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Review Article

Debates Regarding Lean Patients with Polycystic Ovary Syndrome: A Narrative Review

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Abstract

Polycystic ovary syndrome (PCOS) is a complex syndrome showing the clinical features of an endocrine/metabolic disorder, including hyperinsulinemia and hyperandrogenism. Two phenotypes are present, either lean or obese, with different biochemical, hormonal, and metabolic profiles. Evidence suggests many treatment modalities that can be applied. However, many of these modalities were found to be not suitable for the lean phenotype of PCOS. Much contradictory research was found regarding lean patients with PCOS. The aim of this narrative review is to shed light on the debate prevailing regarding characteristics, as well as metabolic, hematological, and potential management modalities. Literature review was performed from January 1, 2000 to March 31, 2017 with specific word search such as lean PCOS, hormonal abnormalities in lean PCOS, and the management of lean PCOS. All retrieved articles were carefully assessed, and data were obtained. We could conclude that the debate is still prevailing regarding this specific lean population with PCOS, especially with regard to their characteristics and management modalities. Further studies are still required to resolve this debate on the presence of PCOS in lean women.

Keywords: *Debate, lean, ovary, polycystic, syndrome*

Introduction

Polycystic ovary syndrome (PCOS) affects approximately 4–12% of women in their reproductive age. It is a leading cause of infertility and is also associated with an increased risk of metabolic syndrome (MBS), diabetes mellitus type 2, cardiovascular disease, and endometrial cancer.[1]

A majority (80%) of women with PCOS have an above average or high body mass index (BMI), insulin resistance (IR), and the typical PCOS symptoms (e.g., ovarian cysts, male pattern baldness, acne, and hirsutism). Many of these women are not diagnosed until fertility issues arise in adulthood. Some women with PCOS having a normal, if not low BMI may or may not have IR and exhibit symptoms that are typical to female pubertal maturation during adolescence (e.g., acne, irregular menstrual cycle, and potentially depression).[2,3]

Materials and Methods

Literature review was performed using PubMed, Google Scholar, Academia, Mendeley, ClinicalKey, and Cochrane Database from January 1, 2000 to March 31, 2017. Specific MeSH words such as lean PCOS, hormonal abnormalities in lean PCOS, the management of lean PCOS, and diet for lean PCOS were used for searching. PCOS was defined according to Rotterdam criteria. All retrieved articles were carefully assessed, and data were obtained.

Insulin resistance in lean women with PCOS

Diabetes mellitus, IR, and metabolic abnormalities are all significantly lower in lean women with PCOS. Although IR (IR) is generally agreed to be an underlying cause of PCOS, there is disagreement among the medical community about whether thin women with PCOS suffer from IR to the same degree as their heavier counterparts. For lean women with PCOS, the prevalence of IR was reported to be 6–22%.[4,5]

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An Indian study proved the presence of abnormal waist circumference and increased waist-to-hip ratio with normal BMI and a very high prevalence of diabetes in the Indian population. They recommended testing all lean women with PCOS for glucose intolerance and the presence of MBSs.[6]

Insulin resistance should be assessed in all women with PCOS, both lean and obese participants. The homeostasis model assessment (HOMA)-M_{120} resulted as a very simple tool, validated specifically for lean women with PCOS whose cardiometabolic impairment is more frequently misunderstood.[7]

Visceral adiposity is another issue of great controversy among these patients. Yildirim *et al.*[8] demonstrated the presence of a higher proportion of preperitoneal and visceral adiposity evidenced by ultrasound compared to weight-matched controls and concluded that lean patients with PCOS have intrinsic IR, whereas obese patients with PCOS have both resistances, intrinsic resistance as a part of the disease and extrinsic resistance due to obesity.

Recent studies demonstrated no difference in abdominal fat distribution among the obese with and without PCOS.[9-11] More recent cross-sectional studies compared fat distribution between lean women with PCOS and controls matched for body composition by magnetic resonance imaging (MRI). The data demonstrated that lean patients with PCOS have less visceral fat when compared with the control patients.[12,13]

Lean patients with PCOS had significantly lower total subcutaneous adipose tissue development, even though height, weight, and BMI did not deviate significantly. Especially on the legs, their subcutaneous adipose tissue layers were significantly lowered, indicating a more "apple-like" fat distribution type.[14,15]

Another study demonstrated that insulin levels were normal in some lean women with PCOS, and women's ovaries were still stimulated by hormonal sensitivities to overproduce excess androgens. Studies have shown that IR can be present in both lean and obese women with PCOS, indicating that other factors cause imbalance in the insulin/glucose mechanism.[16]

Many physicians do not prefer to use the term "insulin resistance" in the absence of obesity; however, thin women with PCOS have higher insulin levels in their blood than those without PCOS.[17,18]

More recently Erol *et al.*[19] conducted a study to investigate betatrophin levels in lean women who were glucose tolerant and had PCOS and to explore the relationships between these levels and anthropometric, hormonal, and metabolic parameters. The study population consisted of 50 lean (BMI $< 25\,kg/m^2$) women diagnosed with PCOS using the Rotterdam criteria and 60 age- and BMI-matched healthy controls without any feature of clinical or biochemical hyperandrogenism. All patients were glucose tolerant. They found that serum betatrophin levels were significantly higher in lean women who were glucose-tolerant and had PCOS than in age- and BMI-matched healthy controls. Elevated betatrophin levels in women with PCOS, in the absence of obesity and glucose intolerance, may reflect a compensatory mechanism to counteract MBS-related risk factors. Similar results were obtained more recently by Li *et al.*[20]

Metabolic and hematological abnormalities

Sharma *et al.*[21] studied the prevalence of MBS in Indian women and saw how it correlated with BMI and PCOS among this population. They found that the prevalence of MBS was significantly higher in the women with PCOS as compared to age-matched controls. Similarly, when BMI was considered, MBS was more prevalent in overweight participants than in lean participants.

Blair *et al.*[22] conducted a study to test the relation of oxidative stress and antioxidant capacity in obese and lean patients with PCOS. They found that antioxidant capacity was lower in the lean PCOS group relative to their weight-matched controls.

Faloia *et al.*[11] conducted a study to evaluate metabolic characters in lean and obese patients with PCOS. Their results did not show significant metabolic alterations in lean women with PCOS. The results indicated that obesity seems to underpin the metabolic alterations exhibited by the overweight/obese patients.

Yilmaz *et al.*[23] conducted a study to assess the effects of rosiglitazone and metformin on cardiovascular disease risk factors such as IR, oxidative stress, and homocysteine levels in lean patients with PCOS. They concluded that elevated IR, oxidative stress, and plasma homocysteine levels, as well as changes in serum lipid profile, were observed in lean patients with PCOS. Rosiglitazone seemed to decrease elevated oxidative stress when compared with metformin treatment in lean patients with PCOS.

Another cross-sectional study was conducted to evaluate the changes in IR and its associations with clinical, biochemical, hormonal, and ultrasound findings in a large cohort of women with PCOS and controls, as they are aging. They concluded that aging increases IR in obese but not in lean and overweight women with PCOS. Because BMI and androgens are positively associated with homeostatic model assessment of insulin resistance (HOMA-IR) and androgens decline through time, it appears that if women with PCOS do not become obese, they may exhibit a better metabolic profile during their reproductive years.[24]

Hematological and lipid abnormalities in lean women with PCOS

Compared with BMI-/age-matched controls, lean women with PCOS have lower levels of high-density lipoprotein, higher levels of very low-density lipoprotein, and higher levels of low-density lipoprotein (LDL) than controls who were lean and were without PCOS. Lean women with PCOS have a 3–10% incidence of undiagnosed diabetes, with higher risk in obese patients.[25,26]

Lean women with PCOS are also exposed to a greater risk of glucose intolerance development and abnormalities in lipid profile than women without PCOS with comparable BMI. Increased levels of proinflammatory cytokines in blood can promote atherosclerosis and cardiovascular disease. An increase in inflammatory markers may be an early indicator of the risk of developing IR and atherosclerosis and may become a useful prognostic and therapeutic tool for monitoring patients with PCOS: lean and those with overweight and obesity. It will also allow appropriate prophylaxis.[27]

Li *et al.*[28] conducted a study to investigate serum lipid profiles in newly diagnosed patients with PCOS using lipidomics and correlated these features with the hyperinsulinemia and hyperandrogenism associated with PCOS and obesity. They found elevation in phosphatidylcholine and a concomitant decrease in lysophospholipid in obese patients with PCOS versus lean controls. Obese patients with PCOS had decreased polyunsaturated fatty acid levels and increased levels of long-chain saturated fatty acids versus lean controls. Serum bioactive lipid levels downstream of arachidonic acid were increased in obese controls but reduced in both obese and lean patients with PCOS versus their respective controls.

Sahin *et al.*[29] conducted a study to investigate the correlation between IR and serum 25-OH-Vit D concentrations and hormonal parameters in lean women with PCOS. They found that an association between 25-OH-Vit D levels and IR was not evident in lean women with PCOS.

Scott *et al.*[30] investigated associations among vitamin D, intramuscular adipose tissue, and IR in a cross-sectional study of 40 women with PCOS and 30 women without PCOS. They found that women with PCOS and low 25OH-D levels have increased IR, which may be partly explained by higher intramuscular adipose tissue. The results are contradictory to those of Sahin *et al.*

Fenkci *et al.*[31] conducted a study to determine serum total l-carnitine levels in nonobese women with PCOS. In that study, 27 nonobese women with PCOS and 30 healthy, age- and BMI-matched controls were evaluated in this controlled clinical study. Serum lipid subfractions, fasting glucose level, insulin and other hormonal levels (gonadotrophins and androgens), and total l-carnitine levels were measured. They found that l-carnitine levels were decreased in lean patients with PCOS, and this may be associated with hyperandrogenism and/or IR.

Simmonds *et al.*[32] conducted a study on lean women with PCOS and age-matched healthy controls to evaluate the physical properties of blood in patients with PCOS. They found that plasma viscosity was significantly increased in women with PCOS. No difference was detected between PCOS and control groups for red blood cell (RBC) deformability measurements. A novel measure indicating the effectiveness of oxygen transport by RBC (the hematocrit-to-viscosity ratio was decreased at all shear rates in women with PCOS. They concluded that in lean women with PCOS a significant hematological impairment was observed. The degree of hematological derangement observed in their study reflected that PCOS is a chronic disease; in addition, their study provided future therapeutic intervention in PCOS.

Rakusa *et al.*[33] found another hematological abnormality in lean patients with PCOS. They conducted a study to assess the relationship of overall hemostatic potential (OHP) with PCOS per se and BMI. They found that significant difference between lean and obese women with PCOS ($P < 0.001$) and between lean and obese controls ($P < 0.001$). The overall coagulation potential also increased with BMI in women with PCOS ($P < 0.001$ for lean vs. obese) and in controls ($P < 0.001$ for lean vs. obese). In addition, the overall fibrinolytic potential decreased with BMI in women with PCOS ($P < 0.001$ for obese vs. overweight vs. lean) and in controls ($P < 0.001$ for obese vs. lean). They concluded that PCOS was not associated with increased OHP compared with BMI- and age-matched controls. However, increase in OHP was positively associated with BMI in women with PCOS and those who were healthy.

Mioni *et al.*[34] found in their study that in relation to BMI, only 24-h, daytime, and nighttime DBP levels were higher in obese than lean patients. At variance, when both hyperinsulinemia and obesity were considered, 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were higher in obese participants with hyperinsulinemia than in the other groups. Insulinemic state and higher nighttime blood pressure and heart rates may represent early markers to identify participants with PCOS prone to high cardiovascular risk.

Psychological/neurological findings in lean women with PCOS

A study was conducted to assess whether the psychological parameters of lean and obese patients

with PCOS are comparably significantly different, and whether there is a correlation between these characteristics and the concentration of various hormones. The study consisted of two groups of BMI-matched patients: 20 patients with diagnosed PCOS and 20 healthy women of similar age. Specific psychological parameters and hormones were estimated in all patients. They found that patients with BMI <25 represented personality traits associated with lower resistance to stress. They also observed significantly higher adrenocorticotropic hormone (ACTH) levels in the same group as compared to patients with BMI >25. A correlation between plasma ghrelin and the severity of anxiety experienced by test participants was also observed. They concluded that the type of personality and emotional disorders in lean patients with PCOS might lead to the activation of the hypothalamic–pituitary–adrenal axis and disturbances in hypothalamic–pituitary–ovary axis with a possibility of the involvement of hypothalamic dysfunction in the pathogenesis of PCOS. Ghrelin is a hormone that may affect the symptoms of PCOS in lean patients. Psychological therapy should be considered as a permanent element in the therapeutic plan provided to patients with PCOS.[35]

Ozgen Saydam *et al.*[36] detected differences in global brain volumes and identified relations between brain volume and appetite-related hormones in women with PCOS compared to BMI-matched controls. They found that total brain volume and total gray matter volume (GMV) were decreased in obese women with PCOS compared to obese controls ($P < 0.05$ for both), whereas lean women with PCOS and controls did not show a significant difference. Secondary analyses of regional brain volumes showed decreases in GMV of the caudate nucleus, ventral diencephalons, and hippocampus in obese women with PCOS compared to obese controls ($P < 0.05$ for all), whereas lean patients with PCOS had lower GMV in the amygdala than lean controls ($P < 0.05$).

Another study showed that β-endorphin serum level as well as pressure pain threshold (PPT) were higher in the lean PCOS group than in controls. We found correlations between β-endorphin levels and PPT in the PCOS group. It may suggest that endogenous opioids play a role in the pathogenesis of PCOS, and that the increases in circulating plasma β-endorphins concentration can increase PPT in this group. β-Endorphins stimulate LH release; therefore, lean patients with PCOS had increased LH levels than classic obese patients. Higher levels of β-endorphins are linked to mood changes in these lean patients.[1,37]

Kiałka *et al.*[38] also found that metformin therapy increases PPT in lean women with PCOS without affecting plasma β-endorphin concentration. Our results may suggest the potential role of metformin in pain therapy. We propose that larger, randomized studies on the impact of metformin on pain perception should be performed.

Hormonal abnormalities in lean women with PCOS

Leptin levels are increased in lean women as evidenced by a study conducted by Chen *et al.*,[39] who found that adiponectin was negatively correlated with IR, BMI, and total testosterone, triglyceride, and LDL levels; conversely, leptin was negatively correlated with adiponectin levels. The adiponectin-to-leptin ratios were significantly lower in women with PCOS than in those without PCOS. Compared to women with non-PCOS, overweight/obese women with PCOS had lower serum adiponectin levels than women without PCOS, which was not the case for lean women. Conversely, lean women with PCOS had higher serum leptin levels than those without PCOS, which was not the case for overweight/obese women.[39]

Milewicz *et al.*[40] studied the relationship between the free androgen index and basal as well as the meal-stimulated level of glucose-dependent insulinotropic peptide (GIP) in lean women affected by PCOS. They found that excess androgen activity might be a factor contributing to alteration in the secretion of incretins in lean women affected by PCOS. However, it could not be ruled out that it is also possible that increased GIP levels might induce hyperandrogenemia in women with PCOS.

Management options for lean women with PCOS

Weight loss

Weight loss is first-line therapy for obese women with PCOS, but is not a therapeutic option for nonobese women with the disorder. The clinical importance of our findings is that they suggest that even normal weight and thin women with PCOS should respond to pharmacological measures to improve insulin sensitivity, such as the administration of agents such as metformin, with decreases in ovarian androgen production and serum androgens.[2]

Lean women with PCOS have lower caloric intake than other lean women, but find it harder to maintain weight. Resistance exercise alone can improve hyperandrogenism, reproductive function, and body composition by decreasing visceral fat and increasing lean muscle mass, but it has no metabolic impact on women with PCOS.[41]

Ovulation inducing agents

Lifestyle modification is recommended as first-line therapy among obese women with PCOS to optimize their outcomes. Among lean and obese women with PCOS, ovulation induction can be achieved with aromatase inhibitors, selective estrogen receptor modulators, insulin sensitizing agents, gonadotropins,

and ovarian drilling with varying rates of ovulation, live birth, and multiple gestations. Assisted reproductive technologies are reserved for women who do not conceive despite the restoration of ovulation or couples with additional factors contributing to their infertility. This review will outline treatment strategies for achieving a healthy pregnancy among lean and obese women with PCOS and infertility.[42]

Obese women with PCOS are more likely to be anovulatory than thin women with PCOS. In addition, overweight women with PCOS are less likely to respond to the pharmacological induction of ovulation.[43]

Popova *et al.*[44] found that lean women with PCOS treated with metformin had menstrual function (55%) and ovulation (45%) restored more often than obese women with PCOS (only one patient (7%) responded to the treatment), $P = 0.018$. A significant decrease in testosterone level (from 3.1 ± 1.0 to 2.7 ± 0.8 nmol/l; $P = 0.049$), fasting glucose (from 5.2 ± 0.4 to 4.9 ± 0.4 mmol/l, $P = 0.013$), and HOMA (from 1.6 ± 0.7 to 1.2 ± 0.7, $P = 0.045$) during metformin treatment was shown only in lean women with PCOS. There was no change in BMI and waist circumference in both groups. They concluded that treatment with metformin 1700 mg daily was more effective in lean than in obese women with PCOS. Its efficacy was independent of the initial surrogate markers of resistance to insulin.

Krohn *et al.*[45] found that in lean patients with PCOS undergoing combined ovulation induction–intra-uterine insemination (IUI), the unadjusted clinical pregnancy rate was 52%; clinical pregnancy rate was comparatively lower in overweight (22%), obese (27%), and morbidly obese (21%) women for all cycles. Adjusting for age and the duration of infertility, the odds of clinical pregnancy after combined ovulation induction–IUI was significantly diminished in overweight (odd ratio, OR = 0.27, confidence interval, CI = 0.12–0.63), obese (OR = 0.41, CI = 0.20–0.83), and morbidly obese women (OR = 0.33, CI = 0.14–0.78) as compared to the lean women with PCOS. A similar but nonsignificant trend was identified in women undergoing oral ovulation induction–IUI.

Metformin

It is still unclear whether metformin is also beneficial for lean women with PCOS. A previous study showed that metformin improved hirsutism scores and ovulation and decreased dehydroepiandrosterone sulfate levels in lean women with PCOS.[46] Similarly, in a recent study performed on lean patients with PCOS without pretreatment IR, metformin improved hyperandrogenemia and anovulation.[47] On the contrary, another study reported no metabolic benefits of metformin treatment in nonobese women with PCOS.[48]

A study suggested that metformin use in patients with PCOS should be restricted to women with glucose intolerance,[49] but others disagreed with this suggestion.[50] We did not document IR in every patient with PCOS, and metformin should be administered to lean patients with PCOS according to the physician's recommendations.[51]

Another study was conducted to compare the ovulation and pregnancy rates in response to metformin therapy in lean and obese women with PCOS. Comparison between lean and obese women was found to be statistically significant. Metformin monotherapy is very effective in improving the ovulation and pregnancy rates in lean women with PCOS as compared with obese women.[52]

Metformin can be given as a first-line drug to all women (obese and nonobese) with PCOS and anovulatory infertility. Although there have been concerns expressed about the risk of hypoglycemia in lean anovulatory women with PCOS on metformin treatment, this risk is low. The risk of hypoglycemia should be extremely unlikely, particularly because IR is linked with anovulation in PCOS, even in lean women. It is, therefore, recommended that all women using metformin must be advised to look out for the signs of hypoglycemia and stop treatment if this is suspected.[53]

Myoinositol

Studies proved that the administration of myoinositol (3 g per day) reduced luteinizing hormone (LH), high-sensitivity C-reactive protein (hs-CRP) (inflammation), and androgens, as well as improved insulin tolerance test, in lean patients with PCOS. The administration of myoinositol, acting as a direct messenger of insulin signaling and improving the glucose uptake in tissues, could improve the IR status of women with PCOS, restoring their hormonal status and restoring the ovulation process.[54-56]

Although some studies discouraged the use of myoinositol in lean patients with PCOS and stated that it may not be suitable or effective for lean patients with PCOS, especially if they do not have IR. Other studies stated that it may – at high dosage – negatively affect oocyte quality.[57-59]

l-Carnitine

Celik *et al.*[60] stated that l-carnitine concentrations were significantly lower in lean patients with PCOS than in lean healthy women. They recommended that l-carnitine could be used as an adjunctive therapy in the management of IR or obesity in women who have PCOS. Further research should be planned to clarify the clinical effects of l-carnitine administration in patients with PCOS with IR and/or obesity.

Assisted reproductive technologies (ART) and lean women with PCOS

Orvieto *et al.*[61] investigated the relation of BMI to In-vitro fertilization (IVF) outcome in patients with PCOS undergoing ovarian stimulation with either gonadotrophin-releasing hormone (GnRH)-agonist (agonist group) or antagonist (antagonist group). The found that in both agonist and antagonist groups, patients with BMI ≤ 25 kg/m^2 had a significantly higher fertilization rate compared with patients with BMI > 25 kg/m^2 ($P < 0.02$ and $P < 0.01$, respectively). Lean patients (BMI ≤ 25) undergoing ovarian stimulation using the GnRH-agonist demonstrated the highest pregnancy rate. They concluded that, in lean patients with PCOS undergoing IVF/embryo transfer cycles, the best results were linked to midluteal long GnRH-agonist suppressive protocol.[61,62]

Diet and lifestyle in lean PCOS

Lifestyle modification is very important in the treatment for PCOS, because weight loss and exercise have been shown to lead to improved fertility and the lowering of androgen levels. It also reduces the long-term risk of diabetes, heart disease, and possibly endometrial cancer.[63]

Evidence-based guidelines recommend that lifestyle modification regimens should incorporate a dietary intake consistent with usual dietary guideline recommendations with modified macronutrient composition. This can be followed by weight maintenance, that is the prevention of weight gain in lean women with PCOS. Tehrani *et al.*[64] claimed that vitamin D and calcium supplementation while on metformin significantly improved menstrual cycle regulation and other PCOS symptoms.

Lifestyle intervention improves body composition, hyperandrogenism (high levels of male hormones and clinical effects), and IR in women with PCOS. There was no evidence regarding the effect of lifestyle intervention on improving glucose tolerance or lipid profiles and no literature assessing clinical reproductive outcomes, the quality of life, and treatment satisfaction.[65]

It is extremely important that lean women with PCOS get a variety of nutrients, minerals, and vitamins in their diet; therefore, they need to make sure that their diet contains plenty of vegetables and some fruit. In addition, because lean patients with PCOS do not need to lose weight, they do not need to restrict their caloric intake.

Complementary to the dietary and lifestyle changes, patients need to focus on supporting their body by promoting healthy hormonal balance, a healthy uterine lining, regular ovulation, improving estrogen metabolism, and ultimately a healthy pregnancy This could be achieved by vitamins and minerals such as calcium and vitamin D, as well as herbs that promote hormonal balance and support regular ovulation such as Vitex (*Vitex agnus-castus*) and maca (*Lepidium meyenii*), licorice root (*Glycyrrhiza glabra*), and white peony (*Paeonia lactiflora*).[66]

Additional nutritional supplements such as essential fatty acids in evening orimrose oil and cod liver oil, saw palmetto (*Serenoa repens*), and d-chiro-inositol and myoinositol improve the previously mentioned benefits of a healthy diet.[67]

Conclusion

Lean women populations with PCOS are a unique group and have different phenotypic, metabolic, hematologic, and neurologic characteristics than obese participants with PCOS. Till recently, there was an ongoing debate regarding the previously mentioned characteristics; in addition, the existing management options are mostly not appropriate for this category of patients with PCOS. Further studies are required to clear and solve this debate.

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Conflicts of interest

There are no conflicts of interest.

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