsulinemia, androgen excess, and increased mechanical loading [18]. In contrast, ovulatory phenotype C, which frequently corresponds to lean PCOS, shows ALMI values comparable to healthy women, suggesting that increased skeletal muscle mass is not a characteristic feature of lean PCOS [18]. Notably, GLP-1 RAs have been associated with preservation of lean mass during weight loss, an effect that may be clinically relevant in lean PCOS where metabolic inflexibility and adverse body composition can coexist despite normal BMI [15,16].
- **Subclinical Organ Risk:** Lean PCOS associates with organ-specific risks not captured by BMI. Alanine Aminotransferase (ALT) is significantly higher in lean PCOS versus controls [19], with Total Testosterone identified as an independent predictor [19]. This suggests hyperandrogenism-driven hepatocellular stress. GLP-1 RAs have demonstrated hepatoprotective effects in metabolic dysfunction-associated steatotic liver disease, reducing ALT and hepatic steatosis independently of weight loss [15]. This raises the possibility that incretin-based therapy could address the hepatic stress observed in lean PCOS, where ALT elevation reflects a hyperandrogenism-driven mechanism distinct from obesity-related NAFLD [15,19].

• **Cardiometabolic Profile:** Meta-analytic data confirm lean PCOS patients have superior cardiovascular indicators than obese counterparts, including significantly lower diastolic/systolic blood pressure, LDL cholesterol, and triglycerides [1]. Nevertheless, GLP-1 RAs have been shown to improve cardiometabolic risk markers across PCOS populations, including blood pressure, lipid profiles, and inflammatory markers [12,13]. In lean PCOS, where baseline metabolic parameters are relatively favorable, the potential for GLP-1 RA therapy to target subclinical inflammation and long-term cardiovascular risk warrants further phenotype-specific investigation [13,16].

2.3. Endocrine and Neuroendocrine Differentiation

Hormonal profiles show consistent distinctions supporting separate primary pathogenic pathways.

• **Gonadotropins:** Lean PCOS patients display elevated LH, FSH, and a significantly higher LH/FSH ratio than obese PCOS, indicating HPO axis dysregulation as a primary driver [1,10].

• **Neuroendocrine Drivers:** Mechanistic studies highlight Anti-Müllerian Hormone (AMH) and Dynorphin as central regulators of the high LH/FSH ratio in lean PCOS. AMH likely functions as a key intermediary, linking HOMA-IR and hyperandrogenism to gonadotropin dysregulation by enhancing GnRH pulsatility. Dynorphin shows direct positive correlation with the LH/FSH ratio [17], suggesting specific KNDy neuron modulation drives LH hypersecretion.

• **Androgen Sources:** Lean PCOS patients have significantly higher Sex Hormone-Binding Globulin (SHBG) and Dehydroepiandrosterone sulfate (DHEAS) than obese PCOS. Elevated SHBG may bind more circulating androgens, mitigating clinical hyperandrogenism, while high DHEAS suggests greater adrenal androgen contribution. Obese PCOS patients typically show higher Free Testosterone due to insulin-mediated SHBG suppression [1,20].

• **Shared Androgen Pathology:** Despite differing sources, androgen excess correlates positively with hyperinsulinemia and endothelial dysfunction irrespective of obesity [21], reinforcing androgen pathways as central, weight-independent pathologies.

2.4. Distinct Sub-Phenotypes and Pathogenic Trajectories

Within lean PCOS, further phenotypic divergence is evident. Adolescent studies confirm that distinct reproductive phenotypes segregate with differences in body weight, further supporting the biologic validity of weight-based stratification [22]. A hypo-androgenic PCOS-like phenotype (H-PCOS) may evolve from the lean hyper-androgenic presentation, typically emerging between the 20s and mid-30s [23]. This trajectory features hypo-androgenism, markedly elevated SHBG and AMH, and immune hyperactivity, potentially driven by adrenal insufficiency [23]. This evolution suggests lean PCOS is not static but may transition into a pathologically distinct late-stage phenotype. Genetic studies using clinical exome sequencing have identified distinct variant profiles in lean versus obese PCOS, reinforcing the biological distinctness of these subgroups [24].

3. Diagnostic Challenges and Classification Frameworks

3.1. Limitations of Current Diagnostic Criteria

The Rotterdam criteria, while widely adopted, exhibit critical limitations in capturing the full metabolic spectrum of PCOS [9]. The framework's exclusive focus on reproductive and androgenic parameters fails to incorporate metabolic status, particularly body weight [9]. This omission results in collapsing metabolically distinct populations (lean vs. obese) into identical phenotypic categories despite vastly different cardiovascular and diabetes risk profiles [9].

The consequence is difficulty establishing clear follow-up strategies and obscuring potential genetic or environmental differences between weight-defined subgroups [9]. International evidence-based guidelines acknowledge these gaps, noting that insulin resistance, while recognized as a key PCOS feature, is not currently recommended for routine clinical measurement due to methodological limitations [2]. This diagnostic inertia prevents appropriate risk stratification, particularly for lean patients whose metabolic dysfunction may be masked by normal BMI.

3.2. Diagnostic Biomarkers Specific to Lean PCOS

Identifying lean PCOS requires a biomarker panel extending beyond Rotterdam criteria to capture neuroendocrine and subclinical metabolic perturbations:

Endocrine Markers:

- **Elevated LH/FSH Ratio:** A hallmark neuroendocrine signature, often >1.5, reflecting HPO axis dysregulation [1,10]
- **Anti-Müllerian Hormone (AMH):** In lean PCOS, AMH acts as a central mediator linking metabolic dysfunction to gonadotropin imbalance and correlates strongly with the LH/FSH ratio [10]. A comparative study further confirms that AMH levels correlate differently with androgens and insulin resistance in lean versus obese PCOS patients, supporting distinct underlying mechanisms [25]. AMH concentrations, however, are not significantly different between lean and obese PCOS groups [1].
- **Adrenal Androgens:** (DHEAS): In lean PCOS, DHEAS levels are significantly higher than in obese PCOS, indicating a greater adrenal contribution to hyperandrogenism [1,20]. Elevated adrenal DHEAS is also implicated as a primary driver of HPO-axis dysfunction in lean PCOS.
- **Sex Hormone-Binding Globulin (SHBG):** Significantly higher than obese PCOS, altering free androgen availability [1]

Metabolic Markers:

- **HOMA-IR:** While lower than obese PCOS, values >2.0 may indicate intrinsic insulin resistance even in lean patients [17]
- **Visceral Adiposity:** Direct measurement via DEXA or MRI reveals increased visceral fat independent of BMI [8]
- **Adipokine Profile:** Adverse adiponectin-to-leptin ratio indicates adipose tissue dysfunction [20,26]

Hepatic and Inflammatory Markers:

- **Alanine Aminotransferase (ALT):** Elevated levels independently predicted by total testosterone, signifying hyperandrogenism-driven hepatocellular stress [19]
- **Gamma Glutamyl Transferase (GGT):** Higher levels in lean PCOS versus controls, indicating cardiovascular risk [20,26]
- **Inflammatory Cytokines:** Chronic low-grade inflammation with elevated markers, plus oxidative stress [8,27]

Genetic/Epigenetic Signatures:

- **Gene Expression:** Upregulation of FTO and INSR genes with downregulation of Nrf2 antioxidant gene distinguishes lean PCOS from healthy controls [27]

3.3. Differential Diagnosis and Exclusion Criteria

Diagnosing lean PCOS requires rigorous exclusion of confounding conditions, particularly in adolescents where diagnostic boundaries blur [26]. Patients with lean PCOS often report prolonged diagnostic delays and dismissive healthcare experiences due to the absence of obesity-related stigmata, highlighting the need for greater clinician awareness [28]. Functional hypothalamic amenorrhea (FHA) represents a key differential diagnosis, as both conditions present with menstrual irregularity and potentially elevated LH/FSH ratios [26]. FHA typically exhibits hypothalamic suppression with low gonadotropins and estrogens, contrasting with PCOS's hyperandrogenism and elevated AMH [26].

Clinical guidelines emphasize that in adolescents, both oligo-anovulation and hyperandrogenism are required for diagnosis, with ultrasound not recommended due to high baseline prevalence of polycystic morphology during puberty [2]. Other exclusionary diagnoses include congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, and thyroid dysfunction—each requiring specific biochemical testing [26]. The challenge intensifies in lean patients where classic metabolic stigmata are absent, necessitating more sensitive biochemical screening to confirm intrinsic insulin resistance and hyperandrogenism [26].

3.4. Proposed Classification Frameworks Incorporating Body Weight

To address diagnostic inadequacies, several classification systems integrate adiposity status:

Carmina and Lobo's Sub-Phenotype Model: This framework divides each Rotterdam phenotype into obese (ob) and lean (l) subgroups (e.g., A-ob, A-l) [9]. Data from Mediterranean cohorts demonstrate nearly equal prevalence of lean (A-l: 31.2%) and obese (A-ob: 23.9%) forms of classic PCOS, underscoring the importance of weight-stratified classification for risk assessment and treatment planning [9].

H-PCOS Evolution Model: The hypo-androgenic PCOS-like phenotype (H-PCOS) represents a distinct late-stage evolution from young lean PCOS [23]. Characterized by hypo-androgenism due to adrenal insufficiency, significantly higher SHBG and AMH, and immune hyperactivity, H-PCOS demonstrates complete reversal of treatment resistance when androgens are reconstituted during IVF cycles [23]. This validates H-PCOS as a unique diagnostic entity within the lean spectrum.

Metabolic vs. Reproductive Subtyping: Genome-wide association studies (GWAS) support two major PCOS clusters: a "reproductive" type with high LH, high SHBG, low insulin, and low BMI (aligning with lean PCOS) versus a "metabolic" type with opposite features [10]. BMI-stratified GWAS has further identified loci specific to lean PCOS (including DENND1A, XBP1, and LINC02905) that are distinct from those in overweight/obese subgroups, confirming a partially distinct genetic architecture [29]. This genetic architecture reinforces that body weight and metabolic status define biologically distinct disease categories that should guide diagnostic workup and therapeutic targeting [10]. Moreover, ART data show that women with a lean/reproductive phenotype have a more favorable IVF profile than obese PCOS patients, including higher ovarian response (more retrieved and mature oocytes), higher cumulative live birth rates (≈ 61.7 % vs 54.0 %), and lower miscarriage rates despite similar embryonic aneuploidy, further underscoring that these biologically distinct clusters also differ in treatment response [30].

International Guideline Recommendations: Current guidelines endorse Rotterdam criteria for adults but acknowledge limitations [2]. They recommend clear phenotypic specification and prioritization of metabolic assessment, though insulin resistance measurement is not yet standardized for routine practice [2]. The guidelines emphasize multidisciplinary care and lifestyle intervention for weight management, implicitly recognizing weight status as a critical classification factor, yet stop short of formally integrating BMI into diagnostic categories [2].

4. Conclusions

Accumulating evidence strongly supports the concept that lean PCOS represents a distinct pathophysiological entity rather than a milder manifestation of obesity-associated PCOS [31]. Evolutionary perspectives further suggest that the neuroendocrine and metabolic features of PCOS may represent ancestral adaptations that become maladaptive under modern lifestyle conditions [32]. This phenotype is primarily characterized by neuroendocrine predominance, reflected by an elevated LH/FSH ratio driven by dysregulation of anti-Müllerian hormone (AMH) and dynorphin signaling, alongside increased adrenal DHEA-S levels, suggesting central hypothalamic-pituitary-ovarian (HPO) axis dysfunction as a principal pathogenic mechanism.

Importantly, lean PCOS is also associated with an intrinsic metabolic defect. Insulin resistance is detectable even during adolescence and appears to be linked to unfavorable adipokine profiles and increased visceral adiposity independent of body mass index (BMI), indicating that normal body weight does not confer metabolic protection in this population. In addition, lean PCOS demonstrates targeted organ-specific vulnerability, as hyperandrogenism contributes to hepatic stress, evidenced by elevated alanine aminotransferase (ALT), and to cardiovascular risk markers, including increased gamma-glutamyl transferase (GGT) and blood viscosity. These alterations differ mechanistically from metabolic disturbances typically observed in obesity-related non-alcoholic fatty liver disease (NAFLD). The recognition of weight-independent insulin resistance and adipose tissue dysfunction in lean PCOS has drawn attention to incretin-based pathways as a potential mechanistic contributor and therapeutic target. Preclinical and clinical evidence indicates that GLP-1 receptor agonists may modulate insulin signaling, adipokine profiles, and hyperandrogenism independently of weight reduction, suggesting relevance even in normal-weight phenotypes [12,14]. However, the current evidence base remains constrained by a lack of phenotype-stratified trials, as most studies have been conducted in overweight or obese populations [13,16].

Molecular data further support phenotypic differentiation, with studies demonstrating specific genetic signatures characterized by upregulation of FTO and INSR expression together with downregulation of Nrf2 compared with healthy controls [27]. Although adiposity status remains the primary determinant of overall

metabolic severity in PCOS [1,9], lean PCOS carries distinct subclinical risks that require targeted diagnostic evaluation [8,26]. While the obese phenotype exhibits profound metabolic impairment across Rotterdam diagnostic categories, lean individuals generally maintain relatively preserved metabolic parameters, but display pronounced neuroendocrine dysregulation and organ-specific susceptibility.

Collectively, these findings support a revised conceptual framework for PCOS classification that formally incorporates adiposity status as a biologically meaningful determinant of disease phenotype, with implications for phenotype-guided therapeutic strategies, including the investigation of incretin-based therapies in appropriately stratified populations.

5. Identified Research Gaps

Despite the growing body of evidence on lean PCOS, several important research gaps remain. Particularly important is the formal incorporation of body weight and metabolic parameters into international diagnostic criteria, which could improve risk stratification and enable more personalized therapeutic management strategies. Further clarification of neuroendocrine mechanisms is also essential, especially regarding alterations in kisspeptin pulsatility and the role of KNDy neurons in generating the elevated LH/FSH ratio characteristic of this phenotype. Emerging evidence also points to the gut-brain axis as a novel avenue for investigation, with recent studies demonstrating altered kisspeptin, ghrelin, and serotonin profiles in PCOS that may contribute to hypothalamic dysfunction independent of body weight [33].

Additionally, long-term prospective studies are required to evaluate cardiovascular risk, cancer incidence, and mortality in lean compared with obese PCOS populations. Future research should also focus on developing evidence-based therapeutic guidelines for normal-weight adolescents, as well as investigating genetic-epigenetic interactions involving FTO, INSR, and Nrf2.

An important direction for further research is the evaluation of the potential role of GLP-1 receptor agonists (GLP-1 RAs) in the treatment of lean PCOS. Most studies to date have included predominantly overweight and obese participants, which limits the applicability of findings to the lean PCOS population [12,13]. Larger prospective studies assessing the efficacy of GLP-1 RAs in improving metabolic function, hyperandrogenism, and menstrual cycle regulation independently of weight reduction are therefore needed [12-16].

Finally, larger prospective studies are necessary to validate diagnostic markers of the hypo-androgenic PCOS-like phenotype (H-PCOS) [23].

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