Editorial

Polycystic ovary syndrome – A metabolic malady, the mother of all lifestyle disorders in women – Can Indian health budget tackle it in future?

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Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in women of reproductive age, and its prevalence is estimated to be 4–8% in studies performed in Greece, Spain and the USA.[1,2] The prevalence of PCOS is increasing the world over and is showing a galloping increase in parallel with the rising prevalence of type 2 diabetes mellitus (T2DM). Use of different diagnostic criteria may partly account for it, as has recently been shown (18%) in the first community-based prevalence study based on current Rotterdam diagnostic criteria.[3] PCOS has also been noted to affect 28% of unselected obese and 5% of lean women. In 2006, based on US data and traditionally lower prevalence estimates, the anticipated economic burden of PCOS in Australia was AU$400 million (menstrual dysfunction 31%, infertility 12% and PCOS-associated diabetes 40% of total costs), representing a major health and economic burden.[4] With regards to fertility, the estimated cost per birth in overweight women with PCOS is high. Although there are no systemic studies from India, the observations by endocrinologists, gynecologists, dermatologists, etc. show a significant rise. The health budget of India is thus unlikely to meet the costs posed to impose lifestyle intervention comprising dietary, exercise and behavioral therapy, tackling fertility, cosmesis, metabolic consequences like glucose intolerance, dyslipidemia, nonalcoholic steatohepatitis, coronary artery disease and consequences thereof.

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Although the exact pathophysiology of PCOS is complex and remains largely unclear, the underlying hormonal imbalance created by a combination of increased androgens and/or serum insulin levels seems to be a central focus. Genetic and environmental contributors along with other factors, including obesity, ovarian dysfunction and hypothalamic pituitary abnormalities, complicate the pathogenic cycle.[5] Probably, the lack of ideal methods to quantitate either hyperandrogenism or insulin resistance has posed a significant impediment to understanding the pathophysiology of this potentially dangerous condition. Insulin resistance is a pathophysiological contributor in around 50–80% of women with PCOS, especially in those with more severe PCOS diagnosed on the basis of National Institutes of Health criteria and in women who are overweight. Insulin resistance contributes not only to metabolic features but also to reproductive features through augmenting androgen production and increasing free androgens by reducing sex hormone binding globulin (SHBG). Obesity increases hyperandrogenism, hirsutism, infertility and pregnancy complications both independently and by exacerbating PCOS. Furthermore, women with PCOS have increased risk factors for T2DM, cardiovascular disease (CVD), impaired glucose tolerance (IGT), and potentially some malignancies. Conversely, lean women and women with milder PCOS diagnosed on newer Rotterdam 2003 criteria appear to have less severe hyperinsulinemia and insulin resistance.

Pathogenesis of PCOS being unclear at the moment, invites many hypotheses. Mechanisms involved in insulin resistance are likely to be complex with genetic and environmental contributors. Specific abnormalities of insulin metabolism identified in PCOS include reductions in secretion,[6] reduced hepatic extraction, impaired suppression of hepatic gluconeogenesis and abnormalities in insulin

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receptor signaling. Interestingly, there is a paradoxical expression of insulin resistance in PCOS whereby insulin-stimulated androgen production persists while its role in glucose metabolism is impaired. Therefore, insulin resistance in PCOS results in hyperinsulinemia with its associated diverse and complex effects on regulating lipid metabolism, protein synthesis and modulation of androgen production. The cause of insulin resistance is likewise complex and multifactorial with genetic and environmental contributors. Lean women with PCOS often, but not always, have abnormalities of insulin secretion and action compared to weight-matched control subjects. Where a woman with PCOS is overweight, she may also demonstrate extrinsic insulin resistance associated with adiposity, which is potentially mechanistically distinct from the insulin resistance present in lean women with PCOS.[7] In women with insulin resistance and PCOS, only a subgroup develops coexistent pancreatic insufficiency with β cell failure and go on to develop T2DM. Women with PCOS also develop abnormal glucose metabolism at a younger age and may demonstrate a more rapid conversion from IGT to T2DM. Women with PCOS also have higher gestational diabetes risk independent of and exacerbated by obesity. IGT has been found to increase the risk of CVD, mortality and progression to T2DM in general populations. Recent population-based data revealed a mortality rate of 5.5% over 5 years for those with IGT versus 1.9% for those with normal glucose tolerance.[8] We earlier studied 168 young women who qualified NICHHD consensus conference criteria for PCOS. Thirty-six percent of PCOS women had IGT and 9% had diabetes with WHO 1999 criteria. With the application of ADA 1997 criteria, the estimation was impaired impaired fasting glucose (IFG) in 15% and T2DM in 3%. Higher body mass index (BMI) and hyperandrogenism was directly correlated with the severity of glucose intolerance. Family history of known diabetes was present in 42.85% subjects and when correlated with oral glucose tolerance test (OGTT) abnormality, it showed no significant correlation, although a rising trend was seen in plasma glucose and plasma insulin levels in subjects with family history of DM in first- and second-degree relatives.[9] There are currently no generic guidelines for IGT screening, except for DM2 based on fasting glucose or more recently on HbA1c as a first line. However, impaired fasting glucose is a poor predictor of IGT in women in general and in women with PCOS. Hence, the ESHRE/ASRM Group recommends an OGTT in all overweight women with PCOS. Furthermore, emerging data show increased risk of metabolic complications in first-degree family members of women with PCOS. Dyslipidemia is common in PCOS women compared to weight-matched controls, with higher triglycerides and lower high-density lipoprotein cholesterol. The causes of dyslipidemia in PCOS are again multifactorial. Insulin resistance appears to have a pivotal role mediated in part by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase. The dyslipidemia occurs independent of BMI; however, there is a synergistic deleterious effect of obesity and insulin resistance. Besides insulin resistance, metabolic syndrome (MS), IGT and T2DM, dyslipidemia women with PCOS also have increased novel cardiovascular risk factors (inflammation, oxidative stress and impaired fibrinolysis) and increased early clinical and subclinical markers of atherosclerosis (endothelial dysfunction, impaired pulse wave velocity, increased carotid intima media wall thickness, presence of carotid plaque and increased coronary artery calcification). There is currently a lack of long-term studies in PCOS to appropriately address CVD risk and data are conflicting.[10] MS has been found to be in 43% which is nearly twofold higher than that reported for age-matched women in the general population by Apridonidze *et al.*, and in 58.5% Sri Lankan women with PCOS, although Carmina *et al.* showed much lower prevalence (8.2–16%) in Italian subjects. Our observation on Indian women with PCOS showed grossly increased prevalence of MS (47.1% by IDF and 50% by WHO criteria) as opposed to 20–30% in non-PCOS Indians data by Misra *et al.* and Deepa *et al.*[11]

Many women with PCOS demonstrate challenges to feminine identity and body image due to obesity, acne and excess hair; also, infertility and long-term health-related concerns compromise the quality of life and adversely impact on mood and psychological well-being. Some authors have shown that women who have PCOS are more prone to depression, anxiety, low self-esteem, negative body image, and psychosexual dysfunction.[12] The other important aspect of psychosocial impact in PCOS is the negative impact of mood disturbance, poor self-esteem and reduced psychological well-being on motivation and on ability to implement and sustain successful lifestyle changes that are critical in this condition.

Management of PCOS is difficult and involves multispecialty approach. Lifestyle change is the first-line treatment in the management of the majority of PCOS women who are overweight, and weight gain should be emphasized in all women with PCOS of normal or increased body weight. Evidence shows that lifestyle change with as little as 5–10% weight loss has significant clinical benefits improving psychological outcomes,[13] reproductive features (menstrual cyclicity, ovulation and fertility) and metabolic features (insulin resistance and risk factors for CVD and T2DM). Standard dietary therapy is a nutritionally adequate, low-fat (approximately 30% of energy, saturated fat approximately 10%), moderate-protein (approximately 15%) and high-

carbohydrate dietary intake (approximately 55%), with increased fiber-rich wholegrain breads, cereals, fruits and vegetables and moderate regular exercise. Fad diets are not encouraged as short-term weight loss, if achieved, is rarely sustainable. Awaiting the full understanding, there is currently no ideal medical therapy for women with PCOS that fully reverses the underlying hormonal disturbances and treats all clinical features. The oral contraceptive pills (OCP) does improve hyperandrogenism, and insulin sensitizers (primarily metformin) reduce insulin resistance in PCOS.[14] Generally, medical therapy is targeted to symptoms and should not be used as an alternative to lifestyle therapy in PCOS. There has been concerning data that the OCP can increase insulin resistance and worsen glucose tolerance. Metformin alone or in combination has had an increasing role in PCOS management, improving the clinical features (ovulation, cycle regulation, and potentially hirsutism) with positive cardiometabolic effects.[15] It is important to note that neither metformin nor the OCP is approved by most regulatory authorities specifically for PCOS, although both treatments are recommended by international and national endocrine societies.

In conclusion, PCOS is a frustrating experience for women, often complex for managing clinicians and is a scientific challenge for researchers. As research in PCOS is rapidly advancing, it is vital that research evidence is translated to knowledge and action among women, healthcare professionals and policymakers. Lifestyle modification and insulin sensitizers are the backbone of treatment, especially for correcting the metabolic derangements. The screening for other metabolic conditions may be also warranted in relatives of women with PCOS, although this requires further research. India, being the diabetic capital of the world, has close relation to PCOS–MS continuum and policymakers should get alarmed to the existence of this metabolic malady and prevent the birth of the consequent disorders.

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