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Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome

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BACKGROUND: Women with polycystic ovary syndrome (PCOS) frequently exhibit central obesity, glucose intolerance, atherogenic dyslipidaemia and hypertension which are characteristic features of the metabolic syndrome (MetS). METHODS: A total of 295 premenopausal Chinese women with PCOS diagnosed by the Rotterdam criteria (mean age: 30.2 ± 6.4 years) and 98 control subjects without PCOS were evaluated for prevalence of MetS and cardiovascular risk factors, including dyslipidaemia and dysglycaemia. RESULTS: Using the 2005 modified Adult Treatment Panel III criteria, MetS (presence of three or more risk factors) was found in 24.9% of PCOS women compared to 3.1% of controls. The prevalence of MetS in PCOS women increased from 16.7% at under 30 years of age to 53.3% at over 40 years. MetS was also more prevalent in overweight and obese (41.3%) than normal-weight PCOS women (0.9%). However, multivariate regression analysis showed that women with PCOS had a 5-fold increase in risk of MetS (odds ratio 4.90; 95% confidence interval: 1.35–17.84) compared with women without PCOS even after controlling for age and BMI, suggesting PCOS alone is an independent risk factor for MetS. CONCLUSIONS: There is high prevalence of MetS in Hong Kong Chinese women with PCOS despite their relatively young age. Recognition of these cardiometabolic risk factors requires a high level of awareness in conjunction with early and regular screening.

Keywords: polycystic ovary syndrome; metabolic syndrome; Chinese

Introduction

Polycystic ovary syndrome (PCOS) is a common gynaecological endocrinopathy affecting 6–12% of premenopausal women (Farah *et al*., 1999; Azziz *et al*., 2004). Despite the diverse phenotypes, it is classically characterized by ovarian dysfunction (oligo-amenorrhoea, anovulatory infertility) in conjunction with the cardinal features of hyperandrogenism and polycystic ovary morphology. Hyperandrogenism, mediated through elevated LH (endocrine pathway) or insulin resistance (metabolic pathway), is an important pathophysiological feature but the relative contribution of these pathways to the disease mechanisms vary in different subjects, thus accounting for its clinical heterogeneity (Balen, 1993; Nestler, 1997; Poretsky and Piper, 1994).

Women with PCOS often present to gynaecologists with menstrual irregularity and reproductive dysfunction early in their reproductive life. However, emerging evidence suggests that PCOS should no longer be considered a purely gynaecological disorder because of its predisposition to various cardiometabolic risk factors (Hopkinson *et al*., 1998). These include obesity, glucose intolerance (Ehrmann *et al*., 1999; Chen *et al*., 2006), atherogenic dyslipidaemia (Sartor and Dickey, 2005; Dokras *et al*., 2005) and hypertension (Dahlgren *et al*., 1992) that are also key components of the metabolic syndrome (MetS). The association of PCOS with MetS and the consequent increase in the long-term risk of Type 2 diabetes and cardiovascular diseases indicates that PCOS carries significant public health implications. Nevertheless, the prevalence of MetS in PCOS women shows a marked variation between countries and ethnic groups, probably due to differences in diet, lifestyle and genetic factors. On the basis of the Adult Treatment Panel III criteria (Lepor and Vogel, 2001), the prevalence of MetS was reported to be 1.6% (Vrbikova *et al*., 2005), 8.2% (Carmina *et al*., 2006) and 43% (Apridonidze *et al*., 2005) in Czech, Italian and US women with PCOS, respectively, but to date there are no data from Chinese subjects. The primary aim of this study was therefore to evaluate the prevalence of the MetS and its individual components in Hong Kong Chinese women with PCOS. We further aimed to test the hypothesis that PCOS women have an increased risk of MetS and to examine the clinical predictors for MetS in these women.

Materials and Methods

Subjects

This was a cross-sectional study conducted in subspecialty gynaecology clinics (combined gynae-endocrinology as well as infertility clinics) at the Prince of Wales Hospital of the Chinese University of Hong Kong from July 2003 to April 2007. A total of 295 consecutive Chinese pre-menopausal women with PCOS were recruited as study subjects. The diagnosis of PCOS was based on the latest 2003 Rotterdam consensus (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004) with at least two of the following features: (i) oligo-amenorrhoea or chronic anovulation, (ii) clinical and/or biochemical hyperandrogenism, (iii) ultrasound appearance of polycystic ovaries, after exclusion of other known causes of hyperandrogenaemia. Amongst these 295 women, 149 (50.5%) had all three clinical features, 110 (37.3%) had anovulation and polycystic ovaries; 30 (10.2%) had anovulation and hyperandrogenism; and 6 (2.0%) had hyperandrogenism and polycystic ovaries. Hence, the proportion of women with a diagnosis of PCOS based on the previous National Institutes of Health (NIH) criteria (Zawadzki and Dunaif, 1992) was 179/295 (60.7%) among this cohort.

Another 98 Chinese pre-menopausal women without PCOS were recruited as control subjects. All of them had regular menstrual cycles and had no hirsutism/acne or ultrasound features of polycystic ovaries. Sixty-one (62.2%) women were healthy volunteers recruited from the community and the remaining were non-PCOS women who presented to the same unit with other gynaecological problems, mostly tubal infertility.

Exclusion criteria for both groups included the use of medications which are known to affect steroid or glucose metabolism (e.g. oral contraceptives, corticosteroids) within the past 3 months. Subjects with hypothyroidism, prolactinoma, non-classical adrenal hyperplasia and Cushing's syndrome were also excluded from the study.

The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong and informed consent was obtained from all subjects.

Clinical, anthropometrical and biochemical parameters

A standard questionnaire was used to document personal, medical and drug history, regularity and length of menstrual cycles, ovulation status, symptoms of hirsutism and acne. Cardiovascular risk factors such as tobacco and alcohol use, physical inactivity and family history of diabetes were also recorded. Physical inactivity was defined as moderate physical activity of less than 30 min per week. Signs of androgen excess were noted in the physical examination. Body weight (kg), body height (m), waist and hip circumferences (cm) were measured. Waist circumference was taken as the narrowest measurement midway between the top of the iliac crest and the lower rib margin, whereas the hip circumference was taken as the widest measurement at the level of the greater trochanters. Sitting blood pressure was measured after a 5-min rest using a standard sphygmomanometer.

Overnight fasting blood specimens were obtained in all women for measurements of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). In 70.2% of study women and 24.5% of control subjects who agreed for a standard 75-g oral glucose tolerance test (OGTT), fasting insulin and 2-h plasma glucose (PG) concentrations were also measured. There were no differences in the clinical or hormonal profiles between women with PCOS who had and those who did not have an OGTT.

Serum LH, FSH and total testosterone concentrations were measured in the early follicular phase of the menstrual cycles or after progestogen-induced menstruation. We defined LH predominance as elevated LH to FSH ratio $\geq$2.5 or increased basal concentrations of LH $\geq$10 IU/l. Biochemical hyperandrogenaemia was defined as elevated total testosterone $\geq$3 nmol/l, the latter being the upper limit of our laboratory range for healthy women.

Laboratory analyses

PG was measured by a hexokinase method (Hitachi 911, analyzer Boehringer Mannheim). Intra- and inter-assay coefficients of variation (CV) were both 2% at 6.6 mmol/l. Insulin was measured by a radioimmunoassay kit (Pharmacia). The lower limit of detection was $<$2 mIU/l and the inter-assay CV was 5%. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald's formula (Friedewald *et al*., 1972). Serum LH, FSH and total testosterone concentrations were measured on an Immulite 1000 semi-automated immunoassay analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). These measurements were performed using standard reagent kits supplied by the manufacturers. The analytical performance of these assays was within the specifications of the analyzers.

Main outcome measures

The occurrences of MetS and other cardiovascular risk factors, including dyslipidaemia and dysglycaemia were studied. MetS was assessed by the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria. Both the original criteria in 2001 and the modified version proposed by the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) in 2005 were included for comparison. The original criteria (ATPIII 2001) (Lepor and Vogel, 2001) defined MetS as the co-occurrence of three or more of the following risk factors:

(i) central obesity with waist circumference $>$88 cm in women;
(ii) elevated systolic and/or diastolic blood pressure $\geq$130/85 mmHg;
(iii) elevated fasting TG $\geq$1.7 mmol/l;
(iv) reduced fasting HDL-C $<$1.3 mmol/l;
(v) impaired fasting glucose $\geq$6.1 mmol/l.

The main changes in the modified AHA/NHLBI definition (ATPIII 2005) (Grundy *et al*., 2005) include:

(i) addressing the ethnic-specific difference in central obesity by using the World Health Organization (WHO) recommendations for waist circumference: $\geq$80 cm in Asian women (World Health Organization, 2000);
(ii) reducing the threshold for impaired fasting glucose to 5.6 mmol/l in accordance with the American Diabetes Association (ADA) revised definition (Genuth *et al*., 2003);
(iii) allowing individual components to be counted abnormal if patients are receiving drug treatment for these conditions.

In addition to MetS, dyslipidaemia was defined by TC $\geq$ 5.2 mmol/l, TG $\geq$ 1.7 mmol/l, HDL-C $<$ 1.3 mmol/l, LDL-C $\geq$ 3.4 mmol/l, or treatment with lipid regulating drugs. Dysglycaemia was based on the revised ADA 2003 definition using 75 g OGTT as appropriate (Genuth *et al*., 2003). These include impaired fasting glucose (IFG: FPG $\geq$ 5.6 and $<$7 mmol/l), impaired glucose tolerance (IGT: 2-h PG $\geq$ 7.8 and $<$11.1 mmol/l), Type 2 diabetes (FPG $\geq$ 7 mmol/l or 2-h PG $\geq$ 11.1 mmol/l) or treatment with anti-diabetic drugs. Homeostasis model assessment of insulin resistance (HOMA-IR), derived from a simplified equation: HOMA-IR = [FPG (mmol/l) $\times$ fasting insulin (μIU/ml)]/22.5 (Matthews *et al*., 1985), was used as a surrogate index of insulin resistance.

Statistical analysis

A pilot study was conducted and the occurrence of MetS in PCOS women was found to be ~25%. A sample size of 300 women with PCOS was needed to estimate the prevalence to within 5% of the true value with 95% confidence.

The prevalence of MetS was reported to be 5–10% in Hong Kong working women (Ko *et al*., 2005). To detect a 15% difference in MetS rate between women with PCOS and control subjects, 100 control women are needed to give the study a power of 80% at the significance level of 0.05.

Statistical analyses were performed using the Statistical Packages for Social Sciences for Windows Version 14.0 (SPSS Inc, IL, USA). Continuous variables are presented as mean ± SD or median (inter-quartile range), and analysed using independent sample *t*-test for normally distributed data or Mann–Whitney *U*-test for skewed data. Categorical variables are expressed as proportion (percentage) and analysed by X^2 or Fisher's exact tests as appropriate. Multivariate logistic regression was used to examine independent predictors of MetS and to adjust for confounding factors. Results are expressed as age and BMI adjusted odds ratio (OR) with 95% confidence interval (CI) or two-sided *P*-value. A *P*-value of less than 0.05 was considered statistically significant and was indicated by an asterisk.

Results

Comparison between women with or without PCOS

Tables I and II compare the clinical characteristics and the prevalence of cardiometabolic risk factors between women with or without PCOS. Compared to the control subjects, women with PCOS were younger, more obese and had higher blood pressures, fasting TG, FPG and lower HDL-C concentrations. They also had a higher prevalence of MetS (ATPIII 2005), dyslipidaemia and dysglycaemia than women without PCOS even after controlling for age and BMI. MetS (ATPIII 2005), defined by co-occurrence of at least three cardiometabolic risk factors, was found in 24.9% of the entire PCOS cohort and 22.9% among those who also met the NIH criteria of PCOS. In addition, 66.5, 46.7, 24.9, 9.6 and 3.3% of women with PCOS had at least one, two, three, four or five components of MetS (ATPIII 2005), respectively. The frequency of each component, in decreasing order, was central obesity (53.1%), elevated blood pressure (29.4%), reduced HDL-C (28.6%), increased TG (21.4%) and IFG (21.4%). Moreover, the prevalence of IFG only, IGT only, IFG plus IGT and Type 2 diabetes among this PCOS cohort was 9.2, 10.5, 4.1 and 7.5%, respectively, based on the 2003 revised ADA criteria using OGTT as appropriate. Our data also suggested that impaired fasting glucose alone, even when a more stringent criterion of ≥5.6 mmol/l was used, only predicted 66 and 86% of those PCOS women with dysglycaemia and Type 2 diabetes.

We next performed stratified analysis, by age group and weight category, as age and BMI are well-known confounding factors for MetS. The age-specific prevalence of MetS is illustrated in Fig. 1. As expected, the prevalence of MetS increased with age and was significantly higher in PCOS women than control subjects in all age groups. Table III compares the individual components of MetS after stratification into subgroups of normal-weight ($BMI < 23\ kg/m^2$) or overweight/obese ($BMI \geq 23\ kg/m^2$) using the WHO Asian definition for obesity (World Health Organization, 2000). When compared with the respective controls, overweight/obese PCOS women were more likely to have multiple cardiometabolic risk factors while normal-weight PCOS women were found to have an increased risk of hypertriglyceridaemia.

Multivariate logistic regression was also performed to examine the independent predictors of MetS in all women with or without PCOS (data not shown). Variables

Table I. Comparison of clinical, anthropometric and biochemical characteristics between women with or without polycystic ovary syndrome.

	PCOS ($n = 295$)	Controls ($n = 98$)	*P*-value
Age (years)	30.2 ± 6.4	33.4 ± 5.9	<0.001*,[a]
BMI (kg/m^2)	25.8 ± 5.9	21.3 ± 2.6	<0.001*,[a]
$BMI \geq 23\ kg/m^2$	178/295 (60.3%)	20/98 (20.4%)	<0.001*,[b]
Waist circumference (cm)	82.3 ± 13.1	71.3 ± 7.8	<0.001*,[a]
Waist-to-hip ratio	0.82 ± 0.07	0.77 ± 0.06	<0.001*,[a]
Ever smoker	35/252 (13.9%)	5/93 (5.4%)	0.028*,[b]
Ever drinker	23/248 (9.3%)	5/93 (5.4%)	0.24[b]
Physical inactivity	141/221 (63.8%)	43/78 (55.1%)	0.18[b]
Family history of diabetes	65/229 (28.4%)	18/92 (19.6%)	0.1[b]
Systolic BP (mmHg)	117.4 ± 17.2	106.7 ± 12.4	<0.001*,[a]
Diastolic BP (mmHg)	71.0 ± 11.1	66.2 ± 8.5	<0.001*,[a]
Total testosterone (nmol/l)	1.7 (1.2–2.4)	1.3 (0.9–1.7)	<0.001*,[c]
LH (IU/l)	7.4 (4.5–11.6)	5.0 (4.0–6.5)	<0.001*,[c]
FSH (IU/l)	5.8 (4.7–6.7)	7.3 (6.1–8.4)	<0.001*,[c]
TC (mmol/l)	4.7 (4.1–5.4)	4.5 (4.1–5.0)	0.077[c]
TG (mmol/l)	1.0 (0.7–1.5)	0.7 (0.6–0.9)	<0.001*,[c]
HDL-C (mmol/l)	1.5 (1.3–1.8)	1.7 (1.5–2.1)	<0.001*,[c]
LDL-C (mmol/l)	2.5 (2.1–3.1)	2.4 (2.1–2.8)	0.047 *,[c]
FPG (mmol/l)	4.9 (4.6–5.4)	4.7 (4.4–5.1)	0.002*,[c]
2-h PG (mmol/l)[ϕ]	6.4 (5.1–8.1)	5.4 (4.9–6.1)	0.012*,[c]
Fasting insulin (μIU/ml)[ϕ]	11.3 (6.2–20.8)	5.1 (4.2–6.7)	<0.001*,[c]

Data were presented as means ± SD, proportion (%) or median (inter-quartile range), and analysed by [a]independent sample *t*-test, [b]X^2/Fisher's exact tests, or [c]Mann–Whitney *U*-test as appropriate. [ϕ]Only around 70.2% of PCOS women and 24.5% of control subjects had OGTT and fasting insulin measurements.
BP, blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; PG, plasma glucose.

Table II. Comparison of cardiometabolic risks factors between women with or without PCOS.

Prevalence (%)	PCOS	Controls	Age and BMI adjusted OR (95% CI)	*P*-value
Dyslipidaemia	154/290 (53.1%)	26/95 (27.4%)	1.99 (1.12–3.53)	0.018*
Dysglycaemia	95/294 (32.3%)	10/98 (10.2%)	2.27 (1.04–4.94)	0.039*
MetS (ATPIII 2001)	52/288 (18.1%)	1/98 (1.0%)	7.78 (0.96–62.82)	0.054
MetS (ATPIII 2005)	72/289 (24.9%)	3/98 (3.1%)	4.9 (1.35–17.84)	0.016*
Individual component of MetS (ATPIII 2005):				
Central obesity	147/277 (53.1%)	14/98 (14.3%)	1.95 (0.77–4.96)	0.16
Elevated blood pressure	86/293 (29.4%)	5/98 (5.1%)	4.56 (1.65–12.61)	0.003*
Increased triglycerides	62/291 (21.4%)	3/98 (3.1%)	6.37 (1.85–21.93)	0.003*
Reduced HDL-C	83/290 (28.6%)	7/95 (7.4%)	2.83 (1.17–6.83)	0.021*
Impaired fasting glucose	63/294 (21.4%)	7/98 (7.1%)	2.33 (0.93–5.85)	0.071

Values are proportion (%) and analysed by logistic regression using age and BMI as covariates.
MetS, metabolic syndrome; ATPIII, adult Treatment Panel III; OR, odds ratio; CI, confidence interval.

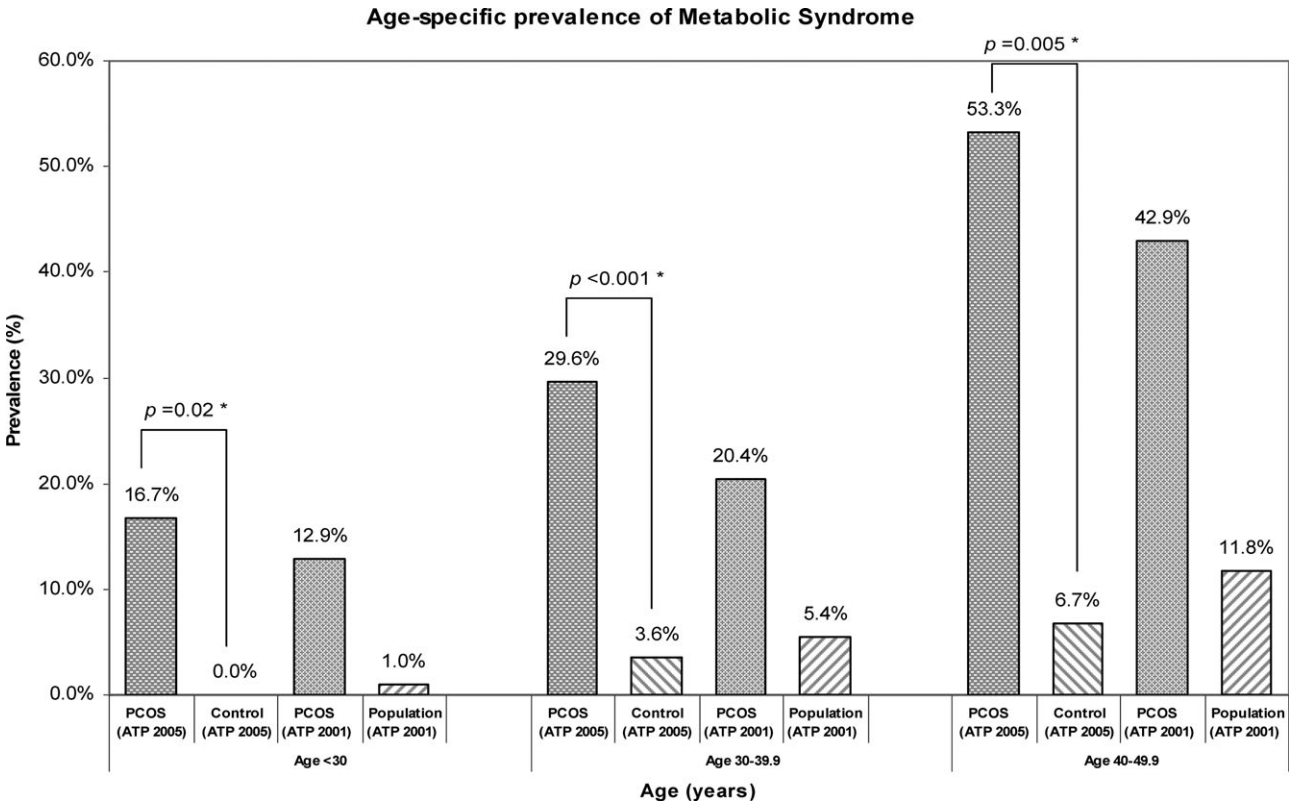

Figure 1: Age-stratified prevalence of MetS in PCOS, control subjects without PCOS (control) and Hong Kong women from the Hong Kong Cardiovascular Risk Factor Prevalence Survey (Population)
Diagnosis of MetS based on both the modified Adult Treatment Panel III (ATP 2005) and the original Adult Treatment Panel III (ATP 2001) criteria. Values are prevalence (%) and analysed by X^2/Fisher's exact tests.

Table III. Comparison of individual components of MetS (ATPIII 2005) in study and control subjects after stratified by weight category.

Prevalence (%)	PCOS normal-weight[a] ($n = 117$) (%)	Control normal-weight[b] ($n = 78$) (%)	*P* (a versus b)	PCOS Overweight/obese[c] ($n = 177$) (%)	Control Overweight/obese[d] ($n = 20$) (%)	*P* (c versus d)
Waist $\geq$80 cm	5.3	3.8	0.74	86.5	55	<0.001*
BP $\geq$ 130/85 mmHg	6.9	6.4	0.89	44.1	0	<0.001*
TG $\geq$ 1.7 mmol/l	9.4	0	0.004*	29.3	15	0.29
HDL-C <1.3 mmol/l	12	3.9	0.07	39.9	21.1	0.14
FPG $\geq$ 5.6 mmol/l	3.4	5.1	0.72	33.3	15	0.13
Fulfilling 3 or more criteria	0.9	0	1.0	41.3	15	0.028 *

Values are proportion (%) and analysed by X^2/Fisher's exact tests.
Normal-weight PCOS compared with overweight/obese PCOS (a versus c)—$P < 0.001$ for all comparisons. Normal-weight subjects are defined as BMI < 23 kg/m^2 and overweight/obese subjects as BMI $\geq$ 23 kg/m^2.

Table IV. Comparison of clinical and biochemical characteristics between PCOS women with or without MetS (ATPIII 2005).

	PCOS with MetS ($n = 72$)	PCOS without MetS ($n = 217$)	P-value
Age (years)	32.6 ± 5.8	29.4 ± 6.3	<0.001*,[a]
BMI (kg/m^2)	30.9 ± 4.4	23.9 ± 5.1	<0.001*,[a]
BMI ≥ 23 kg/m^2	71/72 (98.6%)	101/217 (46.5%)	<0.001*,[b]
Waist circumference (cm)	93.96 ± 8.89	78.46 ± 11.89	<0.001*,[a]
Waist-to-hip ratio	0.87 ± 0.05	0.81 ± 0.06	<0.001*,[a]
Ever smoker	14/64 (21.9%)	21/183 (11.5%)	0.04*,[b]
Ever drinker	5/62 (8.1%)	18/181 (9.9%)	0.66[b]
Physical inactivity	31/46 (67.4%)	109/174 (62.6%)	0.55[b]
Family history of diabetes	18/49 (36.7%)	46/178 (25.8%)	0.13[b]
Total testosterone (nmol/l)	1.7 (1.1–2.4)	1.7 (1.2–2.4)	0.94[c]
Hyperandrogenism	42/67 (62.7%)	139/212 (65.6%)	0.67[b]
LH (IU/l)	6.2 (3.9–10.8)	7.6 (4.8–12.4)	0.039*,[c]
LH predominance	23/68 (33.8%)	87/210 (41.4%)	0.27[b]
Fasting insulin (μIU/ml)	20.2 (14.1–28.9)	8.9 (5.5–13.9)	<0.001*,[c]
HOMA-IR	4.9 (3.4–7.3)	1.9 (1.1–3.4)	<0.001*,[c]

Values are mean ± SD, proportion (%) or median (inter-quartile range), and analysed by [a]independent sample t-test, [b]X^2/Fisher's exact tests, or [c]Mann–Whitney U-test as appropriate. Hyperandrogenism refers to clinical hyperandrogenism and/or biochemical hyperandrogenaemia with total testosterone ≥3 nmol/l. LH predominance is defined as LH ≥10 IU/l or LH to FSH ratio ≥2.5. HOMA-IR is calculated by [FPG (mmol/l) × fasting insulin (μIU/ml)]/22.5. HOMA-IR, homeostasis model assessment of insulin resistance.

independently associated with MetS were older age, higher BMI and presence of PCOS. No interaction was found between age/BMI with PCOS in the prediction of MetS. The presence of PCOS conferred a 5-fold increase in risk of MetS (OR 4.90; 95% CI: 1.35–17.84) as defined by the modified ATPIII 2005 criteria even after adjustment for age and BMI.

Characteristics of PCOS women with or without MetS

Table IV compares the characteristics of PCOS women with or without MetS. Amongst women with PCOS, those with MetS were older, more obese, and were more likely to be smokers. They also had lower LH concentrations and reduced insulin sensitivity as manifested by greater HOMA-IR and higher fasting insulin concentrations than those without MetS. There were no significant differences in serum total testosterone or proportion with hyperandrogenism or LH predominance between those with or without MetS.

Discussion

MetS, characterized by a cluster of cardiometabolic risk factors associated with insulin resistance, is a disease with great health impact as it confers a 5-fold increase in risk of Type 2 diabetes and a 2-fold increase in risk of cardiovascular diseases (Haffner *et al*., 1992; Isomaa *et al*., 2001; Eckel *et al*., 2005). Despite ongoing debate regarding whether the risk associations of MetS are more than the sum of its individual components (Kahn *et al*., 2005), there is a growing consensus on the importance of global cardiometabolic risk assessment in at risk individuals (Despres *et al*., 2006).

In agreement with previous studies (Apridonidze *et al*., 2005; Carmina *et al*., 2006; Hahn *et al*., 2007; Weerakiet *et al*., 2007), we have demonstrated a higher risk of MetS in women with PCOS, independent of, but exacerbated by aging and obesity. The high rates of ATPIII-defined MetS in the entire PCOS cohort (18.1–24.9%) and in those PCOS women younger than 30 years old (12.9–16.7%) are alarming. When compared with the age-matched population controls from the Hong Kong Cardiovascular Risk Factor Prevalence Survey (Thomas *et al*., 2005), the risk of MetS was almost 13-fold higher in those aged <30 years and 3- to 4-fold higher in those aged 40–40.9 years in the presence of PCOS (Fig. 1). The prevalence of Type 2 diabetes (7.5%) was also much higher than that reported from the general population in the same area (0.6% at age under 35 years, Report on Population Health Survey 2003/2004, Department of Health, Hong Kong).

Among the many diagnostic criteria for MetS, the ATP III criterion is the simplest to use in the clinical setting. Other diagnostic criteria from WHO and European Group for the Study of Insulin Resistance include insulin resistance as a diagnostic component and yet measurement of insulin resistance is expensive, labour intensive and difficult to standardize. While another commonly used International Diabetes Federation (IDF) criteria for MetS is based on the same parameters used in the ATPIII criteria, the IDF criteria requires central obesity as an essential and obligatory component for MetS, and has been demonstrated to be deficient in identifying the metabolically abnormal but non-obese patients known to be predisposed to Type 2 diabetes and cardiovascular disease (Yoon *et al*., 2007). Our study also demonstrated that while metabolic derangements occurred more often in overweight and obese PCOS women, non-obese PCOS women also had a significantly higher fasting TG ($P = 0.004$) and a trend towards lower HDL-C concentrations ($P = 0.07$) when compared to their normal-weight counterparts. High TG and low HDL-C are the characteristic types of dyslipidaemia seen in insulin-resistant subjects. This is in line with the current view that although the presence of obesity exacerbates the insulin resistance state associated with PCOS, even lean PCOS women have features of insulin resistance compared to age-matched lean control subjects (Dunaif *et al*., 1989; Dunaif, 1997). Lean PCOS women appear to have an intrinsic form of insulin resistance involving post-binding defects in insulin

receptor signalling (Dunaif *et al*., 2001), while obese women with PCOS not only suffer from the insulin resistance intrinsic to PCOS but also that associated with increased adiposity (Marsden *et al*., 2001).

Conversely, although the original ATPIII criteria proposed in 2001 have been widely used in both clinical practice and epidemiological studies, it has been shown to under-estimate the prevalence of MetS when applied to the Asian population (Tan *et al*., 2004). The use of 2005 AHA/NHLBI modified ATPIII definition, which takes into account ethnicity to define central obesity and the use of a lower cut-off of IFG, identified a higher percentage of PCOS women with MetS, but to our belief, is a more discriminative criterion than its original definition in identifying at risk individuals in our locality. Both of these cut-off values of waist circumference (Ko *et al*., 1996) and FPG (Cockram, 1999) have been validated in the Chinese. However, the diagnostic limitation of using FPG alone without OGTT in the ATPIII definition raises some concern as it has been shown to under-estimate the diabetes and cardiovascular risks especially among obese subjects (Ehrmann *et al*., 1999; Janus *et al*., 2000). Our data also illustrated that fasting glucose alone under-estimates the prevalence of glucose abnormalities, suggesting the need for a complementary OGTT in all women with PCOS.

The finding of an increase risk of MetS in women with PCOS has raised further interest in identifying the predictors for MetS in these women. Insulin resistance, without dispute, is most likely the pathogenic link between PCOS and MetS. The co-morbidities associated with insulin resistance are common to both conditions. All surrogate markers of reduced insulin sensitivity have consistently been found in women with concomitant PCOS and MetS compared to those without MetS, even after controlling for BMI (Dokras *et al*., 2005; Ehrmann *et al*., 2006). However, in contrast to the finding of Apridonidze *et al*. (2005), who described a higher prevalence of hyperandrogenaemia in women with concomitant PCOS and MetS, the study of Dokras *et al*. (2005) as well as our own both failed to demonstrate any significant differences in serum concentrations of free testosterone (Dokras *et al*., 2005) or total testosterone between those PCOS women with or without MetS. In addition, it was shown that lipid abnormalities and hyperinsulinaemia persisted despite suppression of androgens with GnRH agonists in hirsute hyperandrogenic women (Wild *et al*., 1992). It therefore appears that hyperandrogenism, by itself, may not directly contribute to the development of MetS in women with PCOS. As both hyperinsulinaemia and hypersecretion of LH have been proposed as possible mechanisms of PCOS-associated hyperandrogenaemia, the two mechanisms may contribute independently to the metabolic and endocrine abnormalities of PCOS. This is consistent with the finding that while insulin resistance is a common feature in obese PCOS women, elevated LH is more frequently observed in lean women with PCOS (Panidis *et al*., 2005).

The recognition of the role of insulin resistance, rather than hyperandrogenism, as the main culprit in the pathogenesis of MetS in PCOS has important therapeutic implications. The combined oral contraceptive pill, which through its androgen-lowering effect ameliorates androgenic symptoms and regulates menstruation, is currently one of the standard treatments for PCOS. However, it may decrease insulin sensitivity and aggravate metabolic derangements, especially in obese PCOS subjects (Nader *et al*., 2007). With increasing recognition of the importance of its metabolic consequences, future evaluation and therapy for PCOS should go beyond the target of short-term symptom control to the early screening and long-term prevention of cardiovascular risks. Strategies designed to attenuate insulin resistance, such as insulin-sensitizing drugs (Lord *et al*., 2003), used as an adjuvant to lifestyle interventions comprising weight reduction, dietary modification and increased physical activity (Norman *et al*., 2002), which have promising results not only on improvement in reproductive outcomes and hyperandrogenism but also on reduction of metabolic risks, will definitely bring much hope towards the future management of PCOS.

There are several limitations to the present study. First, all PCOS women in this study were recruited from the hospital gynaecology clinics but two-thirds of the control subjects were enrolled from the general population. This may contribute to potential selection bias and over-estimation of the risk of MetS in the PCOS cohort. In addition, PCOS women with predominant hyperandrogenic features may be referred to the medical rather than gynaecology clinics. Nevertheless, the effect of this referral bias was believed to be small as Chinese women with PCOS have been shown to have higher rates of menstrual irregularity and infertility, and relatively low rates of hyperandrogenism (Yan *et al*., 2005). Besides, our combined gynae-endocrinology clinics receive referrals from both specialties. In addition, there was also potential measurement bias as the anthropometric measurements were not blinded. Also, we only measured total testosterone concentrations which may be a less sensitive marker for hyperandrogenism than free testosterone levels. Finally, some subjects declined OGTT, so the frequency of glucose intolerance in these women might have been under-estimated. Despite all these limitations, the present study, being one of the first to report detailed metabolic characterization of a large cohort of Chinese PCOS subjects, may provide valuable insight towards better understanding of the cardiometabolic risk profile in PCOS women in this region, where there is a rising prevalence of diabetes and cardiovascular disease (Gu *et al*., 2003, 2005).

In conclusion, the diagnosis of PCOS in Hong Kong Chinese women is associated with a higher prevalence of MetS and other cardiovascular risk factors irrespective of age and weight. Our results also indicate the need for a comprehensive screening and education programme in these women to identify high-risk individuals for early intervention. Health care professionals should be aware of the evidence that PCOS is not only a gynaecological endocrine disease but also equally important as a metabolic disorder.

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