Polycystic Ovary Syndrome (PCOS) Transition at Menopause

Polycystic ovary syndrome (PCOS) is the most common gynecological endocrinopathy of reproductive age, with a prevalence that ranges from 2% to 15%.[1] The majority are diagnosed in adolescence and early reproductive years either because of cosmetic concerns such as acne, hirsutism or cycle irregularity, weight gain, and infertility. However, the serious health conditions such as obesity and type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, metabolic syndrome (Met S), depression, anxiety, obstructive sleep apnea (OSA), nonalcoholic fatty liver disease, and even endometrial cancer occur or continue well beyond reproductive years into their menopause.[2] For those whose diagnosis has been missed till menopause, identification postmenopause becomes difficult because of the lack of standard criteria. As women with PCOS cross 35 years of age, there is an increase in regular menstrual cycles, decrease in ovarian volume and antral follicle count, and decrease in serum androgen levels. This leads to an amelioration of phenotype and confusion in the diagnosis as a woman approaches her final reproductive years. It is not clear whether this phenotype-amelioration is associated with reduction or increase in other long-term health risks after the menopause. Majority of these women are either not aware of these long-term consequences or are ill-informed about them. As their primary contact, we should be able to provide appropriate counseling, screening, preventive and management options to all PCOS patients in a multi-disciplinary setting irrespective of which indication they first approached us for.

Risk of Type 2 Diabetes Mellitus

Insulin resistance (IR) is defined as a state in which normal concentrations of insulin produce subnormal effects on glucose homeostasis and utilization. Evidence suggests that PCOS and Met S are associated with peripheral IR, and consequent hyperinsulinemia. Obesity, which is common in PCOS and Met S, amplifies the degree of both these abnormalities. IR is present in 65%–80% of PCOS patients, causes early onset hyperglycemia with progression to Type II diabetes and also increases the risk of cardiovascular disease. In the longitudinal Study of Women's Health Across the Nation (SWAN) in the United States, as they went through menopause, those with PCOS had a higher prevalence of impaired glucose tolerance (IGT) compared with control women (25% vs. 9.2%; $P < 0.001$).[3] Multiple studies across different ethnicities and countries collectively demonstrate that the risk of IGT is increased in the reproductive years and the risk of T2DM is increased in perimenopause and beyond in women with PCOS. Although compounded by obesity, studies suggest an obesity-independent association between PCOS had and IGT and T2DM. Based on this independent increased risk, all women with PCOS must be assessed for IR at the outset and then periodically at 1–3 years intervals depending on their individual risk. Keeping in mind the higher risk of T2DM among the South Asian population, it is recommended that this risk should be assessed on an annual basis.

Dyslipidemia

The most prevalent metabolic abnormality in PCOS is dyslipidemia, which is present in 70% of patients. It worsens with aging and obesity and is also a consequence of hyperinsulinemia. Hypertriglyceridemia, elevated low-density lipoprotein (LDL) levels, and low levels of high-density lipoprotein (HDL) predispose to vascular disease and an atherogenic lipid profile. A meta-analysis of 30 studies found higher mean serum LDL-cholesterol, non HDL-cholesterol, and triglyceride levels and lower HDL-cholesterol levels in women with PCOS as compared to the control population.[4] A cross-sectional study of eight cohorts from the Nordic countries compared women with PCOS and control women, including women >39 years of age and reported a higher prevalence of dyslipidemia only in the hyperandrogenic PCOS group after adjusting for body mass index (BMI).[5] There is a paucity of data regarding dyslipidemia in postmenopausal PCOS population. However, there is a strong possibility that premenopausal dyslipidemia in these women continues into menopause.

Hypertension

Hypertension develops due to reduced vascular compliance and endothelial dysfunction. Endothelial dysfunction is proportional to the presence of hyperandrogenemia and IR. Endothelin-1 levels are higher in PCOS patients and correlate positively with free androgen index and negatively with sex hormone-binding globulin. Hyperinsulinemia exerts a hypertrophic effect on the vascular endothelial and smooth muscle cells. There is increased vascular stiffness and a functional defect in the vascular action of insulin in patients with PCOS. IR of the arterial endothelial cells is associated with reduced synthesis of nitric oxide and increased synthesis of vaso-constricting agents.

The Dallas Heart Study reported a higher rate of hypertension in PCOS population compared to the

controls (29.2% vs. 18.8%; $P = 0.03$).[6] In the combined analysis of eight Nordic studies, hyperandrogenic PCOS women >39 years of age had higher risk of hypertension and higher BMI – adjusted systolic blood pressure.[5] There is a higher risk of hypertension beyond menopause in women with PCOS and they need to be adequately counselled and assessed about the same.

Metabolic Syndrome

Met S is a cluster of cardiometabolic abnormalities including central adiposity, hyperglycemia/IR, dyslipidemia, and hypertension. Women with PCOS have a two-fold increased risk of Met S. Menopause increases the incidence of Met S in aging women. There are only a few studies examining the prevalence of MetS in women with PCOS during menopausal transition and some of them do not suggest a higher risk post menopause, while some associate it with hyperandrogenic phenotype only.

Cardio Vascular Risk

The markers for sub-clinical atherosclerosis are carotid intima media thickness and coronary artery calcification (CAC). In the CARDIA cohort, women with PCOS assessed at the age of 45 years had higher mean internal carotid-intima-media thickness than control women.[7] In contrast, in the Rotterdam Study with a mean age 70 years and a follow-up of 12 years, there was no association between presumed PCOS diagnosis and either increased C-IMT or peripheral artery disease.[8] Besides in, women with PCOS in the Dallas Heart Study with a mean age of 40 years showed no difference in the rates of CAC score compared with control women.[6] The jury is still out on whether there is an actual higher risk of subclinical cardiovascular disease and mortality resulting from PCOS beyond menopause.

Anxiety And Depression

Data are scarce as far as postmenopausal anxiety and depression with PCOS is concerned. Analysis of data from the SWAN study with a mean age of 45 years did not find an increased prevalence of high depression scores in women with presumed PCOS compared with control women (29.9% vs. 23.9%; $P = 0.14$).[3]

Obstructive Sleep Apnea

An independent cardiovascular risk factor, OSA is a chronic disorder of partial or complete airway obstruction during sleep which causes hypoxia. Nearly 5% of women with PCOS are affected with OSA. Data are sparse in the postmenopausal population of PCOS. However, a recent Taiwanese study did show an increased risk of OSA in postmenopausal PCOS population.[9]

Cancer

Due to oligomenorrhea and amenorrhea associated with PCOS, there is an unopposed estrogen priming of the endometrium which leads to hyperplasia and cancer and the risk is 2.8-fold. Studies have proved a higher risk of endometrial cancer in PCOS women, but not of ovarian and breast cancers[10-12]

Conclusion

There is robust evidence that PCOS is associated with higher risk of T2DM, hypertension, dyslipidemia, endometrial cancer, and subclinical atherosclerosis. A review done on PCOS and Met S highlights the unhealthy association of the two and emphasizes the importance of early diagnosis, patient education, and long-term follow-up beyond the reproductive age into menopause to prevent the long-term serious comorbidities.[13] Screening for these disorders at the initial contact and periodically thereafter is recommended. Lifestyle modifications, optimization of weight, and incorporation of exercise and healthy eating into basic lifestyle are the mainstay of first-line treatment for the majority of these comorbidities. Screening for and early diagnosis and treatment of various components of Met S may go a long way in the prevention of development of full-blown Met S. We must have large prospective cohort studies across different ethnicities on PCOS women from their early reproductive years well into and beyond menopause to assess the association with different phenotypes and study the end points. All women with PCOS have a right to know about the syndrome beyond their menstrual, cosmetic, and reproductive concerns.

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