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ORIGINAL ARTICLE *Reproductive endocrinology*

Phenotype and metabolic profile of South Asian women with polycystic ovary syndrome (PCOS): results of a large database from a specialist Endocrine Clinic

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BACKGROUND: Compared with other populations, South Asians have a greater propensity to insulin resistance and the metabolic syndrome (MetS). This is the first study to determine the distribution of phenotypes of polycystic ovary syndrome (PCOS) and their relationship to the MetS among indigenous South Asians.

METHOD: An evaluation of the phenotype and metabolic characteristics of PCOS was conducted by recruiting consecutive women diagnosed by Rotterdam consensus criteria from an Endocrine clinic in Colombo, Sri Lanka. Prevalence of MetS was determined, in relation to the phenotypic subgroup of PCOS and compared with ethnically matched, BMI- and age-adjusted controls ($n = 231$).

RESULTS: Acanthosis nigricans (AN) occurred in 64.6% of women with PCOS ($n = 469$). MetS occurred in 30.6% of the PCOS group compared with 6.34% of controls ($P = 0.0001$). Those with PCOS and MetS had significantly higher median BMI, blood pressure (BP), fasting plasma glucose, insulin and triglycerides and lower high-density lipoprotein and sex hormone-binding globulin (SHBG), but similar testosterone concentrations compared with those with PCOS alone. Prevalence of MetS was similar in the four PCOS phenotypes, although oligomenorrhoeic women were more obese compared with the normal cycling hyperandrogenic group. Multivariate logistic regression confirmed age $\geq$35 years, BMI $\geq$25 kg/m^2 and AN as significant predictors of MetS in PCOS. Case–control comparisons showed that the presence of PCOS results in higher odds of having the MetS, a high waist circumference, elevated diastolic BP, abnormal fasting lipids and high fasting insulin and plasma testosterone concentrations.

CONCLUSIONS: Young indigenous South Asians with PCOS have greater odds of being centrally obese, with a third having the MetS that bears no relationship to the androgenic phenotype. Significant predictors for MetS within the PCOS cohort are advancing age, obesity determined by the Asian cut off (BMI $>$25 kg/m^2) and AN, while family history of diabetes, hyperandrogenism and elevated SHBG have no predictive value.

Key words: polycystic ovary syndrome / phenotypes / South Asians / metabolic syndrome

Introduction

Polycystic ovary syndrome (PCOS) is associated with insulin resistance (IR) and the metabolic syndrome (MetS) (Apridonidze *et al*., 2005; Moran *et al*., 2010). We previously demonstrated that migrant South Asians with anovulatory PCOS have more severe symptoms at a younger age, with greater IR than white Europeans (Wijeyaratne *et al*., 2002, 2004). A recent community survey in Sri Lanka found the prevalence of PCOS as 6.3% among women aged 15–39 (Kumarapeli *et al*., 2008). The manifestations of PCOS are heterogeneous, can change during a woman's lifetime (Franks *et al*., 2006), and can impact on health-related quality of life (Ching *et al*., 2007), as well as on long-term cardiovascular health (Teede *et al*., 2010). Although the revised Rotterdam diagnostic criteria led to some controversy about 'over-diagnosis' of PCOS (Azziz, 2006), there are four possible phenotypes based on the presence of oligo-/anovulation (O), hyperandrogenism (H) and PCO (P): (i) classical (O + H + P), (ii) hyperandrogenic (O + H), (iii) ovulatory (H + P) and (iv) non-hyperandrogenic (O + P) (Shroff *et al*., 2007).

Most reports on MetS are from studies carried out in the West (Apridonidze *et al*., 2005; Shroff *et al*., 2007; Goverde *et al*., 2009) and encompass cardiovascular risks such as hyperlipidaemia, hypertension and diabetes mellitus/pre-diabetes that cause endothelial dysfunction and atherosclerosis (Kressel *et al*., 2009). To the best of our knowledge, there are no reports on the prevalence of MetS among South Asian women with PCOS, nor the distribution of the differing PCOS phenotypes. This study aimed for the first time to identify phenotypic subgroups of PCOS and their relationship to the MetS among a large cohort of indigenous women of South Asian descent seeking specialist endocrine care at a single centre in Sri Lanka.

PCOS is reported from many regions of the world (Franks, 1989; Diamanti-Kandarakis *et al*., 1999; Asuncion *et al*., 2000; Azziz *et al*., 2004) with well recognized ethnic variations in its manifestation. Much of our current knowledge is based on evidence from predominantly white European women. Studies of mixed populations residing in the USA, attempted to identify the Asian ethnic subgroup (Ehrmann *et al*., 2006; Legro *et al*., 2006; Lo *et al*., 2006; Welt *et al*., 2006), although migrant Asians comprised <10% of each cohort without detail of their exact geographic origin from Asia, which is the largest continent and has wide variation between its subgroups e.g. East Asians (Chinese/Japanese), South East Asians (Thai/Malay people) and South Asians (Indians/Sri Lankans). Critical appraisal of the expression of PCOS within a distinct ethnic group requires careful and uniform phenotyping of a sufficiently large and representative sample, to evaluate age of manifestation, metabolic characteristics and link(s) between the androgenic, reproductive and metabolic phenotypes. The link between IR and PCOS is strong and has been identified as an important determinant of its phenotypic manifestations and response to treatment (Salley *et al*., 2007; Shroff *et al*., 2007). Recent data on type 2 diabetes mellitus (T2DM) confirms its greater propensity among young adults of South Asia, which is linked to the epidemiological transition and rapid urbanization occurring in the region (Eapen *et al*., 2009; Misra and Khurana, 2009). In view of our previous comparison of migrant South Asians in the UK with indigenous white Europeans, demonstrating a disparity in the phenotypic expression of PCOS (Wijeyaratne *et al*., 2002), an in-depth study of affected indigenous South Asians could shed better light on this subgroup from Asia, and help disentangle possible confounding effects of migration. Finally, it would enable developing evidence-based and ethnically appropriate management guidelines.

Materials and Methods

Objective and study design

Our aim was to determine the distribution of phenotypes of PCOS and their relationship to the MetS among indigenous South Asians. A descriptive cross-sectional study was used for analysis.

Recruitment of subjects

Consecutive women with PCOS diagnosed by Rotterdam criteria (Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group, 2004), and enrolled at the Endocrine Clinic, of the University Obstetrics and Gynaecology Unit, Colombo, Sri Lanka, from April 2003 to November 2009, were invited to participate. Written informed consent was obtained. Concurrently asymptomatic, non-androgenic, normal cycling, unmedicated, consenting young women in whom PCOS was excluded by biochemical and ultrasound testing, were recruited as controls from the community-based study (170) and from the clinic setting (61). Ethical approval for the study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Colombo.

Inclusion and exclusion criteria

Women with any two of the following were included: oligomenorrhoea/oligo-ovulation (O), clinical or biochemical hyperandrogenism (H) and polycystic ovaries on ultrasound (P). Women excluded from the study were those with inherited disorders of IR such as Rabson–Mendenhall syndrome, Cushing syndrome, hyperprolactinaemia, untreated hypothyroidism, congenital adrenal hyperplasia or with an androgen secreting ovarian/adrenal tumour and those taking corticosteroid, antiepileptic or antipsychotic drugs or hormonal contraception and those currently pregnant or in the first postpartum year.

Definitions

Oligomenorrhoea—absence of menstruation for ≥35 days, amenorrhea—no menstruation for >6 months. Clinical hyperandrogenism—modified Ferriman–Gallwey (FG) score ≥8 (Ferriman and Gallwey, 1961), with or without acne and/or androgenic alopecia. Hirsutism was scored by studying terminal hair in nine body areas (upper lip, chin, chest, upper and lower abdomen, upper arms, thighs and upper and lower back) using a grading scale from 0 to 4, and the scores in each area were summed. Terminal hair was defined as pigmented, coarse and longer than 5 mm. Those who had undergone shaving/laser therapy were requested to recall the density of growth. The occurrence of acne was recorded by area(s) of distribution and degree of affection with lesions (comedones, papules, pustules, nodules, abscesses, cysts and scars) categorized simply as mild, moderate and severe.

Acanthosis nigricans (AN)—velvety, dark, skin thickening on the neck, axillae and other sites such as face, chest and knuckles were recorded; we excluded evaluating groin and vulva (due to a common difficulty in clinical differentiation from intertrigo).

All subjects were examined by a single trained endocrinologist (C.N.W.). Co-investigators were trained under the guidance of C.N.W. to help standardize the recognition of skin manifestations such as hirsutism and acne. Reliability was assessed by calculating the inter rate agreement (kappa). Agreement between co-investigators and the consultant Endocrinologist were satisfactory (Cohen's $\kappa = 0.89$).

Biochemical hyperandrogenism—plasma testosterone >90th centile of normal Sri Lankan women of reproductive age.

Polycystic ovaries (PCOs)—ovarian volume >10 cm^3 and/or ≥12 of 2–9 mm follicles in a single ovary by ultrasonography performed within 1 week of last menses (Balen *et al*., 2003).

MetS defined by National Cholesterol Education Program's Adult Treatment Panel III [NCEP (ATP III)] report—presence of three or more of the following risk factors: waist circumference (WC) ≥88 cm, hypertension ≥130/85 Hgmm, fasting plasma glucose (FPG) ≥6.1 mmol/l, triglyceride (TG) ≥1.7 mmol/l and high-density lipoprotein (HDL) <1.3 mmol/l. (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The International Diabetes Federation (IDF) definition of MetS includes the presence of central obesity WC ≥80 cm, with any two of the following: hypertension ≥130/85 Hgmm, FPG ≥5.6 mmol/l, TG ≥1.7 mmol/l and HDL <1.3 mmol/l (Alberti *et al*., 2005).

Data collection

Baseline clinical, biochemical and ultrasound data prior to specific metabolic management were obtained. Those with concurrent subclinical hypothyroidism were included in this analysis, provided they continued to have features of PCOS despite adequate thyroxin replacement (normal thyroid biochemistry) for a minimum of 6 months.

Clinical evaluation

The clinical evaluation first involved a questionnaire-based interview regarding: socio-demographic factors, detailed menstrual and obstetric histories, infertility if relevant, the onset and degree of clinical symptoms of PCOS, drug history, family history of diabetes and other cardiovascular risk factors.

Secondly there was a physical examination of BMI, WC and waist-to-hip ratio (WHR), resting blood pressure (BP) [systolic BP (SBP), diastolic BP (DBP)], hirsutism, frontal balding and distribution of acne and AN. Transabdominal ultrasound examinations, in unmarried women, and transvaginal ultrasounds, in married women, were performed by trained medical doctors (N.K. and C.Y.) as per recommendations (Balen *et al*., 2003).

Biochemical and endocrine evaluation

FPG, insulin, lipid profile, testosterone and sex hormone-binding globulin (SHBG) concentrations were determined in all subjects. While the 75 g oral glucose tolerance test (OGTT) was performed since 2005.

Samples were analysed at the Reproductive Biology and Endocrinology Laboratory, Department of Obstetrics and Gynaecology, Faculty of Medicine in Colombo, using the following techniques: plasma glucose—enzymatic colorimetric assay (Hitachi, Roche), plasma insulin and SHBG—immunometric assay (IMMULITE, Diagnostic Products Corporation, Los Angeles, CA, USA), total testosterone—after organic extraction using immunometric assay (IMMULITE, Diagnostic Products Corporation), and plasma lipids (cholesterol, TGs and HDL)—an enzymatic colorimetric assay (Hitachi, Roche). Laboratory controls were used to monitor accuracy and precision of the analyser, reagents and assay results. Inter- and intra-assay precision checks demonstrated coefficient of variation of 4.8 and 6.9% for plasma glucose, 6.7 and 3.8% for cholesterol, 1.9 and 2.5% for insulin, 3.8 and 3.1% for SHBG and 5.4 and 4.3% for testosterone.

Calculations and data analysis

BMI = weight/height^2 kg/m^2; IR = homeostasis model assessment (HOMA2-IR) (HOMA calculator, Oxford University, 2004). Free androgen index = (testosterone/SHBG) × 100. MetS was determined by NCEP (ATP III) criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) and was used for all analyses and comparisons. The IDF definition (Alberti *et al*., 2005) was applied to compare with the NCEP diagnosis.

Statistical analysis was performed using the computer program Statistical Package for Social Sciences (SPSS® 13.0). The Kolmogorov–Smirnov test was used for normality of distribution for all variables. Age and WC had normal distribution while other variables were skewed. Therefore all data were reported as median and inter-quartile range (IQR).

Prevalence of demographic, clinical and metabolic variables was assessed among women with PCOS. Those with and without MetS were compared for differences in demographic, clinical and metabolic variables. Continuous data were compared by performing Mann–Whitney *U*-test for two medians and categorical data was analysed by performing the χ^2 test. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for selected variables and their significance tested. Comparison of medians between PCOS phenotypes was performed by the non-parametric Kruskal–Wallis test.

A multiple logistic regression (MLR) model was used to test the association between MetS and several potential risk factors. The dependant variable was measured as a binary variable and coded as MetS present = 1 and MetS absent = 0. All predictor variables were included as categorical data. Each predictor variable was stratified into two levels, and the first level was taken as the reference for comparison.

Selection of the variables for the model was based on published literature and those found to be significant in the univariate analysis ($P < 0.05$). Some predictors were also included irrespective of their significance in univariate analysis as they had been identified as important in the literature. The regression model was estimated by carrying out stepwise backward logistic regression. Probability for stepwise backward logistic regression was fixed for entry at level of significance 0.1 and removed at the 0.1 level. Likelihood ratio was used to determine the variables that were retained in the model. Goodness-of-fit of the model was indicated by overall percentage of the predictions that were correctly classified by observed outcomes. Variables selected for the model were: age ≥35 years, oligomenorrhoea since menarche, family history of T2DM, pre-existing diabetes mellitus, presence of acanthosis, BMI ≥25 kg/m^2, hyperinsulinaemia (fasting insulin ≥103.5 pmol/l, 90th centile of controls), high testosterone (≥3.0 nmol/l, 90th centile of controls) and low SHBG (≤12.8 nmol/l, 10th centile of controls). Model χ^2 was 76.23, ($P = 0.0001$), the percentage correctly identified was 22%.

We also performed MLR analysis with both PCOS and control groups to adjust for differences in age and BMI. The dependent variable was measured as a binary variable and coded as PCOS present = 1 and PCOS absent = 0. Age and BMI were included in the model as covariates and were entered as continuous variables. All other predictor variables were included as categorical data, with each predictor stratified into two levels, and the first level taken as the reference for comparison.

Selection of variables for the model was based on those considered important in the literature. The regression model was estimated by carrying out stepwise backward logistic regression. Probability for stepwise backward logistic regression was fixed for entry at 0.1 and removed at 0.1 significance level. The likelihood ratio was used to determine the variables that were retained in the model. Goodness-of-fit of the model indicated the overall percentage of the predictions that were correctly classified by observed outcomes. The variables included in the model were, presence of MetS, WC ≥88 cm, SBP ≥130 mmHg, DBP ≥85 mmHg, FPG ≥6.1 mmol/l, TG≥1.7 mmol/l, HDL <1.3 mmol/l, LDL cholesterol ≥3.9 mmol/l, hyperinsulinaemia, high testosterone and low SHBG. The model χ^2 was 346.99 ($P = 0.0001$), and the percentage correctly identified was 55.7%.

Results

Socio-demographic characteristics

The study included a total of 469 PCOS patients and 231 controls. The racial distribution of the PCOS group was: Sinhalese (86.1%), Muslim/Moors (8.1%), Sri Lankan Tamils (3.8%) and the remainder were Dutch–Burghers. The median age was 25 years (IQR = 9). The controls had similar racial distribution with a median age of 29 (IQR = 13) years.

Oligo/amenorrhoea

Among 433 (92.32%) patients with irregular menses, complete information was available for 426, of whom 211 (49.5%) had oligo/amenorrhoea since menarche and 215 (50.5%) developed it at median age of 19 (IQR = 7) years. There were 36 women with PCOS (7.7%) who had regular cycles. The median longest and shortest cycles were 90 (IQR = 108) and 28 (IQR = 7) days, respectively and the median number of cycles was 6 (IQR = 4) per year.

Hyperandrogenism

Hirsutism occurred in 374 patients (79.7%) and developed at a median age of 17 (IQR = 8) years. Of the PCOS patients, 341 (74.6%) had significant hirsutism (FG ≥8) with a median FG score of 10 (IQR = 5). Acne was present in 184 (39.2%) patients, with common sites being the face (173, 36.9%), anterior chest (60, 12.8%) and back of chest (40, 8.5%).

Infertility

The majority (281, 59.9%) of PCOS patients were unmarried and two were divorced. Of the 188 married women, 68.2% were infertile at a median age of 30 (IQR = 7) years, and 38.3% of these had not sought any medical assistance. The median period of treatment was 4 (IQR = 4) years with clomiphene citrate (46, 43.4%) and/or laparoscopic ovarian drilling (LOD) (32, 30.2%). Those who had undergone LOD had remained infertile after drilling for a median period of 18 months and were also clomiphene resistant. None had received specific metabolic treatment prior to enrolment in this study.

Metabolic features

The distribution of metabolic features among women with PCOS (n = 469) are depicted in Fig. 1.

A family history of T2DM in a first-degree relative was present in 215 (48%) among 446 with reliable information. There were 40 (18.6%) with more than one affected family member. There were 14 (median age 29.5 years) who had previously confirmed T2DM and 12 had pre-existing hypertension, with two having both. The median values for anthropometric measurements among PCOS patients were: BMI = 25.0 (IQR = 6.67) kg/m^2, WC = 87.00 (IQR = 20.75) cm and WHR = 0.87 (IQR = 0.13). AN was present in 303 (64.6%) patients.

Biochemistry

Figure 2 shows the baseline median values of FPG, second hour value of the OGTT and fasting lipid values of the women with PCOS (n = 469). Median values of endocrine and other metabolic parameters were: testosterone 2.93 (IQR 2.25) nmol/l, SHBG 26.4 (IQR 23.05) nmol/l with FAI 10.99 (IQR 15.01); FPG 4.85 (IQR 1.16) mmol/l, 2 h OGTT 6.55 (IQR 2.69) mmol/l, fasting insulin 84.03 (IQR 84.38) pmol/l and HOMA2-IR 1.80 (IQR 1.775). The fasting glucose: insulin ratio was 7.33 (IQR7.15) with G/I ratio <4.5 suggesting IR in 25.3%. A TG/HDL ratio >3.3 was found in 112 (27.93%) patients.

In addition to the 14 (3%) with PCOS and T2DM, this study found an impaired fasting glucose (IFG) (FBG 5.6–6.9 mmol/l) in 64 (13.9%) patients and in diabetic range (FBG ≥7 mmol/l) in another 20 (4.2%) (American Diabetes Association, 2005). Among 226 (48%) screened by OGTT, impaired glucose tolerance (IGT) was detected in 54 (23.8%) and diabetes was detected in 12 (5.38%). The number newly diagnosed as T2DM with PCOS was 27 [by both FPG and 2 h OGTT 5, by FPG alone 15 (among those who did not undergo OGTT), and by abnormal 2 h OGTT only 7 (Fig. 3)].

Ovarian ultrasound

All patients underwent ultrasonography, of whom 387 (82.5%) had PCO by the Rotterdam criteria. Among 204 patients who had detailed baseline ultrasound scanning (transabdominal in 124; transvaginal in 80), the median ovarian volumes were 11.37 (IQR 8.97) and 7.86 (IQR 5.98) cm^3 in the right and left ovaries respectively with PCO present in 167 (81.86%) patients. PCO was present in 30 of 172 (17.4%) control subjects.

Co-morbidities/differential diagnoses

Primary hypothyroidism of autoimmune origin co-existed with PCOS in 28 (5.97%) patients, with their PCOS features unaltered despite adequate thyroxin replacement for 6 months.

The following (n = 11) were excluded from the suspected PCOS group in the clinic during the reported study period: Cushing syndrome 4 (with one having an adrenocorticotrophic hormone secreting pituitary macroadenoma), non-classical congenital adrenal hyperplasia 5, undetected Turner syndrome with gonadoblastoma 1 and a malignant adrenal tumour 1.

Metabolic syndrome

Complete data for NCEP-ATP III criteria was available in 395 (84.2%) patients with PCOS; of whom 121 (30.6%) fulfilled 3 out of 5 diagnostic criteria; while another 227 (57.5%) fulfilled 2 criteria. Complete data for IDF criteria were available in 390 (83.1%); of whom 139 (35.6%) had MetS. Among 205 controls 13 (6.34%) had MetS (NCEP-ATP III) (χ^2 = 46.311, Likelihood ratio = 54.1%, P = 0.0001).

Table I compares clinical and metabolic characteristics of PCOS based on the presence of MetS. Median ages of those detected by NCEP and IDF criteria were similar, and did not differ from those without MetS. The MetS subgroup had significantly higher median BMI and, BP and plasma glucose, insulin and TG and significantly lower HDL and SHBG concentrations but similar plasma testosterone levels. The 2 h OGTT value was significantly greater in those with MetS by IDF criteria.

Further comparison (Table II) demonstrated that having MetS with PCOS is associated with greater odds of being older (≥35 years), being globally obese, by Asian and Western cut offs, and being hyperinsulinaemic, with very high odds of central obesity, pre-hypertension/

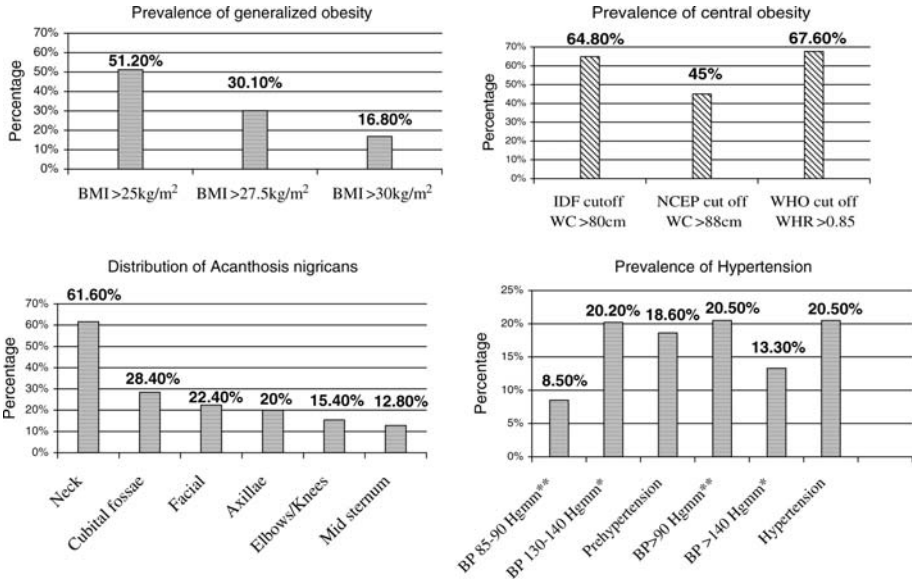

Figure 1 Distribution of metabolic features among women with PCOS ($n = 469$). *SBP, systolic blood pressure; **DBP, diastolic blood pressure; BMI, body mass index (Asian cut off for Class I obesity $\geq$25 kg/m^2; standard cut off for white Europeans $\geq$30 kg/m^2); WC, waist circumference cm (WC > 80 cm recommended for adult Asian women IDF); WHR, waist-to-hip ratio; IDF, International Diabetes Federation; NCEP (ATP III), National Cholesterol Education Program's Adult Treatment Panel III; WHO, World Health Organization.

hypertension, IGT, hypertriglyceridaemia and low HDL. Meanwhile testosterone, SHBG and age of onset of oligomenorrhoea had no effect, based on 90th centile of testosterone and 10th centile of SHBG in controls.

Obesity and the MetS in PCOS

The prevalence of MetS within the PCOS cohort from the lowest to highest quartiles of BMI was 6.7, 22.7, 28.6 and 42.0%, respectively. Increasing BMI was significantly related to an increasing trend in the proportion of women with the MetS ($\chi^2 = 58.5$, $P = 0.0001$). Occurrence of MetS based on the lowest to highest quartiles of WC was 1, 2.9, 14 and 12.9% ($P = 0.0001$).

Fasting insulin, HOMA2-IR, AGT and the MetS in PCOS

Prevalence of MetS among women with PCOS stratified from the lowest to highest quartiles of fasting insulin was 8.5, 18.4, 25.5 and 29.1%, respectively ($P = 0.0001$), without a significant difference between the phenotypes ($P = 0.152$). Fasting insulin was significantly higher in women with higher BMI. Fasting insulin $\geq$75th quartile occurred in 66 of 239 (27.6%) obese PCOS women (Asian cut-off) compared with 12 of 135 (5.4%) non-obese women with PCOS ($P = 0.0001$).

Among those with WC >88 cm, 36.1% had fasting insulin $\geq$75th quartile, compared with 9.7% with WC <88 cm ($P = 0.0001$); corresponding values in those with WC >80 were 29.1 versus 7.44% ($P = 0.0001$). The median HOMA2-IR in those with MetS was 2.60 compared with 1.40 among those without ($P = 0.0001$). Abnormal glucose tolerance was also significantly higher in PCOS with MetS (IGT 39.0% and diabetes 12.1%) compared with PCOS alone (IGT 21.1% and diabetes 2.56%; $P = 0.001$).

Family history of diabetes

A positive family history of T2DM occurred in 84 (61.5%) of women with, and 144 (58.2%) of those without, MetS complicating PCOS, which was not a statistically significant difference ($P = 0.541$).

PCOS phenotypes

Table III shows the distribution and baseline characteristics in the phenotypes. The classical phenotype (O + H + P) occurred in 54.6% of PCOS women. Oligo/amenorrhoea occurred in 92.3%, and the incidence of obesity was significantly greater in these phenotypes (O + H + P, H + O and O + P), when compared with the normal cycling hyperandrogenic women (H + P); the latter were also older, although this was not statistically significant.

MetS and PCOS phenotypes

The Prevalences of the MetS according to PCOS phenotypes were: classical 34.7%, androgenic 31.7%, ovulatory 20.0% and non-hyperandrogenic 23.5% without a significant difference. There were no differences in the occurrence of individual components of MetS between the phenotypes except WC (Table III). More than 60% of all oligo/anovular phenotypes had a WC >80 cm compared with only 40% of the ovulatory phenotype (H + P). The prominent lipid derangement was low HDL cholesterol in >57% of all phenotypes.

MLR showed significant predictive associations with MetS (Table IV) for: age $\geq$35 years ($P = 0.033$, OR = 2.203), AN ($P = 0.027$ OR = 1.837), BMI >25 kg/m^2 ($P = 0.0001$, OR = 2.948), high fasting

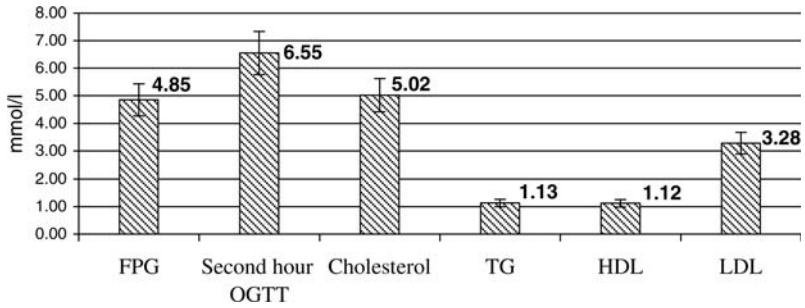

Figure 2 Median values of metabolic parameters in Sri Lankan women with PCOS ($n = 469$). FPG, fasting plasma glucose; OGTT, 75 g oral glucose tolerance test; Cholesterol, fasting value; TG, fasting triglycerides; HDL, fasting high-density lipoprotein cholesterol; LDL, fasting low-density lipoprotein cholesterol.

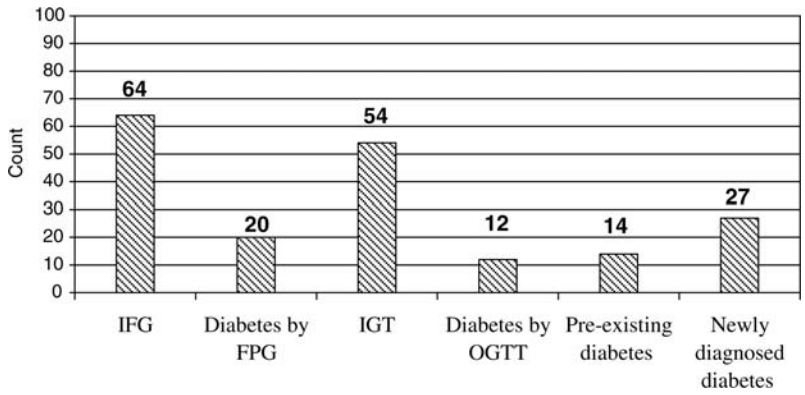

Figure 3 Prevalence of abnormal glucose tolerance among Sri Lankan women with PCOS ($n = 469$). IFG, impaired fasting glucose >5.5 mmol/l and <6.9 mmol; diabetes by FPG ≥7.0 mmol/l; OGTT, 75 g oral glucose tolerance test; IGT, impaired glucose tolerance (second hour value of OGTT) ≥7.8 mmol and <11.1 mmol/l; Diabetes by OGTT = FPG ≥7.0 mmol/l OR 2-h PG ≥11.1 mmol/l.

insulin ($P = 0.0001$, OR = 2.429) and pre-existing T2DM ($P = 0.038$, OR = 3.380). Family history of diabetes, hyperandrogensim and SHBG was not significant. Modelling was also carried out with inclusion of interaction terms. Only age ≥35 and BMI >25 kg/m^2 had a significant interaction. When both conditions were in operation the OR for MetS was higher (OR = 5.855, CI = 1.436–23.864, $P = 0.014$), while the risks for age ≥35 alone (OR = 1.096, CI = 0.447–2.691, $P = 0.841$) or BMI >25 kg/m^2 alone (OR = 0.626, CI = 0.166–2.632, $P = 0.490$) were reduced. None of the other interactions were found to be significant and therefore were not retained in the final model.

PCOS patients compared with controls

Results of MLR performed to adjust the age and BMI of the control group are depicted in Table V.

This showed that the presence of PCOS was associated with greater odds of having the MetS (OR = 6.749, $P = 0.0001$), a high WC (OR = 4.942, $P = 0.0001$), raised DBP (OR = 7.655, $P = 0.0001$) and high fasting insulin (OR = 2.851, $P = 0.002$) and high testosterone (OR = 5.789, $P = 0.0001$) concentrations. Those with PCOS also had higher odds of elevated TG (OR = 2.185, $P = 0.021$), low HDL (OR = 2.484, $P = 0.001$) and elevated LDL cholesterol (OR = 5.274, $P = 0.0001$).

Discussion

Although this study protocol is a descriptive data collection, its large sample size of Sri Lankan women with PCOS enables a reliable assessment of a hitherto unknown area in PCOS research, of problems specific to the indigenous South Asian woman. The study being located in a specialist endocrine clinic is liable to selection bias. Nevertheless, the cohort consists of young and predominantly pre-marital women, with the vast majority being previously uninformed about metabolic treatment and therefore likely to demonstrate the actual metabolic problems of PCOS in South Asians. Moreover, the metabolic differences observed in the group with PCOS, when compared with age- and BMI-adjusted controls from the same ethnic background, confirm that our findings are PCOS specific issues of this ethnic group.

Menstrual irregularity is common, with nearly half commencing from menarche and others from their late teens, with hyperandrogenism occurring in parallel. Our previous study of the classical phenotype,

Table I Comparison of clinical, endocrine and metabolic characteristics of PCOS women with and without MetS (Median, IQR) by NCEP-ATP III and IDF diagnostic criteria.

	Median (IQR) of total sample (n = 395)	Metabolic syndrome (NCEP definition) median (IQR)		P value[a]	Median (IQR) of total sample (n = 390)	Metabolic syndrome (IDF definition) median (IQR)		P value[a]
		Yes (n = 121)	No (n = 274)			Yes (n = 139)	No (n = 251)	
Age (years)	25.00 (9.00)	26.00 (10.00)	25.00 (8.00)	0.177	25.00 (9.00)	27.00 (10.00)	24.00 (8.00)	0.031
BMI (kg/m^2)	24.90 (6.43)	27.39 (4.94)	23.68 (5.7)	0.0001	24.75 (6.63)	27.00 (5.78)	23.00 (5.86)	0.0001
Waist circumference (cm)	86.00 (21.00)	96.00 (14.00)	80.00 (16.00)	0.0001	86.00 (21.00)	95.00 (16.50)	78.00 (16.38)	0.0001
SBP (mmHg)	120.00 (20.00)	130.00 (20.00)	120.00 (10.00)	0.0001	120.00 (20.00)	130.00 (20.00)	120.00 (10.00)	0.0001
DBP (mmHg)	80.00 (10.00)	80.00 (10.00)	80.00 (10.00)	0.0001	80.00 (10.00)	80.00 (10.00)	80.00 (10.00)	0.0001
Fasting plasma glucose (PG) (mmol/l)	4.86 (1.19)	5.10 (1.61)	4.71 (1.01)	0.0001	4.86 (1.22)	5.12 (1.64)	4.71 (1.04)	0.0001
2 h post 75 g OGTT PG (mmol/l)	6.57 (2.52)	6.82 (3.51)	6.44 (2.49)	0.050	6.54 (2.58)	6.93 (3.32)	6.34 (2.42)	0.003
Cholesterol (mmol/l)	5.07 (1.38)	5.33 (1.42)	5.00 (1.38)	0.071	5.06 (1.39)	5.29 (1.33)	4.99 (1.44)	0.163
TG (mmol/l)	1.14 (0.76)	1.67 (1.27)	1.03 (0.63)	0.0001	1.14 (0.76)	1.48 (1.13)	0.99 (0.65)	0.0001
HDL (mmol/l)	1.14 (0.49)	0.98 (0.35)	1.24 (0.54)	0.0001	1.14 (0.47)	1.01 (0.34)	1.26 (0.54)	0.0001
LDL (mmol/l)	3.34 (1.40)	3.45 (1.29)	3.14 (1.42)	0.013	3.30 (1.38)	3.41 (1.28)	3.14 (1.43)	0.141
Fasting insulin (pmol/l)	84.03 (88.89)	122.92 (93.06)	68.06 (67.71)	0.0001	83.68 (87.37)	120.84 (97.92)	68.06 (65.97)	0.0001
HOMA2-IR	1.80 (1.77)	2.60 (1.85)	1.40 (1.40)	0.0001	1.80 (1.70)	2.60 (2.00)	1.40 (1.30)	0.0001
Testosterone (nmo/l)	2.81 (2.16)	3.14 (2.58)	2.74 (1.97)	0.189	2.81 (2.08)	2.95 (2.20)	2.64 (2.04)	0.201
SHBG (nmol/l)	26.40 (22.90)	23.70 (19.43)	29.00 (24.60)	0.013	26.40 (23.10)	22.75 (19.10)	29.9 (26.80)	0.001
FAI	10.83 (14.90)	14.90 (16.76)	10.41 (11.64)	0.061	10.58 (14.41)	14.29 (16.33)	9.55 (11.14)	0.035

NCEP, National Cholesterol Education Program's Adult Treatment Panel III; IDF, International Diabetes Federation; BMI, body mass index (Asian cut off for Class I obesity $\geq$25 kg/m^2; standard cut off for white Europeans $\geq$30 kg/m^2); WC, waist circumference cm (WC $>$80 cm recommended for adult Asian women); SBP, systolic blood pressure; DBP, diastolic blood pressure; OGTT, 75 g oral glucose tolerance test; PG, venous plasma glucose; Cholesterol, fasting value; TG, fasting triglycerides; HDL, fasting high-density lipoprotein cholesterol; LDL, fasting low-density lipoprotein cholesterol; HOMA2-IR, homeostasis model assessment 2-insulin resistance; SHBG, sex hormone-blinding globulin; FAI, free androgen index.

[a]Mann–Whitney U-test with level of significance $P < 0.05$.

Table II Comparison of clinical, endocrine and metabolic characteristics of PCOS women with and without metabolic syndrome.

	Metabolic syndrome (NCEP)		*P* value[a]	Odds ratio	95% confidence interval	
	Yes (121)	No (274)			Lower	Upper
Age ≥35 years	18 (14.9%)	19 (7.0%)	0.013	2.219	1.12	4.36
Age at menarche <median (13 years)	70 (49.6%)	115 (46.2%)	0.264	1.219	0.72	2.06
Oligomenorrhoea since menarche	58 (52.3%)	117 (47.8%)	0.432	1.124	0.719	1.76
Pre-existing diabetes	10 (8.3%)	4 (1.5%)	0.001	6.081	1.86	19.79
Family history of type 2 diabetes	72 (61.5%)	156 (58.2%)	0.541	1.149	0.73	1.79
Presence of acanthosis	97 (80.1%)	158 (57.6%)	0.0001	2.967	1.78	4.92
FG ≥8	92 (76.7%)	192 (70.8%)	0.234	1.407	0.84	2.36
BMI ≥25 kg/m^2	90 (75.6%)	104 (38.7%)	0.0001	4.831	2.97	7.84
BMI ≥27.5 kg/m^2	58 (48.7%)	50 (18.6%)	0.0001	4.004	2.50	6.40
BMI ≥30 kg/m^2	33 (27.7%)	26 (9.7%)	0.0001	3.468	1.97	6.10
Pre-hypertension	88 (77.2%)	42 (18.3%)	0.0001	15.311	8.83	26.55
Cholesterol ≥5.2 mmol/l	65 (58%)	109 (42.2%)	0.005	1.687	1.09	2.06
2 h OGTT ≥7.8 mmol/l	16 (40%)	33 (21.2%)	0.014	2.385	1.14	4.97
Insulin ≥103.5 pmol/l[b]	58 (47.9%)	54 (19.9%)	0.0001	4.214	2.52	7.02
Testosterone ≥3.0 nmol/l[b]	45 (37.1%)	91 (33.5%)	0.258	1.334	0.81	2.19
SHBG ≤12.8 nmol/l[c]	12 (14.63%)	9 (5.96%)	0.027	0.37	0.149	0.919
TG:HDL ≥3.3	58 (47.9%)	46 (16.9%)	0.0001	0.26	0.133	0.351

NCEP, National Cholesterol Education Program's Adult Treatment Panel III; FG, Ferriman–Gallwey score to assess hirsutism; BMI, body mass index (Asian cut off for Class I obesity ≥25 kg/m^2; standard cut off for white Europeans ≥30 kg/m^2); pre-hypertension = resting systolic blood pressure of 120–139 mmHg and/or diastolic blood pressure 80–89 mmHg; OGTT, 75 g oral glucose tolerance test; SHBG, sex hormone-blinding globulin; TG, fasting triglycerides; HDL, fasting high-density lipoprotein cholesterol.
[a]Pearson's χ^2 level of significance $P < 0.05$.
[b]>90th centile for control group.
[c]<10th centile for control group.

found more severe manifestations in younger women and more insulin resistant migrant South Asians (of Pakistani origin) when compared with white Europeans from the same setting in the UK (Wijeyaratne *et al*., 2002). A similar finding in this indigenous group corroborates our previous report of an ethnic difference in the expression of PCOS in South Asians, and excludes migration as a contributor.

Although a high prevalence of PCOS among migrant South Asians has been linked to their ethnic propensity to IR (Rodin *et al*., 1998), a subsequent study in Sri Lanka revealed that the community prevalence of PCOS by Rotterdam criteria as 6.3% among randomly selected semi-urban women with a median age of 25 years (Kumarapeli *et al*., 2008). The prevalence of PCO among asymptomatic women from the same community is 17%, whereas its prevalence in symptomatic women is 82.5%. This suggests ovarian changes occur in parallel with menstrual and hyperandrogenic symptoms in young South Asians. Hyperandrogenism manifests mainly as hirsutism, but with a median FG score of 10 as opposed to our previous report of 18 in Pakistani women. Acne occurs in 39% Sri Lankans while more than two-thirds of migrant Pakistani women had acne. Such variations in hyperandrogenism might suggest intra-regional ethnic differences in its expression or migration as the cause. This can only be resolved by studying indigenous Pakistani women. Interestingly the former result is corroborated by a report of 650 randomly selected indigenous Pakistani women (mean age 27 years) where 79.53% had significant hirsutism with one half having androgenic disorders (Kazmi *et al*., 1993).

Features reported of 'Asians' with PCOS in the USA are short stature, 'lower' BMI and 'milder' phenotype in terms of hyperandrogenism, but with the highest prevalence of MetS (50%) (Lo *et al*., 2006). It is noteworthy that the younger South Asians with PCOS we reported previously had lower BMI (mean 26 kg/m^2) than their older and more obese white European counterparts, but with a greater IR and higher prevalence of MetS (Wijeyaratne *et al*., 2002). In fact, it is their central obesity rather than BMI that correlated strongly with IR and metabolic problems. The current results further strengthen the argument for an ethnic variation in South Asians having a smaller body habitus, but with one half exceeding the Asian cut off for obesity by BMI (World Health Organization expert consultation, 2004), and central obesity having a significant link with the metabolic manifestations and more so with PCOS. It might be argued that such an Asian-specific application for defining obesity is unwarranted, as this disallows direct comparison with other ethnic groups. However, this study shows only 30% of the group exceeded a BMI of 27.5 kg/m^2 and 16% >30 kg/m^2, which is not reflected by the far higher prevalence of MetS. As per NCEP and IDF diagnostic criteria, MetS was present in a third of the sample with significant

Table III Demographic, anthropometric, clinical and metabolic characteristics among women with four different phenotypes of PCOS.

Characteristics	O + H + P *n* = 256 (54.6%)	O + H *n* = 82 (17.5%)	H + P *n* = 36 (7.7%)	O + P *n* = 95 (20.3%)	*P* value
	Median (IQR)				
Age (years)	25.5 (8.0)	24 (6.25)	29.5 (15.5)[a]	25.0 (8.0)	0.35
BMI (kg/m^2)	25.94 (6.31)	25.24 (5.51)	21.98 (4.02)[a]	24.23 (8.06)	0.001
Waist circumference (cm)	88 (20.5)	90 (16.0)	76.0 (21.25)[a]	85.0 (25.5)	0.002
Waist-to-hip ratio	0.89 (0.14)	0.88 (0.13)	0.82 (0.11)[a]	0.86 (0.14)	0.02
FG score	10 (4.75)	10 (4.0)	12 (6.0)[a]	4 (2.0)	0.0001
Age of onset of symptoms (years)					
Menstrual irregularity	14 (7.0)	15 (6.0)	0	14.0 (7.0)	0.770
Hirsutism	17 (8.0)	18 (9.0)	15 (9.0)	18.5 (4.5)	0.970
Characteristics	**No. (%)**				
Family history of type 2 diabetes—number (%)	147 (60%)	55 (67.9%)[b]	21 (58.3 %)	49 (51.6%)	0.018
Prevalence of met syndrome number (%)	86 (34.7%)[b]	22 (31.7%)	9 (20.0%)	24 (23.5%)	0.152
Waist circumference ≥80 cm	169 (66.0%)	62 (75.6%)[b]	14 (40.0%)	58 (60.4%)	0.004
Waist circumference ≥88 cm	121 (47.3%)	43 (52.4%)	10 (27.8%)	37 (38.9%)	0.124
HDL ≤1.3 mmol/l	153 (59.8%)	47 (57.3%)	20 (57.1%)	58 (60.4%)	0.667
TG ≥1.7 mmol/l	55 (21.5%)	11 (13.4%)	5 (14.3%)	13 (13.5%)	0.316
BP ≥130/85 mmHg	80 (31.3%)	29 (35.4%)	10 (28.6%)	27 (28.1%)	0.827
FPG ≥6.1 mmol/l (NCEP)	34 (13.3%)	10 (12.2%)	5 (14.3%)	4 (4.2%)	0.260
FPG ≥5.6 mmol/l ADA criteria (31)	51 (19.9%)	14 (17.0%)	8 (22.2%)	11 (11.6%)	0.633
TG:HDL ≥3.3	69 (26.9%)	17 (20.7%)	5 (13.9%)	21 (22.1%)	0.358

Median values inter-quartile range, IQR; O, oligo/anovulation; H, hyperandrogenism and O, polycystic ovary; classical phenotype = O + H + P; Hyperandrogenic phenotype = O + H; ovulatory phenotype = H + P; non-hyperandrogenic phenotype = O + P; FG, Ferriman–Gallwey score to assess hirsutism; BMI, body mass index; FPG, fasting plasma glucose; NCEP, National Cholesterol Education Program's Adult Treatment Panel III; ADA, American Diabetes Association; TG, fasting triglycerides; HDL, fasting high-density lipoprotein cholesterol.
[a]Kruskal–Wallis test for level of significance ($P < 0.01$).
[b]χ^2 test for level of significance ($P < 0.05$).

Table IV MLR analysis of the PCOS cohort showing the predictive association between clinical, biochemical and endocrine variables and the metabolic syndrome.

Variable	*P* value[a]	Adjusted odds ratio	95% confidence interval	
			Lower bound	Upper bound
Multiple logistic regression				
Age ≥35 years	0.033	2.203	1.066	4.552
Pre-existing diabetes mellitus	0.038	3.380	1.067	10.713
Presence of AN	0.027	1.837	1.071	3.152
BMI ≥25 kg/m^2	0.0001	2.948	1.770	4.912
Insulin ≥103.5 pmol/l[b]	0.0001	2.429	1.506	3.917

BMI, body mass index.
[a]*P*-value significant at 0.05 level.
[b]>90th centile for control group.

relationship with BMI >25 kg/m^2 and central obesity (Table II). This is further supported by the high odds for central obesity in the PCOS cohort as opposed to age and BMI-adjusted women without PCOS ($P = 0.0001$). This proves interesting, since IDF criteria for MetS has a mandatory requirement of high WC, while NCEP criteria includes any combination of its diagnostic components but with a higher cut off for WC (88 versus 80 cm). Therefore, it is reasonable to claim that the current study supports our previous conclusion that migrant South Asians with PCOS have greater central obesity in proportion to a 'lower' BMI, which is linked to their metabolic risk. This highlights the importance of measuring WC of women from high-risk ethnic groups, which must be specifically addressed at diagnosis and during follow up of PCOS.

A notable finding was AN, which was evident in over two-thirds of Lankans with PCOS, with rather extensive distribution including the nasolabial fold that has not been described previously. This mirrors our previous finding in migrant South Asians with PCOS (Wijeyaratne *et al.*, 2002), and is in keeping with reports of its occurrence in other Asian groups with PCOS (Charnvises *et al.*, 2005). In their paper, Charnvises *et al.* describe Thai women who are not strictly comparable with indigenous South Asians due to differing skin colour, body

Table V MLR analysis of differences in characteristics between Sri Lankan women with and without PCOS.

Variable	*P* value[a]	Adjusted odds ratio	95% confidence interval	
			Lower bound	Upper bound
Multiple logistic regression				
Presence of MetS	0.0001	6.749	3.330	13.679
Waist ≥88 cm	0.0001	4.942	2.915	8.380
DBP ≥85 mmHg	0.0001	7.655	2.446	23.957
TG ≥1.7 mmol/l	0.021	2.185	1.123	4.252
HDL <1.3 mmol/l	0.001	2.484	1.483	4.161
LDL ≥3.9 mmol/l	0.0001	5.274	2.741	10.148
Insulin ≥103.5 pmol/l[b]	0.002	2.851	1.475	5.511
Testosterone ≥3.0 nmol/l[b]	0.0001	5.789	3.142	10.663
SHBG ≤12.8 nmol/l[c]	0.027	0.100	0.013	0.774

MetS, metabolic syndrome; BMI, body mass index; DBP, diastolic blood pressure; TG, fasting triglycerides; HDL, fasting high-density lipoprotein cholesterol; LDL, fasting low-density lipoprotein cholesterol; SHBG, sex hormone-blinding globulin.
[a]*P*-value level of significance $P < 0.05$.
[b]>90th centile for control group.
[c]<10th centile for control group.

habitus and expression of hyperandrogenism. The USA-based study also links MetS and AN in PCOS to ethnicity and family history of T2DM (Ehrmann *et al*., 2006). However, our data did not reveal a family history of T2DM as being a significant predictor for MetS in PCOS. Interestingly, our report is the first of a purely South Asian cohort that demonstrates a very high prevalence of acanthosis affecting two-thirds and being a significant predictor. Although acanthosis is not a diagnostic marker of PCOS, their common occurrence supports a policy of training primary healthcare providers in resource-limited countries of South East Asia to evaluate young women with possible PCOS for metabolic risks using simple tools such as WC, BP and AN. Such an approach would enable early institution of cost-effective preventive care.

Although there is a high prevalence of first-degree relatives with diabetes, this was not linked to MetS. However, a large proportion of those without MetS but having two diagnostic criteria, demonstrate their overall high metabolic risk. This is supported by nearly half the cohort having abnormal glucose tolerance as early as their third decade of life and the occurrence of MetS being significantly associated with older age. Therefore, we propose recording a family history of T2DM in a multi-ethnic clinical setting as yet another important simple tool for risk categorization. The associated risk of gestational diabetes and premature T2DM must also be highlighted by incorporating a mandatory 75 g OGTT prior to infertility treatment in high-risk ethnic women (Kousta *et al*., 2000; Wijeyaratne *et al*., 2006, 2004). Longitudinal follow up of such high-risk groups with PCOS for cardiovascular and metabolic outcomes must also be encouraged. The observation that a sizeable number of Sri Lankans with PCOS are hypertensive at this young age supports this.

Although testosterone did not show a linear relationship with the FG score in PCOS, the remarkably low SHBG is similar to that in our previous reports (Wijeyaratne *et al*., 2002, 2004). Since SHBG is a surrogate marker of IR, this further highlights the greater metabolic risk of South Asians with PCOS, and helps explain hyperandrogenic manifestation in >75%. However, measurement of SHBG is costly and requires in-depth study before being adopted as a routine recommendation. The exact interrelationship between androgenic and metabolic problems of PCOS remains unresolved. A large Chinese study reports hyperandrogenaemia, not hirsutism, being independently associated with T2DM (OR = 5.7; $P = 0.028$) (Zhao *et al*., 2010). Others also demonstrate hyperandrogenism related MetS, with the highest prevalence (28.5%) in the classical phenotype (Shroff *et al*., 2007; Zhang *et al*., 2009). However, our current study reveals a similar occurrence of MetS in the four phenotypes of PCOS, with the non-hyperandrogenic phenotype occurring in one-fifth and the normal cycling androgenic group being significantly smaller. This is corroborated by the plasma testosterone being not statistically linked to the occurrence of MetS among Sri Lankans with PCOS.

This observation in South Asians differs from many reports of European groups (Pehlivanov and Orbetzova, 2007; Shroff *et al*., 2007; Goverde *et al*., 2009) and suggests the South Asian propensity to MetS at a younger age is independent of hyperandrogenism. In contrast, a large USA-based study reports approximately a 2-fold risk of MetS in hyperandrogenic women (Shroff *et al*., 2007), who were older and had higher BMIs than the current sample, but also had a higher prevalence of T2DM in family members. Hence, we could hypothesize that young South Asians might manifest a stronger relationship between hyperandrogenism and MetS with ageing. The subgroup with MetS among the Lankans has more women >35 years of age, irrespective of obesity being determined by Asian or Western standards. Moreover, IGT was significantly higher in Lankans with MetS, even though only one half underwent OGTT.

In summary, indigenous South Asians with PCOS manifest early and seek health-care pre-maritally, with irregular menses and hirsutism predominating. They have greater central obesity in proportion to a 'lower' BMI, which is linked to their metabolic risk. MetS affects one-third, with age ≥35 years, AN and BMI ≥25 kg/m^2 (Asian cut off) having significant association. There is no significant association of the occurrence of the MetS with hyperandrogenism, with a similar prevalence in the four phenotypes of PCOS identified by Rotterdam criteria, in contrast to reports among other ethnic groups.

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