ORIGINAL ARTICLE Reproductive endocrinology

Indicators for metabolic disturbances in anovulatory women with polycystic ovary syndrome diagnosed according to the Rotterdam consensus criteria

A.J. Goverde¹, A.J.B. van Koert¹, M.J. Eijkemans¹, E.A.H. Knauff¹, H.E. Westerveld², B.C.J.M. Fauser¹, and F.J. Broekmans¹

¹Department of Reproductive Medicine and Gynaecology, University Medical Centre, PO Box 85500, 3508 GA, Utrecht, The Netherlands
²Department of Internal Medicine, University Medical Centre, Utrecht, The Netherlands
³Correspondence address. E-mail: a.j.goverde@umcutrecht.nl

BACKGROUND: Polycystic ovary syndrome (PCOS) is associated with metabolic abnormalities. It is debated whether all women with PCOS should be screened for metabolic abnormalities as these may vary with PCOS phenotype, age and ethnicity. The aims of this study were to assess the prevalence of metabolic abnormalities in Dutch anovulatory PCOS women and to define criteria for metabolic screening.

METHODS: Anovulatory patients, diagnosed with PCOS according to the Rotterdam consensus criteria, underwent metabolic screening. Through stepwise multivariate analysis patient characteristics associated with metabolic syndrome (MetS) and insulin resistance (IR) were evaluated for their use as selection parameters for metabolic screening.

RESULTS: Overall, prevalence of MetS and IR was 15.9% (n = 25) and 14% (n = 22), respectively, in 157 PCOS women (age 29.0 ± 4.8 years, BMI 26.1 ± 6.7 kg/m²). Anovulatory hyperandrogenic women (with or without polycystic ovaries) had more often MetS and IR (with, 20.8 and 19.8%; without, 100 and 40%, respectively) than non-hyperandrogenic PCOS women (0 and 1.8%; P < 0.001). Waist circumference >83.5 cm along with increased free androgen index (FAI) had the most powerful association with the presence of MetS and IR (area under the receiver operating characteristic curve 0.912) and offered a reduction in the necessity of screening for metabolic derailments of about 50%.

CONCLUSIONS: The hyperandrogenic PCOS phenotypes are highly linked to the presence of MetS and IR in Dutch PCOS women. Waist circumference combined with FAI was identified as an efficient combination test to select those PCOS women who should be screened for the presence of MetS and/or IR.

Key words: insulin resistance / metabolic syndrome / polycystic ovary syndrome / Rotterdam criteria / waist circumference

Introduction

Polycystic ovary syndrome (PCOS) has been strongly associated with metabolic derangements such as the metabolic syndrome (MetS) and insulin resistance (IR) (Korhonen et al., 2001; Apridonidze et al., 2005; Dokras et al., 2005). Both conditions imply changes in carbohydrate and lipid metabolism and a constellation of risk factors for development of cardiovascular disease (Legro et al., 1999; Talbott et al., 2000; Grundy et al., 2004; Orio et al., 2004; Vryonidou et al., 2005; Ehrmann et al., 2006). Progression of IR to overt type 2 diabetes is also frequently observed in PCOS (Ehrmann et al., 1999; Elting et al., 2001; Legro et al., 2005). Like MetS, type 2 diabetes is clearly associated with future cardiovascular disease in women (Lo et al., 2006).

This illustrates the importance of early detection of IR and subsequent application of preventive measures in PCOS women.

With the application of the Rotterdam PCOS consensus (Rott-PCOS) criteria, the group of women diagnosed with PCOS has broadened considerably (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). A greater proportion of women presenting with World Health Organization (WHO) II anovulation (Rowe et al., 1993) are now diagnosed as having PCOS, resulting from the inclusion of polycystic ovaries (PCO) into the set of diagnostic criteria. Women with anovulation and PCO, but without hyperandrogenism, may constitute 16–40% of PCOS patients (Broekmans et al., 2006; Dewailly et al., 2006). This group is leaner and appears to have a more favourable metabolic profile. Inclusion of the latter group has
been suggested to decrease the prevalence of metabolic derangements in PCOS (Broekmans et al., 2006). This can be explained by the contention that higher levels of insulin and androgens combined with the presence of central obesity induce metabolic disturbances in women with PCOS. In view of the presence of different subtypes in the Rotterdam PCOS group, it seems relevant to address the question of whether screening for metabolic dermalion is indicated for every PCOS case.

The first aim of the present study therefore was to assess the prevalence of MetS and IR in anovulatory women diagnosed with PCOS according to the Rotterdam consensus criteria. The second aim was to define readily accessible clinical factors that are predictive of the presence of metabolic disturbances in order to discriminate between those PCOS women who should and those who should not be screened extensively for full lipid profiles and measures of insulin sensitivity.

**Materials and Methods**

**Patient selection and study design**

All women presenting with oligomenorrhoea (mean interval between bleedings ≥35 and <182 days) or amenorrhoea (mean interval between bleedings ≥182 days) were systematically evaluated in our outpatient clinic. Standardized screening was approved by the local Institutional Review Board, and written informed consent was obtained from all participants. Information was obtained regarding age, race, history of cycle abnormality, medical and family history, any previous or current use of medication, presence of acne and hirsutism, BMI, blood pressure, waist and hip circumferences, fasting early morning endocrine profile (including pituitary hormones, ovarian and adrenal steroids), lipids, glucose and insulin. A systematic pelvic ultrasonography was also performed and performed for full lipid profiles and measures of insulin sensitivity.

Clinical hyperandrogenism was defined as the presence of hirsutism (Ferriman–Galwey score >8) and/or acne. Biochemical hyperandrogenism was present if the calculated free androgen index [FAI = (testosterone/sex hormone-binding globulin (SHBG)] > 5.45 (Vermeulen et al., 1999). PCOS was defined as the presence of at least one ovary >10 cm³ in volume and/or at least one ovary with 12 or more follicles measuring 2–8 mm in diameter (Balen et al., 2003; Broekmans and Fauser, 2006).

The diagnosis of PCOS was based on the Rott-PCOS criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). According to these criteria, PCOS was diagnosed if at least two of the following criteria were present: oligo/amenorrhoea, clinical or biochemical hyperandrogenism and PCO on ultrasonography. Other etiology that could mimic PCOS, like Cushing syndrome, late onset adrenal hyperplasia or androgen producing neoplasm had to be excluded. Additionally, Group I or III anovulation according to the WHO criteria (Rowe et al., 1993) had to be ruled out, based on FSH and estradiol (E2) assessment.

Clinical hyperandrogenism was defined as the presence of hyperandrogenism (Ferriman–Galwey score >8) and/or acne. Biochemical hyperandrogenism was present if: (i) waist circumference ≥88 cm, (ii) serum triglyceride ≥1.70 mmol/l, (iii) serum high-density lipoprotein (HDL)-cholesterol <1.30 mmol/l, (iv) the use of lipid lowering medication, (v) blood pressure ≥130/85 mm Hg or the use of anti-hypertensive medication, (vi) fasting plasma glucose ≥6.1 mmol/l.

IR was assessed using the homeostatic model assessment (HOMA-IR: (fasting insulin × fasting glucose)/22.5) (Legro et al., 2004). Although IR is considered a gradual phenomenon, a threshold point of 3.8 was used in this study to enable comparison with the study by Kauffman et al. (2002). Since the same insulin assay was used in this study, correction was not considered necessary. A HOMA-IR value >3.8 probably reflects severe IR, because the HOMA-IR threshold of 3.8 was based on insulin concentrations above the upper limit of normal after a 100 g oral glucose tolerance test as standard test.

A total of 254 women with oligo- or amenorrhoea underwent the screening investigation between September 2004 and April 2006. Only patients for whom the complete panel of physical examination, ultrasound and laboratory data for the classification of PCOS, MetS and IR was available were considered for analysis (Fig. 1). The PCOS phenotype of hyperandrogenism and PCO without anovulation was not present in the current patient population, since cycle abnormalities was the primary inclusion criterion for our screening programme.

**Physical examination, ultrasound and laboratory assessment**

The blood pressure reading was obtained in sitting patients after a 10 min rest. The inflatable cuff size applied was adapted to the upper arm circumference. Waist circumference was measured in the standing position, halfway between the lower ribs and the superior anterior iliac spine of the pelvis. The hip circumference was measured at the level of the pubic symphysis. Hirsutism was established by using the Ferriman–Galwey score.

Transvaginal ultrasonography was systematically performed by the same investigator (E.K.) on a Kretz Voluson 5300, using the 7.5 MHz transvaginal three-dimensional probe. Ovarian volume measurements were carried out by using three perpendicular dimensions and applying the equation for the volume of an ellipsoid [V = (length) × (width) × (height) × (πr/6)]. Antral follicles were measured in three dimensions and those with a mean diameter of 2–9 mm counted.

The laboratory analyses used the following assays to measure the endocrine and metabolic parameters. FSH was assayed in serum with a chemiluminescence FSH assay on the ADVIA Centaur® Automated System (Bayer Corporation, Tarrytown, NY, USA). E2 concentrations were measured by indirect chemiluminescence on the ADVIA Centaur® Automated System (Bayer Corporation). Testosterone was measured on an in-house-developed radio-immunoassay. HDL-cholesterol was quantified using a Konelab 30® (Thermo Clinical Labsystems, Vantaa, Finland). Triglyceride and glucose levels were measured using a VITROS Chemistry System® (Ortho-Clinical Diagnostics, Strasbourg, France). Insulin and SHBG levels 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.

![Figure 1](https://academic.oup.com/humrep/article-abstract/24/3/710/644181/114) An overview of the study cohort, with specification of excluded cases.

PCO, polycystic ovaries; PCOS, polycystic ovary syndrome.
Statistical analysis

Baseline characteristics of the three different PCOS subgroups were analysed by analysis of variance. Proportions were compared using the chi-square test. Univariate logistic regression analysis was applied to quantify the association between several clinical and laboratory variables and the presence of the MetS and/or IR. Variables that appeared to be associated were further analysed using multivariate logistic regression analysis with forward stepwise selection, using a P value for entry of 0.1. Independent predictive factors were subsequently used to establish a predicting model for the presence of the MetS and/or IR. The accuracy of the model was first analysed by using a receiver operating characteristic curve (ROC curve) and the area under this curve (AUC). Secondly, the sensitivity and specificity of the prediction model were calculated at different probability threshold values of the ROC curve to obtain a view on the clinical value of the model. Statistical significance was considered present if the P-value was < 0.05, unless stated otherwise. Statistical Package for Social Sciences (SPSS) was used for statistical analysis (version 11.2, SPSS inc., Chicago, IL, USA). Data are presented as mean ± SD.

Results

Of the 254 women screened, 237 women had oligo- or amenorrhoea; the remaining appeared to have regular menstrual cycles (Fig. 1). Of the 237 women with anovulation, 230 were classified as WHO-II. Two women were diagnosed as WHO-I and WHO-III, respectively, three women appeared pregnant at the time of screening and two remained unclassified. Additionally, 55 women were excluded because of incomplete data (missing ultrasound [n = 41], missing fasting insulin or glucose [n = 11], missing information on hyperandrogenism [n = 1] or missing data to diagnose the MetS [n = 2]). Finally, four women were excluded because of other etiology, which could mimic PCOS. This left 171 cases with WHO-II of whom 157 (92%) were classified as PCOS according to the Rott-PCOS criteria and who comprised the final study cohort (Fig. 1).

The mean age in the study cohort (n = 157) was 29.0 years (range 17–43). The mean BMI was 26.1 kg/m² (range 17–47). Of the 157 Rott-PCOS women, 96 (61%) fulfilled all three Rott-PCOS criteria (i.e. anovulation [AO], hyperandrogenism [HA] and PCO). A total of 56 (36%) women had AO + PCO without HA and 5 (3%) women had AO + HA without PCO. Thus, a total of 101 (64%) women had anovulation with hyperandrogenism and would also have been classified as PCOS according to the National Institutes of Health (NIH) criteria (Zawadski and Dunaif, 1992). Figure 2 presents a flow chart of the study cohort.

Table I presents an overview of the baseline characteristics of the different PCOS phenotype subgroups. BMI varied according to the phenotype. Women with clinical and/or biochemical hyperandrogenism (with or without PCO) had a significantly higher BMI compared with women without hyperandrogenism but with PCO (28.6 and 21.6 kg/m², respectively, P < 0.0001). The mean age did not differ significantly between these two phenotypes. Most of the metabolic variables differed between the cases with and without clinical or biochemical hyperandrogenism. Cases without PCO constituted a small group (n = 5) with very high BMI.

Metabolic syndrome

The overall prevalence of MetS in women with Rott-PCOS was 15.9% (25/157). Of these, 15 cases met three criteria for MetS, 9 cases met four criteria and one case met all five criteria. All women with MetS had increased waist circumference, 90% had reduced fasting plasma HDL-cholesterol concentrations, 80% had high blood pressure, 56% had elevated fasting plasma triglyceride concentrations and 16% had increased fasting plasma glucose concentrations. In PCOS patients with MetS, the BMI was significantly higher compared with the PCOS patients without MetS (24.3 ± 5.8 and 24.6 ± 5.6 kg/m², respectively, P < 0.0001).

The prevalence of the MetS varied significantly according to the specific PCOS phenotypes (Fig. 2). In full-PCOS, the prevalence was 20.8%, in PCOS without hyperandrogenism 0% and in PCOS without PCO 100%. In the group with hyperandrogenism and anovulation (classified NIH), the prevalence of MetS was 24.8% which was significantly higher than 0% in MetS in case of PCOS without hyperandrogenism (Fig. 2, P < 0.0001).

Also, there was a significant difference in the prevalence of MetS between women with PCO with or without hyperandrogenism (20.8 versus 0%, respectively, P < 0.0001). Likewise, for PCOS women with hyperandrogenism, the MetS prevalence differed for those with or without PCO (20.8 versus 100%, respectively, P < 0.001). The logistic regression analysis revealed that both PCO and hyperandrogenism, but also waist and waist-hip ratio (WHR), were associated with the risk of having MetS. There was no significant association for age or race with the MetS in our study group. Multivariate analysis

![Figure 2](https://academic.oup.com/humrep/article-abstract/24/3/710/644181/712)
showed that PCO had the most powerful negative association with the MetS ($P < 0.0001$). Hyperandrogenism was strongly positively associated with MetS ($P < 0.0001$), independently of PCO and BMI.

**Insulin resistance**

IR, defined as HOMA-IR $> 3.8$, was present in 14% of all Rott-PCOS cases. The prevalence of HOMA-IR $> 3.8$ was 19.8% if all three PCOS criteria were present, 1.8% in the group of PCOS without hyperandrogenism and 40% in PCOS without PCO ($P < 0.0001$ PCOS with hyperandrogenism versus PCOS without hyperandrogenism; $P = 0.144$ PCOS with PCO versus PCOS without PCO). In the logistic regression analysis, hyperandrogenism, FAI, race, diastolic blood pressure, waist circumference, WHR, triglycerides and HDL-cholesterol were all associated with IR as defined by HOMA-IR $> 3.8$. We found no association of elevated HOMA-IR with PCO, age and systolic blood pressure. With multivariate analysis, the waist circumference had the most powerful association with the presence of IR defined by HOMA-IR $> 3.8$ ($P < 0.0001$), followed by race and FAI. Both variables showed additional predictive value independently of each other ($P = 0.003$ and $P = 0.045$, respectively).

**Predictive model**

There was some but not a complete overlap between the presence of HOMA-IR $> 3.8$ and the MetS: 25 cases had the MetS, 22 had IR and 12 cases had both. This provided us with the opportunity to perform additional analyses of factors associated with either or both metabolic conditions and to develop a model for the necessity of screening for metabolic derailments.

Univariate logistic analysis revealed an association between the MetS and/or HOMA-IR $> 3.8$ with PCO, hyperandrogenism, FAI, race, waist circumference and WHR. In the multivariate analysis, waist circumference, FAI and WHR were independently associated with the presence of IR and/or the MetS (Table II), although the WHR added marginal information only. The positive predictive value of the waist circumference was used to assess the presence of any of the two metabolic disturbances. When using a waist circumference threshold of 93.5 cm the ROC curve had an AUC of 0.881, with a sensitivity of 97.1% and a specificity of 70% (Fig. 3). The predictive accuracy expressed as the ROC-AUC increased slightly when the waist circumference was combined with FAI (AUC 0.912, sensitivity 97.1% and specificity 75%). The FAI as a single factor produced a slightly poorer predictive accuracy of 0.826 (Fig. 3). The individual ROC curves for the occurrence of MetS and/or IR in relation to waist circumference, FAI and waist circumference in combination with FAI are depicted in Fig. 4.

**Discussion**

We studied the prevalence of MetS and IR in Dutch women diagnosed with anovulatory PCOS according to the Rotterdam criteria. The main findings are that the overall prevalence of MetS and IR in these women is around 16%. Moreover, within this anovulatory cohort, the hyperandrogenic PCOS phenotype is associated with the highest risk of metabolic abnormalities.

We found an overall 15.9% prevalence of clustered metabolic abnormalities consistent with MetS (Expert Panel on the Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) or IR in our study group. In comparison to other studies with similarly diagnosed PCOS women, the prevalence of metabolic abnormalities in our study group is lower than the 35–44% prevalence in American (Shroff et al., 2007) and Australian anovulatory PCOS women (Cussons et al., 2008), comparable to the 16% reported in Taiwanese anovulatory PCOS women (Chen et al., 2006), but higher than the 8.2% reported in Southern Italian women with anovulatory PCOS (Carmina et al., 2006). The diagnosis of MetS in these...
studies was based on the same NCEP ATP III criteria we used, with a
modification for Asian women in the Taiwanese study group (Chen
et al., 2006). Of the subset of patients who were hyperandrogenic
and also would have been diagnosed as having PCOS according to
the NIH criteria, 24.8% had MetS in the present study. This prevalence
is lower compared with other reports in comparably classified PCOS
patient groups in the USA, Germany and Australia (31–46%) (Glueck
et al., 2003; Apridonidze et al., 2005; Dokras et al., 2005; Hahn et al.,

Table II Logistic regression analysis showing the predictive association of several clinical variables and the presence of metabolic derailment (MetS and/or IR)

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>ROC-AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCO (y/n)</td>
<td>&lt;0.0001</td>
<td>0</td>
<td>0.571</td>
</tr>
<tr>
<td>Hyperandrogenism (y/n)</td>
<td>&lt;0.0001</td>
<td>27.91</td>
<td>0.712</td>
</tr>
<tr>
<td>FAI (&gt;4.5 y/n)</td>
<td>&lt;0.0001</td>
<td>1.317</td>
<td>0.826</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.562</td>
<td>1.024</td>
<td>0.531</td>
</tr>
<tr>
<td>Race</td>
<td>0.050</td>
<td>0.609</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 130)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediterranean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asiatic (n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindustanic (n = 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negroid (n = 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arabic (n = 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>&lt;0.0001</td>
<td>1.111</td>
<td>0.881</td>
</tr>
<tr>
<td>WHR (cm/cm)</td>
<td>&lt;0.0001</td>
<td>5.078</td>
<td>0.864</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAI (&gt;4.5 y/n)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR (cm/cm)</td>
<td>0.026</td>
<td>0.927</td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the curve; ROC, receiver operating characteristic; n, no; y, yes; FAI, free androgen index; na, not assumable; WHR, waist/hip-ratio; MetS, metabolic syndrome.

Figure 3 The relationship between free androgen index (FAI) and waist circumference in all study subjects.

The effects of applying the various screening models for identifying women with metabolic disturbances (MetS and/or IR, black dots) are represented by the vertical line (cut-off value of waist circumference), the horizontal line (cut-off value of FAI) and the diagonal line (combination of waist circumference and FAI).

Figure 4 ROC curves of selected variables and presence of MetS and/or IR.

(a) Waist circumference, (b) FAI and (c) combination of waist circumference and FAI as a predictor for metabolic derailments. (a) Waist circumference and presence of MetS and/or IR, (b) FAI and presence of MetS and/or IR, (c) Waist circumference and FAI combined and presence of MetS and/or IR.
Clinical markers of anovulatory polycystic ovary syndrome

2005; Cussons et al., 2008), but higher than found in a South-Italian population (8%) (Carmina et al., 2006). All USA, German and Australian study groups presented with a higher BMI compared with ours, while BMI in the Italian population appeared to be lower compared with that in the present study. The very robust observation that our small subgroup of five women diagnosed with PCOS based on anovulation and hyperandrogenism but without PCO had the highest BMI and presented with the most unfavourable metabolic profile, underlines the role of BMI in the development of metabolic abnormalities. Moreover, BMI might reflect lifestyle and dietary habits of different populations. Indeed, observations suggest that the prevalence of MetS in the normal population is also higher in the USA and Germany (Eckel et al., 2005), whereas the prevalence of MetS in young Dutch adults is ~10% (Ferreira et al., 2005; Ramadhan et al., 2006). This implies that baseline population lifestyle affects the frequency of metabolic derangements in PCOS counterparts.

We found that hyperandrogenism in this Dutch patient group has the strongest association with the presence of MetS and IR. This finding is supported by several other studies (Kauffman et al., 2002; Legro et al., 2004; Broekmans et al., 2006). IR with elevated circulating insulin levels induces unfavourable changes in the lipid metabolism and increased androgen production from theca cells. At the same time androgen excess may support the presence of an unfavourable metabolic state with a tendency towards central obesity and dislipidemia. Especially in obese women excess insulin and androgens may therefore contribute in concert to the development of the PCOS phenotype and the MetS (Eckel et al., 2005; Pasquali, 2006). We found that the presence of PCO was negatively associated with MetS and IR. This is a surprising finding, as the presence of PCO at ultrasound illustrates follicular development arrest, which is associated with increased ovarian androgen production. However, in our study group, 35% of the women presented with anovulation and PCO but without hyperandrogenism. This subgroup is larger compared with other similarly designed studies on metabolic abnormalities in PCOS (Welt et al., 2006; Shroff et al., 2007; Kauffman et al., 2008) in which PCOS cases with hyperandrogenism and PCO but without anovulation were also included. Therefore we cannot exclude some bias in our study group resulting from oligo- or amenorrhea being the first criterion to include women in our study cohort. However, our finding that the group of anovulatory women with PCO but without hyperandrogenism had the least metabolic disturbances is in concordance with some studies (Welt et al., 2006; Shroff et al., 2007) but not with that of Kauffman et al. (2008) who found no striking metabolic differences between the various PCOS phenotypes. In the latter study, BMI was comparable between the different PCOS phenotypes, whereas in the other studies, similar to ours, BMI or waist circumference was lowest in the group of PCOS women characterized by anovulation and PCO without hyperandrogenism.

The current study has some limitations. Especially, the HOMA-IR threshold value used may have underestimated the true prevalence of IR. The gold standard for establishing IR is the euglycemic hyperinsulinemic clamp. This elaborate procedure is not suitable for large-scale clinical use. Therefore, we used the HOMA-IR calculation, which correlates with the euglycemic hyperinsulinemic clamp and is often used as a surrogate marker for IR (Legro et al., 2004). The HOMA-IR threshold level of 3.8 was based on the study by Kauffman et al. (2002). It is important to note that they based this HOMA-IR threshold level on insulin concentrations after an oral glucose tolerance test, which is not the gold standard for the diagnosis of IR. Furthermore, IR is a gradual phenomenon, making threshold levels artificial. PCOS women with HOMA-IR <3.8 may also in some degree be insulin resistant. Finally, several definitions for MetS are in use, of which we selected the NCEP ATP III definition (Expert Panel on the Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) to allow for comparison with a larger body of literature. Had we chosen the International Diabetes Federation (IDF) 2005 definition of MetS (Alberti et al., 2005), 21% (33 out of 157) instead of 15.9% of our study subjects would have been diagnosed with MetS, resulting from the stricter waist circumference criterion in the IDF 2005 definition. It is still unknown why women with PCOS tend to have a more android or central body fat distribution, which favours metabolic disturbances. It has been proposed that antenatal exposure to relatively high concentrations of androgens, a possible explanation for the development of PCOS (Dumesic et al., 2007), might predispose for the android body fat distribution. Moreover, elevated testosterone concentrations in adulthood may induce a more central body fat distribution. The android body fat distribution in PCOS women may be both the result as well as a cause of hyperandrogenism, which precludes a vicious circle of hyperinsulinism, hyperandrogenism and central adiposity and metabolic abnormalities (Barber et al., 2006).

From a clinical point of view, it may be questioned whether all women diagnosed with PCOS should be screened for metabolic abnormalities or whether screening for these abnormalities could be limited to only those women particularly at risk. The Rotterdam consensus meeting recognized the necessity to screen obese PCOS patients for the MetS, but specific criteria or validity were not given. We found that a combination of waist circumference and FAI offers the best selection criterion for the presence of either MetS or IR. Using only the waist circumference >83.5 cm criterion, the same high sensitivity (97%) was achieved, with only a slight reduction in specificity. Selecting all women with a waist circumference above 83.5 cm for further screening seems valid and attractive from a practical point of view. With this threshold level a 52% reduction in the number of women that will be indicated for further screening on metabolic disturbances can be accomplished.

When applying the combined criteria of waist circumference and FAI, screening for MetS and IR could also be limited to half the women with PCOS, but at higher cost. One other study mentioned criteria necessitating screening for MetS in women with PCOS. It has been suggested to use the triglyceride/HDL-cholesterol ratio (TG/HDL-C ratio) >3.2 as a criterion to screen for MetS in hyperandrogenic women (AUC 0.941, sensitivity 90.9%, specificity 87.5%) (Dokras et al., 2005). It is obvious that our proposal of using the waist circumference as the initial screening in all PCOS women has many advantages. It is simple to measure, free of cost and has even a higher sensitivity with comparable specificity than the TG/HDL-C ratio (Dokras et al., 2005).

In conclusion, the prevalence of MetS and IR varies between the different PCOS phenotypes in women, with non-hyperandrogenic anovulatory cases showing only marginal risk. These observations confirm previous findings suggesting that hyperandrogenemia per se is more closely associated with metabolic abnormalities compared with PCO. Waist circumference represents a clinically useful parameter to select those anovulatory PCOS women who should be screened for the presence of MetS or IR.
Funding

A.G. has received fees from Schering/Bayer Schering, and Proctor & Gamble for lectures and advisory committee; B.P. has received fees and grant support from the following companies: Andromed, Ardana, Ferring, Genovum, Merck Serono, Organon, Pantharei Bioscience, Preglem, Schering, Schering Plough, Serono and Wyeth; P.B. is a member of the advisory board of Ferring Pharmaceuticals.

References


Broekmans FJ, Fauser BC. Diagnostic criteria for polycystic ovarian syndrome. Endocrine 2006;30:3–11.


Chen MJ, Yang WS, Yang JH, Hsiao CK, Yang YS, Ho HN. Low sex hormone-binding globulin is associated with low high-density lipoprotein cholesterol and metabolic syndrome in women with PCOS. Hum Reprod 2006;21:2266–2271.


Submitted on June 23, 2008; resubmitted on October 19, 2008; accepted on November 3, 2008