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Review Article

Metabolic syndrome in polycystic ovary syndrome: a review

Kalaivani V., Ushadevi Gopalan*

Department of Obstetrics and Gynaecology, Shri Sathya Sai Medical College and Research Institute, Tamil Nadu, India

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***Correspondence:**

Dr. Ushadevi Gopalan,

E-mail: ushag7@hotmail.com

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ABSTRACT

Polycystic ovary syndrome is one of the most common endocrine abnormalities in women. It affects both reproductive life and overall health of the women including metabolic abnormalities. A multidisciplinary approach is needed in those with metabolic variations to prevent them from the long-term complications like cardiovascular diseases and diabetes mellitus. The objective of this article is to review the association between PCOS and metabolic syndrome.

Keywords: Polycystic ovary syndrome, Metabolic syndrome, Insulin resistance, Dyslipidaemia, Hyperandrogenism

INTRODUCTION

One of the most common endocrine disorders encountered in the reproductive women nowadays is polycystic ovary syndrome with a prevalence ranging from 6-15% worldwide.¹ Polycystic ovary syndrome was described by Stein and Leventhal in the year 1935 and hence it is also called as Stein Leventhal syndrome.² Various factors contribute to the development of PCOS in women but the exact etiology for this disorder is not clearly understood.³ PCOS leads to various complications like metabolic, endocrine, reproductive, psychological disturbances and increased risk of developing endometrial carcinoma.⁴ Metabolic complications are due to insulin resistance, hyperinsulinemia, hyperandrogenism and obesity.

PCOS women are at increased risk of developing type II diabetes and impaired glucose tolerance.⁵ Metabolic syndromes is a group of disorders which include cardiovascular diseases and diabetes mellitus. The common underlying pathophysiology of PCOS and metabolic syndrome is insulin resistance.⁶ The prevalence of metabolic syndrome in PCOS women is about 33%.⁷ Few studies have shown that insulin resistance in PCOS plays an important role in the development of metabolic

syndrome irrespective of lean or obese status of the women.⁸ The risk of diabetes increases in those PCOS women with family history of diabetes.⁹

CRITERIA TO DEFINE METABOLIC SYNDROME

There are various criteria that are used to define metabolic syndrome,

Table 1: International diabetes federation (IDF) 2006.

International diabetes federation (IDF) 2006 ¹⁰	
Waist circumference more than 80cms is a definitive parameter Along with the presence of two or more of the following :	
1	Blood glucose>100mg/dl (5.6mmol/L) or diagnosed diabetes
2	HDL cholesterol<50 mg/dl (1.3mmol/L) or drug treatment for low HDL cholesterol
3	Blood triglycerides>150mg/dl (1.7mmol/L) or drug treatment for elevated triglycerides
4	Blood pressure>130/85 mmHg or drug treatment for hypertension.

Table 2: World Health Organisation (WHO) 1999.

World Health Organisation (WHO) 1999 ¹¹	
Plasma glucose >110mg/dl (6.1 mmol/L), 2-hour glucose >140mg/dl (7.8 mmol/L) or presence of insulin resistance, along with 2 or more of the following	
1	High density lipoprotein (HDL) cholesterol <1.0 mmol/L (<40mg/dl)
2	Serum. triglycerides 1.7 mmol/L (>150mg/dl)
3	BMI >30 kg/m ² or waist hip ratio >0.85
4	Blood pressure >140/90 mmHg.

Table 3: National cholesterol education program (NCEP).

National cholesterol education program (NCEP) ¹²	
3 or more of the following parameter should be fulfilled	
1	Blood glucose > 100mg/dl (5.6mmol/L) or drug treatment for elevated blood glucose
2	HDL cholesterol < 50mg/dl (1.3 mmol/L) or drug treatment for low HDL cholesterol
3	Blood triglycerides >150mg/dl (1.7mmol/L) or drug treatment for elevated triglycerides
4	Waist circumference > 88cms
5	Blood pressure >130/85mmHg or drug treatment for hypertension.

METABOLIC ABNORMALITIES

Metabolism of carbohydrates, proteins, lipid, amino acid and purines are disturbed in PCOS.¹³ This leads to a range of metabolic abnormalities in PCOS women. The pathogenesis of metabolic syndrome is influenced by both genetic and life style factors.¹⁴ The prevalence of metabolic syndrome varies in different regions of the world based on age, race, gender, ethnicity and the different criteria that are used to diagnose.¹⁵

DIABETES

Insulin resistance plays an important role in the development of diabetes mellitus in PCOS women due to the release of excessive free fatty acids. This is due to defect in post receptor signalling pathway associated with auto phosphorylation of the insulin receptor.¹⁶ Free fatty acids are toxic to beta cells of pancreas leading to decrease in the insulin secretion. The risk of diabetes is increased by 5 folds in women with Polycystic ovarian syndrome.⁷ A threefold increase in risk for gestational diabetes has been shown by a meta-analysis. Carbohydrate metabolism is also affected in PCOS contributing to the development of diabetes.¹⁷

DYSLIPIDEMIA

Dyslipidemia is one of the common abnormalities in PCOS women. Decrease in HDL and increase in triglycerides are the common abnormalities noted in

metabolic syndrome. Recent studies have shown that mild hypercholesterolemia has been noted in most of the women with PCOS. Insulin resistance in the adipocytes causes shunting of free fatty acids to the liver which in turn causes production of more VLDL (very high density lipoproteins) in the liver leading to lipid abnormalities and atherogenic dyslipidemia. PCOS also leads to release of inflammatory mediators like cytokines and tumour necrosis factor α which inactivates the insulin receptors in the adipose cells. This inhibits the adiponectin release and increases the lipolysis causing release of excessive free fatty acids.¹⁸

HYPERTENSION

The occurrence of hypertension in PCOS is still not clear. But few studies have shown the association between PCOS and hypertension.¹⁹ Excess production of free fatty acids due to insulin resistance causes vasoconstriction and decrease in insulin production causes loss of vasodilatation effect contributing to the development of hypertension. Alteration in the renin angiotensin aldosterone system also causes endothelial dysfunction and results in hypertension. Angiotensin II that is produced by the adipose tissue activates NADP (nicotinamide adenine dinucleotide phosphate) and releases reactive oxygen species (ROS). This ROS causes endothelial injury, platelet aggregation and fibroblast proliferation causing hypertension.²⁰

CARDIO METABOLIC RISKS

The risk of coronary artery disease and stroke are increased two fold in PCOS women.²¹ Various echocardiographic studies have shown that PCOS women have abnormal myocardial function with increased left ventricular mass and increased left ventricular stiffness. Hyperandrogenism has proven to be associated with cardio metabolic risks in PCOS women. Activation of inflammatory mediators, neuro-hormonal involvement and insulin resistance are the common causes of metabolic syndrome progressing to cardiovascular disease. Obesity increases the Leptin levels and thereby increases the cardiovascular risks. Adiponectin which is a protective factor against diabetes and hypertension is decreased in PCOS due to increase in adipose tissue mass. Fat cells release inflammatory cytokines which also plays a role in the development of cardiovascular risk.²²

VASCULAR RISKS

Increased arterial stiffness has been noted in women with PCOS.²³ Micro vascular and macro vascular endothelial dysfunction leads to atherosclerosis in PCOS women. But the vascular risks are mostly associated with insulin resistance rather than PCOS as such. Interleukin 6 is a cytokine produced by adipocytes and it leads to release of acute phase reactants in the hepatic cells like C-reactive protein (CRP). This increases the fibrinogen levels and causes a prothrombic state. Fibrinolysis inhibitor levels

are also increased causing hypo fibrinolysis in women with polycystic ovary syndrome and leads to atherosclerosis. Coagulation factors like thrombomodulin, Von Willibrands factor, factor VII C, D-dimer and fibrinogen are increased in PCOS. Obesity and insulin resistance results in systemic oxidative stress leading to tissue fibrosis and decreased atherogenic properties.²⁴

SCREENING FOR CARDIO METABOLIC RISKS

All the women with PCOS should be screened for cardio metabolic risks as the long term complications are life threatening. At the time of initial diagnosis of PCOS, OGTT (oral glucose tolerance test) with 75-g glucose should be done. Fasting glucose and HbA1c can be considered when OGTT is not feasible. Fasting lipid profile also should be done at the first visit. If the values are normal, annual screening for high risk women and every three to five years once in those women without any other associated risk factors should be carried out.²⁵

MANAGEMENT OF METABOLIC SYNDROME

Clinicians should also focus on managing metabolic abnormalities apart from treating PCOS alone as the incidence of metabolic abnormalities is on the rise. Management of metabolic syndrome should include both lifestyle modifications and pharmacological interventions.

Lifestyle modifications should include weight reduction of at least 5 to 10%. Few studies have shown that a decrease in weight of about 5–10% shows an improvement in the metabolic risk. Weight reduction also significantly reduces the risk of cardiovascular diseases and diabetes. Aerobic exercises should be advised earlier for women with PCOS. Diet having low glycaemic value and low fat diet should be advised. They should be encouraged to take legumes and fish as it has omega fatty acids which help in decreasing the metabolic risks.²⁶

Pharmacological interventions include Statins which is used to treat dyslipidemia by decreasing the oxidative stress, inflammation, hyper androgenemia and other metabolic derangements. Antiplatelet drugs are used to decrease the prothrombotic risks. Insulin sensitizers like metformin improves the insulin sensitivity and decreases the risk of diabetes. Anti-obesity agents like orlistat can be used to enhance the weight reduction. Bariatric surgery is the last resort in weight reduction and it helps in restoring the hypothalamic pituitary ovarian axis thus correcting the PCOS pathology and its metabolic side effects.²⁷ Nicotinic acid and Vitamin D therapy are also shown to decrease the cardiovascular risks but these are still under research. Various natural agents like omega fatty acids (fish oil), broccoli, cardamom, fenugreek, cinnamon, grapes, ginger and onions are also shown to decrease the metabolic risks but these are used only as adjuvants.²⁸

CONCLUSION

PCOS women are at increased risk of developing cardiovascular diseases, diabetes mellitus, metabolic abnormalities, reproductive problems and psychological disturbances affecting their daily life. Late complications of metabolic syndrome should be kept in mind at the time of initial diagnosis of PCOS and screening should be done for cardio metabolic risks and diabetes mellitus. Early screening, timely intervention and proper management will prevent several long term complications of metabolic syndrome.

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