

PCOS and Metabolic Syndrome: The Worrisome Twosome?

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Abstract

By virtue of insulin resistance being the common etiology for PCOS and Metabolic Syndrome, the cardio metabolic risks of these two syndromes are shared. The usual concerns of a PCOS patient are cosmetic or reproductive. However, there are more serious concerns past the reproductive age. Early treatment of insulin resistance, hypertension, and hyperlipidaemia reduces the long-term risk. This review highlights the unhealthy association of Metabolic Syndrome with PCOS, and emphasizes on early diagnosis, patient education and a long term follow up beyond reproductive age to prevent the co morbidities.

Keywords: PCOS; Metabolic syndrome; Insulin resistance; Dyslipidaemia; Hyperandrogenemia; Hypertension; Sleep apnea

Introduction

Poly-cystic Ovary Syndrome [PCOS] is a gynecological endocrinopathy, and affects 4% to 12% of reproductive age women [1-3]. Since its description in 1935 by Stein and Leventhal [4], it has been a subject of extensive controversy and research.

Metabolic Syndrome [Met S] is a complex cluster of cardio-metabolic risk factors with adipose tissue dysfunction and insulin resistance as the underlying pathology [5]. By virtue of insulin resistance being the common etiology for PCOS and Met S, many features of these two syndromes are shared. Whether PCOS is an early manifestation of Met S or a sex-specific variant, is yet to be ascertained.

Definitions

Keeping in view the complexity of the disorder and in order to have a consensus about the diagnosis, the European Society for Human Reproduction and Embryology [ESHRE] and the American Society for Reproductive Medicine [ASRM], in 2003, recommended that at least **two** of the following three features should be present for PCOS to be diagnosed [6]:

1. Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea
2. Hyper-androgenism [clinical evidence of androgen excess] or hyper-androgenemia [biochemical evidence of androgen excess]
3. Polycystic ovaries [as defined on ultrasonography as presence of 12 or more follicles in each ovary, measuring 2-9 mm in diameter, and/or increased ovarian volume >10 ml].

The definition is not applicable to women taking oral contraceptives, and women with a dominant follicle >10 mm, or a corpus luteum. In these women, the scan must be repeated in the next cycle [6]. It is noteworthy that certain previous diagnostic criteria, such as increased Leutinising Hormone [LH] concentrations, increased LH/FSH ratio are no longer necessary to clinch the diagnosis [6].

Metabolic syndrome [Met S] is a cluster of cardiovascular risk factors. It has been found to be more prevalent in women with PCOS [5].

According to National Cholesterol Education Program [NCEP] Adult Treatment Panel [ATP] III guidelines, the diagnosis of metabolic syndrome is made when **three** or more of the following criteria are present [7]:

1. Waist circumference of >88 cm or >35 inches
2. Fasting plasma glucose of ≥ 100 mg/dl or 6.1 mmol/l
3. Blood pressure $\geq 130/85$ mm Hg
4. Fasting Triglycerides ≥ 150 mg/dl or 1.7 mmol/l
5. High Density Lipoprotein [HDL-C] <50 mg/dl or <1.3 mmol/l

The prevalence of Met S in PCOS is reported to be as high as 43-46%, using the NCEP criteria [5,8].

The definition of Met S by the WHO relies more on insulin resistance as the foremost component. It includes diabetes, impaired fasting glucose, impaired glucose tolerance or insulin resistance and at least two of the following criteria [9]:

PCOS, Metabolic Syndrome: Etiology and Pathophysiology

Women with PCOS have abnormalities in insulin action, metabolism, and in the control of androgen production [10]. These patients have cardiovascular risk factors, similar to Met S, such as insulin resistance, hyper-insulinaemia, obesity, hyper-androgenemia, hyper-lipidaemia, hypertension and sleep disorders [10].

In a prospective, observational cohort study of 101 073 women [11], PCOS patients were found to have a 50% increase in fatal and non-fatal cardiovascular disease compared to age and BMI – matched controls.

Wild et al. [12] studied 319 women with PCOS and 1060 age-matched controls and found an odds ratio of 2.2 for diabetes, 1.4 for hypertension, 3.2 for hypercholesterolemia and 2.8 for cerebrovascular disease in PCOS vs. non-PCOS women.

In postmenopausal women evaluated for ischemia, those with PCOS features were associated with more angiographic coronary artery disease [p=0.04] and worsening cardiovascular event-free survival [p=0.006], compared to the ones without [13]. The most worrisome

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concerns of these patients change with age, from cosmetic troubles like hirsutism and acne, as teenagers, oligomenorrhea and infertility during their reproductive lives, to cardio metabolic disorders following menopause.

Genetics

PCOS arises from an interaction of genetic and environmental factors. It is more likely to be polygenic or oligogenic in origin [14,15]. Genes involved in steroidogenesis, carbohydrate metabolism and major histocompatibility region, SHBG, Insulin receptor, follistatin and CYP17 are likely to be involved [16,17]. In a study of family members of PCOS patients by Carey et al. [18], all the first degree relatives of affected individuals were screened. It was found that there is an autosomal dominant mode of inheritance of PCOS, with 90% penetrance.

The expression of PCOS is varied among different races. Women from South Asia have been found to have worse symptoms, metabolic and hormonal aberrations, and a higher chance of developing type two diabetes when, compared to the Caucasian population [19].

Insulin Resistance

Insulin Resistance [IR] is defined as a state in which normal concentrations of insulin produce subnormal effects on glucose homeostasis and utilization [20,21]. Evidence suggests that PCOS and Met S are associated with peripheral insulin resistance, and consequent hyper-insulinaemia. Obesity, which is common in PCOS and Met S, amplifies the degree of both these abnormalities [10].

In PCOS, there is high responsiveness to insulin by the ovary, contrary to the resistance of the rest of the body. This causes ovarian hyper-androgenemia. Insulin is also responsible for maturation arrest and atresia of ovarian follicles, leading to deficiency of aromatase activity, further aggravating hyper-androgenemia.

Insulin resistance is present in 65-80% of PCOS patients, causes early onset hyperglycemia and progression to type II diabetes, and also increases the risk of cardiovascular disease [19-22].

There is persistence of impaired glucose metabolism after gestational diabetes in women with PCOS, and the relative risk for the composite outcome of glucose metabolism impairment in PCOS women is 3.45 [23-25]. Compared to non-PCOS diabetics, diabetes in PCOS may be a stronger contributing cause of death [12].

Insulin resistance and cardiovascular risk can be determined by Lipid Accumulation Product [LAP] Index, which identifies IR if it is >34.5 [23,24]. LAP is calculated by the formula [Waist circumference [cm] - 58] x fasting triglycerides [mmol/l].

PCOS patients with a high LAP are more insulin resistant and have a higher prevalence of Met S [23].

Elevated homocysteine level, an independent cardiovascular risk factor, contributes to insulin resistance. Comparing the homocysteine levels in normal individuals and those with cardiovascular disease, Clarke, et al. [26] found hyperhomocysteinemia in 16 of 38 patients with cerebrovascular disease [42%], 7 of 25 with peripheral vascular disease [28%], and 18 of 60 with coronary vascular disease [30%], but in none of the normal subjects.

Hyper-insulinaemia contributes to cardiovascular risks in other ways as well. Natriuretic Peptides [NP] are secreted by cardiomyocytes and regulate blood pressure and lipolytic activity. Low levels of NP and reduced lipolytic activity of NP are found in central obesity and

insulin-resistant states. Besides, their clearance is accelerated in a hyper-insulinemic milieu [27].

Obesity

The cause of obesity in PCOS remains unknown but may be the result of hyper-insulinaemia [28]. Weight gain usually precedes the onset of clinical features of PCOS in majority of patients. Fifty percent of PCOS patients are obese, and obesity tends to be abdominal/visceral [28]. Visceral obesity is associated with hyperandrogenemia, insulin resistance and dyslipidemia, and worsens the metabolic and reproductive parameters of PCOS.

Obesity is strongly linked with type II diabetes in PCOS. Comparing the various phenotypes of PCOS in unselected and referral populations, Ezech et al. [29-31] found that women with PCOS seeking medical advice are significantly heavier than their leaner counterparts, who need medical advice at a much later time, if at all. The prevalence of obesity and severe obesity in referral PCOS was 2.3 and 2.5 times greater than that of the same in unselected PCOS and 2.2 and 3.8 times greater than that in non-PCOS controls, respectively.

Fasting and post glucose insulin levels are higher in obese than non-obese PCOS patients [29,30]. Non obese PCOS patients are more insulin sensitive than their obese counterparts. This is partly because of increased production of free fatty acids and lactic acid in obese patients, which alters the metabolism of insulin [31]. The adipose tissue in PCOS has been found to have abnormal function and reduced vascularity. Consequent hypoxia leads to a low-grade inflammation, and an increased production of cytokines and chemokines [30]. C-reactive protein, a marker of inflammation, predicts the cardiovascular risk in PCOS patients. Chronic inflammation is linked with the development of insulin resistance, diabetes mellitus type 2 and other CV risk factors.

Recent developments have shown the association of obesity with ghrelin. Ghrelin is a gastric peptide with orexigenic and adipogenic properties. It exerts a direct effect on gonads and pancreas, and is involved in appetite and weight regulation [32-35]. Low levels of ghrelin have been linked to insulin resistance in PCOS women.

In a prospective study by Basios, et al. [36], levels of adiponectin were found to be reduced in PCOS patients. Adiponectin is an adipokine secreted by the adipose tissue which has an insulin-sensitizing activity.

Hypertension

Hypertension develops due to reduced vascular compliance, and endothelial dysfunction. Endothelial dysfunction is proportional to the level of androgens and insulin resistance [37]. Diamanti, et al. [37] studied the endothelial dysfunction and smooth muscle injury in PCOS patients. Endothelial function was assessed by Flow-Mediated Dilatation [FMD] on the brachial artery and smooth muscle cells injury was excluded by Nitrate-Induced Dilatation [NID]. Flow mediated dilatation was statistically lower in PCOS patients compared to controls. Endothelin-1 levels are higher in PCOS patients and correlate positively with free androgen index and negatively with SHBG [37,38]. Hyperinsulinaemia exerts a hypertrophic effect on the vascular endothelial and smooth muscle cells [39,40].

Kelly et al. [39] studied the cardiovascular risks in PCOS patients in a prospective case-control study and demonstrated increased vascular stiffness and a functional defect in the vascular action of insulin in patients with PCOS. It was found that insulin resistance of the arterial endothelial cells is associated with reduced synthesis of Nitric Oxide [NO] and increased synthesis of vaso-constricting agents.

This leads to increased vascular stiffness, and consequent hypertension. They also found elevated tissue Plasminogen Activator [tPA] levels in such patients, which correlated with BMI and insulin resistance.

Lecke et al. [40,41] demonstrated a link between CYP19 gene expression, aromatase enzyme levels and blood pressure in PCOS patients. CYP19 mRNA was higher in hypertensive PCOS than in control [non PCOS, normotensive] and normotensive PCOS women. Estrogen-to-androgen ratio ≤ 0.06 was observed in 91% of hypertensive PCOS women, vs. 37% and 61% in the control and normotensive PCOS groups.

Using Doppler studies, vascular abnormalities, like increased anteroposterior diameter of abdominal aorta, have been demonstrated in polycystic ovary syndrome patients [42]. The mean anteroposterior diameter of abdominal aorta was 13.87 ± 1.8 mm, while that in controls was 12.18 ± 2.3 mm [p value < 0.01]. Increased anteroposterior diameter could be the earliest pathological clue in the vascular wall, followed by thickening of carotids or femoral arteries. Besides, vascular injury resulting from inflammation could lead to central arterial stiffness, characterized by excessive collagen in the vessel wall [43].

In a cross sectional longitudinal study by Joham, et al. [44], prevalence of hypertension in PCOS and non PCOS women was 5.5% and 2%, respectively [p < 0.001].

In Dutch PCOS population, the prevalence of diabetes and hypertension, respectively, was four and two and half times higher than non PCOS population. Hypertension also occurred significantly more in the younger PCOS age group [45].

In a prospective case-control study, Yarali, et al. [46] found that reduced left ventricular ejection fraction, diastolic dysfunction and increased left ventricular mass index are more common in PCOS women. Women with PCOS are predisposed to macro vascular disease and intra-vascular thrombosis due to increased levels of Plasminogen Activator-I [47-49]. All these parameters contribute to cardiovascular morbidity and mortality.

Dyslipidemia

The most prevalent metabolic abnormality in PCOS is dyslipidemia, which is present in 70% of patients. It worsens with ageing and obesity [50]. Dyslipidemia is a consequence of hyperinsulinaemia. Pasquali R et al and Diamanti et al. in their respective studies, proved that persistent hyperinsulinaemia and hyperandrogenemia lead to dyslipidemia through lipoprotein lipase activity [30,51,52].

Hypertriglyceridemia, elevated low-density lipoprotein levels and low levels of high-density lipoprotein predispose to vascular disease and an atherogenic lipid profile [50]. After controlling the differences in weight and age, pattern of dyslipidemia differs in different ethnicities. US women with PCOS were found to have higher fasting serum triglycerides compared to Italian weight and age-matched controls [51].

Hyper-androgenemia

Ovarian hyper-androgenemia occurs as a direct stimulatory effect of insulin and insulin-like growth factor1 [IGF-1] on ovarian stromal cells. In a systematic review by Azziz, et al. [53], hyper secretion of LH was found in 75% patients, causing hyperplasia of ovarian stromal and thecal cells, which, in turn, worsened hyper-androgenemia. Androgens inhibit the hepatic production of Sex Hormone-Binding Globulin [SHBG] and insulin-like growth factor binding protein- I [IGF-BP-I]. Androgens increase lipolysis, increasing free fatty acids, and causing oxidative stress [54]. Androgens also stimulate hypertrophy of

adipocytes, by influencing the enzymes and proteins involved in the differentiation of pre-adipocytes into mature adipocytes [55].

The long term effects of hyper-androgenism are among the worst, especially from psychological, reproductive and metabolic points of view. The consequences, in the form of hirsutism, acne, excessive weight and infertility, lead to anxiety and depression, thereby affecting the quality of life [31,32].

Sleep Apnea

Obstructive Sleep Apnea [OSA] and daytime somnolence are found to be three times more common in PCOS patients [56,57]. When OSA is suspected, poly-somnography should be done for further evaluation [58]. Gopal et al. [59] studied the prevalence of OSA in PCOS patients, and found that the strongest predictors for sleep apnea are fasting insulin level and glucose to insulin ratio.

Studies link OSA with insulin resistance, diabetes and cardiovascular disease in PCOS women [60]. Continuous Positive Airway Pressure [CPAP] treatment modestly improved insulin sensitivity after controlling for body mass index [P=0.013] and daytime diastolic blood pressure decreased by 2.3 mm Hg after CPAP [P=0.035] in a prospective study of PCOS patients [60].

Treatment

Since IR remains the shared culprit in PCOS and Met S, the treatment implications are shared by the two. Treatment of the components of Met S like impaired glucose tolerance, diabetes, dyslipidemia and hypertension clearly reduces the cardiovascular risk imposed by the Met S [61].

Lifestyle modifications

Lifestyle modification, including diet and exercise, should be considered the first line management of women with PCOS and Met S. [58,62-64]. Weight loss improves insulin resistance, correcting its deleterious consequences on hormonal milieu, ovulation and menstrual regularity [64]. Weight reduction restores spontaneous ovulation in PCOS patients, and should be the first-line management in infertile anovulatory PCOS patients [28]. This fact has been further reinforced in a recent meta-analysis and systematic review by Domecq, et al. [65]. It also leads to improvement in cosmetic disturbances like acne [66].

Hypo caloric diets and exercise, combined with insulin sensitizers prove more effective in inducing and maintaining weight loss in PCOS patients, than utilizing them alone.

Insulin Sensitizers

There is enough evidence to suggest that correction of insulin resistance ameliorates hyperandrogenism, menstrual irregularity, and restores ovulation, thereby correcting the cardiovascular risks [67-69].

Metformin, is it the Holy Grail?

Metformin is the most widely used and trusted insulin sensitizer, belonging to the biguanide class [70]. It reduces insulin resistance, decreases LH hypersecretion and restores ovulation.

In women with PCOS, metformin treatment has also been found to have a comprehensive benefit by improving reproductive and metabolic functions and promoting weight loss. However, metformin has not been found to be effective for cosmetic concerns like hirsutism [71]. Metformin has a beneficial effect on blood pressure and improves endothelial function [72,73].

Metformin improves ovulation rates in women with PCOS when given alone or along with CC [70]. Metformin was found to be safe for use in pregnancy by Thatcher et al. [74] in a meta-analysis on pregnancy outcome in infertile patients with PCOS, treated with the drug.

Boomsma et al. [75] in their meta-analysis of pregnant patients with PCOS, and Glueck et al. [76] found that metformin decreases the risk of spontaneous miscarriages and development of gestational diabetes. However, the Royal College of Obstetricians and Gynaecologists [RCOG], even in its most recent guideline on PCOS, does not recommend the use of metformin in pregnancy [77].

Thiazolidinediones [TZDs] are used more sparingly, but have been found to improve the metabolic and hormonal aberrations, resulting in spontaneous ovulation. They work at the peroxisome-activated receptor level to improve insulin metabolism [78,79]. However, they cause fluid retention, thereby increasing weight [80]. These drugs are hepatotoxic, and should not be given to patients with deranged liver profile. TZDs are Category C drugs, and should be avoided in patients planning a pregnancy [58]. Troglitazone has been withdrawn from the market due to marked toxicity on liver. Pioglitazone and rosiglitazone are the newer agents being used, and have, till date, impressively improved hyperinsulinaemia, hyper-androgenism and irregular menstruation.

Among newer agents used in PCOS is D-chiro-inositol, which is an insulin sensitizer, working on thecal steroidogenesis to improve ovulation [81,82].

More often than not, in PCOS, treatment is symptom-tailored, and may have detrimental effects on the cardiometabolic aspects. As far as symptoms and signs of hyperandrogenism are concerned, insulin sensitizers are inferior to Combined Oral Contraceptives [COCs], especially the ones containing drospirenone and Cyproterone acetate [CPA]. These COCs exert a positive effect on atherogenic lipid and metabolic profiles [73,83]. Hormonal contraceptives have been found to have limited effect on carbohydrate metabolism in women without diabetes [84]. OC use was significantly associated with an increase in high-density lipoprotein cholesterol [85].

For hyper androgenic symptoms, COCs with Ethinyl Estradiol [EE] and CPA may be considered as the first line therapy [83,86]. Drospirenone containing COCs are inferior to CPA containing COCs, according to a consensus statement by Androgen Excess and Polycystic Ovary Society [86,87]. From cardiometabolic point of view, Cyproterone acetate in high doses has been shown to worsen triglyceridemia and is associated with venous thrombosis [88].

Anti-androgens like flutamide, finasteride and spironolactone have been used in treatment of hirsutism, either alone, or in combination with the COCs, for more effective symptom relief [89-91]. Spironolactone decreases insulin resistance and hyperinsulinaemia in obese PCOS patients [92]. Flutamide improves lipid profiles, insulin sensitivity and reduces visceral fat content in PCOS patients [93].

Joint British Societies' guidelines recommend that hypertension be treated if found to be greater than or equal to 140 mm Hg systolic, and/or 90 mm Hg diastolic, despite lifestyle modifications. Therapy may be considered earlier in presence of additional risk factors like diabetes [94].

Usually, there is significant improvement of dyslipidemia with dietary modifications and exercise. RCOG recommends treatment with statins by a specialist if atherogenic lipid profile doesn't improve with such measures. Lipid-lowering treatment should be considered earlier in cases where there are additional risk factors like smoking and family

history of cardiovascular disease. Statins also exert a positive effect on correcting hyper-androgenemia in such patients [95,96].

For morbidly obese patients with a Body Mass Index [BMI] of 40kg/m², especially the ones with Met S, bariatric surgery is a good option. Weight loss of 14-25% may be expected in such cases [97-99]. Legro et al suggested that bariatric surgery prevents or reverses metabolic syndrome and has reproductive benefits as well [100]. Anti-obesity drugs like sibutramine and orlistat have not been extensively evaluated in PCOS patients, but should not be used long term [101]. Orlistat is a pancreatic lipase inhibitor which reduces body weight and improves insulin resistance, hormonal and metabolic parameters [102]. Sibutramine should be used with caution because of the rise in blood pressure with its use.

Conclusions

PCOS is referred to as the Met S of gynaecology, and sometimes, as a 'sex-specific form of Met S' [28].

A majority of PCOS patients seek medical advice for cosmetic reasons like hirsutism and acne, infertility and menstrual irregularity. This could be used as a potential opportunity to educate and evaluate the patients, and to prevent the various facets of Met S, by intervening at the earliest. The unhealthy association of PCOS with Met S poses serious cardio-metabolic risks beyond the usual concerns of a PCOS patient. The follow up of PCOS patients should, therefore, continue well beyond their reproductive age, focusing on long-term cardiovascular consequences.

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