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Review

Lean Polycystic Ovary Syndrome: A Narrative Review

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Abstract

Objectives: (1) To delineate the differences between lean and obese polycystic ovary syndrome (PCOS). (2) To review different modalities for management of infertility associated with PCOS. **Mechanism**: Literature review of PubMed from 2000 to 2023. **Findings in Brief**: Body weight is more important than the Rotterdam phenotype in influencing the metabolic status. Both the lean and obese PCOS groups exhibit individual differences in body composition and other parameters: clinical signs, psychological, hormonal, metabolic, and genetic profiles. Lean PCOS differs from lean non-PCOS regarding metabolic profile, hepatic impairment, and cardiovascular risks. Management: lifestyle modifications serve as first-line therapy, emphasizing weight maintenance with a high caloric intake during breakfast and reduced intake at dinner. Additionally, micronutrients supplementation and resistance exercise are recommended. Induction of ovulation through the administration of as adjunctive therapies letrozole, clomiphene citrate, and metformin may be considered. Laparoscopic ovarian drilling (LOD) may be considered in cases where medical induction of ovulation failed. Intrauterine insemination is associated with promising results. Assisted reproductive techniques (ART) are recommended for women who fail to conceive despite the restoration of ovulation, or when additional factors contribute to their infertility. **Conclusions**: A significant proportion of patients with PCOS exhibit normal body mass index (BMI). The management of PCOS-associated infertility should be individualized based on the patient's BMI.

Keywords: PCOS; lean; infertility

1. Introduction

Polycystic ovary syndrome (PCOS) is a diverse endocrinopathy that affects 4–8% of women of reproductive age. PCOS is the most common cause of anovulatory infertility, affecting approximately 90–95% of women with anovulatory infertility seeking treatment at infertility clinics [1,2]. Polycystic ovaries, menstrual irregularities, and hyperandrogenism are all hallmark characteristics of PCOS. Up to 70% of hyperandrogenic women exhibit hirsutism, or extra hair on their bodies. Acne is a rare and less specific marker of hyperandrogenism [3]. Obese women are more likely to be diagnosed with PCOS [4]. Obesity has been reported in 25–70% of PCOS women, yet a significant proportion of patients are affected by PCOS despite of having a normal body mass index (BMI) ($\leq$25 kg/m^2). These outcomes make determining its diagnostics and treatment strategy more challenging. These thin PCOS patients may or may not have traditional signs, such as irregular menstruation and acne. Medical professional must first rule out other endocrine and genetic disorders that manifest comparable clinical symptoms before implementing appropriate treatment strategies. Despite the fact that obesity is a well-established risk factor for PCOS, the number of lean women with the condition is increasing [5].

2. Lean *vs.* Obese PCOS

Carmina and Lobo [6] started comparing lean and obese PCOS in various PCOS phenotypic traits. They discovered that body mass exerts a greater influence on metabolism than the Rotterdam trait. Rotterdam phenotypes effectively distinguish among PCOS individuals on the basis of ovulatory sequence and androgen efflux but underperform to distinguish among obese patients with abnormal metabolic trends and lean patients with normal metabolic trends. As such, a new classification of PCOS patients is required, one that incorporates the influence of body weight on energy metabolism trends of PCOS patients.

Dadachanji *et al.* [7] proposed categorizing PCOS into lean and obese groups, as the cardiometabolic statuses of PCOS phenotypes are equal when BMI-matched. However, they observed that all PCOS women have important metabolic and endocrine dysfunction compare to BMI-matched controls. Once BMI is matched, only a few PCOS-related traits vary across phenotypes. Obesity is a major predictor of PCOS-related characteristics, and BMI-based classification could aid in better understanding pathogenic pathways, long-term risks, therapeutic approaches, and outcomes. PCOS is mostly associated with obesity, but it also affects numerous PCOS lean patients. Despite some similarities in their metabolic profiles, each group has unique differences in body composition as well as other variables [8].

(1) Clinical signs: menstrual disorder (79.2% overweight and 44% lean) and hyperandrogenism (74.2% overweight and 50.6% lean) were significantly more preva-

lent in the overweight group of women [9–11]. In PCOS, there is a link between hyperandrogenism and chronically low-grade inflammation [12]. In lean reproductive-age women, hyperandrogenism sensitizes mononuclear cells to glucose-induced inflammation. Endometrial hyperplasia was more prevalent (relative risk (RR) = 2.8), but not statically relevant (p = 0.055) [10,11]. Even though hormonal and metabolic imbalances occur in lean women with PCOS, they are more extreme in obese people with the endocrinopathy.

(2) Psychological profile: patients with BMI <25 exhibited personal characteristics linked to reduced stress tolerance [13]. Adrenocorticotropic hormone (ACTH) levels were significantly higher in the same group when compared to patients with a BMI greater than 25. Additionally, a correlation was observed between plasma ghrelin and the anxiety level. Personality and emotional abnormalities observed in lean PCOS patients may lead to stimulation of the hypothalamic-pituitary-adrenal (HPA) axis and disruptions in the hypothalamic-pituitary-ovary (HPO) axis. The results indicate that primary hypothalamic dysfunction contributes to the development of PCOS in patients exhibiting a particular phenotype. Ghrelin is a hormone that may influence PCOS symptoms in individuals with a lean body composition. Psychological management should be viewed as a lasting component of the treatment plan for PCOS patients.

(3) Hormonal profiles: there was no significant distinction in the luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio between the two groups (2.76 *vs.* 2.79, p = 0.48) [14]. There was no link found between BMI and the LH/FSH ratio, prolactin, or thyroid-stimulating hormone (TSH) levels. According to the documentation, BMI is not linked to a higher LH/FSH ratio. Because LH/FSH ratio was the same in normal body weight women, healthcare providers must consider ways to normalize this ratio other than weight loss.

Dehydroepiandrosterone sulfate (DHEAS) levels were higher in lean PCOS females compared to both obese-PCOS and non-PCOS females. Nevertheless, receiver operating curve (ROC) analysis revealed that DHEAS is a less reliable predictor of PCOS compared to the free androgen index and the modified Ferrymen and Gallwey score [15].

(4) Metabolic profile: due to methodological limitations, quantifying insulin resistance (IR) in PCOS is challenging. However, IR appears to be prevalent in both lean and obese PCOS (83.3% *vs.* 93.1%) [15]. Obese women with the disorder had a higher level of IR. Women with PCOS commonly exhibit IR, which subsequently leads to hyperinsulinemia [16]. The evaluated prevalence of IR in lean and overweight/obese PCOS women was 9.3 and 57%, respectively, using a homeostatic model assessment of insulin resistance (HOMA-IR) cutoff value of 3.15 [17].

Diabetes mellitus, impaired glucose tolerance, and IR are far less prevalent in young lean PCOS women than in obese PCOS women. These finding suggest that in lean women with PCOS, either IR testing or a 2-hour oral glucose tolerance test (OGTT) may be inappropriate. In women with PCOS, BMI serves as a strong predictor of insulin and glucose levels [18]. However, on the other hand, some authors recommended early determination of IR in PCOS, even in women with low BMI and normal glucose tolerance [19]. All women with PCOS, regardless of their weight (lean and obese), should undergo testing for IR. Collection of information is necessary to determine whether an OGTT is required in slender women with PCOS. Overweight/obese PCOS patients were discovered to be significantly more likely than lean PCOS patients to progress to type 2 diabetes [20]. BMI and serum leptin were discovered to have a positive correlation [21]. Leptin levels in thin and morbidly obese PCOS patients differ from those in regularly menstruating normal-weight participants, suggesting that leptin may be an innovative, independent risk factor for PCOS. Obese women with PCOS have significantly lower vascular smooth muscle function compared to lean women with PCOS. Obesity and IR emerged as significant modulators of vascular function, but not hyperandrogenism [22].

Saturated fat consumption in PCOS activates a molecular pathway of inflammatory response known to perpetuate atherogenesis [12]. This effect takes place in lean women with PCOS but not in lean ovulatory control subjects, indicating that it is independent of overweight. The cumulative impact of PCOS and obesity are more severe than the impact of obesity alone.

(5) Genetic profile: PCOS is a complicated multigenic disorder, and women with PCOS may experience a number of chronic conditions [5]. The assessment of differentially expressed genes (DEGs) across different tissues revealed a that large number of genes with differential expression for lean and obese PCOS were negatively regulated. Numerous popularly dysregulated genes were found in both ovarian and endometrial tissues, indicating that shared PCOS pathophysiology mechanisms are present across various body tissues. Numerous cellular homeostasis pathways recognized to be impacted in PCOS, including inflammation and immune response, insulin signaling, steroidogenesis, hormone levels, energy metabolism signaling, regulation of gonadotrophic hormone secretion, as well as cell structure and signaling, were discovered to be enriched in our gene expression profiling of lean and obese PCOS. Obese PCOS has a denser gene-disease network and a higher comorbidity scoring system compared to lean PCOS.

3. Lean PCOS *vs.* Lean Non-PCOS

(1) Metabolic Profile: Alebić *et al.* [17] discovered that plasma insulin levels two hours after glucose administration were significantly higher in lean PCOS patients when compared to healthy controls. Low-density lipoprotein (LDL) and total cholesterol levels were also considerably higher in lean PCOS patients compared to con-

trols. The prevalence of IR did not differ significantly among lean controls (5%) and lean PCOS (9.3%). Lean PCOS women have lower high-density lipoprotein (HDL) size, higher very-low-density lipoprotein (VLDL) particle amount, higher LDL particle number, and borderline lower LDL size compared to lean controls [23].

Leptin and Vitamin D (VD) may play a role in the progression of lean PCOS [24]. VD levels in the lean PCOS group were found to be lower than in the control group. According to the study, low VD levels and IR are independent features of body size in PCOS patients [24]. This assertion is crucial because many PCOS women have IR but are not obese [25]. Serum leptin levels were discovered to be substantially higher in lean PCOS patients than in control groups. Alatas *et al*. [26] recently discovered that serum adiponectin values in lean PCOS women were considerably lower than in lean controls.

Mammadova *et al*. (2021) [27] investigated the gut microbiome of lean PCOS patients. They found that compared to controls, patients have similar bacterial richness and diversity, and hyperandrogenism was associated with dysbiosis.

(2) Cardiovascular risk: Gamma-glutamyl transferase (GGT) levels in plasma, which are better indicators of heart disease, were significantly higher in both lean and overweight PCOS phenotypes compared to controls.

When compared to controls, blood viscosity was substantially higher in the lean PCOS group at lesser shear rates [26]. Endothelial dysfunction, coronary artery calcification, and venous thromboembolism [27] are all considered to be increased risks in PCOS.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were also linked to higher IR, dyslipidaemia, decreased insulin sensitivity, and hyperandrogenism [28]. Lean PCOS patients have higher cardiovascular disease (CVD) risk factors, and these risk factors are linked to NT-proBNP levels. Patients with lean PCOS should be assessed for CVD. More prospective controlled studies are required to anticipate the long-term likelihood of developing CVD in patients with lean PCOS.

The research by Öztürk *et al*. [29] recommended that pregnancy-associated plasma protein-A (PAPP-A) could serve as a clinical predictor in PCOS, indicating a higher risk of metabolic syndrome and cardiovascular events. A group of young patients with a BMI of 27 kg/m^2, in particular, may benefit from the cardiovascular risk assessment using PAPP-A, which provides prognosis for high risk in the onset of heart disease.

Although lean phenotypic expression PCOS patients had comparable heart rate variability (HRV) variables as controls at baseline, the exercise challenging task regimen led to decreased sympathetic drive, as evidenced by lower low-frequency (LF) power in the patient group [29]. This could be due to latent autonomic dysfunction in "lean" PCOS, which is revealed by exercise challenging task. The assessment of HRV response to exercise could be a sensitive screening tool for detecting early cardiovascular disorders in recently diagnosed lean PCOS patients.

(3) Liver function impairment threat: a significant increase of alanine aminotransferase (ALT) was found in lean PCOS patients [30]. In lean PCOS, BMI, white blood cell count, lymphocyte count, aspartate aminotransferase (AST), uric acid, and total testosterone were all closely linked to ALT. After several linear regressions, it was found that total testosterone and AST were independently associated with the development of lean PCOS, coupled with ALT. In earlier times, there may have been a risk of liver disorder in lean PCOS women. As soon as PCOS is diagnosed, early evaluation and interference may be required to prevent or delay the development of liver problems. Functional hypothalamic amenorrhea may be difficult to be differentiated from PCOS [31].

4. Treatment of Infertile Lean PCOS

While both lean and obese reproductive-aged women with PCOS experience anovulatory infertility, obesity has been linked with resistance to oral ovulation induction agents, lower conception rate, and a higher risk of pregnancy complications [32].

4.1 Lifestyle Modifications

(1) Maintain weight: weight loss is regarded first-line therapy in women with the obese phenotype of PCOS, but not in lean women with the syndrome [8,33]. Caloric restrictions are unnecessary because lean women may not need to lose weight. Conversely, lean PCOS women should strive to keep their weight stable. A high-calorie consumption at breakfast and lower calorie consumption at dinner enhances insulin sensitivity indices and decreases cytochrome P450c17 activity, which alleviates hyperandrogenism and increases ovulation frequency. For women with lean PCOS, meal duration and dispersion should be regarded as a treatment approach.

(2) Macronutrients: regardless of not being envisioned for weight loss, improving the macronutrient delivery in the dietary regimen could help the constant inflammatory state associated with lean PCOS [8].

The Mediterranean diet is a plant-based, antioxidant-rich diet associated with numerous health advantages. It is distinguished by a high daily consumption of whole cereals, fruit and vegetables, vegetables, tree nuts, legumes, and olive oil; moderate consumption of fish and poultry; and an inadequate intake of milk products, red meat, processed meat, and sweet. This dietary pattern is regarded nutritionally comprehensive and adequate because it is simple to follow and based on traditional foods eaten by people in their home countries [34]. According to international guidelines, no single dietary type is recommended in PCOS.

(3) Micronutrients supplementation: it is critical that lean women with PCOS consume a variety of nutrients,

minerals, and vitamins; therefore, they must ensure that their diet includes plenty of vegetables and fruit. For example, calcium and VD, encourage hormonal balance and assist with normal ovulation [35].

VD is involved in a number of metabolic processes, such as glucose metabolism. The process underlying this impact is unidentified; however, the immunomodulatory function is well established [8].

Tehrani *et al*. [36] reported that taking VD and calcium alongside metformin enhanced menstrual cycle regulation and other PCOS symptoms. Vitamin D may play a role in many aspects of PCOS, including infertility, hirsutism, IR, and CVD risk. Supplementing with VD, for example, may enhance reproductive function in women with PCOS by restoring regular menstrual cycles [36]. In order to characterize the significance of VD in PCOS, additional randomized experiments in well-defined and identified communities are required.

Ağar *et al*. [37] recently investigated the impact of VD replacement therapy on serum nuclear factor-kappa (NF-k) levels in lean and obese PCOS women. VD replacement therapy improves subfertility and metabolic disparity in both lean and obese women with PCOS by lowering serum NF-k levels. Additional nutritional supplements, including essential fatty acids, enhance the advantages of an already balanced diet [38].

(4) Resistance exercise: physical activity was demonstrated to enhance multiple PCOS-related factors, including ovulation rates, menstrual regularity, CVD risk [10], waist circumference, weight, and total fat mass, making exercise a beneficial non-pharmacological lifestyle change for PCOS. International guidelines suggest varying the intensity and duration of exercise as a lifestyle approach for enhancing health in general in individuals with PCOS [11].

4.2 Induction of Ovulation

Ovulation initiation can be accomplished in lean and obese women with PCOS using aromatase inhibitors, selective estrogen receptor modulators, insulin sensitizing agents, gonadotropins, and ovarian drilling, with different rates of ovulation, live birth, as well as multiple gestations.

(1) Clomiphene citrate (CC) was and still is the first treatment option for lean women with PCOS [39]. The CC dose needed to induce ovulation is positively associated with body weight.

(2) Letrozole was previously suggested as first-line therapy (over CC) only for women with a BMI greater than 30 kg/m^2, but it is now suggested for all women with PCOS, irrespective of BMI [11]. Letrozole and laparoscopic ovarian drilling (LOD) are both successful in patients with CC resistant PCOS [40].

(3) Metformin is an insulin-sensitizing agent that lowers serum glucose levels by increasing glucose uptake and utilization in the peripheral tissues while decreasing the output of glucose from the liver. There are no metabolic advantages in the treatment of lean PCOS [41]. Metformin should only be used by women who have glucose intolerance. In the presence of IR or impaired glucose tolerance (IGT), metformin should not be as the primary therapy alone, but ought to be combined with letrozole, CC, or gonadotropins [11]. According to a Cochrane systematic review published in 2019, it remains uncertain whether metformin in addition to CC improves live birth rate (LBR) in comparison to CC by itself, but digestive adverse reactions rise with combined therapy. The findings varied according to BMI, emphasizing the significance of stratifying outcomes by BMI [42]. Magzoub *et al*. [43] conducted a meta-analysis of 21 randomized controlled trials (RCTs), including 2638 patients with lean PCOS. When contrasted with letrozole, the combination of metformin and CC has been associated with decreased clinical pregnancy rate (CPR) and multiple births.

(4) Inositol: inositol stereoisomers, including Myo-inositol (MYO-INS) and D-chiroinositol (DCI), are now being utilized for treating PCOS by enhancing IR and lowering risk factors for CVD [43]. Certain investigations have advised against using MYO-INS in lean PCOS patients, claiming that it may not be appropriate or efficient, particularly if they do not have IR [44]. Additional research determined that elevated doses of MYO-INS may have an adverse impact on oocyte quality. MYO-INS should be considered experimental in PCOS, according to international guidelines lines [11], and more research is needed. Jethaliya *et al*. [45] conducted a meta-analysis of 17 RCTs involving 1083 PCOS patients. In PCOS patients, after MYO-INS therapy. BMI, fasting insulin, fasting glucose, HOMA, LH, FSH, estradiol, sex hormone-binding globulin (SHBG), Dehydroepiandrosterone (DHEA), testosterone, anthropometric, metabolic, and endocrine outcomes [45] did not improve significantly. Greff *et al*. [46] conducted a meta-analysis of 26 RCTs incvolving 1691 PCOS patients. In most results, inositols are non-inferior to metformin.

(5) L-carnitine: according to Celik *et al*. [19], l-carnitine levels were substantially reduced in lean PCOS patients than in lean healthy women. They suggested that l-carnitine be used as an adjunctive therapy in the management of IR or obesity in PCOS women. More research is needed to determine the clinical consequences of l-carnitine management in patients with PCOS, IR, and/or obesity.

(6) Gonadotropins: obese PCOS women require higher gonadotrophin doses than lean PCOS women. Gonadotropins are used as a last resort after first-line oral ovulation induction therapy has failed [11]. Because lean PCOS women are more likely to develop ovarian hyperstimulation syndrome (OHSS), lower gonadotropin dosages are recommended. The chronic low-dose protocol is the preferred protocol. When compared to non-PCOS women, it results in obtaining more follicles and oocytes.

(7) LOD is as effective as FSH in inducing ovulation, especially in lean individuals who have elevated LH levels. A recent meta-analysis [47] discovered that unilateral

or bilateral LOD had been linked with a comparable percentage of successful pregnancies. LOD is no longer the preferred treatment method. It may be employed with the assistance of other factors, such as tubal factor with CC resistant PCOS. According to a Cochrane systematic review (2020), LOD with and without medical ovulation induction may reduce LBR in women with anovulatory PCOS and CC resistance compared to medical ovulation induction alone [48]. There is little or no difference in clinical pregnancy rates among treatments (low-quality evidence). LOD lowers OHSS and the percentage of concurrent pregnancies.

4.3 Intrauterine Insemination (IUI)

When compared to their overweight, obese, and morbidly obese counterparts, lean women with PCOS had greater CPR after IUI. Patients with a lean PCOS phenotype could benefit more from this therapy strategy [49].

4.4 Assisted Reproductive Technologies (ART) are Designated for Women who are Unable to Conceive Despite Ovulation Restoration or for Couples who Have other Variables Leading to Their Infertility

(1) Pretreatment: metformin is not suggested as a prior treatment in the gonadotropin releasing hormone antagonist (GnRH) antagonist protocol since it could decrease LBR [49]. We are uncertain whether a long GnRH agonist protocol enhances LBR. Metformin lowers the risk of OHSS and is suggested for women with BMI $\geq$26. In accordance with Cochrane systematic review (2018) we are uncertain whether inositol improves LBR or CPR in PCOS patients undergoing *in vitro* fertilization (IVF). In women with PCOS, there is insufficient proof to support their use as a pretreatment prior to IVF/intracytoplasmic sperm injection (IVF/ICSI) [50].

(2) Controlled ovarian stimulation (COS): GnRH antagonist protocol is suggested for COS [51]. It is more secure, more efficient, and less expensive than the long GnRH agonist protocol. To prevent OHSS, the use of an agonist trigger followed by embryo freezing (freeze-all strategy) may be recommended. The addition of CC to gonadotropin, the natural cycle, or the modified natural cycle is not advised.

(3) Oocyte retrieval: even though acute hemorrhage after transvaginal oocyte retrieval is uncommon, lean patients with PCOS are at much greater risk for this type of problem [52].

(4) Outcome: individuals with lean and obese PCOS have distinct IVF results [53]. When contrasted with obese PCOS, lean PCOS has a higher incidence of OHSS, CPR, and LBR. In a study that included a total of 1395 patients who underwent 2348 IVF cycles, the LBR was higher in lean PCOS: 61.7% *vs*. 54.0% [54]. Miscarriage rates were significantly higher for obese-PCOS: 19.7% *vs*. 14.5%. Lean PCOS is associated with a significantly higher LBR compared to obese PCOS.

5. Conclusions

Regardless of experiencing an adequate BMI of 25 kg/m^2, a significant proportion of patients have PCOS. The prevalence of lean PCOS is increasing. Body weight has a greater influence on metabolic status than the Rotterdam phenotype. Obese and lean PCOS share several metabolic characteristics. Each group differs in terms of body structure and other variables such as clinical signs, psychological factors, hormonal profiles, metabolic, and hereditary profiles. In terms of metabolic outline, liver dysfunction, and risk factors for CVD, lean PCOS differs from lean non-PCOS. Anovulatory infertility is a prevalent complication of lean PCOS. Maintaining weight with an elevated calorie count at breakfast and a lower consumption at dinner, supplementing with micronutrients, and resistance exercise are first-line therapies for PCOS management. Letrozole, CC, and metformin may be used to induce ovulation medically. LOD can be considered if medical induction of ovulation failed. IUI has been correlated with positive outcomes. ART are reserved for women who are unable to get pregnant despite of restoring ovulation and addressing other factors contributing to their infertility.

Author Contributions

All work was conceived and completed by AE.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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