PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors

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Objective The current report aims to compare the prevalence of polycystic ovary syndrome (PCOS) diagnosed according to the new Rotterdam criteria (Rott-PCOS) versus the previous criteria as formulated by the National Institutes of Health (NIH) (NIH-PCOS) in women with normogonadotropic (WHO-II) anovulation and assess the frequency of obesity and related factors determined in these women.

Design Cohort study based on large anovulation screening database.

Setting Two large tertiary referral centres for reproductive medicine.

Population WHO-II normogonadotropic, anovulatory, infertility cases.

Methods WHO-II cases were extracted from the screening database and classified according to both the Rotterdam and NIH criteria for PCOS. Within these two classes, the prevalence of obesity, hyperglycaemia and insulin resistance was assessed and compared and their relation to the difference in diagnostic criteria applied was analysed.

Main outcome measures Prevalence of diagnosis PCOS in the WHO-II anovulation group. Prevalence of obesity, hyperglycaemia and insulin resistance in the two diagnostic classes.

Results The Rott-PCOS group appeared to be more than 1.5 times larger than the group classified as NIH-PCOS (91 versus 55% of the WHO-II cohort). Especially, women with ovarian dysfunction and polycystic ovaries at ultrasound scan, but without hyperandrogenism, were added to the PCOS diagnostic group. The Rott-PCOS exhibited a lower frequency of obesity, hyperglycaemia and insulin resistance compared with the NIH-PCOS group. Obese women in the Rott-PCOS group without androgen excess had a different metabolic profile compared with obese women in the NIH-PCOS group, with lower rates of hyperglycaemia and hyperinsulinism, despite comparable distributions of body weight.

Conclusion The present findings indicate that with the new Rotterdam consensus criteria, oligo/anovulatory women with less severe metabolic derangement will be added to the heterogeneous group of women with PCOS.

Keywords Consensus, hyperglycaemia, insulin resistance, PCOS, WHO-II.

Introduction

In 1935, Stein and Leventhal1 described several women presenting with oligo/amenorrhoea combined with the presence of bilateral polycystic ovaries (PCO) established during surgery. Three of these seven women also presented with obesity, while five showed signs of hirsutism. Only one woman was both obese and showed hirsutism. These findings imply that in case PCO is diagnosed by morphology in women with oligo/anovulation, not all the features which are believed to be associated with PCOS need to be present.2,3 Likewise, with the use of transvaginal ultrasonography it has become evident that women with oligo/amenorrhoea, obesity and hirsutism do not all have the typical PCO morphology.4,5 The occurrence
of a considerable heterogeneity in clinical symptoms and endocrine features associated with polycystic ovary syndrome (PCOS) implies that some women with PCO on ultrasound scan may even exhibit none of the other features of PCOS.

Diagnostic criteria for PCOS have been subject of lengthy debates among clinicians. Specialty groups still tend to differ in their use of diagnostic criteria and diagnostic work up, as well in their choice of first- and second-line treatment. In the 1990 National Institutes of Health (NIH) sponsored conference concerning PCOS, it was concluded that for the diagnosis of the syndrome, evidence should be present of both hyperandrogenism and ovarian dysfunction and that presence of PCO morphology was not required (Figure 1). In contrast, it was consented during the 2003 Rotterdam consensus workshop that PCOS should be considered a syndrome of ovarian dysfunction, features of hyperandrogenism and PCO morphology (Figure 1). Taking the heterogeneity of the syndrome into consideration, none of the criteria was considered absolutely required for the diagnosis. The new criteria broadens rather than replaces the previous NIH criteria for PCOS diagnosis. Under the new criteria, the prevalence of PCOS among the general female population could well rise up to 10%. The additional phenotypes which are diagnosed as PCOS under the revised criteria have given rise to considerable debate in recent literature.

According to the Rotterdam consensus criteria, additional PCOS phenotypes include PCO and hyperandrogenism in women with normal menstrual cycles and especially women presenting with PCO and anovulation without androgen excess. It remains to be established whether these additional phenotypes present with features associated with long-term health risks: obesity, insulin resistance and the metabolic syndrome. Increased body weight has been one of the features for the diagnosis of PCOS in the classical description by Stein and Leventhal. Among diagnosed PCOS cases today, indeed, obesity (body mass index [BMI] > 27 kg/m²) is very common. It is stated that some 50% of women with PCOS are obese. Increased body weight in PCOS is often due to increased visceral fat, i.e. central obesity, characterised by increased waist-to-hip ratio or waist circumference. As this type of overweight is particularly associated with increased risk of cardiovascular disease and type II diabetes, obesity is often defined as a waist circumference of more than 88 cm (35 inches) in classifications that serve the diagnosis of the metabolic syndrome.

Although the cause for the occurrence of obesity in women with PCOS remains largely unknown, androgen excess and insulin resistance are considered as the main independent factors that contribute to the development of central obesity. A specific role of leptin in PCOS-related obesity remains uncertain. At the same time, obesity induces, through the path of insulin resistance, high levels of insulin-related growth factors. These will stimulate theca cells to produce supranormal amounts of androgens and will reduce sex hormone binding globulin (SHBG) synthesis by liver cells, a normal amount of androgens, thereby raising the proportion of free circulating testosterone. The resulting androgen excess is considered to contribute to the presence of increased numbers of follicles in all stages, as well as arrested maturation of follicle-stimulating hormone (FSH) sensitive follicles on their way to gain dominance. Insulin-sensitising treatment like caloric restriction, even with mild body weight reduction, or metformin will frequently lead to restoration of ovarian function.

Women with PCOS and obesity tend to have more pronounced endocrine disturbances. They more often suffer from hyperinsulinaemia, have more suppressed SHBG levels and exhibit higher androgen and estradiol (E2) levels compared with their lean counterparts with PCOS. This eventually will result in more pronounced disturbance of ovarian function, exemplified by a higher rate of amenorrhoea in obese women with PCOS. Moreover, it has been shown that in obese women with PCOS and more severe cycle disturbance, there is need for higher dosages of ovulation induction drugs and an increased risk of nonresponse to such treatment.

It is the aim of the present report to study the prevalence of obesity and related factors in PCOS cases diagnosed according to the new Rotterdam criteria, using a large cohort of WHO-II anovulation women.

Figure 1. Diagnosis of PCOS, according to the 1990 NIH and the 2003 Rotterdam consensus criteria.
Material and methods

At the Departments for Reproductive Medicine of the University Medical Centre, Utrecht and Erasmus Medical Centre, Rotterdam, all women with the clinical suspicion of oligo/ anovulation (mean cycle length > 35 days [oligomenorrhoea] or >180 days [amenorrhoea]), with or without desire to have children or with infertility are systematically screened under the same standardised protocol. Approval for this screening was obtained from the ethical boards of both centres and all women gave written informed consent. The screening includes recording of age, duration and type (primary versus secondary) of infertility if appropriate, history of cycle length, obstetric and medical history, family history, any previous or current use of medication, BMI, waist–hip ratio and blood pressure. Hirsutism is scored using Ferriman–Gallwey score. Systematic transvaginal sonography includes measurement of double endometrial thickness, ovarian volume and the total number of antral follicles sized 2–10 mm. Comprehensive early morning endocrine screening comprises pituitary hormones, ovarian and adrenal steroids, fasting glucose and insulin, lipids and carbohydrates. All data are systematically entered into a database. During the 2003 Rotterdam consensus meeting, it was agreed that PCOS should be diagnosed if at least two of the following three features are present: (1) oligo/amenorrhoea, (2) clinical or biochemical signs of androgen excess and (3) PCO at ultrasound scan. Women are to be classified as with NIH-PCOS if they present with (1) oligo/amenorrhoea and (2) clinical or biochemical hyperandrogenism. The current database allows for the assessment of PCOS according to both the NIH and Rotterdam criteria in women presenting with ovarian dysfunction.

From the database, a total of 869 cases were used for analysis. Information regarding cycle length, BMI, Ferriman–Gallwey score, FSH, E2, Testosterone, SHBG, fasting insulin and glucose and assessment of PCO by ultrasound scan was available. First, assignment of the diagnosis PCOS was performed using the criteria defined by the NIH as well as the criteria from the Rotterdam consensus. The precise way these criteria were applied is depicted in Table 1. In short, WHO-II cases (i.e. serum FSH and E2 levels within the normal limits applied in the centre) were first extracted from the database. Subsequently, all WHO-II women displaying clinical and/or biochemical signs of androgen excess were recorded as with NIH-PCOS, while those with either hyperandrogenism or PCO on ultrasound scan or both were listed as with Rott-PCOS.

Defining androgen excess by the single measurement of circulating androgen levels may be cumbersome due to the inaccuracy and variability of the laboratory methods used and the presence of circadian, cyclic and lifetime variation. Also, normative ranges have not been well-established using well-characterised control populations. We chose to use the calculated free androgen index (FAI) to define hyperandrogenism because it is the non-protein-bound fraction that represents the biologically active fraction of testosterone. The FAI shows appropriate correlation with free testosterone levels measured by equilibrium dialysis. Although the cutoff used for biochemical hyperandrogenism may not be universally applicable, in the present comparative data, this issue will not be of great importance.

For both diagnostic groups, the prevalence of obesity (BMI > 27 kg/m²) was assessed and compared. In addition, for evaluation of carbohydrate metabolism, the rates of

### Table 1. Criteria for PCOS diagnosis according to NIH and Rotterdam consensus

<table>
<thead>
<tr>
<th>Factor</th>
<th>Definition and cutoff</th>
<th>NIH-PCOS (Rott-PCOS, no PCO)</th>
<th>Rott-PCOS no hyperandrogenism</th>
<th>Rott-PCOS normal cycle</th>
<th>Rott-PCOS full</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligo/anovulation</td>
<td>WHO-II classification: Oligomenorrhoea (35–182 days) oramenorrhoea (&gt;182 days) and FSH 1–10 U/l, with normal E2</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperandrogenism</td>
<td>Clinical: hirsutism (Ferriman–Gallwey score ≥ 9) and/or biochemical: FAI* &gt; 4.5</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCO on transvaginal sonography</td>
<td>Volume: one or two ovaries &gt; 10 cm³ and/or follicle count (2–9 mm); one or two ovaries ≥ 12 follicle</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FAI = (Total testosterone × 100)/SHBG.
abnormal fasting hyperglycaemia (≥6.1 mMol/l)3,9,15,16 or insulin resistance (fasting glucose/insulin ratio < 0.25 mMol/mU or <4.5 mg/µU)14,41,42 were compared. Assessment of insulin resistance by the use of fasting glucose/insulin ratio becomes hampered in cases with hyperglycaemia, and the cutoff for abnormality has shown to be population dependent.41,42 The current cohort of cases is predominantly white women, and as the use of the fasting glucose/insulin ratio was solely used for group comparisons and not for patient management, the role of hyperglycaemia therefore was disregarded. Statistical analysis was performed using the statistical package for social sciences (SPSS for Windows, version 12.1; SPSS Inc., Chicago, IL, USA). Chi-square tests were used for first comparisons of proportions. In addition, logistic regression analysis was applied to compare the associative relation of several classification parameters regarding metabolic factors and to assess their relative value, using a P level of 0.05 as cutoff for significance.

Assays used to measure the endocrine and metabolic parameters were as follows. FSH was assayed in serum with a chemiluminescence FSH assay on the ADVIA Centaur® Automated System (Bayer Corporation, Tarrytown, NY, USA) in Utrecht and on an Immulite™ platform (Diagnostic Products Corporation, Breda, the Netherlands) in Rotterdam. E2 concentrations in Utrecht were assayed using the ADVIA Centaur® Automated System (Bayer Corporation) and in Rotterdam with a radio-immunoassay (RIA) (Diagnostic Products Corporation, Breda, the Netherlands). RIAs of testosterone levels were performed on an in-house-developed RIA (with extraction) in Utrecht and in Rotterdam using the RIA of Diagnostic Products Corporation. Glucose levels were measured using a VITROS Chemistry System® (Ortho-Clinical Diagnostics, Strasbourg, France) (University Medical Centre, Utrecht) or a Hitachi® 917 analyzer (Roche Diagnostics, Almere, the Netherlands) (Erasmus Medical Centre). Insulin and SHBG levels were quantified using an Immulite™ platform (Diagnostic Products Corporation) in both the centres.

**Results**

From a total of 869 women with oligo/amenorrhoea, 827 were classified as WHO-II, 12 as WHO-I and 30 as WHO-III according to the FSH and E2 levels measured (Table 1). From the 827 WHO-II women, 456 (55%) were classified as NIH-PCOS according to the criteria listed in Table 1 (Figure 2). In contrast, 754 (91%) women were recorded as with Rott-PCOS, an increase by 65%. The absolute difference of 36% was statistically significant (chi-square test: P = 0.001). Of those classified as with NIH-PCOS, 404 (89%) also were diagnosed with PCO at ultrasound scan and as such fitted all three criteria for Rott-PCOS (Figure 2). The 298 additional women according to the Rotterdam criteria were thus classified based on the presence of PCO at ultrasound scan but without clinical or biochemical evidence of androgen excess (Figure 2).

In the WHO-II group as a whole the prevalence of obesity was 42% (Table 2). In the groups classified as NIH-PCOS and Rott-PCOS, a clear difference was observed in the prevalence of obesity, as shown in Table 2. From multivariable logistic regression analysis, it was shown that the presence of obesity was mainly related to the presence of hyperandrogenism and not with the finding of PCO at ultrasound scan. As expected, in the cases categorised on the basis of PCO and anovulation alone (n = 298), the rate of obesity was even more reduced compared with the NIH-PCOS group (21 versus 61%, P = 0.000; Table 2).

Regarding carbohydrate metabolism, the prevalence of elevated fasting blood glucose and insulin resistance among WHO-II women was 2.4 and 17%, respectively. In the NIH-PCOS group, the rate of elevated blood glucose was doubled compared with the women classified as with Rott-PCOS, while the proportion of insulin-resistant women rose by almost 10% (Table 2). Both differences were significant statistically (P = 0.001). Univariate logistic regression analysis revealed that hyperandrogenism and obesity both were related to the presence of hyperglycaemia and hyperinsulinaemia (Table 3). The finding of PCO at ultrasound scan appeared to have no significant relation to either of the two carbohydrate metabolism factors. Multivariable analysis showed that associations with hyperglycaemia were not strong and statistically not significant. For insulin resistance, there appeared to be a most powerful relation with obesity. Hyperandrogenism showed additional relational value, independently of obesity, while PCO did not (Table 3).

In the Rott-PCOS group, obese women appeared to have the same rate of hyperglycaemia and insulin resistance compared with the obese women in NIH-PCOS group. However, obese women with Rott-PCOS without hyperandrogenism seemed to have a more moderate frequency of carbohydrate metabolism abnormalities compared with the obese women.
with hyperandrogenism, while no differences were found in the body weight distribution (Table 2).

**Discussion**

The current report is the first to provide information concerning the effects of the application of the Rotterdam criteria for the diagnosis of the PCOS upon the prevalence of this syndrome among WHO-II anovulation cases. As expected from the way the new criteria are formulated, the group of PCOS cases has widened considerably compared with the group classified according to the NIH criteria with hyperandrogenism. The increase by roughly 65% has been mainly achieved by the inclusion of cases with anovulation and PCO at ultrasound scan without the presence of clinical or biochemical hyperandrogenism. This figure is clearly higher than those suggested in other reports, where not more than 3% failed to show clinical and biochemical hyperandrogenism.

The question can be asked whether the added group, based solely on PCO morphology and anovulation, differs from the ‘classical’ NIH group in terms of response to ovulation induction treatment and the presence of long-term health risk conditions. As the first item lies beyond the scope of this report, we will mainly focus on the health risk issues.

### Table 2. Prevalence of obesity and carbohydrate metabolism features according to anovulation classification and according to the presence of obesity within the subclasses

<table>
<thead>
<tr>
<th>Classification</th>
<th>Obesity, BMI &gt; 27 kg/m²; n (%)</th>
<th>Hyperglycaemia, fasting glucose &gt; 6.1 mMol/l; n (%)</th>
<th>Insulin resistance, fasting glucose/insulin ratio &lt; 0.25 mMol/mU; n (%)</th>
<th>Body weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-II (n = 827)</td>
<td>345 (42)</td>
<td>19 (2.4)</td>
<td>139 (17)</td>
<td>75 ± 18</td>
</tr>
<tr>
<td>NIH-PCOS (n = 456)</td>
<td>280 (61)</td>
<td>16 (4)</td>
<td>123 (27)</td>
<td>81 ± 19</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rott-PCOS (n = 754)</td>
<td>336 (45)</td>
<td>15 (5.2)*</td>
<td>104 (37)**</td>
<td>92 ± 15***</td>
</tr>
<tr>
<td>Obese</td>
<td>1 (1.8)*</td>
<td>8 (14)**</td>
<td>89 ± 11***</td>
<td></td>
</tr>
<tr>
<td>Rott-PCOS, no hyperandrogenism (n = 298)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>15 (5.2)*</td>
<td>104 (37)**</td>
<td>92 ± 15***</td>
<td></td>
</tr>
</tbody>
</table>

Comparison of obese women with Rott-PCOS and no hyperandrogenism versus obese women with NIH-PCOS.

*P = 0.4.

**P = 0.001.

***P = 0.27.

### Table 3. UVA and MVA logistic regression analysis showing the associational relation between three PCOS-related factors and the presence of hyperglycaemia and insulin resistance

<table>
<thead>
<tr>
<th>Hyperglycaemia (fasting glucose &gt; 6.1 mMol/l)</th>
<th>Insulin resistance (fasting glucose/insulin ratio &lt; 0.25 mMol/mU)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odds ratio</strong></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>Factors in UVA</td>
<td></td>
</tr>
<tr>
<td>Obesity (y/n)</td>
<td>4.1</td>
</tr>
<tr>
<td>Hyperandrogenism (y/n)</td>
<td>4.5</td>
</tr>
<tr>
<td>PCO (y/n)</td>
<td>0.85</td>
</tr>
<tr>
<td>Factors tested in MVA</td>
<td></td>
</tr>
<tr>
<td>Obesity (y/n)</td>
<td>2.9</td>
</tr>
<tr>
<td>Hyperandrogenism (y/n)</td>
<td>2.9</td>
</tr>
<tr>
<td>PCO (y/n)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

MVA, multivariate; n, no; UVA, univariate; y, yes.

Significance was set at the P level of 0.05.
In the present report, the rate of obesity has been almost reduced to half by the application of the new criteria. Also, in the newly added group with anovulation and PCO without androgen excess, the rate of obesity is only 56 in 298 cases (21%). This finding confirms the causal inter-relationship between androgen excess and overweight, as discussed in the Introduction. As the criterion of PCO at ultrasound scan has been met in the vast majority of Rott-PCOS cases (93%), the PCOS group according to the new criteria, indeed, now roughly represents a merging of hyperandrogenic and nonhyperandrogenic anovulation states, which display quite pronounced differences in the rate of health-risk-related conditions. This seems to be supported by the observation that nonhyperandrogenic women with anovulation present with a low rate of hyperglycaemia (0.6%) and insulin resistance (5%). Moreover, even in obese women without hyperandrogenism, the effect upon the carbohydrate metabolism also seems to be mitigated in spite of the fact that these women have a body weight distribution that is comparable with obese women with NIH-PCOS. All this implies that in the ‘new PCOS’, the occurrence of the so-called metabolic syndrome will be less frequent as obesity of the visceral type, insulin resistance and impaired glucose tolerance are key features of this syndrome (report of the National Cholesterol Education Program, recently adjusted as for the treatment approach). The group classified as NIH-PCOS, the Rotterdam criteria will automatically be fulfilled. In ~90% of these classical PCOS cases, the criterion of PCO at ultrasound scan has also been met. This means that in women with PCOS with androgen excess, the ovaries will generally show the typical PCO morphology. This may contrast with earlier reports where only partial overlap with cases presenting biochemical hyperandrogenism was observed. Still, considering that the vast majority of NIH cases had PCO, the rate of hyperandrogenism was indeed very much comparable to earlier published data and seems perfectly in line with a recent report. The finding may also be biologically plausible as the production and release of androgens from the theca cells of antral follicles is held responsible for the biochemical hyperandrogenism. Next to altered signalling towards the theca cells by elevated endogenous luteinising hormone and insulin-related growth factors, increased antral follicle numbers may be considered as consistently related to the androgen excess.

In the present study, no women with regular cycles, PCO at ultrasound scan and hyperandrogenism were included. Much debate has been put forward as to the helpfulness of incorporation of these women in the syndrome definition. As recently summarised, there are strong arguments to conclude that women with PCO indeed have many of the biochemical and endocrine features of the PCOS and this has also been suggested in other studies. Still, women with regular cycles will present a lower risk for the presence of insulin resistance or type II diabetes compared with women with PCOS with oligo/amenorrhoea, and as such the relation between ovarian dysfunction and metabolic dysfunction becomes apparent.

The fact that under the new diagnostic criteria, the prevalence of metabolic disturbances and androgen excess becomes decreased and may also have consequences on the way women with PCOS will behave in ovulation induction treatment. From several reports in the recent literature, it has been shown that next to factors like higher female age and longer duration of infertility, hyperandrogenism and overweight will substantially reduce the chances for success in the establishment of ovulation and pregnancy. As many of the new PCOS cases do not have androgen excess and tend to have lower rates of obesity and hyperinsulinaemia, they may be expected to respond better to ovulation induction regimens. Future research on anovulation treatment in subgroups of the currently defined PCOS will unravel whether this assumption holds.

In conclusion, this report shows that by applying the new criteria for PCOS according to the Rotterdam consensus, the frequency of diagnosis of the syndrome greatly increases. The occurrence of obesity and carbohydrate derangements under the new diagnostic approach is considerably lower and related to the attainment of women with ovarian dysfunction and PCO at ultrasound scan without the presence of hyperandrogenism. These findings need to be considered in the health risk and infertility management of the women with PCOS.

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