Polycystic ovary syndrome (PCOS) was first described in 1935 by Stein and Leventhal (1) in a case series of seven women with amenorrhea, hirsutism, obesity, and ovaries with a gross polycystic appearance. The syndrome is one of the most common endocrinopathies in women of child-bearing age, and over the past few decades its metabolic, cardiovascular, and reproductive risks have been further defined (2).

There has been significant controversy regarding the diagnosis of PCOS, primarily owing to heterogeneous manifestations, which may change during a woman’s lifetime. An expert conference in 1990 sponsored by the National Institute of Child Health and Human Development (NICHD) was therefore convened to obtain consensus on the diagnostic criteria for PCOS. The following two criteria were considered central to the diagnosis of PCOS: 1) clinical and/or biochemical hyperandrogenemia; and 2) clinical or anovulation, with exclusion of other known disorders such as congenital adrenal hyperplasia and androgen-producing tumors (3). Of note, the finding of polycystic ovaries on ultrasound (PCO-US), a clinical feature recognized to be associated with PCOS, was rejected at the NICHD conference as an essential component of the diagnostic criteria. In the decade following the implementation of the NICHD criteria, it was recognized that a broader spectrum of PCOS existed, extending beyond the diagnostic criteria put forth in 1990. In 2003, a conference was held in Rotterdam, The Netherlands, cosponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, and workshop participants debated that PCO-US should now be considered as one of the criteria for the diagnosis of PCOS. The revised diagnostic criteria (Rotterdam criteria) of PCOS include any two of the following three features: 1) oligo- or anovulation; 2) clinical and/or biochemical hyperandrogenemia; and 3) PCO-US with exclusion of other etiologies as mentioned in the NICHD criteria (4). It is important to recognize that the new Rotterdam criteria have not nullified the NICHD criteria; rather, they have served to expand the diagnosis of PCOS to include the NICHD phenotype and other new phenotypes namely; 1) complete phenotype: oligo/anovulation, hyperandrogenism, and PCO-US (O+H+P); 2) ovulatory phenotype: hyperandrogenemia and PCO-US (H+P); and 3) nonhyperandrogenic phenotype: oligo/anovulation and PCO-US (O+P).

The diagnosis of PCOS carries significant implications for future metabolic consequences (2). Evidence suggests that hyperinsulinemia plays a central role in the pathogenesis of PCOS. Women with PCOS demonstrate a significantly higher prevalence of impaired glucose tolerance and noninsulin dependent diabetes mellitus (NIDDM) compared with age- and
weight-matched control subjects (5). More recently, we reported that the risk of metabolic syndrome is 11-fold higher in women with PCOS compared with age-matched controls (6). In addition, we found those women to have an increased risk for cardiovascular disease, as indicated by an elevated triglycerides (TG)/high-density lipoprotein (HDL) ratio (7). Other cardiovascular risk factors reported in this population include lipid abnormalities, hypertension, carotid and coronary atherosclerosis, and endothelial dysfunction (8–11). The majority of this data is based on studies defining women with PCOS by the NICHD criteria. Some studies specifically recruited women with biochemical hyperandrogenism to represent the more hyperandrogenic profile. There are limited data on metabolic complications in women belonging to the newer PCOS phenotypes as defined by the Rotterdam criteria, especially the nonhyperandrogenic phenotype (12). For these reasons, the widespread application of these criteria to clinical practice and research protocols has been cautioned against (13). The present study was undertaken to characterize the prevalence of metabolic complications, primarily metabolic syndrome, in all phenotypes of PCOS per the Rotterdam criteria and compare these risks with control subjects.

### MATERIALS AND METHODS

#### Subjects

All patients aged 18–45 years seen at the University of Iowa Reproductive Endocrinology Clinic from 2002 to 2005 and diagnosed with PCOS were identified through the ICD-9 coding system of the hospital medical records. All charts were reviewed to re-evaluate the diagnosis of PCOS based on the Rotterdam criteria with women satisfying at least two of the following three criteria: 1) oligomenorrhea/oligo-ovulation (O); 2) clinical or biochemical hyperandrogenism (H); 3) polycystic ovaries on transvaginal ultrasound (P) and exclusion of related disorders such as hypothyroidism, hyperprolactinemia, and adrenal hyperplasia (4). As a result, only patients who had a complete PCOS work-up, including a transvaginal ultrasound, physical exam, and laboratory tests, were included in the study. None of the subjects were postmenopausal.

Of approximately 800 charts reviewed, 258 subjects had adequate data to be accurately classified according to the Rotterdam criteria (4) and had laboratory testing to define the presence or absence of metabolic syndrome. Participants were classified as having metabolic syndrome if they met three of the following five criteria: body mass index (BMI) >30, serum TG ≥150 mg/dL, serum HDL-cholesterol <50 mg/dL, blood pressure ≥130/85 mm Hg or on antihypertensive medication, and fasting blood glucose ≥100 mg/dL or the presence of NIDDM (14). A lower cut-off for glucose was used, based on recent guidelines (15).

In addition, control subjects were selected from women who had regular menses and no hirsutism and who were being seen for an annual examination in the Gynecology Clinic at the University of Iowa during the same time period as the PCOS subjects. An attempt was made to mimic the BMI distribution of the general population in this geographic area. A total of 110 subjects had sufficient data to classify the presence or absence of metabolic syndrome and were seen by two healthcare providers in the gynecology clinic. Other data collected from each patient’s medical record included tobacco and alcohol use, family history of coronary artery disease and NIDDM. This study was approved by the Institutional Review Board at the University of Iowa.

### Laboratory Tests

Laboratory tests to establish the diagnosis of PCOS included TSH, PRL, total/free T, DHEAS, and 17-OHP levels. In addition, PCOS and control subjects had fasting glucose and lipid panels. In PCOS subjects, insulin resistance (IR) was estimated using fasting insulin, homeostasis model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI). The HOMA-IR was calculated with the formula (fasting insulin [U/mL] × fasting glucose [mmol/dL])/22.5; percentage β-cell function = (20 × insulin [μU/mL]/(glucose [mg/dL] × 0.05551) − 3.5; the QUICKI was derived by calculating the inverse of the sum of logarithmically expressed values of fasting insulin and glucose.

### Statistical Analysis

We had 80% power to detect a difference of 25% in the prevalence of metabolic syndrome with 5% prevalence in the control subjects (n = 100) and n = 35 in the study groups at the Bonferroni adjusted significance level of .05. Multiple logistic regression model was used to compare prevalence of metabolic syndrome among the phenotype groups and controls, with age as a covariate. Bonferroni adjustment was used for multiple comparisons. Chi-squared test was used to determine the difference in prevalence for impaired fasting glucose and NIDDM. For comparisons across the four PCOS groups, a natural log transformation was used for variables, and then analysis of covariance was used with age as the covariate. If there was a significant group effect, pairwise mean comparison of the groups was performed using Tukey test. Significance was determined to be at P < .05.

### RESULTS

Of the 258 PCOS subjects studied, the largest phenotype group included women with all three features, namely O+H+P (58%, Table 1). Interestingly, 14% satisfied the NICHD criteria (O+H) but did not meet the criteria for PCO-US; therefore, we classified these subjects separately. Another 14% had H+P (ovulatory phenotype), and 13% had O+P (nonhyperandrogenic phenotype). The latter two groups represent the newer phenotypes created by the Rotterdam criteria. Baseline characteristics for all four groups are shown in Table 1. The mean age at screening for all PCOS phenotypes was lower than the control subjects (Table 1).
Other group-specific demographic characteristics are included in Table 1.

Figure 1 depicts the prevalence of metabolic syndrome in all four PCOS phenotypes and control subjects. The age-adjusted prevalence of metabolic syndrome was 36.1% for women with O+H+P (odds ratio [OR] 6.3 [95% confidence interval 2.1–18.9]), 41.3% for women with O+H (OR 7.8 [2.2–27.5]), and 42.3% for women with H+P (OR 8.2 [2.2–29.5]). For these three phenotypes, the prevalence of metabolic syndrome was significantly higher than the control subjects (8.3%; P < .001). The age-adjusted prevalence of metabolic syndrome in women with O+P (20.3%) was not statistically different compared with the control subjects (P = .14).

We next examined the prevalence of each of the abnormalities of metabolic syndrome in the different phenotypes. As has been shown previously in North American women with PCOS (6, 16), obesity was the most common abnormality in most phenotypes (66%–70%) except the O+P group (Table 2). In the latter group, a low HDL value was more common (55%) than obesity. A high TG value was the third most common abnormality in all groups. An elevated glucose value was the least common abnormality in all groups, including the control subjects.

To explore the role of BMI in the prevalence of metabolic syndrome, we examined women with obesity (BMI >30) separately. No women in any of the phenotype groups with a BMI <30 had metabolic syndrome. The age-adjusted OR for metabolic syndrome in obese women was 3.5 (1.04–11.94; P < .04) in the complete phenotype (O+H+P), in H+P was 5.12 (1.2–22.7; P < .02), 3.81 (0.95–15.4; P < .06) in O+H, and 5.32 (0.78–36.4; P = .12) in O+P compared with the control group (23.5%).

We next examined the risk of diabetes in the four PCOS phenotypes. A higher proportion of PCOS women had NIDDM (3%–6%), except for the O+P phenotype, where no subjects had a fasting glucose level ≥126 mg/dL (Fig. 2). The prevalence of impaired fasting glucose (IFG, fasting glucose 100–125 mg/dL) in women with O+H+P, O+H, and H+P (16%–17%, Fig. 2) was higher than in the phenotype O+P (6%), although this was not statistically significant. The mean fasting glucose level was not significantly lower in the control group (90.6 ± 12.5) compared with all 4 phenotype groups (Table 3). There was no significant difference in mean fasting glucose levels among the four phenotype groups after adjusting for age and BMI.

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A large proportion of women with PCOS exhibit insulin resistance. We used a variety of surrogate markers of insulin
resistance to compare the differences in insulin sensitivities across the 4 PCOS groups. The measures of insulin resistance QUICKI and ratio of fasting glucose to insulin (17) were not significantly different among the four PCOS subgroups (Table 3). The mean HOMA-IR levels in all four groups were not significantly different. The percentage of women with an abnormal HOMA-IR (>1.0 mol·L⁻¹) was similar in all groups (84.6%–94.1%). Beta-cell function was also similar in all four groups, and the percentage of subjects with abnormal HOMA β-cell (<100%) were similar in all groups (18.8%–24.1%). We did not have fasting insulin levels in the control subjects to compare with the PCOS phenotypes.

We next examined the lipid profiles and found the mean cholesterol levels to be similar in women with all phenotypes compared to controls (Table 4). The mean TG levels were also significantly higher in phenotype O+H+P than in the control subjects (P<.01). The mean HDL levels were significantly lower in women with H+P and O+H+P than in control subjects (P<.01) but not different compared with the other two phenotypes. Mean LDL levels did not vary significantly among the five groups. The TG/HDL ratio is reflective of small atherogenic LDL particles (7) and has recently been shown to be a simple means of identifying insulin-resistant individuals at high risk for cardiovascular disease (19). We have previously shown a significant linear relationship between insulin resistance (measured by QUICKI) and TG/HDL levels in women with PCOS (6). The TG/HDL ratio was significantly higher in women with PCOS phenotypes O+H+P and H+P (P<.05) compared with the controls (Table 4).

**DISCUSSION**

The present study aimed to characterize the metabolic complications of the four PCOS phenotypes as proposed by the Rotterdam criteria and compare their prevalence with control subjects. The complete phenotype (O+H+P), the hyperandrogenic phenotype (H+P), and the NICHD phenotype (O+H) all had a six- to eightfold increased risk of metabolic syndrome compared with the control group. The reported prevalence of metabolic syndrome in women with PCOS varies between 30% and 47% (6, 16, 20), depending on the criteria used for defining both PCOS and metabolic syndrome. Some studies recruit PCOS women with only biochemical hyperandrogenism, making direct comparisons between studies difficult. The present study found a similar risk of metabolic syndrome (35%–44%) in the three PCOS phenotypes mentioned (based on the Rotterdam definition) but a lower risk in the nonhyperandrogenic PCOS phenotype (O+P, 20%). Although this lower prevalence was not significantly different from our geographically matched controls, it is higher than age-matched female participants from the NHANES population (6%–15%) (21). In addition, the O+P phenotype had similar mean TG and HDL levels and TG/HDL ratio compared with the control group. This suggests that O+P phenotype women may have fewer cardiovascular risk factors. These data collectively suggest that the nonhyperandrogenic phenotype (O+P), one of the new phenotypes created by the Rotterdam Criteria, may represent a form of PCOS associated with a milder metabolic profile.

As reported previously, we did not find metabolic syndrome in any women with BMI <30, suggesting that in this

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**TABLE 2**

Prevalence of components of metabolic syndrome in each PCOS phenotype and controls.

<table>
<thead>
<tr>
<th></th>
<th>H + O + P</th>
<th>O + H</th>
<th>H + P</th>
<th>O + P</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &gt; 30</td>
<td>95 (66.4%)</td>
<td>28 (75.7%)</td>
<td>26 (70.2%)</td>
<td>16 (47.1%)</td>
<td>41 (39%)</td>
</tr>
<tr>
<td>HDL &lt; 50 mg/dL</td>
<td>70 (56.5%)</td>
<td>17 (50.0%)</td>
<td>18 (51.4%)</td>
<td>15 (55.6%)</td>
<td>27 (22.5%)</td>
</tr>
<tr>
<td>TG ≥ 150 mg/dL</td>
<td>46 (35.4%)</td>
<td>11 (33.3%)</td>
<td>15 (44.1%)</td>
<td>9 (29.0%)</td>
<td>15 (22%)</td>
</tr>
<tr>
<td>BP ≥ 130/85 mm Hg</td>
<td>35 (24.5%)</td>
<td>9 (24.3%)</td>
<td>10 (27.0%)</td>
<td>4 (11.8%)</td>
<td>12 (10.9%)</td>
</tr>
<tr>
<td>Glucose ≥ 100 mg/dL</td>
<td>17 (12.5%)</td>
<td>5 (14.3%)</td>
<td>5 (13.9%)</td>
<td>1 (3.1%)</td>
<td>5 (5.7%)</td>
</tr>
</tbody>
</table>

*Note: BP = blood pressure; HDL = high-density lipoprotein; TG = triglycerides; other abbreviations as in Table 1.*


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**FIGURE 2**

Prevalence of impaired fasting glucose (IFG) and DM in PCOS phenotypes and controls.

[Graph showing prevalence of IFG and DM in different PCOS phenotypes and controls.]

young population obesity is an important determinant of metabolic syndrome (6). Women with O+H+P, O+H, and H+P had a significantly higher BMI compared with control subjects. However, women with O+P had a significantly lower BMI compared with the other three phenotype groups. It is not clear if this reflects an inherent difference in this phenotype or a selection bias in our study. The risk of metabolic syndrome in women with PCOS is increased independent of BMI (17). We also noted a higher prevalence of metabolic syndrome in obese PCOS women (O+H+P, H+P) compared with obese controls. Our sample size in the obese groups was, however, small, and larger studies will be needed to validate these results.

An increased risk for impaired glucose tolerance and NIDDM in women with PCOS (NICHD criteria with biochemical hyperandrogenism) has been reported (5). The present study shows a trend toward a higher risk for IFG and NIDDM in all PCOS phenotypes, except women with nonhyperandrogenic phenotype (O+P), compared with control subjects. However, the study was not powered to determine differences in these outcomes. We used different surrogate markers to examine insulin resistance in the four phenotypes and were unable to detect a significant difference. Although we did not measure insulin sensitivity directly, HOMA-IR has been shown to correlate significantly with the insulin sensitivity index in women with PCOS (22). Insulin resistance and compensatory hyperinsulinemia appears to play a significant role in the pathophysiology of metabolic syndrome. The presence of clinical versus biochemical hyperandrogenism appears to be associated with the degree of insulin resistance in this population (18). Those authors (18) suggest that the clinical phenotype may arise, at least in part, from differences in the degree of metabolic dysfunction. It is interesting that we did not observe a decrease in insulin resistance in the O+P group.

Lipid abnormalities in the PCOS population include increased LDL and TG and low HDL levels (8). We recently examined the relationship between TG/HDL ratio and QUICKI in women with PCOS ($r = -0.554; P<.001$) (6). The TG/HDL ratio $>3.2$ had a 90.9% sensitivity and a 7.5% false negative rate to detect metabolic syndrome in that population. In the present study, all phenotypes except O+P had significantly elevated TG/HDL ratio. The TG/HDL ratio has been identified as a simple test to detect insulin-resistant individuals at increased risk of cardiovascular disease (19). It is possible that the TG/HDL ratio may also be a better indicator of underlying insulin resistance in women with PCOS.

We studied the complete phenotype (H+P+O+) separately from the NICHD phenotype (H+P), because there are conflicting data regarding the metabolic significance of PCO-US. The odds of women with PCOS based on NICHD criteria having polycystic ovaries are very high (23). In the present study also, most women with H+P had PCO-US and therefore were included in the complete group. We did not find a difference between these two groups for all parameters examined. These findings are similar to an earlier study that found no differences in insulin sensitivities, integrated OGTT glucose and insulin responses in women with PCOS (NICHD) and PCO-US or women with PCOS (NICHD) minus PCO-US (23).

The data on metabolic complications in the ovulatory PCOS phenotype (H+P) are conflicting. One study reported significantly higher serum insulin levels, lower glucose/insulin ratios, and an atherogenic lipid profile in overweight women with hyperandrogenism and PCO-US ($n = 22$) compared with control subjects (24). The same authors recently reported a larger group of ovulatory PCOS subjects ($n = 50$) with an intermediate metabolic profile compared with the NICHD (H+O) phenotype and control subjects (25). In another study, in the H+P group (defined by biochemical hyperandrogenism) the lipid levels and glucose and insulin concentrations were not significantly different from control subjects (12). The present findings suggest that women with H+P have a similar prevalence of metabolic syndrome, IFG, DM, and lipid abnormalities as the complete phenotype

### TABLE 3
Comparison of glucose levels and markers of insulin resistance in the PCOS phenotypes.

<table>
<thead>
<tr>
<th></th>
<th>H+O+P</th>
<th>O+H</th>
<th>H+P</th>
<th>O+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dl</td>
<td>92 ± 13</td>
<td>97 ± 26</td>
<td>97 ± 30</td>
<td>89 ± 10</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>18.2 ± 14.8</td>
<td>18.3 ± 14.7</td>
<td>18.4 ± 18.8</td>
<td>13.9 ± 10.5</td>
</tr>
<tr>
<td>Glucose/insulin</td>
<td>6.3 ± 4.3</td>
<td>6.8 ± 4.8</td>
<td>7.1 ± 4.9</td>
<td>8.4 ± 6.5</td>
</tr>
<tr>
<td>QUICKI</td>
<td>1.7 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>HOMA–IR (mol μU/mL)</td>
<td>3.97 ± 3.25</td>
<td>4.74 ± 5.24</td>
<td>5.80 ± 11.7</td>
<td>3.67 ± 2.88</td>
</tr>
<tr>
<td>HOMA–β-cell (%)</td>
<td>193.1 ± 971.6</td>
<td>228.2 ± 171.7</td>
<td>201.9 ± 111.6</td>
<td>227.6 ± 159.0</td>
</tr>
<tr>
<td>HOMA–β-cell % of abnormal parameters (&lt;100%)</td>
<td>19 (18.8%)</td>
<td>6 (23.1%)</td>
<td>5 (19.2%)</td>
<td>7 (24.1%)</td>
</tr>
</tbody>
</table>

**Note:** Values are mean ± SD. Abbreviations as in Table 1.

and the NICHD phenotype. There are conflicting reports regarding the association of hyperandrogenemia with increased risk for metabolic syndrome in women with PCOS (6, 26). Because >70% of hirsute women are hyperandrogenic (27), we used clinical and/or biochemical hyperandrogenism as a diagnostic criterion in the present study and found no significant difference in the prevalence of metabolic syndrome among the phenotypes that include women with hyperandrogenemia.

There are limited data in the literature on the nonhyperandrogenic phenotype (O+P). Polycystic ovaries may be found in up to 23% of women (28), associated with eating disorders, hyperprolactinemia, and functional hypothalamic amenorrhea. In an Australian study, women with PCO-US only (n = 15) had a similar metabolic profile as control subjects (12). In the same study, women with PCO-US and cycle irregularity (O+P; n = 6) had evidence of hypertriglyceridemia and insulin resistance compared with control subjects. In contrast, we found the O+P group to have the lowest risk for metabolic syndrome, NIDDM, IFG, and lipid abnormalities, specifically the TG/HDL ratio. These findings suggest that the O+P phenotype may have an intermediate risk for metabolic complications compared with the other phenotypes and control subjects. Larger studies are needed to determine the precise metabolic risks in this specific phenotype to appropriately counsel this population.

The present study has some limitations. We retrospectively reviewed charts and redefined subjects as PCOS based on the Rotterdam criteria. Our distribution of subjects in the four PCOS phenotypes may therefore not be accurate, and prospective studies will need to confirm the distribution of women with PCOS in these phenotypes. We had adequate power to compare differences in metabolic syndrome, but the study was not adequately powered for differences in IFG and NIDDM. Additionally, the majority of patients seen in our clinic are caucasian (>95%), and the distribution of the PCOS phenotypes in other ethnic groups, especially those with higher metabolic complications (i.e., African Americans and Hispanic Americans) needs to be evaluated.

The strength of the present study is the inclusion of a geographically matched contemporary control group. During the expansion of the PCOS criteria, the expert panel agreed that the clinical evidence of hyperandrogenism is an important feature of patients with PCOS, notwithstanding its limitations. Therefore, in the present study the PCOS subjects were not preselected to have biochemical hyperandrogenism or any other specific characteristic, making them more likely to represent typical patients managed in a gynecology/endocrinology facility. Also, our control subjects were not preselected to exclude hypertension or diabetes and therefore represent the general population.

In conclusion, it is evident that the diagnosis of PCOS has life-long implications for a woman’s health and possibly that of her relatives and offspring. Polycystic ovary syndrome is a significant economic burden to the modern health care system, underscoring the importance of accurate identification of women with the diagnosis (29). Along with making the diagnosis, we need to be able to accurately counsel these women about their long-term risks. The present study is the first to provide information on prevalence of metabolic complications in all PCOS phenotypes based on the Rotterdam criteria in a North American population. These findings suggest that the ovulatory PCOS subjects (H+P) have similar risks as the complete phenotype (H+O+P) and the NICHD phenotype (H+O). However, the nonhyperandrogenic (O+P) phenotype may represent a form of PCOS with an intermediate or milder metabolic risk profile. Larger studies are needed to validate our findings.

REFERENCES