Comparison of the phenotype of Chinese versus Dutch Caucasian women presenting with polycystic ovary syndrome and oligo/amenorrhea

M. Guo1, Z.J. Chen2*, M.J.E. Eijkemans1,3, A.J. Goverde1, B.C.J.M. Fauser1, and N.S. Macklon1,4

1Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands 2Center for Reproductive Medicine, Provincial Hospital Affiliated to Shandong University, Jinan, China 3Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands 4Division of Developmental Origins of Adult Diseases (DOHaD), Princess Anne Hospital Affiliated to University of Southampton, Southampton, UK

*Correspondence address. E-mail: chenzijiang@hotmail.com

Submitted on June 30, 2011; resubmitted on November 6, 2011; accepted on November 29, 2011

BACKGROUND: Polycystic ovary syndrome (PCOS) is a complex disorder with variable prevalence and clinical presentation in different populations, which may be mediated by geographical and ethnic background.

METHODS: We performed a comparison of phenotypic characteristics between 547 Chinese and 427 Dutch women with PCOS and oligo/amenorrhea attending University Reproductive Centers in China and the Netherlands.

RESULTS: Chinese women presenting with a clinical diagnosis of PCOS were observed to have a higher incidence of hyperandrogenism (HA) (P < 0.001) and amenorrhea (P < 0.001) compared with Dutch women, but no difference was observed in the incidence of polycystic ovaries (PCOs). Using population-specific cut-off values, Chinese women with PCOS demonstrated a higher incidence of increased BMI (P < 0.001), waist circumference (WC) (P < 0.001) and waist–hip ratio (P < 0.001) than Dutch women. In both groups, HA was associated with increased age, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and serum LH while PCOs correlated with BMI, WC, HOMA-IR, fasting insulin and elevated total testosterone. Associations specific for ethnic background were found between LH and HA, and between both BMI and HOMA-IR, and PCOs.

CONCLUSIONS: Reproductive and metabolic characteristics differed between the two ethnic groups. Chinese women were found to present more frequently with a phenotype associated with increased risk of metabolic complications later in life, compared with Dutch Caucasian women. Ethnicity seems to determine part of the specific phenotypical presentation of PCOS.

Key words: anovulation / ethnicity / infertility / polycystic ovary syndrome / phenotype

Introduction

Polycystic ovary syndrome (PCOS) is a complex disorder predominantly characterized by ovarian dysfunction (oligo-/anovulation), hyperandrogenism (HA) and polycystic ovaries (PCOs) (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

In addition, PCOS is associated with obesity, insulin resistance (IR), dyslipidaemia and hypertension (Ehrmann et al., 2006; Goverde et al., 2009). In complex disorders, the clinical presentation is the result of the interplay between genetic susceptibility and environmental factors. As a result, the prevalence and the clinical presentation of PCOS in different populations may be influenced by geographical and ethnic background. Most knowledge regarding PCOS is derived from studies reporting on Caucasian women in western societies, and there is therefore a need for more studies in women of other ethnic backgrounds and geographical origin.

The prevalence of PCOS diagnosed according to the 1990 National Institutes of Health (NIH)-sponsored conference criteria (Zawadski and Dunai, 1992) is 5–8% in several Caucasian populations (Knocchenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Azziz...
et al., 2004; Escobar-Morreale and San Villan, 2007). A PCOS prevalence as high as 12% has been reported in the Australian population using the Rotterdam diagnostic criteria (March et al., 2010); however, in South China, using the same diagnostic criteria, a prevalence of just 2.2% has been reported (Chen et al., 2008a,b). Moreover, when using the Rotterdam diagnostic criteria, women of different ethnicities with PCOS may show different phenotypic patterns in relation to HA, menstrual dysfunction, body weight and IR (Carmina et al., 1992; Dunäf et al., 1993; Norman et al., 1995).

It has been suggested that East-Asian women with PCOS present less often with clinical features of HA (Chae et al., 2008). Indeed, in a report from mainland China, none of the women diagnosed with PCOS presented with hirsutism (Chen et al., 2008a,b). This was also the case in a study of Taiwanese Chinese women (Hsu et al., 2007). However, acne has been reported to be a prominent expression of clinical HA in Chinese women with PCOS (Welt et al., 2006; Li et al., 2007; Chen et al., 2008a,b; Liou et al., 2009). PCOs are also frequently present in East-Asian women with PCOS, although lower diagnostic cut-off levels for ovarian volume and follicle number have been suggested (Ng et al., 2006; Chen et al., 2008a,b). The association of PCOS with metabolic abnormalities is reported similarly in Asian and Caucasian women. Asian women with PCOS demonstrate a higher degree of IR than those without PCOS (Carmina et al., 2003; Welt et al., 2006; Chae et al., 2008), while those with PCOS have been shown to be more insulin-resistant if they are also hyperandrogenic (Park et al., 2007; Lam et al., 2009). Our group has recently reported a low prevalence of metabolic syndrome in a Chinese population (Guo et al., 2010); within this population, the incidence of metabolic syndrome did not appear to vary significantly with the specific PCOS phenotype.

Information regarding variability of PCOS presentation resulting from ethnic or geographical differences is scant, and cross-population studies are necessary to ascertain key differences in phenotypes that may point to genetic variability or genetic or environmental modifiers of PCOS. In turn, these data could guide appropriate health screening policies for women with PCOS depending on geo-ethnic origin.

No direct comparison of phenotypic characteristics between Asian and Caucasian women with PCOS has been performed. We therefore set out to evaluate the phenotypic differences in presentation of Chinese and Caucasian Dutch women with PCOS associated with oligo/amenorrhea according to the 2003 revised Rotterdam criteria, which requires the presence of two out of the three following features for the diagnosis of PCOS: (i) oligo and/or amenorrhea, (ii) clinical and/or biochemical signs of HA and (iii) echographic PCO, after the exclusion of other related pathologies (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), and to explore the relationship of the clinical phenotypic features of PCOS and biophysical characteristics of these two ethnically different groups. Although this study was limited to women presenting with oligo/amenorrhea, this is a major subgroup of women with PCOS and likely to manifest key differences related to ethnic origin if present.

Materials and Methods

Between January 2004 and January 2007, women presenting with oligomenorrhea (mean interval between bleedings 35–182 days) or amenorrhea (interval between bleedings ≥182 days) and a diagnosis of PCOS were systematically evaluated in an outpatient setting at the Department of Reproductive Medicine of Shandong University, Jinan, China, and the Department of Reproductive Medicine and Gynecology of the University Medical Center in Utrecht. Data collected from the cohort of 547 Chinese women cohort have been published previously by our group (Guo et al., 2010). During the same period, similar data were collected from 427 consecutive Dutch women presenting similarly at the Netherlands.

Information on cycle abnormality, medical and family history, and any previous or current use of medication was obtained by standardized questionnaires. Physical examination included assessment of race, acne, hirsutism and acanthosis nigricans, and measurement of height, weight, waist and hip circumferences and blood pressure (BP). Pelvic ultrasonography was performed for the evaluation of the internal genitalia. In addition, all women underwent early morning blood sampling after an overnight fasting for assessment of the endocrine (including pituitary hormones, ovarian and adrenal steroids) and metabolic (including lipids, glucose and insulin) profile. Approval of the local Institutional Review Committees at both sites was obtained for this standardized evaluation of women in whom PCOS was suspected. All women participating in this study had given written informed consent.

Women were diagnosed as having PCOS if at least two of the following criteria were present: oligo/anovulation (OA) clinical and/or biochemical HA or PCOs on ultrasonography (Balen et al., 2003), as determined by the Rotterdam consensus PCOS criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Other aetologies which could mimic PCOS, such as Cushing’s syndrome, late-onset adrenal hyperplasia or androgen-producing neoplasm, were excluded with appropriate tests. Women with oligo/amenorrhea related to hyper- or hypogonadotropic disorders were excluded, as were those with ultrasound evidence of intrauterine abnormalities underlying their cycle disorder.

In order to evaluate the role of ethnicity, each of the two groups consisted of women of one racial background only. In the Jinan cohort, women were Han Chinese and the Dutch cohort was exclusively Caucasian.

Physical examination and ultrasound assessment

In both study groups, BP was measured in a sitting position after a 10 min rest using an electronic BP monitor with an inflatable cuff size appropriate for the upper arm circumference. In case the reading was abnormal, a second measurement was taken after 1 min, and the average of both measurements was used. Anthropometric variables, such as body height (in cm), weight (in kg with 1 decimal), waist circumference (WC, in cm) and hip circumferences (HC, in cm), were measured. WC was measured in the standing position, halfway between the lower ribs and the superior anterior iliac spine of the pelvis. HC was measured at the level of the pubic symphysis. Hirsutism was assessed according to the modified Ferriman–Gallwey (FG) score (Ferriman and Gallwey, 1961). The Dutch women were diagnosed as hirsute, when the FG score was >8. The exact FG score was only calculated in women meeting this criterion. Missing values for those not diagnosed as hirsute were interpolated. The presence of acanthosis nigricans was determined according to the clarification description of the Andrews’ Diseases of the Skin (James et al., 2005).

Transvaginal ultrasonography was systematically performed on a Kretz Voluson 530, using the 7.5 MHz transvaginal probe in Dutch women and LogIQ-200 Pro series ultrasonic machine (GE Company, New York, NY, USA) with a 6.5 Hz vaginal probe in Chinese women. Follicles were measured in three dimensions and those with a mean diameter of 2–9 mm counted.
Lipid profiles including high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and total cholesterol were quantified using a Konelab 30w (Thermo Clinical Labsystems, Vantaa, Finland). Triglyceride (TG) was measured using a VITROS Chemistry System (Ortho-Clinical Diagnostics, Strasbourg, France). Insulin and glucose were quantified using an Immulite platform (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra- and inter-assay coefficients of variation were <10% for all assays performed.

Table I Baseline clinical and biochemical characteristics of Chinese women and Dutch women with PCOS and oligo/amenorrhea.

<table>
<thead>
<tr>
<th></th>
<th>Chinese women (n = 547)</th>
<th>Dutch women (n = 427)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.3 ± 3.4</td>
<td>29.0 ± 5.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.7 ± 12.2</td>
<td>74.9 ± 20.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 4.3</td>
<td>26.3 ± 6.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Increased BMI (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥26 kg/m²</td>
<td>40%</td>
<td>42%</td>
<td>0.2666</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>15%</td>
<td>28%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>82.5 ± 10.8</td>
<td>86.0 ± 19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased WC (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80 cm</td>
<td>54%</td>
<td>59%</td>
<td>&lt;0.045</td>
</tr>
<tr>
<td>≥88 cm</td>
<td>32%</td>
<td>36%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>97.3 ± 9.4</td>
<td>104.1 ± 17.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist–hip ratioa</td>
<td>0.85 ± 0.06</td>
<td>0.82 ± 0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferriman–Gallwey score</td>
<td>3.6 ± 4.9</td>
<td>5.2 ± 5.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119 ± 11</td>
<td>125 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 10</td>
<td>79 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH (IU/l)b</td>
<td>6.9 ± 15.3</td>
<td>1.0 ± 15.3</td>
<td>0.244</td>
</tr>
<tr>
<td>LH (IU/l)b</td>
<td>10.4 ± 6.3</td>
<td>10.8 ± 8.9</td>
<td>0.469</td>
</tr>
<tr>
<td>Total testosterone (nmol/l)</td>
<td>2.3 ± 1.3</td>
<td>2.3 ± 2.1</td>
<td>n.a.</td>
</tr>
<tr>
<td>Prolactin (pmol/l)</td>
<td>787.0 ± 582.6</td>
<td>165.2 ± 156.5</td>
<td>n.a.</td>
</tr>
<tr>
<td>Estradiol (pmol/l)</td>
<td>222.8 ± 186.9</td>
<td>319.7 ± 297.7</td>
<td>n.a.</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>4.8 ± 0.7</td>
<td>5.2 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (mmol/l)b</td>
<td>10.2 ± 7.5</td>
<td>9.8 ± 9.6</td>
<td>0.002</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.2 ± 1.9</td>
<td>2.4 ± 2.8</td>
<td>0.219</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.7 ± 0.9</td>
<td>4.7 ± 1.0</td>
<td>0.463</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)b</td>
<td>1.1 ± 1.0</td>
<td>1.0 ± 0.7</td>
<td>0.144</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.7 ± 0.4</td>
<td>1.5 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.0 ± 1.1</td>
<td>2.8 ± 1.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/l)</td>
<td>2.9 ± 1.0</td>
<td>3.2 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean ± SD. Asia criteria: BMI ≥ 26 kg/m² (Ko et al., 2001); WC ≥ 80 cm (ATPIII-WPRO, 2000). Western criteria: BMI ≥ 30 kg/m² (World Health Organization, Global Database on BMI, 2009); WC ≥ 88 cm (ATPIII, 2001). HOMA-IR, Homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein. All analyses by Student’s t-test. *Statistical analysis after square root transformation to correct for non-normal distribution. **Analysis after logarithmic 10 transformation.

Laboratory assessment

Dutch women

FSH, LH and prolactin were assayed in serum with chemiluminescence assays, and estradiol (E₂) concentrations were measured by indirect chemiluminescence, all on the ADVIA Centaur Automated System (Bayer Corporation, Tarrytown, NY, USA) until 30 November 2006. From 1 December 2006 onwards, these assays were performed on the DXi (Beckman, Fullerton, CA, USA). All concentrations measured with the Centaur were recalculated to DXi outcomes according to the following equations:

\[ \text{LH} \times \text{DXi} = 0.88 \times \text{Centaur} + 0.87 \text{U/l} \]
\[ \text{FSH} \times \text{DXi} = 1.16 \times \text{Centaur} + 0.46 \text{U/l} \]
\[ \text{prolactin} \times \text{DXi} = 0.82 \times \text{Centaur} - 0.11 \text{U/l} \]
\[ \text{total testosterone} \times \text{DXi} = 0.77 \times \text{Centaur} + 0.5 \text{nmol/l} \]
\[ \text{E}_2 \times \text{DXi} = 0.76 \times \text{Centaur} + 25 \text{pmol/l} \]

Total testosterone was measured by radioimmunoassay (developed in-house) after organic solvent extraction (normal values for women 0.5–2.0 nmol/l).
Definitions
Clinical HA was defined as the presence of hirsutism, which was set at a modified FG (mFG) score of >8 for Dutch women and of ≥ 6 for Chinese women (Hatch et al., 1981; Knochenhauer et al., 1998; Yang et al., 2010) and/or acne. Biochemical HA was defined as a total testosterone >2.08 nmol/l in Chinese women and >2.0 nmol/l in Dutch women, according to the normal upper reference limit of the different assays used at each onsite laboratory. The presence of these cycle abnormalities indicates OA (Burgers et al., 2010). PCO was defined as the presence of at least one ovary with 12 or more follicles measuring 2–9 mm diameter and/or ovarian volume >10 ml (Balen et al., 2003). IR was assessed using the homeostatic model assessment of IR (HOMA-IR), calculated as (fasting insulin × fasting glucose)/22.5 (Legro et al., 2004). Obesity and increased WC were defined according to the specific ethnic population criteria, since the proportion of body fat which is itself a predictive factor for development of metabolic disease has been shown to differ between ethnic groups of the same BMI (Ko et al., 2001; WHO Expert Consultation, 2004; Rahman and Berenson, 2010). For Chinese women, obesity was defined as BMI ≥ 26 kg/m² (Ko et al., 2001) and increased WC as WC ≥ 80 cm (NIH ATP III-WPRO, 2000). For Caucasian Dutch women, obesity was defined as BMI ≥ 30 kg/m² (World Health Organization, 2009) and increased WC as WC ≥ 88 cm (ATP III, 2001).

Statistical analysis
Data are presented as mean ± SD. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows version 11.2 (SPSS Inc., Chicago, IL, USA). For Dutch women, initially mFG scores were only recorded if >8 as an expression of hirsutism. This resulted in scores only being recorded in half of the Dutch study cases. To extrapolate to the whole study cohort, mFG scores were calculated after multiple imputation with the expectation-maximization algorithms (Azar et al., 2001). Continuous variables were analysed with the Kolmogorov–Smimov statistical test. Differences between two groups were analysed with the independent sample t-test after square transformation of the waist–hip ratio and logarithmic transformation of LH, fasting insulin and TG. The independent t-test for biochemical values was performed only when assays were comparable, which was not the case for total testosterone, prolactin and E₂.

Proportions were explored using the χ² or Fisher’s exact test as appropriate. Logistic regression was used to evaluate the contribution of these variables to the presence of HA. Independent variables were the presence or absence of amenorrhea and PCO, physical examinations (such as age, BMI, WC), serum profiles (HOMA-IR, fasting insulin, fasting glucose, LH), the origin of the data (Chinese or Dutch) and the interaction of data origin and each of the independent variables. Similar analyses were applied with PCO and oligomenorrhea, with increased total testosterone (yes/no) included as the independent variable for its contribution to the presence of hirsutism, as the dependent variable. Statistical significance was considered at the two-tailed P-value of 0.05.

Results
Baseline characteristics of the 547 Chinese and 427 Dutch women with oligo/amenorrhea diagnosed with PCOS are depicted in Table I. The mean age of the Chinese cohort was lower than that of the Dutch women. Although absolute BMI and WC measurements were lower in Chinese women, when adjusted for regional standards, the relative prevalence of obesity and increased WC was higher in Chinese women and their mean waist–hip ratio was greater compared with Dutch women. On the other hand, Chinese women had lower systolic and diastolic BP than Dutch women.

The distribution of the three PCOS phenotypes with oligo/amenorrhea known to be associated with ovulatory disorders in the two ethnic groups is depicted in Fig. 1. In both Chinese (81%) and Dutch (55%) women with PCOS, the phenotype characterized by OA + HA + PCO was most frequently identified. The phenotype characterized by OA + PCO occurred in 9% of Chinese and in 35% of Dutch PCOS women, and 10% of both Chinese and Dutch PCOS women presented with HA + OA.

The prevalence of PCO did not differ between the two groups (89.9 versus 90%, P = 0.958) (Fig. 2). However, Chinese women presented more often with amenorrhea (74.8 versus 26.8%, P < 0.001) and with HA (91.0 versus 64.3%, P < 0.001), although this difference was in clinical features of HA (51.5 versus 28.5%, P < 0.001) such as hirsutism (corrected for ethnicity; 20.8 versus 10.2%, P < 0.001), acne (40.8 versus 19.8%, P < 0.001) and/or acanthosis nigricans (21.4 versus 0.3%, P < 0.001). No significant difference was found in the prevalence of biochemical HA (57.2% in Chinese versus 50.8% in Dutch women, P = 0.053).
Endocrine and metabolic serum profiles of the two groups are shown in Table I. Chinese women had higher fasting insulin and HDL cholesterol, as well as lower fasting glucose and non-HDL cholesterol than Dutch women, even after controlling for age.

In the logistic regression analysis, we explored the relationship between the reproductive and metabolic characteristics. We also assessed the effect of ethnicity by setting the interaction of profiles with case origin as independent covariates. For HA (clinical and/or biochemical HA) as a dependent variable, PCO, oligomenorrhea or amenorrhea, age, BMI, WC, HOMA-IR, fasting insulin, fasting glucose, LH and increased total testosterone (yes/no) were used as the independent variables. HA was negatively associated with age but positively related with fasting insulin, HOMA-IR and LH. LH had the independent variables. HA was negatively associated with age or amenorrhoea, age, BMI, WC, HOMA-IR, fasting insulin, fasting glucose, LH and increased total testosterone (yes/no) were used as the independent variables. HA was negatively associated with age but positively related with fasting insulin, HOMA-IR and LH. LH had a stronger effect on the occurrence of HA in Dutch women than Chinese women. For clinical HA, a negative association was found for age [P = 0.02, odds ratio (OR) = 0.962], while BMI was associated positively (P = 0.03, OR = 1.028). Similar analyses were performed for PCO and oligomenorrhea. PCO was negatively related with BMI, WC, HOMA-IR, fasting insulin and increased total testosterone. An increased BMI, fasting insulin and HOMA-IR had a stronger association with the occurrence of PCO in Chinese women than Dutch women. No association was found for oligomenorrhea and any clinical or biochemical factor (Table II).

Discussion

We present the first direct comparison of phenotypic and clinical characteristics between Chinese and Dutch Caucasian women diagnosed with PCOS associated with oligo/amenorrhoea. Chinese women with PCOS more often presented with HA, amenorrhea, obesity and increased waist–hip ratio. Significant differences between Dutch and Chinese women were found for fasting glucose, insulin and HDL and non-HDL concentrations, although overall these measurements were within normal ranges. In Dutch Caucasian women, LH had a stronger association with HA than in Chinese women. On the other hand, in Chinese women with PCOS, the presence of PCO was more strongly associated with an increased BMI and altered HOMA-IR than in Dutch women.

Table II Outcome of testing for association of PCOS criteria with clinical and biochemical variables by logistic regression in the combined Dutch (n = 427) and Chinese (n = 547) patients.

<table>
<thead>
<tr>
<th>Components</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.961</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>0.107</td>
<td>0.095</td>
</tr>
<tr>
<td>BMI</td>
<td>0.899</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>0.092</td>
<td>0.03</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.875</td>
<td>0.004</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>0.488</td>
<td>0.036</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>0.964</td>
<td>0.014</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>0.512</td>
<td>0.062</td>
</tr>
<tr>
<td>Elevated total testosterone</td>
<td>1.854</td>
<td>0.009</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>0.991</td>
<td>0.967</td>
</tr>
<tr>
<td>Hyperandrogenism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.919</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>5.417</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>1.045</td>
<td>0.002</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>2.024</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.153</td>
<td>0.005</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>5.840</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH</td>
<td>1.053</td>
<td>0.002</td>
</tr>
<tr>
<td>Source of data (Chinese/Dutch)</td>
<td>10.786</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Beneath each clinical association, the odds ratio for the association differing in the Dutch dataset from the Chinese is given. For logistic regression, each independent variable, the source of data and their interaction were set as covariates with 'Enter' at the first block and their interaction set as covariates at the second block screened with 'Forward LR'. Dependent variables: HA, PCO. Independent variables: age, HA, PCO, oligomenorrhea, BMI, WC, HOMA-IR, fasting insulin, fasting glucose, LH and increased total testosterone.

The interaction of variable by the source of data (Chinese/Dutch) (P-values): 1BMI by source of data 0.042. 2HOMA-IR by source of data 0.034. 3Fasting insulin by source of data 0.04. 4LH by source of data 0.005.

A higher percentage of Chinese women presented with (clinical) HA than Dutch Caucasian women, with both acne and hirsutism more often observed in the Chinese than in the Dutch study group. However, it should be noted that a lower cut-off for the FG score was used to determine hirsutism in Chinese women, as East-Asians are reported to have a less dense hair pattern than Euro-Americans (Ewing and Rouse, 1978; Azziz et al., 2009). The prevalence of HA in our cohort of Chinese women is comparable with that reported in Taiwanese and Hong Kong Chinese women (Lam et al., 2005; Hsu et al., 2007). With a cut-off for the FG score at 6, 20.8% of the Chinese women in this study were diagnosed with hirsutism, whilst 10.2% in Dutch. This is in sharp contrast to a report from a similar ethnic and geographical Chinese cohort in which no woman diagnosed with PCOS presented with hirsutism (Chen et al., 2008a,b). However, that study assessed the prevalence of PCOS in an unselected community cohort of which only a limited number of women were actually diagnosed with PCOS.
Body composition in the Chinese women of this cohort was less favourable as shown by higher waist–hip ratio and obesity rate, as well as increased WC rate corrected for ethnicity. However, in contrast with these clinical signs, Chinese women did not present with an unfavourable metabolic profile compared with their Dutch counterparts. In fact, Dutch women had higher BP and a less favourable lipid profile, although overall these levels were within normal ranges. HOMA-IR ratios were not significantly different between the two study groups and did not indicate severe IR. Although not a direct comparative study, the IR and its related metabolic abnormalities were reported to be less frequent in Dutch women with PCOS than in Americans with the same diagnosis (Goverde et al., 2009). This may reflect the higher prevalence of obesity in the Dutch group.

The relatively higher (abdominal) obesity rate found in the Chinese women of this study may have favoured their hyperandrogenic presentation, since abdominal adiposity has both a direct (Barber et al., 2006) and an indirect effect on androgen levels (Sam and Dunaf, 2003; Escobar-Morreale and San Villan, 2007). This also explains the higher prevalence of acanthosis nigricans, which is frequently caused by IR in Chinese women. Acanthosis nigricans appears to be especially associated with upper body obesity, where there is increased peripheral aromatization of androgens to estrogens (Diamanti-Kandarakis and Berliec, 2001; El Safoury et al., 2010). The neck is also considered to be an androgen-dependent area, similar to the axillae and the groins, though hairless (Ozdemir et al., 2010). However, the prevalence of abnormal metabolic laboratory parameters was much lower in Chinese women which was not consistent with these mechanisms. An explanation for these contrasting observations could be that in the Chinese women, the metabolic action of insulin is maintained at a higher level, while its reproductive negative effects can already be recognized at relatively low insulin concentrations. This may reflect an ethnic difference in insulin receptor action in PCOS (Cohan et al., 2000). In general, hyperinsulinaemia is attributed to an adaptive mechanism to compensate for lower insulin sensitivity by increased insulin secretion. It has also been demonstrated that diminished insulin clearance is an important underlying mechanism in various IR conditions, notably obesity (Shapiro et al., 1988; Jones et al., 1997). Insulin sensitivity index and β-cell function have been shown to be variable in different ethnicities (Chiu et al., 2000). It can therefore be postulated that lower insulin sensitivity and decreased insulin clearance maybe the explanation for the higher fasting insulin found in Chinese women.

The association between the specific PCOS phenotype and degree of metabolic disturbance has been reported previously (Goverde et al., 2009). While the subphenotype of PCOS with oligo/amenorrhea without HA is associated with fewer metabolic disturbances and lower BMI and WC (Welt et al., 2006; Shroff et al., 2007; Goverde et al., 2009), HA (clinical and/or biochemical HA) has been demonstrated to be positively correlated with parameters of IR and BMI (Gambinen et al., 2002; Hsu et al., 2009; Yang et al., 2010). In the present study, HA was more strongly correlated to the degree of metabolic disturbance in the Chinese cohort than the Dutch. PCO was negatively correlated with BMI and HOMA-IR in both cohorts, but this was found to be more marked in Chinese women.

When drawing conclusions from this study, a number of limitations need to be considered. First, the inclusion of only women with oligo/amenorrhea into the study cohorts may have introduced a selection bias as many ovulatory women with PCOS were thus excluded, and unfortunately, no control group data were available. Although the systematic evaluation in China and the Netherlands contained many identical elements, no a priori alignment in the data to be collected was performed. Each site of recruitment carried out their own laboratory analyses, resulting in the need for calibration prior to analysis. Unfortunately, no accurate data on biochemical HA are available for the Chinese women in this study. In this group, testosterone was used owing to its simplicity and because of evidence that it is a better discriminator between PCOS and mild Cushing’s syndrome (Pall et al., 2008). Better sensitivity and specificity has been reported by measuring bioavailable testosterone and free androgen index (Rosner et al., 2007; Hahn et al., 2007). Therefore, we were unable to perform a direct comparison between Chinese and Caucasian women for biochemical HA.

Despite employing different BMI cut-off points to define obesity, depending on ethnic origin (WHO/IASO/IOTF, 2000), no differences in metabolic profiles were observed between our two study groups. This finding, in well described and ethnically homogenous groups, would appear to provide an additional rationale for the current advice from the World Health Organization not to adapt cut-off BMIs to define the degree of obesity in Asian populations (World Health Organization, 2010).

Despite the limitations stated, this large cross-sectional comparison of two populations of women with PCOS did reveal a number of significant differences between the two ethnic groups. These are summarized in Table I. A key novel finding was the less favourable body composition observed in the Chinese group, contrasted with the less favourable metabolic profile identified in the Dutch group. Increasing awareness of the long-term health implications of PCOS and the need to identify women at particular risk has led to increased interest in identifying clinical parameters and specific PCOS phenotypes which may predict long-term morbidity. Our findings demonstrate that women with PCOS who come from different ethnic backgrounds may have different metabolic risk profiles and that the relative weight given to individual screening parameters as predictors of long-term disease may require to be adjusted according to ethnic origin. Moreover, this work suggests that it may be important to screen some women with PCOS more aggressively for certain diseases based on their ethnic background. Further work is required in order to ascertain whether the difference in risk factors identified is translated into differences in long-term morbidities. Only then can ethnic population-specific prediction models, designed to identify women in need of aggressive monitoring and intervention, be developed and validated.

**Acknowledgements**

Thank you very much for all the cooperative authors’ great job on this paper. And we are very appreciative for the help from PCOS research groups of the Center for Reproductive Medicine, Provincial Hospital Affiliated to Shandong University, and the Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht.
Authors’ roles

M.G.: design of the study, data analysis, writing the manuscript. Z.J.C.: data collection, writing the manuscript. Y.H.S.: data collection. M.J.E.: data analysis. B.C.J.M.F.: design of the study, data analysis, writing the manuscript. A.J.G.: design of the study, data analysis, writing the manuscript. N.S.M.: design of the study, data analysis, writing and approval of final draft of the manuscript.

Funding

A.J.G. has received fees from Schering/Bayer Schering for lectures and advisory committee. B.C.J.M.F. has received fees and grant support from the following companies (in alphabetic order): Andromed, Ardana, Ferring, Genovum, Glycotope, Merck Serono, Organon, Pantharei Bioscience, Philips, PregLem, Schring, Schering Plough, Serono and Wyeth. A.J.G. has received fees from Bayer Schering, IBSA, Procter and Gamble and Schering Plough for lectures and advisory committee. N.S.M. has received research funding and consultancy fees from Merck Serono, MSD, Organon, Schering Plough, Anecova and Ferring.

Conflict of interest

B.C.J.M.F. has received fees and grant support from the following companies (in alphabetic order): Andromed, Ardana, Ferring, Genovum, Glycotope, Merck Serono, Organon, Pantharei Bioscience, Philips, PregLem, Schring, Schering Plough, Serono and Wyeth. A.J.G. has received fees from Bayer Schering, IBSA, Procter and Gamble and Schering Plough for lectures and advisory committee. N.S.M. has received research funding and consultancy fees from Merck Serono, MSD, Anecova and Ferring.

References


Ng EH, Chan CC, Ho PC. Are there differences in ultrasound parameters between Chinese women with polycystic ovaries only and with polycystic ovary syndrome? *Eur J Obstet Gynecol Reprod Biol* 2006; 125:92–98.


