CLINICAL STUDY

The clinical significance and primary determinants of hirsutism in patients with polycystic ovary syndrome

Dimitrios Panidis, Konstantinos Tziomalos¹, Efstathios Papadakis, Panagiotis Chatzis, Eleni A Kandaraki, Elena A Tsourdi, Christos Vosnakis and Ilias Katsikis

Division of Endocrinology and Human Reproduction, Second Department of Obstetrics and Gynecology, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece and ¹First Propedeutic Department of Internal Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, 1 Stilponos Kyriakidi Street, 546 36 Thessaloniki, Greece

(Correspondence should be addressed to K Tziomalos; Email: ktziomalos@yahoo.com)

Abstract

Objective: Hirsutism is frequently present in patients with polycystic ovary syndrome (PCOS) and is a major sign of hyperandrogenism. However, other disorders frequently present in PCOS, particularly abdominal obesity and insulin resistance (IR), have also been implicated in the development of hirsutism in this population but relevant data are limited. We aimed to define the determinants of the presence of hirsutism in PCOS.

Design: Observational study.

Methods: We studied 1297 patients with PCOS (age 24.3 ± 5.8 years, BMI 26.8 ± 6.9 kg/m²). Hirsutism was defined as a modified Ferriman–Gallwey score ≥ 8 .

Results: Women with hirsutism were younger, had greater BMI, and had higher levels of circulating androgens than women without hirsutism; markers of IR did not differ between the two groups after adjustment for age and BMI. The prevalence of hirsutism progressively declined with age, was lower in normal-weight women than in overweight and obese women, and was comparably prevalent in the hyperandrogenemic phenotypes of PCOS. In binary logistic regression analysis, independent predictors of the presence of hirsutism were younger age, larger waist circumference (W), and higher serum testosterone levels. In stepwise linear regression analysis, the Ferriman–Gallwey score independently correlated with age, W, free androgen index, and serum Δ_4 -androstenedione and DHEAS levels.

Conclusions: Besides hyperandrogenemia, abdominal obesity, and young age are independently associated with the presence of hirsutism. In contrast, the relationship between IR and hirsutism appears to be mediated by the more severe obesity of insulin-resistant patients with PCOS.

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Introduction

Androgen excess is a pivotal characteristic of polycystic ovary syndrome (PCOS) (1). It has been argued that PCOS is primarily a disorder of androgen excess and that hyperandrogenemia or clinical hyperandrogenism is sine qua non for the diagnosis of the syndrome (2). Even though this position is a matter of controversy, clinical or biochemical signs of hyperandrogenism are included in the current diagnostic criteria of PCOS (3).

Hirsutism is a major sign of hyperandrogenism and is defined as excessive terminal hair that appears in a male pattern in a woman (4). Androgens play a major role in the development of hirsutism (5). However, other disorders frequently present in patients with PCOS, particularly abdominal obesity and insulin resistance (IR), have also been implicated in the development of hirsutism in this population (6, 7, 8, 9, 10, 11). However, only a limited number of small studies have evaluated the characteristics of hirsute

patients with PCOS and have yielded conflicting results (6, 7, 8, 9, 10, 11).

The determination of the endocrine and metabolic characteristics of hirsute patients with PCOS is an important aspect of the management of this disorder because hirsutism is highly prevalent in this population (6, 7, 8, 12, 13), adversely affects health-related quality of life (14), and might play a role in the increased cardiovascular risk of these patients (15, 16). Accordingly, we aimed to define the characteristics of hirsute patients with PCOS in a large cohort of patients with this syndrome.

Materials and methods

Subjects

We studied 1297 women with PCOS (age 24.3 ± 5.8 years, BMI 26.8 ± 6.9 kg/m²). All of them were outpatients at the Gynecological Endocrinology Infirmary of the

Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece.

Diagnosis of PCOS was based on the revised criteria of Rotterdam, which require the presence of at least two of the following three features: i) oligo- or anovulation (<8 spontaneous hemorrhagic episodes/year); ii) biochemical hyperandrogenemia (defined in our population as early follicular phase testosterone >60 ng/dl, corresponding to the mean + 2 s.d. testosterone levels in 200 control subjects measured in our laboratory) or clinical manifestations of hyperandrogenemia (Ferriman–Gallwey score ≥ 8); and iii) polycystic ovaries on ultrasound (≥ 12 small follicles in at least one ovary and/or ovarian volume >10 cm³) (3).

None of the women studied had galactorrhea or any endocrine or systemic disease that could possibly affect reproductive physiology. No woman reported use during the last semester of any medication that could interfere with the normal function of the hypothalamic–pituitary–gonadal axis. When basic 17 α -hydroxyprogesterone (17 α -OHP) levels were >1.5 ng/ml, the Synacthen test (0.25 mg/1 ml; Novartis Pharma S.A., Rueil-Malmaison, France) was performed to rule out congenital adrenal hyperplasia. Other causes of hyperandrogenemia, including prolactinoma, Cushing's syndrome, and androgen-secreting tumors, were also excluded.

Informed consent was obtained from all women, and the study was approved by the Institutional Review Board. The study met the requirements of the 1975 Helsinki guidelines.

Study protocol

In all women, body weight, height, waist circumference (W), and hip circumference (H) were measured. Body weight was measured with analog scales and in light clothing; height was measured barefoot with a stadiometer. The BMI was calculated by dividing weight (kg) by height squared (m²) to assess obesity. The W was obtained as the smallest circumference at the level of the umbilicus and the H was measured at the level of the widest diameter around the buttocks. The W/H was calculated by dividing W by H.

Hirsutism was defined as a modified Ferriman–Gallwey score ≥ 8 (17, 18). None of the patients had

received oral contraceptives or other antiandrogens in the past.

Baseline blood samples were collected between 3 and 7 days after a spontaneous bleeding episode, after an overnight fast. The circulating levels of FSH, LH, prolactin (PRL), testosterone, Δ_4 -androstenedione (Δ_4 -A), DHEAS, 17 α -OHP, sex hormone-binding globulin (SHBG), glucose, and insulin were measured. Immediately after the baseline blood sampling, an oral glucose tolerance test was performed; 75 g glucose were administered orally and serum glucose levels were determined after 30, 60, 90, and 120 min. On the same day, transvaginal ultrasonography was performed and the volume of each ovary was determined, as well as the number of follicles in each ovary.

The study population was divided according to: i) age in ≤ 20 years old ($n=381$), 21–30 years old ($n=717$), and >30 years old ($n=199$); ii) BMI in normal weight (i.e. with BMI <25.0 kg/m²; $n=679$), overweight (i.e. with BMI 25.0–29.9 kg/m²; $n=277$), and obese (i.e. with BMI ≥ 30.0 kg/m²; $n=341$); iii) PCOS phenotype in women with phenotype 1 (i.e. with oligo- or anovulation, hyperandrogenism, and polycystic ovaries; $n=653$), phenotype 2 (i.e. with oligo- or anovulation and hyperandrogenism but without polycystic ovaries; $n=408$), phenotype 3 (i.e. with hyperandrogenism and polycystic ovaries but without oligo- or anovulation; $n=131$), and phenotype 4 (i.e. with oligo- or anovulation and polycystic ovaries but without hyperandrogenism; $n=105$) (Table 1) (3); and iv) hyperandrogenism in women with clinical but not biochemical hyperandrogenism ($n=136$) and women with both clinical and biochemical hyperandrogenism ($n=644$).

Methods

Serum glucose, insulin, FSH, LH, PRL, androgens, and 17 α -OHP concentrations were measured as described previously (19). Free androgen index (FAI) was determined as follows: FAI=testosterone (nmol/l) $\times$ 100/SHBG (nmol/l) (20). The homeostasis model assessment of IR (HOMA-IR) index was calculated as follows: HOMA-IR=fasting insulin (mIU/l) $\times$ glucose (mg/dl)/405 (21). The quantitative insulin sensitivity check index (QUICKI) was calculated according to the following formula: QUICKI = 1/(log insulin (mIU/l) + log glucose (mg/dl)) (22).

Table 1 Definition of the phenotypes of the polycystic ovary syndrome (PCOS).

PCOS phenotype	Anovulation	Biochemical hyperandrogenemia or clinical manifestations of hyperandrogenemia	Polycystic ovaries in transvaginal ultrasonography
1 (severe PCOS)	+	+	+
2 (anovulation and hyperandrogenemia)	+	+	–
3 (ovulatory PCOS)	–	+	+
4 (mild PCOS)	+	–	+

Table 2 Characteristics of women with polycystic ovary syndrome (PCOS) and hirsutism and of women with PCOS without hirsutism.

	Women with hirsutism (n=780)	Women without hirsutism (n=517)	P (adjusted for age and BMI)
Age (years)	23.8±5.6	25.1±5.9	<0.001
BMI (kg/m ²)	27.3±7.0	25.9±6.8	<0.001
Waist (cm)	84.9±15.6	81.9±15.0	NS
W/H	0.79±0.07	0.79±0.29	NS
Ferriman–Gallwey score	11.4±2.5	3.4±2.4	<0.001
FSH (mIU/ml)	5.8±1.7	6.0±1.9	NS
LH (mIU/ml)	7.8±5.9	7.7±4.9	NS
Prolactin (ng/ml)	14.4±7.3	13.6±7.1	NS
Testosterone (ng/dl)	78.4±32.5	68.6±26.9	<0.001
Δ_4 -A (ng/ml)	2.9±1.2	2.7±1.0	0.001
DHEAS (ng/ml)	3057.4±1283.6	2755.9±1246.3	0.001
FAI	9.92±7.99	6.75±5.04	<0.001
17 α -OHP (ng/ml)	1.1±0.5	1.1±0.6	NS
SHBG (nmol/ml)	38.0±23.8	47.9±27.3	<0.001
Glucose (mg/dl)	97.8±33.3	97.5±12.1	NS
Insulin (μ IU/ml)	13.5±13.8	11.7±8.9	NS
Glucose/insulin	11.01±7.29	12.48±8.69	NS
AUC OGTT	15 491.9±3200.4	15 161.3±3319.6	NS
HOMA-IR	3.35±3.80	2.89±2.51	NS
QUICKI	0.33±0.03	0.34±0.03	NS
Ovarian volume (cm ³)	7.9±3.5	8.6±4.7	0.006
Ovarian follicles	11.0±4.8	12.0±6.6	<0.001

NS, not significant; W/H, waist:hip ratio; Δ_4 -A, Δ_4 -androstenedione; FAI, free androgen index; 17 α -OHP, 17 α -hydroxyprogesterone; SHBG, sex hormone-binding globulin; AUC OGTT, area under the curve of the oral glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

Transvaginal ultrasonography

Transvaginal ultrasonography was performed by an experienced operator in all women. Ovarian volume was calculated as follows: ovarian volume=($\pi/6$) $\times$ ovarian length $\times$ ovarian height $\times$ ovarian width. The presence of polycystic ovaries was diagnosed by the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume (>10 cm³).

Statistical analysis

Data analysis was performed with the statistical package SPSS (version 17.0; SPSS, Inc., Chicago, IL, USA). Data are reported as mean $\pm$ s.d. Differences in continuous variables between groups were assessed with analysis of covariance adjusting for age and BMI. Differences in the prevalence of hirsutism between the age and BMI groups and the PCOS phenotypes were assessed with the χ^2 test. Binary logistic regression analysis was used to identify independent predictors of the presence of hirsutism.

Correlations between the Ferriman–Gallwey score and other parameters were assessed with Pearson's correlation. Parameters that were significantly correlated with the Ferriman–Gallwey score according to Pearson's correlation were included in a stepwise linear regression analysis model to identify parameters

that were independently correlated with the Ferriman–Gallwey score. In all cases, a *P* value <0.05 was considered significant.

Results

The mean Ferriman–Gallwey score was 8.2 $\pm$ 4.6 and hirsutism was present in 60.1% of the study population. Characteristics of women with hirsutism and of those without hirsutism are shown in Table 2. Women with hirsutism were younger and had greater BMI (*P*<0.001 for both comparisons). In age and BMI-adjusted comparisons, women with hirsutism had higher levels of circulating androgens (serum testosterone, Δ_4 -A, and DHEAS levels and FAI) than women without hirsutism. In contrast, markers of IR did not differ between women with hirsutism and those without hirsutism.

Anthropometric parameters and markers of IR in women with clinical but not biochemical hyperandrogenism and in women with both clinical and biochemical hyperandrogenism are shown in Table 3. Women with clinical but not biochemical hyperandrogenism were older and had smaller BMI and W than women with both clinical and biochemical hyperandrogenism (*P*<0.001, *P*<0.001, and *P*=0.038 respectively). In age- and BMI-adjusted comparisons, none of the markers of IR differed between these two groups.

Table 3 Anthropometric parameters and markers of insulin resistance in women with clinical but not biochemical hyperandrogenism and in women with both clinical and biochemical hyperandrogenism.

	Women with clinical but not biochemical hyperandrogenism (n=136)	Women with both clinical and biochemical hyperandrogenism (n=644)	P (adjusted for age and BMI)
Age (years)	25.7±6.5	23.4±5.3	<0.001
BMI (kg/m ²)	25.2±6.7	27.8±7.0	<0.001
Waist (cm)	80.3±14.4	85.9±17.4	0.038
W/H	0.77±0.07	0.79±0.08	NS
Ferriman–Gallwey score	10.6±2.1	11.5±2.6	0.009
Glucose (mg/dl)	97.4±11.7	97.8±36.2	NS
Insulin (μIU/ml)	11.0±9.9	14.1±14.4	NS
Glucose/insulin	13.42±8.66	10.50±6.88	NS
AUC OGTT	15 205.5±2775.3	15 561.7±3294.5	NS
HOMA-IR	2.69±2.51	3.49±4.01	NS
QUICKI	0.34±0.03	0.33±0.03	NS

NS, not significant; W/H, waist:hip ratio; AUC OGTT, area under the curve of the oral glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

The prevalence of hirsutism progressively declined with age, being 65.6, 60.1, and 50.0% in women ≤20, 21–30, and >30 years old respectively ($P=0.001$). In addition, the prevalence of hirsutism was similar in overweight and obese women (67.1 and 65.6% respectively) but was significantly lower in normal-weight women (54.6%; $P<0.001$, compared with overweight and obese women). Finally, hirsutism was comparably prevalent in phenotypes 1, 2, and 3 (64.6, 67.6, and 62.6% respectively). By definition, none of the patients with phenotype 4 had hirsutism ($P<0.001$ compared with the other phenotypes). The Ferriman–Gallwey score did not differ significantly between phenotypes 1, 2, and 3 (8.7 ± 4.4 , 8.6 ± 4.5 , and 8.4 ± 4.7 respectively) but was significantly lower in patients with phenotype 4 (3.1 ± 2.4 , $P<0.001$, vs all other phenotypes). In binary logistic regression analysis, independent predictors of the presence of hirsutism were age, W, and serum testosterone levels ($P<0.001$ for all parameters; Table 4).

Correlations between the Ferriman–Gallwey score and other parameters in univariate analysis in the total study population ($n=1.297$) are shown in Table 5. In stepwise linear regression analysis, the Ferriman–Gallwey score independently correlated with age, W, FAI, and serum Δ_4 -A and DHEAS levels ($P<0.001$, $P=0.002$, $P=0.001$, $P=0.019$, and $P=0.022$, respectively; Table 6). In the subpopulation of women with clinical but not biochemical hyperandrogenism ($n=136$), in univariate analysis, the Ferriman–Gallwey score correlated only with the FAI ($r=0.187$, $P=0.029$).

Discussion

Patients with hirsutism had higher serum testosterone, Δ_4 -A and DHEAS levels, and FAI than patients without hirsutism. Moreover, the Ferriman–Gallwey score independently correlated with serum Δ_4 -A and DHEAS levels and the FAI. These findings are in

agreement with previous reports (6, 7, 11) and are somewhat expected given that hirsutism is a major clinical sign of hyperandrogenism (5, 18). Notably, only two small studies in patients with PCOS ($n=24$ and 58 respectively) did not identify significant differences in circulating androgens between patients with hirsutism and those without hirsutism, but this was probably due to the small sample size (8, 23). On the other hand, we should emphasize that circulating androgens were measured by an immunoassay method that has poor specificity and accuracy for androgens at low circulating concentrations (24). This represents a limitation of our study.

Patients with hirsutism were more obese in our study and the prevalence of hirsutism was lower in normal-weight women than in overweight/obese women. Moreover, W was an independent predictor of the presence of hirsutism and correlated with the Ferriman–Gallwey score independently from circulating androgens. Previous studies also reported an association between obesity and more severe hirsutism (6, 7). In addition, lifestyle changes aiming at weight loss also reduced the Ferriman–Gallwey score (25). However, in other studies in women with PCOS, the Ferriman–Gallwey score did not correlate with WHR (8) or with BMI (9). However, the former study included mostly normal-weight women (8) and the latter (9) did not assess the correlation between the Ferriman–Gallwey score and W or WHR, which appear to be more sensitive markers of abdominal obesity than BMI (6, 26).

Table 4 Independent predictors of the presence of hirsutism in women with polycystic ovary syndrome.

Variable	Odds ratio	95% CI	P
Age	0.962	0.942–0.982	<0.001
Waist	1.008	1.004–1.012	<0.001
Testosterone	1.016	1.008–1.025	<0.001

IR appears to aggravate hyperandrogenemia in patients with PCOS (1). In addition, insulin-sensitizing agents have a small beneficial effect on hirsutism in this population (27). However, markers of IR did not differ between patients with hirsutism and those without hirsutism in our study after adjustment for age and BMI. Moreover, none of the markers of IR predicted the presence of hirsutism nor correlated with the Ferriman–Gallwey score after adjusting for W and circulating androgens. These findings are in agreement with most previous studies, which did not detect differences in markers of IR between patients with hirsutism and those without hirsutism but with similar BMI (8, 10). In reports that showed more severe IR in patients with hirsutism, the former were also more obese than patients without hirsutism (11). However, in a smaller study in 130 patients with PCOS, those with hirsutism were more insulin resistant than those without hirsutism even though the BMI and W were similar in the two groups (6). Overall, most data do not suggest an independent association between hirsutism and IR in patients with PCOS but more studies are needed to evaluate this relationship.

We observed a progressive decline in the prevalence of hirsutism with age. Moreover, age was an independent predictor of the presence of hirsutism and independently correlated with the Ferriman–Gallwey score. We are not aware of other studies that assessed the relationship between age and hirsutism in patients with PCOS. The improvement in hirsutism with age might be due to the progressive decline in circulating androgens during reproductive age in women with PCOS (28, 29). Given the adverse effects of hirsutism on quality of life in patients with PCOS (14), informing hirsute women with PCOS about the gradual decline in the prevalence of hirsutism with aging might have beneficial effects on their psychosocial status.

Table 5 Correlations between the Ferriman–Gallwey score and other parameters in univariate analysis in the total study population ($n=1297$).

Parameter	<i>r</i>	<i>P</i>
Positive correlations		
BMI	0.125	<0.001
Waist circumference	0.117	<0.001
Testosterone	0.221	<0.001
Δ_4 -Androstenedione	0.144	<0.001
DHEAS	0.170	<0.001
Free androgen index	0.280	<0.001
17 α -Hydroxyprogesterone	0.061	0.027
Insulin	0.097	<0.001
Homeostasis model assessment of insulin resistance	0.080	0.004
Negative correlations		
Age	−0.132	<0.001
FSH	−0.085	0.002
Sex hormone-binding globulin	−0.224	<0.001
Glucose:insulin ratio	−0.119	<0.001
Quantitative insulin sensitivity check index	−0.106	<0.001

Table 6 Stepwise linear regression analysis of the correlation between the Ferriman–Gallwey score and other parameters.

Model	Predictors	<i>R</i> ²
1	FAI	0.55
2	FAI, age	0.64
3	FAI, age, DHEAS	0.69
4	FAI, age, DHEAS, W	0.75
5	FAI, age, DHEAS, W, Δ_4 -A	0.79

FAI, free androgen index; W, waist circumference; Δ_4 -A, Δ_4 -androstenedione.

In our study, the prevalence of hirsutism and the Ferriman–Gallwey score did not differ significantly between women with the different hyperandrogenemic phenotypes of PCOS (i.e. phenotypes 1, 2, and 3). This is in agreement with previous reports (30, 31), whereas other groups reported a higher Ferriman–Gallwey score in patients with phenotypes 1 or 2 than in patients with phenotype 3 (32, 33) and in patients with phenotype 1 than in patients with phenotype 2 (34). Hyperandrogenemia was more pronounced in phenotypes characterized by more severe hirsutism in the latter studies (32, 33, 34), whereas circulating androgens did not differ between phenotypes 1, 2, and 3 in studies that did not identify differences in hirsutism between these phenotypes (30, 31). In contrast, in our study, despite the similar Ferriman–Gallwey score in phenotypes 1, 2, and 3, circulating androgens were higher in phenotypes 1 and 2 than in phenotype 3 and were also higher in phenotype 1 than in phenotype 3 (data not shown). Therefore, our findings suggest that the Ferriman–Gallwey score is not adequately sensitive to detect subtle differences in circulating androgens between the hyperandrogenemic phenotypes of PCOS.

In conclusion, besides hyperandrogenemia, abdominal obesity and young age are independently associated with the presence of hirsutism. In contrast, the relationship between IR and hirsutism appears to be mediated by the more severe obesity of insulin-resistant patients with PCOS. Given the beneficial effects of lifestyle changes on both circulating androgens and obesity (25), they should represent the first-line management of hirsutism in PCOS. In addition, as hirsutism appears to be associated with increased cardiovascular risk in patients with PCOS (15, 16), lifestyle changes might also prevent or delay the progression of atherosclerosis in this population.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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