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Phenotypic Variation in Hyperandrogenic Women Influences the Findings of Abnormal Metabolic and Cardiovascular Risk Parameters

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In hyperandrogenic women, several phenotypes may be observed. This includes women with classic polycystic ovary syndrome (C-PCOS), those with ovulatory (OV) PCOS, and women with idiopathic hyperandrogenism (IHA), which occurs in women with normal ovaries. Where other causes have been excluded, we categorized 290 hyperandrogenic women who were seen consecutively for this complaint between 1993 and 2004 into these three subgroups. The aim was to compare the prevalence of obesity, insulin resistance, and dyslipidemia as well as increases in C-reactive protein and homocysteine in these different phenotypes with age-matched ovulatory controls of normal weight (n = 85) and others matched for body mass index (BMI) with women with C-PCOS (n = 42). Although BMI affected fasting serum insulin and the Quantitative Insulin-Sensitivity Check Index, these markers of insulin resistance were greatest in C-PCOS (n = 204), followed by OV-PCOS (n = 50) and then IHA (n = 33). Androgen levels were similar in OV-PCOS and IHA but were higher in C-PCOS, whereas gonadotropins were similar in all groups. Lipid abnormalities were highest in C-PCOS and OV-PCOS and were normal in IHA. C-reactive protein was elevated in C-PCOS and OV-PCOS but not IHA. Homocysteine was elevated only in C-PCOS. Overall, the prevalence of obesity (BMI > 30) was 29% in C-PCOS, 8% in OV-PCOS, and 15% in IHA and insulin resistance (Quantitative Insulin-Sensitivity Check Index < 0.33) was 68% in C-PCOS, 36% in OV-PCOS, and 26% in IHA. The prevalence of having at least one elevated cardiovascular risk marker was 45% in C-PCOS 38% in OV-PCOS and was not increased on IHA (6%). These results suggest that among hyperandrogenic women the prevalence of abnormal metabolic and cardiovascular risk parameters is greatest in C-PCOS, followed by OV-PCOS and then women with IHA. Moreover, in that in OV-PCOS and IHA, ages and weights were similar yet the prevalence of metabolic and cardiovascular risk was greater in OV-PCOS, the finding of polycystic ovaries may be a significant modifying factor. (*J Clin Endocrinol Metab* 90: 2545–2549, 2005)

THE DIAGNOSIS OF polycystic ovary syndrome (PCOS) has undergone several changes in recent years. Whereas the clinical presentation of chronic anovulation and hyperandrogenism has been stressed as the major diagnostic criteria (1), in recent years the occurrence of normal ovulatory function in women with PCOS has been acknowledged (2–4). In 2004 new diagnostic criteria were established, placing all these factors together, with a special emphasis placed on the finding of polycystic ovaries on ultrasound (5, 6).

Using these criteria, PCOS may be diagnosed in women having three different phenotypes: hyperandrogenism and chronic anovulation; hyperandrogenism and polycystic ovaries but with ovulatory cycles; and chronic anovulation and polycystic ovaries, without requiring clinical hyperandrogenism. With these different phenotypes, it is not clear whether the usual characteristics of increased insulin resistance (IR) and metabolic and cardiovascular (CV) risk markers may be found in all groups. Previously we found mild IR and some lipid abnormalities in young ovulatory normal overweight women who had polycystic ovaries and/or exaggerated responses of 17-hydroxy progesterone and androgen to GnRH agonist challenge (3).

To this end, we reevaluated the diagnosis of PCOS in 290 hyperandrogenic women and divided them into three groups: classic (C)-PCOS (*i.e.* patients with hyperandrogenism and chronic anovulation), ovulatory (OV)-PCOS (*i.e.* patients with hyperandrogenism and polycystic ovaries but with normal ovulatory cycles), and patients with idiopathic hyperandrogenism (IHA) (*i.e.* patients with hyperandrogenism but with ovulatory cycles and normal ovaries) in whom enzymatic defects or tumor had been ruled out. We sought to distinguish between these different phenotypes on the basis of their endocrine and metabolic features and their circulating markers of CV risk.

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Abbreviations: BMI, Body mass index; C, classic (PCOS); CRP, C-reactive protein; CV, cardiovascular; DHEAS, dehydroepiandrosterone sulfate; HDL, high-density lipoprotein; IHA, idiopathic hyperandrogenism; IR, insulin resistance; LDL, low-density lipoprotein; OV, ovulatory (PCOS); PCOS, polycystic ovary syndrome; QUICKI, Quantitative Insulin-Sensitivity Check Index; T, testosterone; WM, weight matched.

Subjects and Methods

Subjects

Two hundred ninety hyperandrogenic women were studied. These patients were referred to the Departments of Endocrinology and Clinical Medicine of the University of Palermo between 1993 and 2004 because of symptoms and/or signs of hyperandogenism and were found to be hyperandrogenic (increased total testosterone and/or elevated unbound testosterone and/or dehydroepiandrosterone sulfate). Eight-four percent (n = 243) of the patients had hirsutism as their major complaint,

whereas in 12% (n = 35) only acne was the complaint and in 4% (n = 12) only alopecia was the concern.

No patients with adrenal enzymatic deficiencies, Cushing's syndrome, or androgen-secreting tumors were included in this study. Normal circulating levels of 17-hydroxyprogesterone were used to exclude the diagnosis of nonclassic 21-hydroxylase deficiency, whereas clinical findings and/or urinary free cortisol assessment were used to exclude the diagnosis of Cushing's syndrome (7). Patients with androgen-secreting tumors were excluded on the basis of the elevations in androgen levels and the use of computed tomography scan or magnetic resonance imaging when levels were suspicious (7).

Independent of the original diagnosis, the diagnosis of these patients was reevaluated according to the European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) criteria for the diagnosis of PCOS (5, 6). The presence of polycystic ovaries was determined by intravaginal sonography using the new criteria as described here. We required the finding of increased ovarian size and/or at least 12 follicular cysts measuring 2–9 mm (8). The patients in this study were divided into two groups: women with the diagnosis of PCOS (n = 254) and women with IHA (hyperandrogenism with normal ovulatory cycles and normal ovaries) (n = 36). Ovulatory cycles were confirmed by finding serum progesterone levels greater than 7 ng/ml in at least two consecutive cycles.

Women with PCOS were further divided into two subgroups according their phenotype: 204 women had hyperandrogenism and chronic anovulation (C-PCOS) and 50 women with hyperandrogenism and polycystic ovaries but with normal ovulatory cycles (OV-PCOS) as assessed using the above criteria. Anovulation was defined as serum P less than 3 ng/ml. In patients with normal menses, at least two consecutive low levels of serum P (<3 ng/ml) were needed to make a diagnosis of anovulation.

Eighty-five women of similar age and with normal weight [body mass index (BMI) between 20 and 25], with normal ovulatory cycles and no findings of hyperandrogenism were selected as normal controls. In addition, 42 women of similar age, with ovulatory cycles and no hyperandrogenism who were matched for body weight with patients with C-PCOS were also studied and are reported as weight-matched (WM) controls.

Institutional review board approval was obtained, and all patients and controls gave written consent. All subjects were sedentary and were not participating in any specific diet plans. Nevertheless, diets of all subjects were Mediterranean in nature as described by us previously (9).

Protocol

Fasting blood was obtained between 0800 and 1000 h, during the follicular phase (d 5–6) of a spontaneous or progestin-induced menstrual cycle. LH, FSH, testosterone (T), dehydroepiandrosterone sulfate (DHEAS), glucose, insulin, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, C-reactive protein (CRP), and homocysteine were measured. In all patients, gonadotropins, androgens, glucose, insulin, and lipids were determined at the time of the original diagnosis, and all assays used were constant throughout the study period. CRP and homocysteine were measured in stored frozen sera from patients presenting between 1993 and 2002 or at the time of presentation after 2002. The assays used for all samples are described below.

Serum LH, FSH, T, and DHEAS were measured by RIA using previously described methods (10, 11). Insulin was determined with a double-antibody method using reagents obtained from Linco Research, Inc. (St. Charles, MO). IR was calculated by the Quantitative Insulin-Sensitivity Check Index (QUICKI) (12). In all hormonal assays, the intraassay coefficient of variation was less than 6%, and the interassay coefficient of variation was less than 15%.

Blood glucose was determined using the glucose oxidase method. Total cholesterol was determined using the cholesterol esterase method on an automated chemistry analyzer (Roche, Stockholm, Sweden). HDL-cholesterol was determined using the cholesterol esterase method following selective precipitation of apolipoprotein-B containing lipoproteins with a polyanion solution. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald equation (13). Triglycerides were determined enzymatically as glycerol on a Roche automated chemistry analyzer after hydrolysis with lipase. All lipid analyses had intra- and interassay variations of less than 3%. Serum CRP was assessed by a highly sensitive immunoturbidimetric assay (14). The detection limit was 0.115 mg/liter. Total plasma homocysteine was measured by a fluorescence polarization immunoassay (Abbott Diagnostics, Abbott Park IL) (15).

Statistical analyses

ANOVA was used for comparisons. *Post hoc* testing was carried out by Student's *t* test with log transformation. Analysis of covariance was used to evaluate the role of BMI on metabolic and CV markers. Pearson product moment correlation and stepwise multivariate linear regression analysis with forward selection was used to analyze correlations. $P < 0.05$ was considered statistically significant. All data are expressed as mean ± SD.

Results

Serum insulin and insulin sensitivity (by QUICKI) of normal women, WM controls and the three groups of patients (C-PCOS, OV-PCOS, and IHA) are depicted in Table 1. Patients with C-PCOS had significantly ($P < 0.01$) increased BMI and insulin and reduced insulin sensitivity in comparison with normoweight controls as well as with patients with OV-PCOS and IHA. In comparison with WM controls (matched for BMI), patients with classic PCOS had significantly ($P < 0.01$) increased serum insulin and reduced insulin sensitivity.

Women with OV-PCOS had lower insulin and higher QUICKI levels compared with C-PCOS but had higher serum insulin and lower QUICKI in comparison with normoweight controls ($P < 0.01$) and patients with IHA ($P < 0.01$ for differences in serum insulin, $P < 0.05$ for differences in QUICKI). Women with IHA had higher insulin ($P < 0.05$) and lower insulin sensitivity ($P < 0.05$) compared with normoweight controls.

The endocrine parameters (gonadotropins and androgens) are depicted in Table 2. Patients with C-PCOS had significantly ($P < 0.01$) increased levels of LH, LH/FSH, T, and

TABLE 1. Clinical and metabolic characteristics of normal controls, WM controls, and hyperandrogenetic patients (C-PCOS, OV-PCOS, and IHA)

	Number	Age (yr)	BMI	Insulin (μU/ml)	QUICKI
Normal controls	85	24.9 ± 5.2	22.9 ± 1.9[a]	8.7 ± 1.9[a,b,d]	0.360 ± 0.021[a,b,d]
WM controls	42	24.6 ± 4.5	28.0 ± 3.3	11.3 ± 5.5[a]	0.342 ± 0.021
Classic PCOS	204	24.8 ± 5.6	28.1 ± 5.8	17.8 ± 7.4	0.319 ± 0.019
OV-PCOS ovulatory	50	24.6 ± 4.6	23.8 ± 4.6[a]	13.5 ± 7.7[a]	0.333 ± 0.021[a]
IHA ovulatory	33	24.2 ± 4.5	24.2 ± 4.5[a]	10.8 ± 4[a,b]	0.344 ± 0.021[a,c]

[a] $P < 0.01$ *vs.* C-PCOS.
[b] $P < 0.01$ *vs.* OV-PCOS.
[c] $P < 0.05$ *vs.* OV-PCOS.
[d] $P < 0.05$ *vs.* IHA.

TABLE 2. Serum gonadotropins and androgens in normal controls, WM controls, and hyperandrogenic patients

	LH (mIU/ml)	FSH (mIU/ml)	LH/FSH	T (ng/dl)[a]	DHEAS (μg/ml)[b]
Normal controls	6 ± 1.3[c]	6.2 ± 2.4	1 ± 0.5[c]	37 ± 15[a,d]	1.8 ± 0.7[c,d]
WM controls	6.5 ± 2[c]	6.3 ± 1.9	1 ± 0.6[c]	38 ± 16[c,d]	2 ± 0.5[c,d]
Classic PCOS	8.7 ± 5.3	6.1 ± 1.3	1.6 ± 1.1	88 ± 33	3.1 ± 1.3
OV-PCOS	6.8 ± 2.6	6.3 ± 2.6	1.1 ± 0.5[c]	79 ± 16[e]	2.8 ± 1.1
IHA	6.2 ± 1.9[c]	6.1 ± 2.5	1.1 ± 0.5[c]	75 ± 15[c]	2.5 ± 0.9[c]

[a] Multiply by 34.67 for picomoles per liter.
[b] Multiply by 2721 for nanomoles per liter.
[c] $P < 0.01$ *vs.* C-PCOS.
[d] $P < 0.01$ *vs.* OV-PCOS and IHA.
[e] $P < 0.05$ *vs.* C-PCOS.

DHEAS in comparison with normoweight controls, WM controls, and patients with IHA. In comparison with patients with OV-PCOS, C-PCOS had increased ($P < 0.05$) LH to FSH ratios ($P < 0.01$) and serum T ($P < 0.05$). Women with OV-PCOS and IHA had similar gonadotropins and androgens and in comparison with normoweight controls had higher androgens but similar gonadotropins.

Lipid profiles in normal controls, WM controls, and hyperandrogenic patients are depicted in Table 3. Patients with C-PCOS had increased ($P < 0.01$) total cholesterol, LDL-cholesterol, and triglycerides and lower HDL-cholesterol when compared with normoweight controls and patients with IHA. In comparison with WM controls, C-PCOS had increased total and LDL-cholesterol ($P < 0.01$) but similar HDL-cholesterol and triglycerides. In comparison with patients with OV-PCOS, patients with C-PCOS had higher triglycerides ($P < 0.01$) and lower HDL-cholesterol ($P < 0.05$) but similar cholesterol and LDL-cholesterol. Finally, patients with OV-PCOS had increased total and LDL-cholesterol, compared with normoweight controls ($P < 0.01$) and patients with IHA ($P < 0.05$). No differences in serum lipids were observed between normoweight controls and patients with IHA.

Circulating levels of CRP and homocysteine are reported in Table 4. Women with C-PCOS had increased levels of CRP in comparison with normoweight controls ($P < 0.01$), WM controls ($P < 0.01$), those with idiopathic hyperandrogenism ($P < 0.01$), and patients with OV-PCOS ($P < 0.05$). Patients with OV-PCOS had increased levels of CRP in comparison with normoweight controls ($P < 0.05$) and patients with IHA ($P < 0.05$).

Patients with C-PCOS had increased levels of homocysteine in comparison with normoweight controls ($P < 0.01$), WM controls ($P < 0.05$), patients with OV-PCOS ($P < 0.01$), and patients with IHA ($P < 0.01$). Women with OV-PCOS and IHA had similar homocysteine compared with normoweight controls.

Prevalence of obesity, insulin resistance, and markers of CV risk with the various phenotypes

All hyperandrogenic women were analyzed to assess their prevalence of obesity, insulin resistance, and/or altered markers of CV risk. The following criteria were considered as being abnormal: obesity, BMI 30 or more; insulin resistance, QUICKI 0.330 or less (16); dyslipidemia, total cholesterol, 200 mg/dl or more and/or HDL-cholesterol, 40 mg/dl or less, and/or LDL-cholesterol, 130 mg/dl or more, and/or triglycerides, 150 mg/dl or more. Altered inflammatory factors included: CRP, 3 mg/liter or more and homocysteine, 13 μmol/liter or more.

Obesity

Obesity was found in 29% of women with C-PCOS and was present in 8 and 15% of women with OV-PCOS and IHA, respectively (Table 5).

Insulin resistance

Using criteria we established of QUICKI values less than 0.330, we found that 68% of women with C-PCOS had evidence of insulin resistance. This occurred in only 36 and 26% of women with OV-PCOS and IHA, respectively (Table 5).

CV risk factors

The most frequent alteration was dyslipidemia occurring in 36% of patients with C-PCOS, whereas increased CRP and homocysteine were found in 20% of these patients (Table 5). Women with OV-PCOS, despite being less obese and having less insulin resistance, had a similar prevalence of dyslipi-

TABLE 3. Serum lipids in normal controls, WM controls, and hyperandrogenic patients

	Cholesterol (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)	Triglycerides (mg/dl)
Normal controls	160 ± 19[a,b]	52.5 ± 11[a]	96 ± 12[a,b]	72 ± 23[a]
WM controls	162 ± 11[a,b]	50.4 ± 5.1	101 ± 8[c]	90 ± 7
Classic PCOS	177 ± 40	48.4 ± 10.1	111 ± 36	93 ± 38
OV-PCOS	178 ± 31	51.9 ± 10[d]	107 ± 35	76 ± 28[a]
IHA	163 ± 26[a,c]	54.5 ± 10[a]	95 ± 24[a,c]	78 ± 21[c]

[a] $P < 0.01$ *vs.* classic PCOS.
[b] $P < 0.01$ *vs.* OV-PCOS.
[c] $P < 0.05$ *vs.* OV-PCOS.
[d] $P < 0.05$ *vs.* classic PCOS.

TABLE 4. Serum CRP and homocysteine in normal controls, WM controls, and hyperandrogenic patients

	CRP (mg/liter)	Homocysteine (μmol/liter)
Normal controls	$1.52 \pm 0.45^{a,b}$	9.9 ± 1.4^{a}
WM controls	$1.45 \pm 0.48^{a,b}$	10.2 ± 2.2^{c}
Classic PCOS	2.05 ± 0.79	10.9 ± 3.1
OV-PCOS	1.78 ± 0.74^{c}	9.8 ± 1.4^{a}
IHA	$1.51 \pm 0.41^{a,b}$	10.0 ± 1.5^{a}

[a] $P < 0.01$ *vs.* C-PCOS.
[b] $P < 0.05$ *vs.* OV-PCOS.
[c] $P < 0.05$ *vs.* C-PCOS.

demia (32%) but a lower prevalence of other markers (10 and 5% for CRP and homocysteine, respectively) (Table 5). In women with IHA there were only minor abnormalities: 6, 3, and 3% for dyslipidemia, CRP, and homocysteine, respectively (Table 5).

In assessing how many patients had at least one altered CV marker, we found that 45% of patients with C-PCOS and 38% of patients with OV-PCOS had an alteration of at least one CV marker (Fig. 1). Alterations of these markers were uncommon in IHA and similar to the prevalence in normoweight controls.

Correlations

In these hyperandrogenic women, BMI correlated significantly ($P < 0.01$) with serum insulin (r = 0.38) and QUICKI (r = −0.38). BMI did not correlate with LH, the LH to FSH ratio, or androgens, whereas serum insulin correlated with serum LH (r = 0.3, $P < 0.01$) and serum T (r = 0.3, $P < 0.01$).

BMI correlated negatively with HDL-cholesterol (r = −0.31, $P < 0.01$) but not with the other markers of CV risk.

Insulin correlated with serum homocysteine (r = 0.31, $P < 0.01$) and negatively with HDL-cholesterol (r = −0.23, $P < 0.01$). The correlations of insulin with HDL-cholesterol, homocysteine, and T were lost if these correlation were corrected for BMI.

Discussion

Using the new ESHRE/ASRM criteria for the diagnosis of PCOS (5, 6), 88% of the hyperandrogenic women of this study were considered to have PCOS. Twelve percent did not have PCOS and, because other causes of hyperandrogenism were ruled out, were considered affected by a non-PCOS form of hyperandrogenism, for which we have used the term IHA, understanding that this definition is relatively arbitrary. Among the 254 women with PCOS, 80% had a phenotype characterized by hyperandrogenism and chronic anovulation and were considered to have C-PCOS (1), whereas 20% had OV-PCOS, characterized by a phenotype of hyperandrogenism and polycystic ovaries with ovulatory cycles. These patients are considered to have PCOS using the new diagnostic criteria (5, 6) but would not have been included using older criteria (1). Whereas this study was not designed to assess the relative prevalence of the different phenotypes among women with PCOS, the ratio 4:1 between classic and OV-PCOS in unselected women presenting with hyperandrogenism to our center in Palermo, Italy, is similar to our previous experience (17).

TABLE 5. Percentage of hyperandrogenic women having obesity, insulin resistance, dyslipidemia, or increased CRP and homocysteine

	Obesity	Insulin resistance	Dyslipidemia	Increased CRP	Increased homocysteine
Classic PCOS	29	68	36	21	18
OV-PCOS	8	36	32	10	5
IHA	15	26	6	3	3

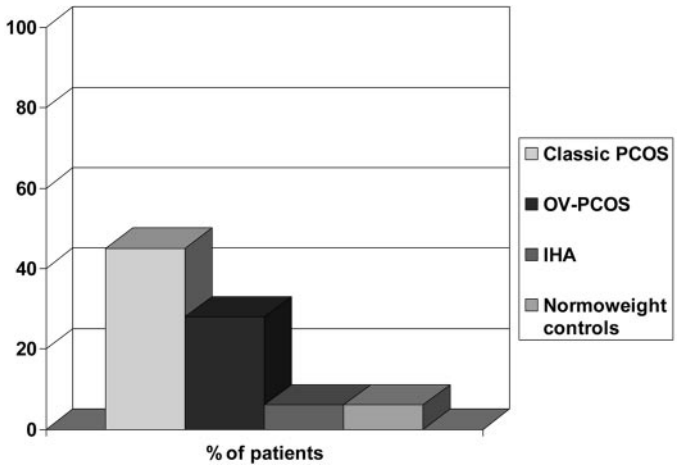

FIG. 1. Prevalence of altered risk parameters (dyslipidemia and/or increased CRP and/or increased homocysteine) in the various groups of women and normoweight controls.

Our data show that the various hyperandrogenic phenotypes, independent of the specific diagnosis, have similar endocrine and metabolic findings yet varying in the degree of severity. Women with C-PCOS had higher androgen levels, insulin, and IR, compared with the other two groups (OV-PCOS and IHA). Women with IHA had the mildest alterations of these parameters, and the profiles of women with OV-PCOS appeared to be intermediate.

Differences in BMI and serum LH and the LH to FSH ratio were found to be abnormal only in patients with C-PCOS. Whereas it is possible that the alterations in LH and LH to FSH may contribute to the anovulation of patients with PCOS, it is also likely that these changes reflect the consequences of changes in ovarian steroid secretion (18) and/or insulin parameters. Serum LH was significantly correlated with insulin, suggesting that higher insulin levels may result in higher LH, which may contribute to anovulation. Insulin in turn is highly correlated with the high BMI of these women.

Whereas in our study, only 29% of women with PCOS were obese (BMI > 30), the mean BMI of patients with C-PCOS was significantly higher, compared with not only normal controls but also patients with OV-PCOS, and IHA. Obesity was uncommon in the two other groups of hyperandrogenic patients. In addition, most women with C-PCOS were considered overweight (with only 30% being normoweight). Because of the strong correlation between BMI and serum insulin, it is possible that increased body weight is the major factor influencing the hyperandrogenic phenotype modifying the degree of IR and the occurrence of anovulation.

Differences in body weight and endocrine and metabolic parameters also appear to modify CV risk parameters in the three groups of women with hyperandrogenism. Women with C-PCOS had increased levels of all parameters measured, whereas women with IHA had normal CV risk markers and women with OV-PCOS had increased levels of total cholesterol, LDL-cholesterol and CRP. Whereas in many women, the absolute values of the CV risk markers were in the normal range, the most common alterations (low HDL-cholesterol, high LDL-cholesterol, and high CRP) were not correlated, and 45% of patients with C-PCOS but also 38% of patients with OV-PCOS had an increase of at least one circulating marker of CV risk. Clearly, one of the limitations of this report is that we did not have the opportunity to assess other markers that might provide a more comprehensive risk profile.

It is interesting to note that, in our patients with C-PCOS, the HDL-cholesterol levels were higher and the triglyceride levels were lower than those reported in other studies of women with PCOS (19). However, these data are similar to that of our previous report (9), reflecting differences in lipid profiles between U.S. and Italian women. We observed that in U.S. women with PCOS, a much higher quantity of saturated fat is ingested, compared with Italian women. The quantity of saturated fat correlated negatively with HDL-cholesterol. This suggests that lifestyle factors may have an important effect on the phenotype of women with PCOS and that in some populations (possibly in U.S. women) CV risk in women with PCOS may be higher than what we observed in this report.

A comment should be made regarding the significance of finding polycystic ovaries on ultrasound. Women with OV-PCOS and IHA had similar gonadotropins, androgens, and BMI, and both groups were ovulatory. The major difference between these subgroups is the presence of polycystic ovaries in OV-PCOS. In that this latter group (OV-PCOS) had more IR and higher CV risk markers suggests that the polycystic ovary may be a significant factor in determining metabolic and CV risk through mechanisms that, as yet, are unclear.

In conclusion, we have described three phenotypes of hyperandrogenic women applying the new ESHRE/ASRM criteria for the diagnosis of PCOS. These three different phenotypes vary in their prevalence of abnormalities in IR and CV risk markers, which are partially dependent on the variable of increasing BMI. In this regard, women with C-PCOS have the most abnormal findings, followed by women with OV-PCOS and women with IHA having the mildest abnormalities.

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