Objectives. To identify the characteristics of Hong Kong Chinese women with polycystic ovarian syndrome and to compare different diagnostic criteria.

Design. Retrospective study.

Setting. Gynae-endocrinology Clinics in the Prince of Wales Hospital, Hong Kong.

Patients. Ninety Hong Kong Chinese women with polycystic ovarian syndrome who were diagnosed according to the hospital’s criteria.

Main outcome measures. Prevalence of typical features of polycystic ovarian syndrome, including anovulation and hyperandrogenism (with other endocrine causes excluded), polycystic ovarian features on ultrasonography, luteinising hormone predominance, obesity, and insulin resistance.

Results. Almost all (98.9%) patients with polycystic ovarian syndrome presented with anovulation, only 48.9% of them had clinical or biochemical evidence of hyperandrogenism. Typical ultrasound appearances of polycystic ovaries were observed in 86.7% of patients. Luteinising hormone predominance and insulin resistance were demonstrated in 67.8% and 40.7% of the cohort, respectively. Eight-six (95.6%) patients should have also been diagnosed with polycystic ovarian syndrome based on the 2003 Rotterdam new criteria. About 60% of patients who screened positive for insulin resistance had normal fasting serum glucose levels. The same proportion who had full screening for insulin resistance by oral glucose tolerance tests and fasting serum glucose to insulin ratios had discordant results of these two tests.

Conclusions. The 2003 Rotterdam new diagnostic criteria for polycystic ovarian syndrome are generally applicable to the Hong Kong Chinese population. Early detection of insulin resistance in patients with polycystic ovarian syndrome can be ensured by performing an oral glucose tolerance test combined with measurement of fasting serum glucose to insulin ratio.
Introduction

Polycystic ovarian syndrome (PCOS) is a complex heterogeneous endocrine disorder. It is a syndrome, thus no single diagnostic criterion is sufficient for clinical diagnosis. During the first international conference on PCOS at the National Institutes of Health (NIH) in 1990, three key features of PCOS were generally agreed: chronic anovulation, hyperandrogenism (clinical or laboratory evidence), and the absence of other endocrine disorders (eg congenital adrenal hyperplasia, hyperprolactinaemia, or thyroid abnormalities).1 Nonetheless, this definition has been criticised. The presence of polycystic ovaries on ultrasonography was not included in the definition although it is a mandatory finding in many centres. Moreover, the assessment of clinical hyperandrogenism may be difficult, especially in the Chinese population where the prevalence of hirsutism is low.2 In addition, defining biochemical hyperandrogenaemia is limited by the inaccuracy and variability in the measurement of circulating androgen levels.3,4

In the last 10 years, the author’s unit has modified the criteria used to diagnose PCOS. The characteristic features of PCOS are considered major or minor. Two major criteria include chronic anovulation and hyperandrogenism with other endocrine causes excluded. Three minor criteria include appearance of polycystic ovaries on ultrasonography, luteinising hormone (LH) predominance, and obesity or insulin resistance. Using local criteria, PCOS is diagnosed if at least one major together with one major or minor criteria are met.

The 2003 Rotterdam PCOS consensus workshop proposed new diagnostic guidelines for PCOS.5 A diagnosis can be reached when at least two of three elements are present: chronic anovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries.5 These new guidelines are more flexible and permit the diagnosis to be made in patients previously excluded by the 1990 NIH criteria, which include anovulatory normoandrogenic women with polycystic ovaries or ovulatory hyperandrogenic women with polycystic ovaries. It remains to be seen whether the 2003 Rotterdam new guidelines are applicable to the Chinese population.

We conducted a retrospective review of medical records to examine the clinical features of a cohort of Hong Kong Chinese women with PCOS. We also compared the three diagnostic guidelines in this cohort.

Methods

Patients

The medical records of all women with PCOS seen in the Gynae-endocrinology Clinic in the Prince of Wales Hospital (PWH) during a 1-year period from July 2003 to June 2004 were reviewed. Women had been referred from various clinics: primary care clinics, medical clinics, and general gynaecology clinics. The criteria for referral to the Gynae-endocrinology Clinic in PWH included amenorrhoea or oligomenorrhoea, hirsutism, galactorrhoea, recurrent miscarriage, and an established diagnosis of PCOS—hyperandrogenism or hyperprolactinaemia. Women with PCOS and infertility were assessed at the Fertility Clinic, unless they had co-existing endocrine problems such as diabetes mellitus (DM). We identified 90 women with PCOS who were subsequently recruited to the study.

Diagnostic workup for polycystic ovarian syndrome

The hormonal profile was checked in all patients regardless of whether PCOS had been confirmed. The profile included serum concentrations of follicle-stimulating hormone (FSH), LH, and oestradiol in the early follicular phase of an ovarian cycle, serum prolactin level, thyroid function test, and serum concentrations of total testosterone. Predominance of LH was defined as increased serum LH levels (≥10 IU/L) or increased ratios of serum concentrations of LH to FSH (≥2.5) while the serum FSH level was normal. Hyperprolactinaemia or thyroid abnormalities as the cause of anovulation were excluded. Biochemical hyperandrogenaemia was defined as an elevated serum concentration of total testosterone (≥2.5 nmol/L). Other causes of hyperandrogenaemia such as adult-onset congenital adrenal hyperplasia and Cushing’s syndrome were excluded by further assessment by an endocrinologist and additional investigations.
as indicated such as serum concentration of 17-
hydroxyprogesterone and overnight dexamethasone
suppression tests.

Body weight and height were measured: obesity
was defined as a body mass index (BMI) of greater
than 25 kg/m². An ultrasound scan of the pelvis, pref-
erably transvaginal, was performed to identify polycy-
cystic ovaries, typical appearance of which included
multiple tiny cysts in the periphery and increased strom-
al echogenicity in the centre. The details of diagnos-
tic criteria for the ultrasound appearance of polycystic
ovaries were not available in the records for all patients.
Those with suspected PCOS were also screened for
DM or insulin resistance using fasting serum glucose
levels alone, 75 g oral glucose tolerance tests (OGTT),
and/or fasting serum glucose to insulin (G:I) ratios.
Insulin resistance was diagnosed if the fasting serum
levels or the OGTT revealed abnormal
results, either impaired glucose tolerance (IGT) or
frank DM, or the fasting serum G:I ratios of less
than 4.5 mg/10⁻⁴ U (the conversion factor for glucose
concentrations in mmol/L to mg/dL was 18.0).

Major diagnostic criteria of PCOS included
chronic anovulation and clinical or biochemical
hyperandrogenism with other endocrine causes
excluded. Chronic anovulation presented as a
menstrual disturbance such as oligomenorrhoea or
amenorrhoea while hyperandrogenism presented as
hirsutism or acne. Oligomenorrhoea was arbitrarily
defined as the repeated occurrence of prolonged
menstrual intervals ranging from 6 weeks to 3 months.
The severity of clinical hyperandrogenism (hirsutism
and acne) was graded subjectively by the patients.
Mild hirsutism needed no or occasional shaving;
moderate hirsutism needed regular shaving; severe
hirsutism was very distressing to the patient. Mild
acne consisted of papules or pustules on the face only
and was not distressing to the patient; moderate
acne consisted of papules or pustules on the face that
caused distress to the patient; acne was considered
severe if it involved the face and the trunk. Minor
criteria included appearance of polycystic ovaries on
ultrasonography, LH predominance in the early follicular
phase, and obesity or insulin resistance. A
diagnosis of PCOS was confirmed if at least two of
the above criteria, including at least one major criterion,
were met.

Patients with PCOS were also screened for
dyslipidaemia by measuring fasting serum concen-
trations of total cholesterol (TC), low-density-
lipoprotein cholesterol (LDL-C), triglyceride (TG), and
high-density-lipoprotein cholesterol (HDL-C). Dyslipidaemia was defined as a TC level of 5.2 mmol/L
or higher, LDL-C level of 3.4 mmol/L or higher, TG
level of 2.0 mmol/L or higher, and/or HDL-C level
below 1.0 mmol/L.

Outcome measures
The main outcome measures were the prevalence of
typical features of PCOS, including anovulation and
hyperandrogenism (with the exclusion of other causes),
appearance of polycystic ovaries on ultrasonography,
LH predominance, obesity, and insulin resistance. The
three diagnostic criteria of PCOS, namely 1990 NIH
criteria, local PWH criteria, and 2003 Rotterdam
criteria, were also compared. The screening methods
for insulin resistance were examined and the preva-
ence of dyslipidaemia assessed.

Statistical analysis
Statistical analyses were performed using the Statisti-
cal Package for the Social Sciences (Windows
version 11.0; SPSS Inc, Chicago [IL], US). Results
were analysed by descriptive statistics. Differences
between groups were tested statistically using the
Chi squared test for categorical data. Logistic regres-
sion analysis was performed to test the potential
predicting variables and to determine the association
of each independent variable with the outcome vari-
able. Data were considered statistically significant
when the P value was 0.05 or less. The cut-off point of
predicting variables with optimal sensitivity and
specificity for screening of the outcome variable was
determined by the receiver operating characteristic
curve analysis.

Results

Patient characteristics
The mean age of women was 28.6 years (standard
deviation [SD], 6.9 years; 10th, 50th, and 90th
percentiles were 19, 29, and 37 years, respectively).
Their mean BMI was 26.6 kg/m² (SD, 7.1 kg/m²; 10th,
50th, and 90th percentiles were 18.0, 25.9, and
37.2 kg/m², respectively). The mean serum concen-
tration of total testosterone was 2.5 nmol/L (SD,
1.3 nmol/L; 10th, 50th, and 90th percentiles were 1.1,
2.2, and 4.6 nmol/L, respectively).

The proportion of the cohort fulfilling each of the
PWH diagnostic criteria for PCOS is shown in the
Table. All except one of the cohort presented with
menstrual disturbances. A 17-year-old girl presented
with primary amenorrhoea while 63 (70.0%) other
women presented with secondary amenorrhoea.
Oligomenorrhoea was present in 23 (25.6%) patients and two (2.2%) had irregular menstruation. One patient with a regular menstrual cycle presented with clinical and biochemical hyperandrogenism. Clinical or biochemical evidence of hyperandrogenism was present in only 44 (48.9%) patients. Among them, 24 patients had biochemical hyperandrogenism and 40 had clinical hirsutism and/or acne. Of the 33 patients with clinical hirsutism, 25 (75.8%) were mild, seven (21.2%) were moderate, and one (3.0%) was severe. For the 17 patients with acne problems, 12 (70.6%) were mild, five (29.4%) were moderate, and none were severe. Other endocrine causes of anovulation and hyperandrogenism were excluded.

Increased serum LH levels (≥10 IU/L) or increased ratios of serum concentrations of LH to FSH (≥2.5) were observed in 61 (67.8%) patients. Typical ultrasound appearance of polycystic ovaries was demonstrated in 78 (86.7%) patients. A BMI of higher than 25 kg/m² was present in 46 (51.1%) patients. Nine patients defaulted or refused screening for insulin resistance; of the remaining 81 patients, 33 (40.7%) were screened positive for insulin resistance. Seven were diagnosed with frank DM while 17 patients had IGT, nine patients had fasting serum G:I ratios below 4.5 mg/10⁴ U.

Fasting lipid profiles were measured in 55 patients with dyslipidaemia established in 31 (56.4%)—21 (38.2%) patients had elevated fasting TC level (≥5.2 mmol/L); 13 (23.6%) patients had elevated fasting LDL-C level (≥3.4 mmol/L); 10 (18.2%) patients had elevated fasting TG level (≥2.0 mmol/L); and 10 (18.2%) patients had reduced fasting HDL-C level (<1.0 mmol/L).

Comparisons of different diagnostic criteria
In this cohort, only 43 (47.8%) should have been diagnosed with PCOS based on the 1990 NIH criteria of having both chronic anovulation and hyperandrogenism. Nonetheless based on the 2003 Rotterdam criteria, 86 (95.6%) should have been diagnosed with PCOS—36 women had all three features of PCOS (chronic anovulation, hyperandrogenism, and polycystic ovaries on ultrasound scan) while the remaining had only two of them. There were 41 anovulatory normoandrogenic women with polycystic ovaries, one ovulatory hyperandrogenic women with polycystic ovaries, and eight had chronic anovulation and hyperandrogenism but no polycystic ovaries. For the remaining four whose symptoms did not satisfy the 2003 Rotterdam criteria, a diagnosis of PCOS was based on the evidence of chronic anovulation with other endocrine causes excluded and increased serum LH levels in the early follicular phase. Two of them were also obese.

Screening for insulin resistance
Screening for insulin resistance was performed in 81 patients—38 (46.9%) underwent fasting serum glucose levels alone; 12 (14.8%) were by OGTT alone; 5 (6.2%) were by fasting serum G:I ratios alone; and 26 (32.1%) had full screening by both OGTT and fasting serum G:I ratios. Among the 33 patients screened positive for insulin resistance, 23 (69.7%) had normal fasting serum glucose levels. Of the 26 patients in whom full screening for insulin resistance was performed by OGTT and fasting serum G:I ratios, 16 (61.5%) had discordant results—seven had abnormal OGTT results but normal fasting serum G:I ratios, while nine had normal OGTT results but abnormal fasting serum G:I ratios.

Predictors for insulin resistance
Binary logistic regression analysis was performed to determine the importance of each independent variable in the occurrence of insulin resistance: independent variables included age, BMI, serum concentrations of LH and total testosterone, and obesity. Insulin resistance was associated with obesity (regression coefficient=8.16; standard
error=4.17; P≤0.05) but no other predicting variables (all P>0.05). Obese patients with PCOS had a significantly higher prevalence of insulin resistance than non-obese ones (62.2% vs 13.9%, P<0.01). Using obesity (BMI>25 kg/m²) as a screening cut-off, insulin resistance can be predicted with 85% sensitivity and 67% specificity.

Discussion

Polycystic ovarian syndrome is the most common reproductive endocrinopathy of women during their childbearing years, with a reported prevalence of 4% to 8%. 6-8 Diagnosis is primarily dictated by typical features of anovulation and hyperandrogenism. Associated findings include LH predominance as well as obesity and insulin resistance with compensatory hyperinsulinaemia. In addition, the ovaries display a typical morphological pattern that appears to be unique to the disorder. As such a complex heterogeneous disorder, the diagnostic criteria for PCOS have long been a source of controversy. Ethnicity has a great impact on the presentation of PCOS. 9 In our cohort, almost all women presented with menstrual disturbances while less than half had clinical or biochemical evidence of hyperandrogenism. This probably relates to the low prevalence of hirsutism in the Chinese population 2 as well as the measurement by our unit of total testosterone instead of circulating free testosterone levels. These limitations render the 1990 NIH diagnostic criteria of PCOS inapplicable to our local population. Nonetheless, typical ultrasound appearances of polycystic ovaries were demonstrated in the majority of this study cohort. The 2003 Rotterdam criteria could have diagnosed PCOS in more than 95% of our cohort.

The 2003 Rotterdam criteria are more flexible and address the problem of heterogeneous presentations, nonetheless they impose some practical difficulties and give cause for further debate. The detection of ultrasound of ovaries that appear polycystic requires experience and can be operator-dependent. Transvaginal ultrasound scans are practically difficult in patients without previous sexual experience and transabdominal scans are of a less high resolution, especially in obese patients. In addition, accumulating evidence confirms that insulin resistance is central to the pathogenesis of PCOS, 10-12 yet this feature is excluded from these new guidelines. In our opinion, the 2003 Rotterdam criteria are generally applicable to our population provided their limitations are acknowledged.

More than half of all women with PCOS have some degree of insulin resistance, 10,13 and this probably contributes to the hyperandrogenism that is responsible for the clinical features of PCOS. 14,15 Early detection of insulin resistance in this high-risk population has both prognostic and therapeutic implications. Glucose intolerance has long been recognised as a strong risk factor for type 2 diabetes and cardiovascular disease, 16,17 and a study has shown that progression to diabetes is delayed by both lifestyle and pharmacological intervention. 18 Over the last decade, the use of insulin-sensitising agents such as metformin prescribed to women with PCOS has produced promising results. 19,20 Identification of patients who are at increased risk of the metabolic sequelae of PCOS may allow better selection of patients most likely to respond to treatment with insulin-sensitising drugs. In our cohort, a varying degree of insulin resistance was observed in about 40% of women with PCOS.

Despite the importance of assessing insulin sensitivity in subjects with PCOS, there remains no consensus as to the best method. Although the hyperinsulinaemic-euglycaemic clamp technique is the gold standard for measuring insulin sensitivity, it is too expensive, time-consuming, and labour-intensive to be of practical use in an out-patient setting. 21 Homeostatic measurements such as fasting serum G:I ratio and insulin sensitivity indices derived from OGTT are the easiest office-based assessments of insulin resistance in PCOS patients. 22,23 In women with PCOS, a cut-off value of fasting G:I ratio of less than 4.5 mg/10⁴ U can detect insulin resistance with the sensitivity of 95% and specificity of 84%, compared with the gold-standard measurement by frequently sampled intravenous glucose tolerance test. 24 In this study, the use of fasting serum glucose levels in isolation would have failed to detect the majority of cases with insulin resistance whilst OGTT and fasting serum G:I ratios are complementary to each other. We recommend full metabolic screening by OGTT together with measurement of fasting G:I ratios, especially in obese women.

There were several limitations of this retrospective study. Not all women with PCOS were seen in the Gynae-endocrinology Clinic and this resulted in potential selection bias. For example, women with mild menstrual disturbances might be assessed in other gynaecology clinics prior to a diagnosis of PCOS. This may have accounted for the high prevalence of amenorrhoea and oligomenorrhoea in our cohort. In addition, exclusion of infertile women with PCOS but no endocrine problems might result in an over-
estimation of the prevalence of insulin resistance. Incomplete metabolic screening might have resulted in an underestimation. In particular, almost half of this cohort underwent screening for insulin resistance using fasting serum glucose levels only. In spite of these limitations, this study provides important information about the clinical characteristics of Chinese women with PCOS that is crucial when defining diagnostic criteria for a local population. Consensus in diagnostic criteria for PCOS is crucial for further development in the clinical management as well as research activities on this area.

In conclusion, PCOS is a heterogeneous endocrine disorder that requires uniform and definitive criteria for its diagnosis. The 2003 Rotterdam criteria represent a credible first step and are generally applicable to our local population. Early detection of insulin resistance in PCOS patients has great prognostic and therapeutic implications: screening should be by OGTT together with measurement of fasting G: I ratios.

References