Chapter 3

Lean Women with Polycystic Ovary Syndrome

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Abstract

Most of the time, polycystic ovary syndrome (PCOs) is considered as an obese women disease; lean PCOs patients need to evaluate and treat completely as a neglected subgroup. Androgen excess signs and symptoms, insulin resistance (IR) and its consequences, cardiometabolic risks, and regular exercise must be noted and managed carefully.

Keywords: lean, non-obese, androgen, insulin, PCO

1. Introduction

Polycystic ovary syndrome (PCOs) is the most common reason of androgen excess in reproductive-age women with a prevalence of 6.5–8% according to clinical appearance [1] or even up to 20% by sonographic evidence [2].

For the first time, Stein and Leventhal described it in the year 1935 [3]. Year after year, the description of the disease developed; in 1990, the National Institutes of Health (NIH) mentioned oligo-ovulation and hyperandrogenism with or without hyperandrogenemia (HA) must be together (of course, after exclusion of another causes of androgen excess) [4].

Another expert meeting in 2003 expanded the NIH definition of PCOs by adding the sonographic aspect of the disease (Rotterdam criteria) [5]. According to their criteria, two of three signs/symptoms are necessary for PCOs diagnosis; therefore, PCOs woman can be ovulatory with regular menstruation.

More recently, the Androgen Excess Society (AES) advocated that all of the signs and symptoms should be present for the confirmation of diagnose [6] (**Table 1**).

Contrary to physicians' and patients' belief, weight or body mass index (BMI) had never been a part of PCOs definition.

NIH Criteria 1990 (all of them)	ESHRE[1]/ASRM[2] (Rotterdam) 2003 (two of three)	AES 2006 (all of them)
Hyperandrogenism ± hyperandrogenemia	Hyperandrogenism±hyperandrogenemia	Hyperandrogenism ± hyperandrogenemia
Oligo-ovulation	Menstruation abnormality	Ovarian dysfunction ± sonographic aspect
	Sonographic aspect of poly cystic ovary	

Exclusion of other androgen excess conditions is necessary for all of definition: (21-hydroxylase deficient, thyroid dysfunction, nonclassical adrenal hyperplasia, hyper prolactinemia, drug-induced androgen excess, androgenic neoplasm, Cushing syndrome, growth hormone excess).
[1]European Society for Human Reproductive Medicine.
[2]American Society for Reproductive Medicine.

Table 1. Different definition of polycystic ovary syndrome.

According to epidemiological data, there is a wide variation in the prevalence of obese and non-obese PCOs women: in Korean population 20%, in Europe 27–50.5%, and in USA 67% of PCOs woman are obese [7–11]. Regarding to different ethnicity, the prevalence of normal weight and underweight patients with PCOs has been reported 1.5–6.6% [12, 13]. Entirely, by using Rotterdam criteria, the overall prevalence of PCOs is increasing because ovulatory or non-hyper androgen PCO patients also are considered [14].

By definition, women with BMI ≤ 25 are non-obese and with BMI > 25 considered obese.

Although at now, we have a few reports about the prevalence of non-obese PCOs patients, but attention toward those patients and their metabolic and health problems are enhanced day by day.

The pathophysiology of PCOs is multifactorial and manifests the final effect of genetic, fetal, environmental, and metabolic factors. As a result of weakness or strength of each factor, clinical and subclinical character and their response to therapeutic efforts will be different.

2. Genetic and PCOs

Obvious familial clustering of PCOs and higher prevalence of its sign and symptom, like type 2 diabetes mellitus (T2DM) and hyperandrogenemia in first-degree relatives of women with PCOs, demonstrate its genetic origin [15, 16]. Also, in the Dutch twin study, higher degree of heritability was shown [17]. Initially, autosomal dominant mode of inheritance was suggested [18]; but after a while, researches demonstrate it has more complex inheritance pattern. Despite the progress in genes or loci study, no single gene has been successfully described as the certain responsible gene among all studies [19]. According to microarray analysis results, 14 important genes were recognized: 6 genes were identified as down-regulated genes and 8 genes as up-regulated genes [20]. Another proposed genes are *CYP11A*, the insulin gene, and a region near the insulin-receptor gene [21]. Also, controlling genes in folliculogenesis and LH receptor and coding genes for TNF-alpha, IL-6, and IL-6 receptor can be involved in the pathogenesis of this syndrome [22].

3. Insulin and PCOs

For the first time in 1980, the relation between this syndrome and insulin was determinate [23]. Clinically insulin resistance (IR) is specified as inability of a known amount of endogenous or exogenous insulin to enhance glucose uptake and consumption. As a result of a misbelief that IR always accompanies with obesity, in clinical practice, IR is underestimated in non-obese PCO women. IR is a common character between obese and non-obese PCO patients and its overall prevalence is 50–75%. Up to 35% of PCOs women have IGTT and 7–10% are type 2 diabetes mellitus (T2DM) [24].

At now, the most used IR indices are homeostasis-model assessment (HOMA) and insulinemic 2-h area under the curve (AUCi 2 h), both derived from oral glucose tolerance test (OGTT) [25]. The 120-min glucose and insulin evaluation (HOMA-M_{120}) is the best IR index in lean PCOs women according to Morciano et al. study [26]. Meanwhile, there are several earlier studies about IR evaluation in lean PCOs women [27–29]. Although, a study in a large group of European lean PCOs patients displayed that this group had significantly less IR compared with obese PCO women [30]; but, instead of it, there is evidence that in American and Asian PCOs women, IR is independent from BMI [31]. It seems that dietary composition and ethnic background associated with this discrepancy.

Owing to another recent study, the crucial role of insulin in PCO pathogenesis emphasized that IR shall be evaluated even in normal weight and lean PCOs patients [12].

As suggested in the earlier study [32], hyperinsulinemia stimulates ovarian P450c17 alpha activity in non-obese women with PCOs, which means more conversion of progesterone to androstenedione which is changed to testosterone. In granulosa cell, insulin intensifies their response to LH. Therefore, these cells experience premature arrest of follicular growth and abnormal differentiation, and thus anovulation. Also, elevated insulin resistance causes hyperglycemia which leads to hyperinsulinemia and it can increase LH action on theca cells and subsequent elevation in androgen level. Hyperinsulinemia, insulin resistance, and enhancement in androgen production are the famous pathophysiology triads in PCOs. From another side, elevated level of insulin prevents hepatic sex hormone-binding globulin (SHBG) production, which can lead to elevated free androgen and again elevated level of insulin, a positive feedback in an undesirable circle. Thus, IR and hyperinsulinemia are the principal pathological causes of this syndrome, and hyperandrogenemia is their consequence.

As insulin resistance has fundamental role in non-obese PCOs patients, then metformin administration have a beneficial effect on them and regulate their menstruation cycle [33]. As well, there is a new therapeutic option: inositol, a precursor component of second messenger for follicle-stimulating hormone (FSH), *thyroid - stimulating hormone* (TSH), and insulin receptor. This drug can overcome IR from another way [34]. It is important to mention that only 15% of women with IR are having PCOs criteria; therefore, insulin resistance cannot be the only pathophysiologic pathway [35] and metformin administration may not be effective in all of lean PCOs.

4. Androgens and PCO

About 10–12% of women in reproductive age suffer from androgen excess sign and symptom. It can be caused by androgen overproduction (from ovary or adrenal gland) or secondary to increased sensitivity of pilosebaceous unit (with normal level of androgens). Hyperandrogenemia is another hallmark of PCOs; mainly by ovarian resource and less by adrenal. In PCOs women, 60% of serum androstenedione and testosterone (T) are secreted by ovary. Surprising, ovarian androgens will not prominently affect LH production, thus an elevation in free testosterone or androstenedione will not decrease ovarian synthesis of these androgens in women, contrasting to men.

As mentioned before, in PCO women, insulin in a solitary manner or with synergetic effect of LH induces androgen production by ovaries. Even in lean PCOs women with normal metabolic insulin sensitivity and insulin levels, decline of insulin secretion with diazoxide (like metformin) prominently reduce levels of free T and androstenedione and meaningfully increased SHBG [36]. In these women, hyperandrogenemia is seen because of augmented sensitivity of their androgenic pathway to insulin and dysregulation of steroidogeneses enzymes based on genetic predisposition [37]. Therefore, even in PCOs patients with normal insulin metabolic and without clinical approved IR, local resistance in the ovaries increased androgens production [38].

Androgen excess or hyperandrogenemia (HA) in PCOs women contribute in exacerbation of metabolic abnormalities, such as insulin resistance in adipose tissue and skeletal muscle and elevation in lipid metabolism in visceral fat, decreased lipolysis in subcutaneous fat, increased low-density lipoprotein cholesterol (LDL-C) levels decreased HDL-C levels. Besides that, androgens may be involved in possible direct vascular action [39]. There are some studies, in which hyperandrogenemia was accompanying with metabolic syndrome (MetS) in non-obese PCOs more than obese PCOs women [40, 41].

Hyperandrogenemia or androgen access clinical signs are mainly cutaneous manifestations: hirsutism, acne, androgenic alopecia, acanthosis nigricans (AN), and seborrhea. In one study, their prevalence in PCOs women was: 78, 48, 31, 30, and 29% (in mentioned order) [42]. In another study, the prevalence of acanthosis nigricans in obese PCO was 42.5% compared to 28% in non-obese [43]. One published paper shows that AN is a marker of hyperinsulinemia in both obese and non-obese PCO patients rather than a sign of androgen excess and the only sex steroid associated with histological AN is dehydroepiandrosterone sulfate (DHEAS) [44].

Pharmacological management of hyperandrogenic skin symptoms has two targets: firstly, decrease the level of circulating androgens, and secondly prevent their effect at tissue level. Cyproterone acetate/ethinylestradiol has beneficial effect in non-obese PCO women with hyperandrogenic skin symptoms [45].

5. Inflammation and PCO

There are many published studies about proinflammatory or inflammatory situations in PCOs woman. Increased level of circulatory inflammatory markers like C-reactive protein (CRP),

tumor necrosis factor-alpha (TNF-α), interleukins (IL-16 and -18), and plasminogen activator inhibitor in PCO patients accompany with abdominal obesity and more specific with visceral fat [46]. Low-grade inflammation situation by increased level of adiponectin, resistin, IL-6, and TNF-α in non-obese PCO women have been approved [47]. Also, it has been shown that inhibition of nutrient-induced inflammation decreases ovarian androgen secretion and induces ovulation in lean PCOs woman without clinical IR or abdominal adiposity. Therefore, inflammation directly encourages ovarian dysfunction in PCOs women distinctly from insulin resistance or excess adiposity [48]. There is evidence that non-steroidal anti-inflammatory agent administration in lean PCO women can reduce androgen secretion from ovary [49].

Dose inflammation have pathophysiologic role in this syndrome or may be its consequence remain still unclear. Inflammation as a chronic immune activation, prevents ovulation, increases androgen production by ovary and adrenal gland and disrupts hormonal receptors. Most of long-term complications of PCOs like cardiovascular disease (CVD) are consequences of inflammatory state [50].

In non-obese PCO patients, visceral fat distribution, waist to hip ratio (WHR), and abdominal obesity have relation with inflammatory situation. In one study, in lean PCOs, level of white blood cell (WBC) has a positive predictive value with insulin resistance, while the neutrophil to lymphocyte ratio has a negative predictive value [51]. Also, it has been demonstrated that in clomiphene citrate (CC)-resistant patients, regardless to BMI, inflammatory markers like TNF-α are too high, and TNF-α serum level may be used as a clinical predictive indicator before CC useless administration [52].

6. Weight and PCO

Even in lean PCO women, we can see higher waist to hip ratio, greater intra peritoneal and visceral fat, and percentage of body fat in comparison with BMI matched non-PCO women. Accumulation of small subcutaneous abdominal fat in those patients shows spoiled adipogenesis and hyperandrogenism [53]. Also, abnormal gene expression in stem cell of subcutaneous abdominal fat in normoandrogen and ovulatory lean PCO women display abnormal vacuolization and angiogenesis, which may reflect metabolism alter in those women [54]. From another side, adiponectin, a protein which is involved in regulating glucose levels and fatty acid breakdown, is produced by omental fat and dysregulated by high level of insulin; thus, even in lean PCOs women, inappropriate metabolism of glucose and lipid can be explained [55]. In respect with a new randomized controlled trial, arranged and regular physical exercise can ameliorate insulin sensitivity, hyperandrogenemia, and menstrual regularity in lean PCO women [56].

7. Metabolic disorders and PCO

PCOs is considered by multiple metabolic disorders which may associate to increase risk of hypertension and cardiovascular disease. One study used menstrual irregularity as a predictive

factor for assessment of cardiovascular events in a 15-year period, in PCOs women. There was an insignificant increase in overall stroke risk and in ischemic stroke risk associated with "very irregular" menstrual cycles [57]. In PCO women, higher prevalence of hypertension is related to insulin. Hyperinsulinemia have been connected with an increase in intracellular sodium and calcium, along with vascular smooth muscle hypertrophy due to insulin-like growth factor-1 (IGF-1) activity [58]. Simultaneously, androgen excess stimulates sympathetic nerve activity, as another etiology of hypertension in this population [59].

PCOs is also associated with elevated levels of plasma endothelin-1 (ET-1), one of several circulating indicators of endothelial injury and dysfunction. One study found that impairment of endothelial function is more severe in lean than obese women with PCOs, and that ET receptor downregulation plays an essential role in this probably adverse cardiovascular outcome [60].

The increase in carotid intima-media wall thickness (CIMT) in PCOs women has been associated in different studies with higher levels of insulin, hyperandrogenism, LDL level, and abdominal obesity; which is an early marker of atherosclerosis [61].

Meanwhile, impaired nitric oxide (NO) production as a consequence of elevated androgen levels in PCOs women contribute to endothelial dysfunction [62].

Elevated plasma viscosity as a result of increased plasma fibrinogen concentration in PCOs patients exacerbates vascular dysfunction because autoregulation of vasomotor tone may not be able to adjust with compromised physical properties of blood [63]. Some possible reasons for increased plasma fibrinogen are: increased inflammatory processes [64], decreased fibrinolysis [65], and as an acute phase reactant. Enhancement in fibrinogen level stimulates RBC aggregation and significantly increased resistance in blood flow [66]. Low SHBG and high insulin stimulate prothrombotic state in all of PCOs women by increased plasminogen activator inhibitor 1 (PAI-1) activity and fibrinogen in a BMI-independent way [67].

Dyslipidemia including elevated low-density lipoprotein (LDL), triglyceride levels and decreased high-density lipoprotein (HDL) are often seen in PCO women as a result of hyperandrogenism and insulin resistance in both lean and obese PCO patients [68].

Owing to many evidence about vitamin D deficiency and metabolic syndrome; there are many studies about 25(OH) D levels and PCOs. There are some evidences which support this relationship and encourage vitamin D administration in all of deficient PCOs women [69], whereas some studies do not support it [70].

From another site, insulin resistance, increased central adiposity, higher levels of testosterone, and dyslipidemia beside oxidative stress and low grade inflammation contribute to cause hepatic steatosis or fatty liver in PCOs women. Advanced stage of this disease characterized by necrosis and steatohepatitis which called non-alcoholic fatty liver disease (NAFLD) and has prevalence about 40% in lean PCOs women [71].

After blow-by-blow discussion about all of aspects in lean PCOs women, we cannot consider this syndrome as just a part of infertility or menstrual abnormality assessment, but should be accepted as an alarm sign for serious health problem.

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