Marked hyperandrogenemia and acne associated with polycystic ovaries in Greek women with polycystic ovary syndrome

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Summary

PCOS represents the commonest endocrinopathy among women of reproductive age. We conducted this study to evaluate the association between polycystic ovaries and clinical and biochemical features of the syndrome. TVS was performed in 74 women with the clinical diagnosis of PCOS. The findings were compared to biochemical, hormonal and clinical features of the syndrome. Statistical analysis revealed a significantly higher prevalence of acne, LH/FSH ratios and testosterone levels in women with PCO compared to those with normal ovarian morphology. In the subgroup analysis, total ovarian volume correlated significantly with hirsutism scores. Our study revealed a great prevalence of polycystic ovaries in Greek women with PCOS, and emphasizes the significance of transvaginal ultrasound in establishment of the diagnosis of the syndrome. The presence of PCO may not be clinically important when present alone without clinical manifestations but reflects the underlying hyperandrogenemia in PCOS women, representing a useful tool in the management of these patients.

Key words: Polycystic ovaries; Hyperandrogenemia; Acne; PCOS; Testosterone.

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy of women in reproductive age with a reported prevalence of 5-10% [1]. Despite the high prevalence of PCOS, the diagnosis and differential diagnosis remain confusing.

In 1936 Stein and Leventhal first described the syndrome in women with anovulation and/or hirsutism who had bilateral enlarged so-called scerocystic (poly cystic) ovaries [2]. The heterogeneity of the syndrome was evident even at the initial description of seven women, with three of the women being obese, four hirsute (one obese), and one acneic. Thus began the description of a disorder that was eventually recognized to have significant reproductive, metabolic, and dermatological consequences.

The definition of PCOS most commonly used today arose from the proceedings of an expert conference sponsored by the NIH in April 1990 (*i.e.*, NIH 1990 criteria) [3]. The proceedings were then summarized into the following major research criteria: 1) hyperandrogenism and/or hyperandrogenemia, 2) oligoovulation, and 3) exclusion of known disorders, such as Cushing's syndrome, hyperprolactinemia, and CAH. Another expert conference was organized in Rotterdam in May of 2003, sponsored in part by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine [4]. The new 'Rotterdam criteria' allow a diagnosis of PCOS to be made when two out of three clinicopathological features are present: 1) oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, or 3) polycystic ovaries. It should be noted that the Rotterdam 2003 criteria did not replace the NIH 1990 criteria because all women diagnosable by those criteria would also meet the Rotterdam definition. Rather, it expanded the definition of PCOS, adding two additional phenotypes as PCOS, including women with: 1) polycystic ovaries and clinical and/or biochemical evidence of androgen excess, but without ovulatory dysfunction, and 2) polycystic ovaries and ovulatory dysfunction, but without hyperandrogenemia and/or hirsutism. This revised classification supports the objective role of ultrasound in the diagnosis of PCOS which should include either 12 or more follicles measuring 2-9 mm in diameter or an increased ovarian volume > 10 cm^3 in at least one ovary [5].

Multiple studies have been conducted to evaluate the correlation between ovarian morphology and clinical and biochemical findings of the syndrome. Results have been controversial and the argument among scientists regarding the significance of gynecological ultrasound in the diagnosis of the syndrome still goes on.

We conducted this study to estimate the correlation between polycystic ovaries (PCO), when present, and typical clinical and laboratory findings among Greek women with PCOS. More specifically we turned to the question whether there is an association between polycystic ovaries, and clinical or biochemical hyperandrogenism in a group of PCOS affected women.

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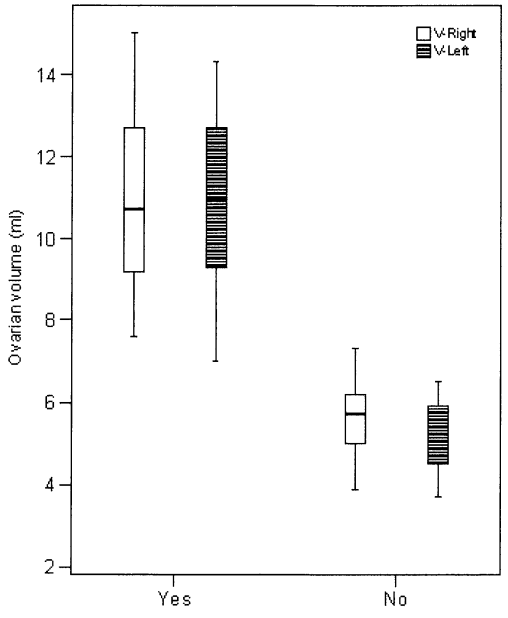
Fig. 1



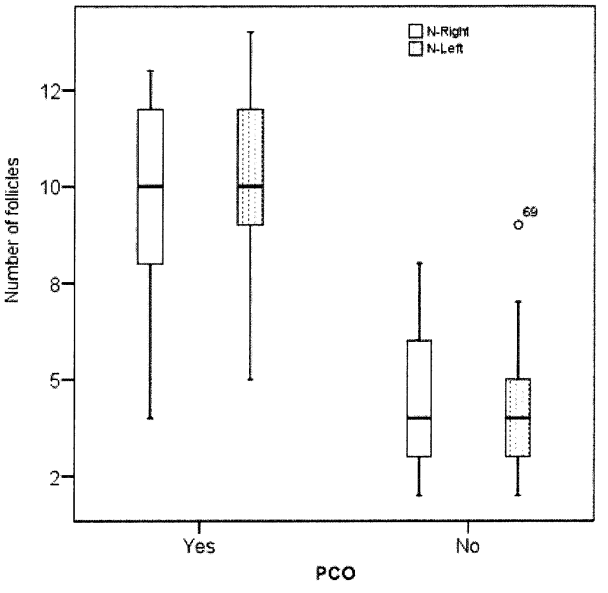


Fig. 2

Figure 1. — Ovarian volume in PCOS women with and without polycystic ovaries (PCO).
Figure 2. — Number of ovarian follicles in PCOS women with and without polycystic ovaries (PCO).

Materials and Methods

Patients presenting to the Gynecological Endocrinology Department of the University hospital of Alexandroupolis with the provisional diagnosis of PCOS, seeking medical advice for infertility, cycle abnormalities, persisting acne and hirsutism were voluntarily recruited in our study over a two year period (2008-2010). The diagnosis of PCOS was established initially with the NIH criteria, when oligo (cycle > 35 days) or amenorrhea (less than 2 cycles in the last 6 months) and clinical or biochemical hyperandrogenism was found with the exclusion of other pituitary, adrenal or ovarian disease when possible. Clinical details were recorded on all subjects. The body mass index (BMI) was calculated (weight (kg)/height (m^2) and BMI greater than 25 was defined as overweight. Hirsutism was evaluated with the Ferriman Gallwey score (FG) and was diagnosed when the FG score was greater than 6. Presence and severity of acne was also evaluated. Clinical personal and family history was recorded for all patients. Each subject underwent a transvaginal ultrasound (TVS) examination and blood was collected for the assesstment of endocrine status. Both TVS and blood sampling were performed during the first eight days of the follicular phase of the cycle in subjects who were menstruating and at any convenient time in those who were amenorrheic. All subjects were screened for the absence of hyperprolactinemia, hypercortisolemia, thyroid dysfunction and 21-hydroxylase deficiency. Clinical and endocrine data were analyzed retrospectively.

Ultrasound examination

In all women TVS was performed by two trained gynecologists with many years of experience in real-time gynecological TVS. A high frequency (4-8 MHz) transvaginal transducer (GE Voluson 730 BT05 Expert 4D) was used and data is collected. Women were examined in the first eight days of the follicular phase. The parameters that were important for our study were identification of both ovaries, maximum diameter of the three planes, longitudinal, anterior-posterior and transverse, and follicle count. The ovarian volume was calculated by astraia software. Follicle number was calculated as the maximum number of follicles from inner to outer margin in one ultrasonographic plane. The ovaries were defined as polycystic when they had a volume of at least 10 ml or more than 12 follicles (diameter 2-9 mm), (ESHRE/ASRM criteria) [5].

Endocrine assessment

In all women, serum concentrations of the following hormones were measured: LH, FSH, fasting glucose, fasting insulin, testosterone, sex hormone binding globulin, dehydroepiandrosterone sulphate (DHEAS), estradiol and 17OH-progesterone. The LH/FSH ratio was also calculated. All the measurements were made in the first eight days of the follicular phase or at an appropriate time for amenorrheic women. Subjects taking contraceptive pills were excluded from the study because of possible interference with hormonal rates. Hormonal values were also evaluated for the exclusion of thyroid, ovarian or adrenal dysfunction, but data was not included in the analysis.

Statistical methods

All data were represented by a box plot and the frequencies or means were tabulated as appropriate. Differences between the examined groups were evaluated with the Mann-Whitney U test for continuous data types since most of the variables were not normally distributed. Correlations between variables were examined by Spearman's correlation coefficient (rs) since data was not normally distributed. Regarding categorical data the chi-square test was used; p values were considered statistically significant when < 0.05. Analysis was performed with SPSS 17.

Statistical analysis

The cohort consisted of 74 (n = 74) PCOS patients initially diagnosed with the NIH criteria. All patients underwent gynecological TVS. Polycystic ovaries were identified in 57 women

(77%) while 17 (23%) had normal ovarian morphology. As expected mean ovarian volume (for left and right ovaries) was significantly greater in women with PCO than in women with normal ovaries ($p < 0.001$). In addition patients with PCO had significantly more ovarian follicles ($p < 0.001$), (Figures 1 and 2).

Between the two groups there were no differences regarding age and other anthropometric and metabolic variables like glycemia and fasting insulin (Table 1).

Concerning the analysis of endocrine parameters, women with PCO had significantly higher LH/FSH ratios ($p = 0.006$) and testosterone levels ($p = 0.049$) compared to patients with normal ovarian morphology. Levels of DHEAS, progesterone and estradiol did not differ in the two groups. Also remarkable was the SHBG count which was higher in the non PCO group and very close to statistical significance (Table 2).

A significantly higher prevalence of acne was found in women with PCO compared to those without ($p = 0.042$) (Table 3) but no considerable differences were observed regarding severity in the presentation of the symptom.

In all PCOS women with PCO, total ovarian volume (sum of left and right) correlated significantly with hirsutism scores ($r_S = 0.324$, $p = 0.014$). Total number of ovarian follicles (sum of left and right) correlated with glucose levels ($r_S = 0.319$, $p = 0.015$).

In the subgroup with PCO, 16 women (28%) had less than 12 follicles but an increased ovarian volume greater than 10 ml (V-group), 12 women (21%) had 12 or more follicles but normal ovarian volume (F-group) and 29 women (51%) had both increased number of follicles and increased ovarian volume (VF-group).

Comparisons of all three groups by the Kruskal-Wallis test revealed significant differences in FG scores. In the V-group hirsutism was present in 11 out of 16 (68%) PCOS women, in four out of 12 (33%) in the F-group and in 24 out of 29 in the VF-group (82%). Prevalence of acne, amenorrhea and other parameters did not differ among the three groups (Table 4).

Table 1. — *Median and range of anthropometric and metabolic characteristics of PCOS women with and without PCO.*

	PCOS with PCO (n = 57)	PCOS without PCO (n = 17)	*p*
Age	25 (17-39)	24 (18-40)	0.827
BMI (Kg/m^2)	30 (19-35)	29 (19-34)	0.862
Fasting insulin (pmol/l)	98.5 (20.3-567.0)	126 (36-432.5)	0.867
Fasting glucose (nmol/l)	91 (73-115)	87 (73-101)	0.342

Table 2. — *Median and range of endocrine characteristics of PCOS women with and without PCO.*

	PCOS with PCO (n = 57)	PCOS without PCO (n = 17)	*p*
SHBG (nmol/l)	76.5 (11.8-139.5)	100.9 (28.4-140.0)	0.06
Estradiol (pmol/l)	268.3 (101.6-803.0)	212.7 (109.7-826.0)	0.85
170H progesterone (nmol/l)	2.8 (1.1-41.0)	3.8 (1.3-9.0)	0.09
LH/FSH ratio	2.5 (0.5-13.0)	1.5 (0.1-4.3)	0.006
DHEAS (μmol/l)	0.8 (0.0-1.5)	1.1 (0.0-1.5)	0.34
Testosterone (nmol/lit)	3.3 (0.9-5.4)	2.7 (0.4-4.2)	0.049

Table 3. — *Clinical characteristics and family history of PCOS women with and without PCO.*

	PCOS with PCO (n = 57)	PCOS without PCO (n = 17)	*p*
Oligomenorrhea	39 (68%)	13 (77%)	0.524
Amenorrhea	18 (32%)	4 (24%)	0.524
Acne	36 (63%)	21 (37%)	0.042
Hirsutism FG > 6	39 (68%)	11 (65%)	0.774
FG score	8 (1.0-31.0)	7 (0.0-24.0)	0.260

Table 4. — *Subgroup analysis of endocrine and metabolic characteristics of PCOS women with PCO.*

	PCOS-VF (n = 29)	PCOS-V (n = 16)	PCOS-F (n = 12)
Testosterone	3.4 (0.9-35.0)	3.25 (0.9-5.0)	2.95 (0.9-5.2)
170H Progesterone	2.45 (1.2-9.0)	3.4 (1.5-41.0)	3.0 (1.1-8.0)
LH/FSH	2.6 (0.5-13.0)	2.65 (0.7-6.0)	1.35 (0.5-5.4)
FG score	10.0 (1.0-23.0)	8.5 (1.0-31.0)	5.5 (10-19.0)
BMI	30.0 (23-34)	29.5 (24-35)	29.0 (19-34)

Discussion

In accordance with other cohorts [6], our study demonstrates a high prevalence of PCO in Greek women with PCOS, even when the selection is made with the NIH criteria, independently of ultrasonographic findings. In a large percentage of our patients the ovarian volume and number of follicles were greater for the right ovary, also in accordance with other studies [7, 8]. As concerns the inter- intraobserver variability, use of the Rotterdam criteria, requiring one out of two criteria (1) > 10 ml ovarian volume and 2, ≥ 12 number of follicles, is more likely to reduce variability. Older studies have shown significant inter- and intraobserver variability but using two out of three of the following criteria to define PCO: 1) increased echogenic stroma, 2) ≥ 10 small peripheral cysts and 3) increased ovarian volume [9].

In our cohort, women with PCO did not differ in anthropometric and metabolic characteristics (age, BMI, fasting glucose and fasting insulin) in accordance with literature [6, 10].

Significant differences were found when studying clinical parameters. There was a statistically significant difference in acne presentation between the two groups. PCO women presented more often with acne, a sign of the underlying hyperandrogenemia. According to O'Driscoll *et al.*, PCO occur more often in women with clinical signs of hyperandrogenism like hirsutism and acne [11].

Testosterone levels were statistically greater in PCO women. Puzica and co-workers reported that elevated ovarian volume is a predictor of assessed androgen production, in accordance with our findings [12]. The same findings came out in a study of 90 women by Van der Westhuizen and Van der Sprui [13]. However, Legro *et al.* did not find the same results. Testosterone values in their study were comparable between women with PCO and those without [6] but results could be quite different if undergoing follicle count. Pachè *et al.* [14] revealed a correlation between ovarian volume, follicle number and stromal echogenicity with androgen levels in PCOS women. Carmina *et al.* in contrast did not find differences between women with and without polycystic ovaries [3] as concerns the androgen profile.

Our Greek PCOS women compared with the PCO group were found to present with significantly higher LH/FSH ratios. These findings are in accordance with the literature [3, 13].

Puzigaca and co-workers reported that ovarian enlargement was a marker of excessive androgen production and menstrual disturbance in PCOS, findings that are in keeping with those of our study [12].

High resolution TVS has enhanced our awareness of polycystic ovaries both in our study population and among women with no symptoms in the general population [15]. Many authors have advised the use of a variety of endocrine tests to evaluate the severity of the disease or to confirm the diagnosis, and have emphasized the difficulty in relying on laboratory findings alone to assess the severity of ovarian changes [16]. Our final results demonstrate a clear correlation between women with PCOS and PCO and some important clinical and biochemical features such as acne and hirsutism scores. It must be stressed though that there is great difficulty in predicting endocrinopathy based only on ovarian morphology. In addition, marked ovarian changes in the sense of PCO may be clinically unimportant in the absence of symptoms and endocrine disturbancies.

Conclusion

When the diagnosis of PCOS is suspected clinically, we believe TVS evaluation of the patient is of great importance to establish the diagnosis. Prognostic accuracy in terms of clinical manifestation and underlying endocrinopathy is poor. Each patient should be thoroughly examined and individually assessed, given the great variability in the presentation of the syndrome.

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