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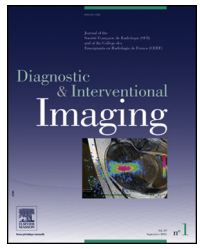

ORIGINAL ARTICLE /*Genito-urinary imaging*

Adrenal gland volume assessed by magnetic resonance imaging in women with polycystic ovary syndrome

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Abstract
Purpose: To determine adrenal gland volume (AGV) in women with polycystic ovary syndrome (PCOS) by comparison with healthy control subjects and to investigate the relationship between AGV and hormonal status.
Patients and methods: AGV was measured on transverse sections of T1-weighted MRI imaging data in 27 PCOS patients and 40 age-matched control subjects for this prospectively designed study. A comparative analysis of AGV in PCOS and controls was performed and possible correlations between AGV and hormonal parameters were evaluated.
Results: PCOS patients had significantly larger AGV compared to controls ($(11.7 \pm 4.4$ cm^3, 7.2 ± 1.9 cm^3, respectively, $P < 0.001$). A significant positive correlation was found between total AGV and dehydroepiandrosterone sulfate, 17-OH progesterone, and total and free testosterone levels in the PCOS group ($r = +0.51$, $+0.48$, $+0.43$, $+0.62$, respectively; P values < 0.05).

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In addition, AGV was significantly negatively correlated with LH and LH/FSH ratio in the PCOS group ($r = -0.55$, $P = 0.02$; $r = -0.51$, $P = 0.01$, respectively).
Conclusions: PCOS patients have significantly increased AGV as well as a positive correlation of AGV and androgens. We conclude that the assessment of AGV with MRI shows a significant correlation with the androgenic activity of the gland, and that hypertrophy of the adrenal gland may be involved in the pathogenesis of PCOS.

Polycystic ovary syndrome (PCOS), also called hyperandrogenic anovulation, is the most frequent endocrine disorder, affecting approximately 5—10% of women of reproductive age [1]. It is not a simple pathophysiologic process, being characterized by anovulation, irregular menstruation, hypergonadotrophism, hirsutism, obesity and excess androgenic hormones and is commonly associated with infertility [1,2].

Androgen excess is the principal characteristic of the disease and it has been suggested that PCOS should primarily be regarded as a disorder of increased androgen synthesis, use, or metabolism [2]. While the ovary is generally considered the principal source of androgens in most of these patients, over 50% of patients with PCOS also demonstrate excess levels of adrenal androgens (AAs), particularly dehydroepiandrosterone sulfate (DHEA-S) [3,4]. These patients show hypersecretion of adrenocortical products, both in basal conditions and in response to stimulation of adrenocorticotropic hormone (ACTH) [5—9].

Some signs of hyperactivity of the adrenal glands should be present if the AA excess plays a major role in the pathogenesis of PCOS. It has been suggested that disorders that are accompanied by chronic activation of the HPA axis are generally associated with enlargement of the adrenal glands [10—13]. Thus, AGV may represent a non-invasive measure of HPA axis tone and is suggested to be an indicator of adrenal gland activity [12—15].

Although CT is the preferred primary modality for adrenal imaging due to its outstanding spatial resolution, MRI is also considered to be a potentially reliable technique for adrenal imaging, without using radiation. Additionally, with improvements in magnetic resonance volumetric analysis, MRI has become a useful alternative method for assessing a pathological change in adrenal size, particularly in exploratory studies. With this background, we have measured the volumes of adrenal glands in PCOS patients using MRI and have investigated the correlation of adrenal volumes with adrenal androgens.

The purpose of the present study was to evaluate the effect of PCOS on adrenal gland volume and to elucidate whether possible morphologic abnormalities of adrenal glands could explain the hyperandrogenism in PCOS. Additionally, we aimed to explore the hypothesis that AGV could provide a surrogate measure of androgenic activity of the gland. To the best of our knowledge, this is the first study investigating the possible morphological changes of adrenal glands and the relationship between AGV and androgens in women with PCOS.

Patients and methods

Patients

This prospectively designed cross-sectional study was carried out between June 2014 to August 2014 in the radiology department of our university hospital. The study was performed in accordance with the Declaration of Helsinki and was approved by the local Ethical Committee. Informed consent was obtained from all included subjects before participation in the study. All women with PCOS were recruited from those who visited our obstetrics and gynecology outpatient facility with a chief complaint of irregular menstrual cycles and/or clinical hyperandrogenism. All participants underwent a gynecologic examination, including transvaginal/pelvic ultrasound to investigate ovarian morphology. The diagnosis of PCOS was based on the Rotterdam criteria [16].

The patient group consisted of 27 normal-weight women with PCOS (mean age 22.1 ± 3.8 years) and 40 aged and BMI-matched female volunteers with normal ovulating cycles (28 ± 2 days, blood progesterone levels > 10 ng/ml in two consecutive cycles), no signs of hyperandrogenism, and normal ultrasonographic appearance of the ovaries.

Body mass index (BMI, kg/m^2) was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2) to assess obesity. All the study population had a normal abdomen MRI as evaluated by a radiologist. Also, none of the women studied had any systemic disease that could possibly affect their reproductive physiology. Exclusion criteria for all women were age < 16 or > 35 years, body mass index (BMI) < 17.5 kg/m^2 or > 25 kg/m^2 and possible causes of adrenal enlargement such as: congenital adrenal hyperplasia, Cushing's syndrome, primary aldosteronism, multiple endocrine neoplasia type 1, chronic infection, neoplastic processes, type 2 diabetes and depression.

MRI data acquisition

All subjects underwent non-contrast MRI of the abdomen on a 1.5-Tesla Philips Intera MR unit (Philips Medical Systems, Amsterdam, The Netherlands) on the 3^{rd}—7^{th} day of

their spontaneous menstrual cycle. The adrenal glands were imaged using T1-weighted fast spin echo technique with the following parameters: repetition time (TR) = 450 ms, echo time (TE) = 5.2 ms, matrix = 574 × 574, flip angle = 10°, field of view = 300 mm, slice thickness = 2 mm. The MRIs were blindly assessed by an experienced radiologist (E.K), i.e., the radiologist did not know whether the abdominal MRI scans belonged to a patient with PCOS or to a subject from the healthy control group.

Image analysis

The MRI data were transferred to a DELL Precision Workstation for anatomical volume measurements of the right and left adrenal glands. Each adrenal gland was manually traced on axial slice of T1 sequence MRI. A segmentation process was performed in order to use images for 3D reconstruction. Segmentation was performed on a slice-by-slice basis using manual tools to define the contour around the gland. Collection of data and the segmentation process were performed using Mimics 10.1 software (Materialise, Leuven, Belgium). The segmentation process was converted to a 3D mesh model using an adapted marching cubes algorithm and the volume value was obtained (Fig. 1) [17]. Measurements were performed by two radiologists with segmentation experience (EU, MBA). The overall Pearson correlation for interobserver reliability, assessed on 10 randomly selected images, was 0.95 and intrarater reliability, based on 10 scans measured twice by the same rater (EU) was 0.97. All these values are well within acceptable limits.

Serum hormone level measurements

Fasting blood samples were collected for measurements of serum levels of FSH, LH, estradiol, DHEA-S, 17-OH progesterone, total testosterone (Ttest), free testosterone (Ftest) and prolactin between the 3rd and 7th days of the menstrual cycle in controls and after a spontaneous bleeding episode in patients with PCOS. Also, a 1-mg dexamethasone suppression test was performed to exclude Cushing's syndrome.

Statistical analysis

Statistical analysis was performed using SPSS, version 19.0 (SPSS, Chicago, IL). Mann-Whitney U test was used for comparison of groups for variables that were inconsistent with a normal distribution. Independent student *t*-test was used for comparison of groups for variables that were consistent with a normal distribution. $P < 0.05$ was considered statistically significant.

A multiple linear regression model was used for determination of the relation between adrenal volume and independent variables. Pearson's correlation coefficient and Spearman's correlation coefficient test were used for comparisons of adrenal volume alterations with age and hormonal parameters. Intra-observer reliability was evaluated with use of the Pearson correlation coefficient.

Results

Baseline characteristics of patients with PCOS and controls are presented in Table 1. Patients with PCOS had a total AGV of 11.7 cm^3, whereas healthy control subjects had a volume of 7.2 cm^3. Statistical analysis showed total adrenal volume to be significantly higher in patients with PCOS than in healthy control subjects ($P < 0.001$) (Fig. 2). Correlation analysis showed that in PCOS subjects, total AGV was significantly higher in older individuals ($r = 0.42$, $P = 0.05$), whereas healthy control subjects showed a trend toward decreasing AGV with age but without reaching statistical significance ($r = -0.05$, $P = 0.7$, Pearson correlation coefficient) (Table 2) (Fig. 3). Serum LH, LH/FSH ratio, DHEA-S, 17-OH progesterone and Ftest levels were significantly higher in the PCOS group ($P < 0.05$).

AGV correlated strongly with DHEA-S levels ($r = 0.51$, $P = 0.008$), and also with Ftest, Ttest ($r = 0.43$, $P = 0.03$ and $r = 0.62$, $P = 0.002$, respectively) and 17-OH progesterone plasma levels ($r = 0.48$, $P = 0.01$). However, there was a significant negative correlation between LH, LH/FSH ratio and AGV ($r = -0.55$, $P = 0.02$, $r = -0.51$, $P = 0.01$, respectively) (Table 2). There was no significant correlation between AGV

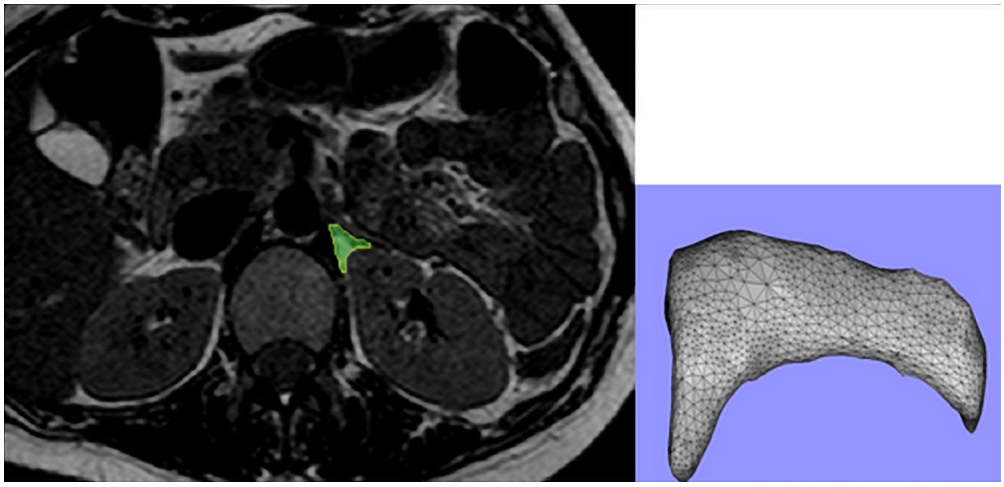

Figure 1. Each adrenal gland was manually traced on axial slice of T1-weighted MR sequence. A segmentation process was performed in order to use images for 3D reconstruction and was converted to a 3D mesh model using an adapted marching cubes algorithm.

Table 1 Baseline characteristics of patients with PCOS and controls.

	PCOS ($n=27$)	Control ($n=40$)	P-value
Age (years)	22.1 ± 3.8	23.1 ± 1.5	0.1[a]
BMI (kg/m^2)	24.5 ± 2.1	22.1 ± 1.7	0.8[a]
Adrenal volume (cm^3)	11.7 ± 4.4	7.2 ± 1.9	0.00*[a]
LH (mIU/ml)	10 ± 10.8	5 ± 6.8	0.00*[b]
FSH (mIU/ml)	6.1 ± 2.1	5.2	0.7[a]
LH/FSH	1.59 ± 1.82	0.9 ± 0.8	0.03*[b]
DHEAS (μg/dL)	311 ± 133	242 ± 100	0.01*[a]
Free testosterone (ng/dl)	2.7 ± 2.3	1.0 ± 0.4	0.00*[a]0.2[b]
Total testosterone (ng/dl)	37.9 ± 23.6	35 ± 28.6	
Estradiol (pg/ml)	39.3 ± 33	42.5 ± 35	0.9[b]
17-OH progesterone (ng/ml)	0.95 ± 0.4	0.39 ± 0.7	0.03*[a]

BMI: body mass index; LH: luteinizing hormone; FSH: follicle-stimulating hormone; DHEA-S: dehydroepiandrosterone sulfate.
*Significant differences were signed (if $P<0.05$).
[a] Independent sample t-test (was used for normally distributed variables that was showed as mean ± standart deviation).
[b] Mann Whitney U-test (was used for not-normally distributed variables that was showed as median (interquartile range) (IQR).

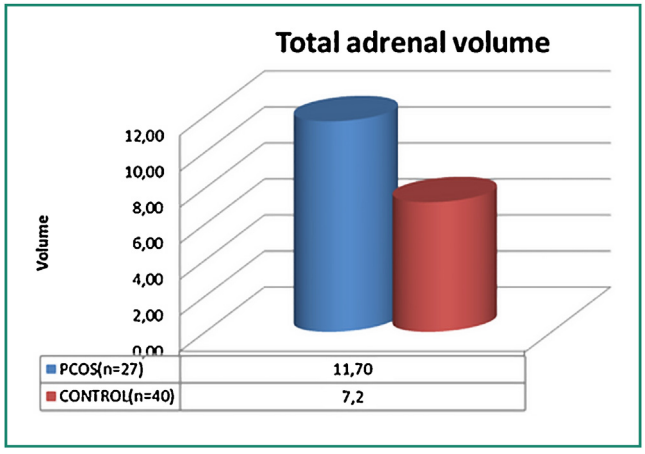

Figure 2. Adrenal gland volumes across groups. Adrenal volumes are significantly higher in patients with PCOS than in healthy control subjects ($P<0.00$).

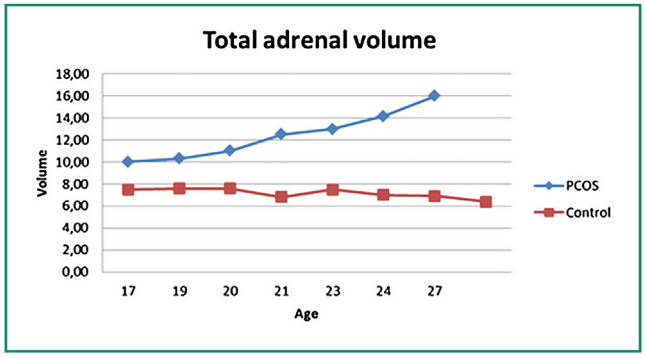

Figure 3. Correlations of adrenal gland volumes with age. Total adrenal gland volume was significantly higher in older individuals in patients with PCOS ($r=0.42$, $P=0.05$) whereas healthy control subjects showed a trend toward decreasing gland volume with age (r: −0.05, $P=0.7$).

and hormonal parameters in the control group ($P>0.05$). On the other hand, LH was also negatively correlated with DHEA-S in women with PCOS ($r=-0.46$, $P=0.01$, Spearman Correlation Coefficient) whereas there was no significant correlation between LH and DHEA-S in healthy control subjects ($r=0.09$ $P=0.6$). Also, multiple linear regression model results showed that there were no independent variables affecting AGV.

Discussion

The main findings of the present study were as follows: an increase in AGV in normal weight PCOS patients compared with age and BMI matched healthy controls was noted. Furthermore, AGV's were positively correlated with DHEA-S,

Table 2 Correlation coefficients between total adrenal volume and age, hormonal parameters in women with PCOS.

	Rho	P
Age (years)	0.42	0.05[a]
LH (mIU/ml)	−0.55	0.02[b]
LH/FSH	−0.51	0.01[b]
DHEA-S (μg/dL)	0.51	0.008[a]
Free testosterone (ng/dl)	0.43	0.03[a]0.002[b]
Total testosterone (ng/dl)	0.62	
Estradiol (pg/ml)	−0.18	0.3[b]
17 OH progesterone (ng/ml)	0.48	0.01[a]

LH: luteinizing hormone; DHEA-S: dehydroepiandrosterone sulfate.
[a] Pearson's correlation coefficient.
[b] Spearman's correlation coefficient.

17-OH progesterone, Ttest, and Ftest and were negatively correlated with LH levels in PCOS patients, but there was no significant correlation between these parameters in healthy subjects. Finally, a significant positive correlation between AGV and age was noted in PCOS patients, whereas non-significant trends toward a decrease in AGV were found in the healthy group. The findings were consistent with our previous hypothesis that increased androgen levels in PCOS are associated with hypertrophy of the adrenal gland, which can be an issue in PCOS pathogenesis.

As is well known, approximately half of PCOS women have functional adrenocortical hyperandrogenism [3]. These women vary in their presentation [18], but are most commonly identified by increased basal levels of DHEA-S both in the basal condition [4,19] and in response to ACTH stimulation [5,9,20,21]. The mechanisms underlying the exaggerated response to ACTH in PCOS are still uncertain. While some studies showed high ACTH levels [6,8] and hyperresponsiveness of ACTH to corticotropin-releasing hormone (CRH) [22], others showed normal ACTH plasma levels [2,22—26] or hyperresponsiveness of the adrenal to ACTH [5,8,9,22] in PCOS patients. Briefly, the larger question is whether the hyperandrogenic state is due to abnormalities of hypothalamic-pituitary control or due to an alteration in the intrinsic behaviour of the adrenal cortex.

Although many studies have examined AA excess in patients with PCOS [3—5,7—9,22—24], the role of the adrenal gland in the genesis of PCOS and the mechanisms responsible for the adrenal hyperandrogenism in these women are still unresolved problems. To date, the main focus of interest concerning patients with PCOS has been on metabolic and hormonal alterations and thus, these have been extensively studied. Since AA overproduction plays a major role in the pathogenesis of PCOS, some signs of hyperactivity of the adrenal glands should exist. Our analysis showed that volume of the adrenal gland, which we investigated by means of 1.5 T MRI, was significantly larger in patients with PCOS than in control subjects. To the best of our knowledge, this is the first study showing objective measurable morphological changes in the adrenal gland and its relationship to androgens in women with PCOS.

In the present study, volumes of the adrenal glands were measured by means of MRI. Basically, CT is the preferred imaging modality for adrenal glands because of its better spatial resolution, low cost and broad availability. However, despite these benefits of CT, the major disadvantage is the inevitable patient exposure to ionizing radiation. Thus, MRI is a useful alternative modality in clinical practice, especially with the need of repeated assessment of the adrenal gland, for instance, for follow-up of tumor size. Additionally, MRI is considered to be a potentially reliable technique for adrenal imaging because of its high-contrast, high-resolution and multiplanar imaging capability. To date, there have been only a few volumetric studies using MRI for measuring AGV [13—15,25,26]. This may be partly due to the paucity of information about the reliability of MRI volumetric analysis. However, a recent research report sought to determine the intra- and inter-observer variation and repeatability of MRI measurements of AGV and suggested that MRI has become a potentially alternative imaging modality for the measurement of AGV in humans, due to the increasing capabilities of MRI volumetric analysis [26].

The mean volumes of adrenal glands in healthy adults reported in previous studies were variable, with a median left adrenal volume of 2.53 ± 0.80 ml [12], 5.7 ± 4.9 ml [27] and 4.23 ± 0.74 [28]. Also, a recent study performed by Grant et al. reported that adrenal volume varied from 0.63 cm^3 to 3.68 cm^3 [26]. Another volumetric study of an Asian population measured AGV using CT, and noted that the left, right, and total AGV were 4.23 ± 0.74 (range: 2.85—5.83) cm^3, 4.26 ± 0.86 (2.59—6.56) cm^3, and 8.50 ± 1.40 (5.80—11.39) cm^3, respectively [28]. In our study, healthy control subjects had a mean total AGV of 7.2 cm^3, whereas patients with PCOS had significantly enlarged adrenal glands with a total AGV of 11.7 cm^3.

Under normal conditions, HPA axis activation, in response to physiological or psychological stress, results in release of CRH from the hypothalamus, which stimulates the production of ACTH from the anterior pituitary. Subsequently, ACTH stimulates the zona fasciculata of the adrenal cortex to produce more glucucorticoids. However, chronic activation of the HPA axis results in an increase of AGV because of the trophic effects of ACTH on the adrenal cortex. Thus, AGV is accepted as a non-invasive measure of HPA axis tone (11, 13).

Adrenocortical hyperplasia may result from endocrine abnormalities such as Cushing's syndrome, primary aldosteronism, CAH or multiple endocrine neoplasia type 1 [29]. It has also been demonstrated that 11.3% of patients undergoing CT without endocrine disease have adrenal enlargement as an incidental radiological finding [30]. This group includes benign adrenocortical hyperplasia, which is defined as radiographic adrenal enlargement of unknown cause, also inflammation, neoplastic processes [31—34], type 2 diabetes [11], or psychiatric disorders, such as depression [12] and blumia [13]. It has been suggested that there could be upregulation of the HPA axis and this could reflect overworking of the adrenal glands, making them enlarged or swollen. In addition, in all these disorders, the increased AGV is thought to be due to chronic ACTH elevation. However, in previous studies, no significant differences were found in terms of ACTH levels between PCOS patients and the healthy population [4,22—24]. Azziz et al. suggested that high levels of adrenal androgens in PCOS patients were the result of increased zona reticularis mass, which we also found in the present study. These authors also concluded that AA excess in PCOS was not due to increased ACTH levels or increased sensitivity of these androgens to ACTH stimulation [4]. In our recent study on PCOS, we found that PCOS women had higher pituitary volumes than healthy women, as well as a positive correlation between pituitary gland volume and LH levels [35]. We also demonstrated that PGV began to rise before ovarian volume increased, suggesting this as an early finding of PCOS. Thus, we concluded that chronic stimulation with LH may lead to an increase in ovarian volume in later stages of the disease. Similarly, in the present study, it seems likely that subtle but chronic stimulation with ACTH, as a result of overactivity of the HPA axis, may result in subclinical hypertrophy and/or hyperplasia of the zonae reticularis/fasciculata.

DHEA-S is the most abundant androgen produced by the adrenal cortex and, therefore, is used as a marker of AA secretion. Also, 17-OH progesterone is primarily produced in the adrenal glands and to some degree in the gonads

[1]. Our analysis showed that serum DHEA-S, 17-OH progesterone and Ftest levels were significantly higher in the PCOS women, and that patients with higher DHEA-S and 17-OH progesterone levels had larger adrenal volumes. Our study also demonstrated that Ftest and Ttest levels showed positive correlations with DHEA-S levels and with AGV in PCOS women, but no correlations were found in controls. This was an expected finding since DHEA and its sulfate ester, DHEA-S, may undergo continuous interconversion and also convert to testosterone and androstenedione in peripheral tissues [36]. Although the ovaries are known to be the major source of testosterone, 50% of circulating testosterone is derived from the conversion of AAs in normal women of reproductive age [37]. Hence, high levels of AAs may always be accompanied by elevated gonadal androgen levels, as also shown in our study.

In addition, we found a significant negative correlation between DHEA-S and LH levels. These findings are inconsistent with some human and animal studies [38—40] that found a positive correlation between LH and DHEA-S levels and support the idea that high LH levels might be responsible for the adrenocortical hyperactivity. In contrast, the present study showed that higher DHEA-S levels were associated with lower LH levels in patients with PCOS. We suggest that high testosterone levels, which are the result of increased peripheral conversion of high DHEAS levels, give rise to a decrease in LH levels because of a negative-feedback effect.

Our analysis showed that PCOS patients showed a significant increase in adrenal volume with age. However, in our control group, AGV did not change significantly with age but showed a trend toward decreasing with age, which is in line with the findings of Wang et al. [28]. Puurunen et al. found that serum adrenal steroid production capacity remained enhanced at least up to menopause in women with PCOS [9]. Therefore, it is reasonable for us to speculate that enlargement of the adrenal gland with age in PCOS may reflect more chronically elevated levels of DHEA-S and an ongoing process of gland hypertrophy in the course of time and duration of the disease from puberty to menopause.

Additionally, but beyond the scope of this paper, is the fact that there is growing evidence of a link between PCOS and depression, anxiety, bipolar disorder and binge eating disorder. On the other hand, patients suffering from adrenal hyperplasia are often mistakenly thought to have PCOS because of the excess production of androgen and hyperandrogenism [34]. Although all other causes of adrenal enlargement as we discussed above were excluded from our study, it could be hypothesized that all these diseases that are associated with each other may be a reflection of a common pathogenesis.

There are limitations of the present study that should be noted. Firstly, we designed our study with basal androgens and routine hormonal parameters, which was sufficient for the diagnosis of PCOS. For this reason, laboratory findings concerning, insulin and IGF-1 levels, which may contribute to adrenal gland enlargement, and also ACTH levels, were not available. Although our study was performed with normal-weight women to exclude the possibility of hyperinsulinemia, further research with a full endocrine assessment is warranted. The other weakness of our study was the limited number of subjects fulfilling the inclusion criteria (BMI, hormonal status, and age). On the other hand, statistically significant correlations were found even though the sample size was small.

In conclusion, we have found a significant increase of AGV in patients with PCOS compared to healthy control individuals, previously not reported, as well as a positive correlation of adrenal gland size and androgens. Adrenal androgen excess in PCOS appears to be due to an alteration in the intrinsic behavior of the adrenal cortex (subclinical hypertrophy and/or hyperplasia of zonae reticularis/fasciculata) and hyperactivity of the adrenal glands. Understanding the relationship between adrenal volume and adrenal steroidogenesis in PCOS might provide novel insights into the pathophysiology of the syndrome.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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