

PCOS - Syndrome XX or sex-limited metabolic syndrome

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Metabolic syndrome variously called as insulin resistance syndrome (IRS), Reaven's Syndrome, or syndrome X is a cluster of traits including hyper-insulinemia, dyslipidemia, hypertension and obesity, is associated with significantly increased risk of cardiovascular and all-cause mortality(1). Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting women in their reproductive years and has many metabolic constellations similar to IRS. PCOS was first reported in 1935 by Stein and Leventhal(2) as amenorrhea and polycystic ovaries but now the disorder is considered to have a wide clinical spectrum. Although many metabolic disorders manifest in women with PCOS, the degree of expression is highly variable between individuals(3). Among the metabolic disorders obesity, hyperlipidemia, hyperinsulinemia, insulin resistance and impaired beta cell insulin secretion and type 2 diabetes are common in addition to increased cardiovascular disease risk factors and possibly breast and endometrial cancer. Among these most common epidemiologically are obesity, insulin resistance, and glucose tolerance abnormality(4-6). Hyperinsulinemia secondary to poorly characterized disorder of insulin action is a documented feature of PCOS(7). Obesity in subjects with PCOS appears to have a synergistic deleterious effect on glucose homeostasis and predispose them to increase risk of development of frank type 2 diabetes(8).

IRS and PCOS etiopathogenically undefined disorders with many common dysmetabolic features are currently considered different disorders and have strict respective definitions. In 1990 a consensus was reached regarding the definition of PCOS in NIH/NICHHD sponsored conference and the diagnostic criteria were established(9), which include 1) ovulatory dysfunction 2) clinical / biochemical evidence of hyperandrogenism and 3) exclusion of related disorders, such as hyperprolactinemia,

thyroid disorders, non-classical adrenal hyperplasia and drugs causing either disorder. Since the adoption of the consensus on the diagnosis of PCOS, most of the epidemiological studies have been based on these diagnostic criteria. The 2003 Rotterdam criteria for PCOS, however, included polycystic ovary morphology as one of the criteria(10). Insulin resistance means reduced ability of insulin to control the processing of glucose by the body. Using the "euglycemic clamp technique" Hollenbeck and Reaven observed a two and half fold difference in the mean insulin sensitivity between subjects in the most sensitive compared to the least sensitive quartile(11). At the first world congress on the IRS held at Los Angeles in November 2003, varieties of definitions of insulin resistance syndrome were discussed and are presented below:

- a) The Adult Treatment Panel (ATP) III: The presence of three of the following factors defines a person as having the metabolic syndrome: waist circumference of >102cms in men and > 88 in women; serum triglyceride level of >150 mg/dl; high density lipoprotein cholesterol of < 40 mg/dl in men and < 50 mg/dl in women; blood pressure of >135/>85 mmHg; fasting plasma glucose of >110 mg/dl(12).
- b) The American Association of Clinical Endocrinologists: recognizes a person to have insulin resistance syndrome when he or she has at least one of i) diagnosis of cardiovascular disease, hypertension, polycystic ovarian syndrome, nonalcoholic fatty liver disease or acanthosis nigricans, ii) family history of type 2 diabetes, hypertension, or cardiovascular disease, iii) history of gestational diabetes or glucose intolerance, iv) non-Caucasian ethnicity) sedentary life style, vi) body mass index of > 25 kg/m² or waist circumference of > 102cms in men and 88 cms in women and vii) age > 40 years, together with at least two of i) serum triglycerides

- > 150 mg/dl, ii) HDL cholesterol < 40 mg/dl, iii) blood pressure > 130/85 and iv) fasting blood glucose of 100-125 mg/dl or 2 hour post glucose challenge value of 140-200 mg/dl(13).
- c) The European group for the study of insulin resistance (EGIR): characterizes any individual to have the insulin resistance syndrome if he or she has fasting insulin levels in the highest 25 centiles together with any two of i) fasting plasma glucose of > 6.1mmol/L (excluding diabetes), ii) blood pressure of > 140/90 mmHg or history of being treated for hypertension, iii) plasma triglyceride level of > 2mmol/L or HDL of < 1.0 mmol/L or history of being treated for dyslipidaemia, and iv) waist circumference of > 94 cms in men and > 80 cms in women(14).

The WHO defines metabolic syndrome as presence of diabetes mellitus, impaired fasting glucose, impaired glucose tolerance or homeostasis model assessment (HOMA) insulin resistance together with any two of i) waist-hip ratio of > 0.9 in men and 0.85 in women ii) serum triglyceride level of >150 mg/dl or HDL-cholesterol <35 mg/dl in men and <39mg/dl in women iii) urinary albumin excretion rate of > 20 µg/minute and iv) blood pressure of >140/90 mmHg(15).

By ATP III(12), the National Health & Nutrition Examination Survey III, estimated that 22% of the US adults (~ 47 million people) had IRS in 1988-1994(16): although the prevalence was highest in the 60-69 years age group, disturbingly it was found to be 5-10% among those aged 20-29 years. There are large ethnic differences in prevalence of insulin resistance which underlie the disparate prevalence of type 2 diabetes in different ethnic group(16). Recently the evaluation of the prevalence of cardiovascular morbidity and mortality associated with metabolic syndrome as defined by WHO(17) in 4000 high risk Scandinavians revealed that metabolic syndrome was present in approximately 10% of subjects with normal glucose tolerance, 50% of those with impaired glucose tolerance, and 80% of patients with type 2 diabetes(18); subjects with the syndrome had a three fold increased risk of coronary heart disease and stroke and their cardiovascular mortality was markedly increased (12% vs. 2.2%) underscoring the importance of identification, risk assessment and treatment of patients with the syndrome.

Since MS and the PCOS have a significant overlap in the derangements, various researchers have tried estimate the prevalence of one disorder in the other or vice versa. Reviews have been written on the existing data regarding the prevalence, characteristics, and treatment of the metabolic syndrome in women with PCOS(19). The prevalence of the metabolic syndrome in PCOS is approximately 43-47%, a rate 2-fold higher than that for women in the general population. In indigenous Sri Lankan PCOS women 3 years postpartum MS was shown to be significantly higher in those with previous GDM compared with ethnically matched controls confirming association between GDM and

subsequent PCOS and MS (20). In one study 51 hirsute PCOS patients and 63 weight-matched female controls significantly lower adiponectin levels were demonstrated in addition to other risk factors for the metabolic syndrome. Furthermore, ghrelin levels showed negative correlation with testosterone independent of body composition(21).

An observational study conducted on four subgroups of subjects with PCOS defined by 1) irregular menses (IM), hyperandrogenism (HA), and polycystic ovary morphology (PCOM, n = 298); 2) IM/HA (n = 7); 3) HA/PCOM (n = 77); and 4) IM/PCOM (n = 36) and a group of controls (n = 64), aged 18-45 year, were examined. They concluded that the subjects with PCOS defined by IM/HA are the most severely affected women on the basis of androgen levels, ovarian volumes, and insulin levels. Their higher body mass index partially accounts for the increased insulin levels, suggesting that weight gain exacerbates the symptoms of PCOS(22).

Study of mothers of women with PCOS was done to test the hypothesis that dyslipidaemia is a heritable trait in families of women with PCOS. Fasting blood was obtained in 215 non-Hispanic white mothers of women with PCOS and 62 control women. The prevalence of metabolic syndrome was compared with that in non-Hispanic white women of comparable age from the National Health and Nutrition Examination Survey III. Mothers had higher total ($p < 0.001$) and low-density lipoprotein (LDL) cholesterol levels ($p = 0.007$), whereas high-density lipoprotein and triglyceride levels did not differ compared with control women. A history of menstrual irregularity identifies mothers with features of PCOS. Obese mothers have a very high prevalence of metabolic syndrome. These findings suggest that both the reproductive and metabolic abnormalities persist with age in PCOS(23). In a recent study Apridonidze et al conducted a retrospective chart review of all women with PCOS seen over a 3-yr period at an endocrinology clinic. Of the 161 PCOS cases reviewed, 106 met the inclusion criteria. The women were divided into two groups: 1) women with PCOS and the MS (n = 46); and 2) women with PCOS lacking the MS (n = 60). Prevalence of the MS was 43%, nearly 2-fold higher than that reported for age-matched women in the general population. Women with PCOS and the MS had significantly higher levels of serum free testosterone and lower levels of serum SHBG than women with PCOS without the MS. No differences in total testosterone were observed between the groups(24). In another recent study by Rossi B et al in a cross-sectional study of overweight and obese PCOS adolescents and BMI matched controls, 74 subjects (43 with PCOS and 31 controls) they observed that the PCOS group had larger ovarian volume, higher measures of total testosterone and free androgen index than controls, but there were no differences in waist circumference, fasting glucose, blood pressure, or lipids. PCOS adolescents demonstrated more glucose abnormalities and higher PAI-1. By pediatric criteria,

53% of the PCOS and 55% of the control adolescents had MS. By adult criteria 26% of PCOS and 29% of controls met diagnostic criteria for MS. They concluded that the obese adolescent women have a high prevalence of MS, and PCOS does not add additional risk for MS and PCOS is associated with increased incidence of glucose intolerance and increased PAI-1 levels(25).

Our population belongs to an ethnic group where insulin resistance has been demonstrated to be very high(26). Glucose intolerance in North Indian women in the adolescent PCOS has been demonstrated to be very high. The study carried out to estimate the prevalence of glucose intolerance and insulin sensitivity in young women with PCOS examined one hundred sixty eight young women who attended AIIMS endocrine center for hirsutism and / or oligomenorrhea were enrolled for the study. NICHHD consensus conference criteria were used for diagnosis of PCOS. Results indicated higher prevalence glucose intolerance even at younger age in PCOS females. 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 fasting plasma glucose (IFG) in 15% and diabetes in 3%. Higher 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 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(27). In a recent study by our group in adolescent north Indian PCOS girls also showed 50.0%, 47.3% and 23.68% had MS by IDF, WHO, and ATP III criteria respectively. The study comprised of 477 adolescent girls and young women with PCOS diagnosed by NICHHD 1990 criteria and 100 healthy controls whose age ranged from 15 to 29 years (23.55 ± 4.2) in PCOS women as compared age range of 17 to 30 (26.24 ± 8.2) in controls. Mean BMI of study subjects was 23.22 ± 3.92 ($15.2-29.9$) as compared 23.13 ± 3.13 ($17.3-28.8$) in the controls. Diabetes mellitus was diagnosed in twenty-six cases and four controls. Family history of known type 2 DM in a first and second-degree relatives was noted in 153/477 women (32.07%) and 90/477 (18.86%) controls. HOMA values were 1.12 in PCOS subjects and 28.94% had moderate to severe insulin resistance. The conclusion was that the prevalence of MS in adolescent girls and young women with PCOS by IDF, WHO, and ATP III criteria were 50.0%, 47.3% and 23.68% respectively. The ATP III prevalence of MS in controls was estimated to be 16%(28).

In conclusion it appears that various components of MS are universal in PCOS and the prevalence comes to less than 100% since the criteria used depend on existence of many components at a time. The data may support the fact that the PCOS falls somewhere on the trail of spectrum from single metabolic abnormalities to a full blown picture of Syndrome

XX that is why some authors have coined a term of Syndrome XX in place of PCOS(29). The PCOS can be viewed as a sex limited metabolic syndrome.

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