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Elevated and diagnostic androgens of polycystic ovary syndrome

Ibrahim A. Abdelazim[1,2], Ahmed Alanwar[1], Mohannad AbuFaza[2], Osama O. Amer[3], Yerbol Bekmukhambetov[4], Gulmira Zhurabekova[5], Svetlana Shikanova[6], Bakyt Karimova[6]

[1]Department of Obstetrics and Gynecology, Ain Shams University, Cairo, Egypt

[2]Department of Obstetrics and Gynecology, Ahmadi Hospital, Kuwait Oil Company (KOC), Ahmadi, Kuwait

[3]Department of Oncology, Ghamra Military Hospital, Cairo, Egypt

[4]Department of Oncology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

[5]Department of Normal and Topographic Anatomy, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

[6]Department of Obstetrics and Gynecology No. 1, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

Abstract

Introduction: A genetic variation at the level of aromatase enzyme and/or androgen receptors was suggested in polycystic ovary syndrome (PCOS).

Aim of the study: To determine the androgens elevated and diagnostic for PCOS.

Material and methods: A total of 120 PCOS women were compared to non-PCOS controls in this study. The studied women were evaluated thoroughly, including: day 2-3 hormonal profile and any hormonal change confirmed by two laboratory results eight weeks apart. Collected data were analysed to determine the androgens elevated and diagnostic for PCOS.

Results: The luteinising hormone (LH) and LH/follicle stimulating hormone (FSH) ratio were significantly high in the studied PCOS group compared to controls (p = 0.02 and 0.01, respectively). In addition, total and free testosterone and androstenedione were significantly high in the studied PCOS group compared to controls (p = 0.001, 0.003, and 0.02, respectively).

The studied PCOS group had higher relative risk (RR) and odds ratio (OR) of elevated total testosterone (2.4 and 5.7, respectively), elevated free testosterone (2.9 and 4.9, respectively), and elevated androstenedione (3.0 and 4.8, respectively), compared to controls.

Conclusions: Testosterone (both total and free testosterone) and androstenedione were the main elevated androgens and were diagnostic for excess ovarian androgens in the studied PCOS women, whereas dehydroepiandrosterone (DHEA) was not elevated and/or diagnostic for excess ovarian androgens in the studied PCOS women.

Key words: elevated, diagnostic, androgens, PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a multiple endocrine disorder associated with significant reproductive (anovulation and hyperandrogenism) and metabolic manifestations (insulin resistance [IR] and glucose intolerance) [1-3].

The prevalence of PCOS is about 15-20% according to the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) diagnostic criteria [1].

PCOS is a multifactorial disorder, involving interactions between certain genes, and pituitary and hypothalamic dysfunction [2, 4].

A genetic variation at the level of aromatase enzyme and/or androgen receptors was suggested in PCOS [5-7].

The aromatase enzyme gene and/or androgen receptor variation lead to aromatase deficiency or reduced activity with subsequent increased ovarian androgen [6, 7]. Therefore, this prospective multicentre study was designed to determine elevated androgens and diagnostics for PCOS.

Material and methods

This prospective multicentre study was conducted after approval of the institutes' Ethical Committee and after informed consent.

Women ≥ 20 years < 35 years old presenting with infertility and/or irregular menses and diagnosed as PCOS were included in the study group (120 women).

Corresponding author:
Ibrahim A. Abdelazim MD, Department of Obstetrics and Gynecology, Ain Shams University, Cairo, Egypt and Ahmadi Kuwait Oil (KOC) Company Hospital, P.O. Box: 9758, 61008 Ahmadi, Kuwait,
e-mail: dr.ibrahimanwar@gmail.com

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Women ≥ 20 years < 35 years old presenting with infertility and/or irregular menses were included as controls after exclusion of PCOS (120 women).

Women with thyroid dysfunction, Cushing's syndrome, hyperprolactinaemia, and women receiving contraceptives pills, steroids, or with ovulation induction during the last six months were excluded from the study.

Participants were evaluated thoroughly, including: history, calculation of body mass index (BMI), waist circumference, and ultrasound diagnostic criteria of PCOS.

Evaluation of the day 2-3 hormonal profile including: follicle stimulating hormone (FSH), luteinising hormones (LH), prolactin, thyroid stimulating hormone (TSH), total and free testosterone, androstenedione, dehydroepiandrosterone (DHEA), and 17-hydroxy (OH) progesterone was performed using the enzyme-linked immunosorbent assay (ELISA) [8].

Any hormonal changes from the normal value (FSH, LH, prolactin, TSH, and androgens) were confirmed by two laboratory results eight weeks apart.

PCOS was defined by the ESHRE/ASRM criteria as the presence of any two of the following three criteria: (1) polycystic ovaries, (2) oligo-/anovulation, and/or (3) clinical or biochemical evidence of hyperandrogenism after exclusion of other causes of hyperandrogenism such as late-onset congenital adrenal hyperplasia (CAH), androgen-secreting ovarian or adrenal tumours, and Cushing's syndrome/disease [2].

BMI was calculated using the weight in kilograms divided by the square of the height in metres (kg/m^2) (18.5-24.9 = normal BMI, 25-29.9 = overweight, and ≥ 30 = obese) [2].

Waist circumference was measured midway between the upper border of the iliac crest and the lower rib margin (> 35 inches means increased waist circumference) [2].

Ultrasound diagnosed criteria of PCOS ≥ 10 small follicles measuring 2-8 mm in both ovaries [1-3].

Women with prolactin level twice the normal (normal value < 29 ng/ml [< 614 mIU/ml]) were evaluated for pituitary micro- and/or macroadenoma using the pituitary magnetic resonance imaging (MRI) according to the hospitals protocol. CAH as a cause of excess androgen was excluded by the measurement of the serum 17-OH progesterone (normal value < 200 ng/dl or < 6.06 nmol).

According to the hospital's protocol, women with elevated total testosterone > 200-250 ng/dl were screened for ovarian or adrenal androgen secreting tumours using pelvi-abdominal MRI. Androgen secreting adrenal tumours were suspected when the DHEA-sulphate (DHEA-s) was high with > 200-250 ng/dl total testosterone. Androgen secreting ovarian tumours were suspected when the total testosterone was > 200-250 ng/dl with normal DHEA-s.

Cushing's syndrome/disease as a cause of excess androgen was excluded by history of external glucocorticoids, 24-hour urinary cortisol, and dexamethasone suppression test [2]. Collected data were analysed to determine the androgens elevated and diagnostic for PCOS.

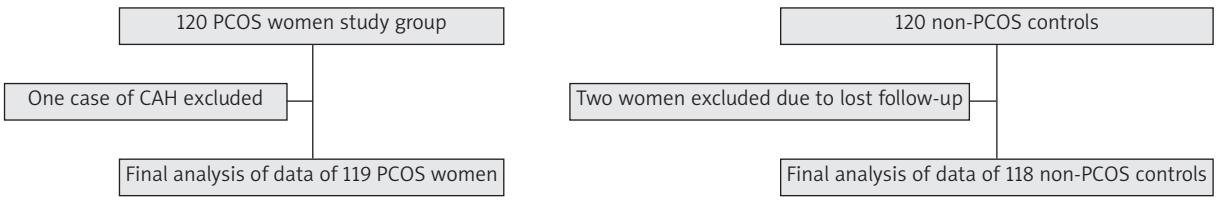
Sample size and statistical analysis

G Power software version 3.17 (Heinrich Heine Universität; Düsseldorf; Germany) was used for calculation of the required sample size. An effective sample include > 220 women was needed to produce a statistically acceptable figure. Collected data were analysed using the Statistical Package for Social Science (SPSS) (Chicago, IL, USA). χ^2 test was used to compare qualitative variables and Student's *t*-test was used to compare quantitative variables. Logistic regression analysis was used to calculate the relative risk (RR) and odds ratio (OR) of elevated and diagnostic androgens of PCOS. *P* values < 0.05 were considered significant.

Results

A total of 120 women aged ≥ 20 < 35 years diagnosed as PCOS were included in the study group, and one of them was excluded from the final analysis because of a confirmed diagnosis of late-onset CAH (119 PCOS women finally analysed). Two women from non-PCOS controls were lost during the follow-up, with final analysis of data for 118 controls (Fig. 1).

There was no significant difference between the studied PCOS and controls regarding the mean age (p = 0.9), while the BMI was significantly high in the studied PCOS group compared to the controls (30.7 ±6.0 vs. 24.5 ±4 kg/m^2, respectively; p = 0.001).



PCOS – polycystic ovary syndrome, CAH – congenital adrenal hyperplasia

Fig. 1. Study flow-chart

Table 1. Age, body mass index, and hormonal profile of the two studied groups

Variable	PCOS women (study group) (n = 119)	Non-PCOS controls (n = 118)	p-value (95% CI)
Age (years)	24.2 ±3.6	26.3 ±5.4	0.9 (–3.3, –2.1, –0.9)
BMI (kg/m^2)	30.7 ±6.0	24.5 ±4.5	0.001* (4.8, 6.2, 7.6)
FSH (mIU/ml)	6.5 ±4.6	5.3 ±4.3	0.2 (0.06, 1.2, 2.3)
LH (mIU/ml)	18.7 ±7.5	5.9 ±6.2	0.02* (11, 12.8, 14.6)
LH/FSH ratio	2.8 ±3.3	1.1 ±2.7	0.01* (0.9, 1.7, 2.5)
Total testosterone (ng/dl)	92.5 ±9.1	44.3 ±6.9	0.001* (46.1, 48.2, 50.3)
Free testosterone (pg/ml)	5.7 ±3.6	2.5 ±2.8	0.003* (2.4, 3.2, 4.03)
Androstenedione (ng/ml)	4.2 ±2.9	2.3 ±2.4	0.02* (1.22, 1.9, 2.58)
DHEA (ng/l)	8937 ±2.9	5491 ±3.7	0.99 (3445.1, 345, 3446.9)

BMI – body mass index, FSH – follicle stimulating hormone, LH – luteinising hormone, DHEA – dehydroepiandrosterone (normal 1330-7780 ng/l), PCOS – polycystic ovary syndrome, CI – confidence interval. Total testosterone normal value 6-86 ng/dl, free testosterone normal value 0.7-3.6 pg/ml, androstenedione normal value 0.7-3.1 ng/ml. Student's t-test used for statistical analysis. * Significant difference. Data presented as mean ±standard deviation (SD)

Table 2. Body mass index, waist circumference, and androgen profile of the two studied groups

Variable	PCOS women (study group) (n = 119)	Non-PCOS controls (n = 118)	p-value
BMI 25-29.9 kg/m^2	53 (44.5)	17 (14.4)	0.0001*
BMI ≥ 30 kg/m^2	42 (35.3)	12 (10.2)	0.0002*
Waist circumference > 35 inches	49 (41.2)	15 (12.7)	0.0001*
Total testosterone > 86 ng/dl	83 (69.8)	34 (28.8)	0.002*
Free testosterone > 3.6 pg/ml	61 (51.3)	21 (17.8)	0.0001*
Androstenedione > 3.1 ng/ml	55 (46.2)	18 (15.3)	0.001*
DHEA > 7780 ng/l	15 (12.6)	13 (11)	0.7

BMI – body mass index, DHEA – dehydroepiandrosterone (normal 1330-7780 ng/l), PCOS – polycystic ovary syndrome. Total testosterone normal value 6-86 ng/dl, free testosterone normal value 0.7-3.6 pg/ml, androstenedione normal value 0.7-3.1 ng/ml. χ^2 test used for statistical analysis. * Significant difference. Data presented as number and percentage (%)

There was no significant difference between the studied PCOS and controls regarding the mean FSH (6.5 ±4.6 vs. 5.3 ±4.3 mIU/ml, respectively; p = 0.2), while the LH and LH/FSH were significantly high in the studied PCOS group (18.7 ±7.5 and 2.8 ±3.3, respectively) compared to controls (5.9 ±6.2 mIU/ml and 1.1 ±2.7, respectively) (p = 0.02 and 0.01, respectively).

Total and free testosterone were significantly high in the studied PCOS group (92.5 ±9.1 and 5.7 ±3.6, respectively) compared to controls (44 .3 ±6.9 ng/dl and 2.5 ±2.8 pg/ml, respectively) (p = 0.001 and 0.003, respectively). Androstenedione was significantly high in the studied PCOS group (4.2 ±2.9) compared to controls (2.3 ±2.4 ng/ml) (p = 0.02), while there was no significant difference between the two studied groups regarding the DHEA (p = 0.99) (Table 1).

The number of over-weight and obese women (BMI 25-29.9 and ≥ 30 kg/m^2, respectively) was significantly high in the studied PCOS group (44.5% and 35.3%, respectively) compared to controls (14.4% and 10.2%, respectively) (p = 0.0001 and 0.0002, respectively). 41.2% of the studied PCOS group had waist circumference > 35 inches compared to 12.7% in the controls (p = 0.0001; significant difference). Number of women with high total and free testosterone (> 86 ng/dl and > 3.6 pg/ml, respectively) was significantly high in the studied PCOS (69.8% and 51.3%; respectively) compared to controls (28.8 and 17.8%, respectively), (p = 0.002 and 0.0001, respectively), and the number of women with high androstenedione (> 3.1 ng/ml) was also significantly high in the studied PCOS group compared to controls (46.2 vs. 15.3%, p = 0.001) (Table 2).

The studied PCOS group had significant higher relative risk (RR) of overweight (RR 3.1 [95% CI: 1.9-5.0]; p < 0.0001), obesity (RR 3.5 [95% CI: 1.93-6.3]; p < 0.0001), and waist circumference > 35 inches (RR 3.2 [95% CI: 1.9-5.4]; p < 0.0001) compared to controls. In addition, the studied PCOS group had higher RR of elevated total testosterone (RR 2.4 [95% CI: 1.8-3.3]; p < 0.0001), elevated free testosterone (RR 2.9 [95% CI: 1.9-4.4]; p < 0.0001), and elevated androstenedione (RR 3.0 [95% CI; 1.9-4.8]; p < 0.0001) compared to controls (Table 3).

The studied PCOS group had significant higher odds ratio (OR) of overweight (OR 4.8 [95% CI: 2.6-8.9]; p < 0.0001), obesity (OR 4.8 [95% CI: 2.4-9.8]; p < 0.0001), and waist circumference > 35 inches (OR 4.8 [95% CI: 2.5-9.2]; p < 0.0001) compared to controls. In addition, the studied PCOS group had higher OR of elevated

Table 3. Relative risk of overweight, obesity, and elevated androgens in the two studied groups

Variable	PCOS women (study group) (*n* = 119)	Non-PCOS controls (*n* = 118)	Relative risk (95% CI); *p*-value
BMI 25-29.9 kg/m^2 BMI < 25 kg/m^2	53 (44.5) 66 (55.5)	17 (14.4) 101 (85.6)	3.1 (1.9-5.0); < 0.0001*
BMI ≥ 30 kg/m^2 BMI < 30 kg/m^2	42 (35.3) 77 (64.7)	12 (10.2) 106 (89.8)	3.5 (1.93-6.3); < 0.0001*
Waist circumference > 35 inches Waist circumference < 35 inches	49 (41.2) 70 (58.8)	15 (12.7) 103 (87.3)	3.2 (1.9-5.4); < 0.0001*
Total testosterone > 86 ng/dl Total testosterone < 86 ng/dl	83 (69.8) 36 (30.2)	34 (28.8) 84 (71.2)	2.4 (1.8-3.3); < 0.0001*
Free testosterone > 3.6 pg/ml Free testosterone < 3.6 pg/ml	61 (51.3) 58 (48.7)	21 (17.8) 97 (82.2)	2.9 (1.9-4.4); < 0.0001*
Androstenedione > 3.1 ng/ml Androstenedione < 3.1 ng/ml	55 (46.2) 64 (53.8)	18 (15.3) 100 (84.7)	3.0 (1.9-4.8); < 0.0001*
DHEA > 7780 ng/l DHEA < 7780 ng/l	15 (12.6) 104 (87.4)	13 (11.0) 105 (89.0)	1.2 (0.59-2.4); 0.66

BMI – body mass index, DHEA – dehydroepiandrosterone, PCOS – polycystic ovary syndrome, CI – confidence interval. * Significant difference. Data presented as number and percentage (%)

Table 4. Odds ratio of overweight, obesity and elevated androgens in the two studied groups

Variable	PCOS women (study group) (*n* = 119)	Non-PCOS controls (*n* = 118)	Odds ratio (95% CI); *p*-value
BMI 25-29.9 kg/m^2 BMI < 25 kg/m^2	53 (44.5) 66 (55.5)	17 (14.4) 101 (85.6)	4.8 (2.6-8.9); < 0.0001*
BMI ≥ 30 kg/m^2 BMI < 30 kg/m^2	42 (35.3) 77 (64.7)	12 (10.2) 106 (89.8)	4.8 (2.4-9.8); < 0.0001*
Waist circumference > 35 inches Waist circumference < 35 inches	49 (41.2) 70 (58.8)	15 (12.7) 103 (87.3)	4.8 (2.5-9.2); < 0.0001*
Total testosterone > 86 ng/dl Total testosterone < 86 ng/dl	83 (69.8) 36 (30.2)	34 (28.8) 84 (71.2)	5.7 (3.3-99.9); < 0.0001*
Free testosterone > 3.6 pg/ml Free testosterone < 3.6 pg/ml	61 (51.3) 58 (48.7)	21 (17.8) 97 (82.2)	4.9 (2.7-8.8); < 0.0001*
Androstenedione > 3.1 ng/ml Androstenedione < 3.1 ng/ml	55 (46.2) 64 (53.8)	18 (15.3) 100 (84.7)	4.8 (2.6-8.9); <0.0001*
DHEA > 7780 ng/l DHEA < 7780 ng/l	15 (12.6) 104 (87.4)	13 (11.0) 105 (89.0)	1.2 (0.5-2.6); 0.7051

BMI – body mass index, DHEA – dehydroepiandrosterone, PCOS – polycystic ovary syndrome, CI – confidence interval. * Significant difference. Data presented as number and percentage (%)

total testosterone (OR 5.7 [95% CI: 3.3-99.9]; $p < 0.0001$), elevated free testosterone (OR 4.9 [95% CI: 2.7-8.8]; $p < 0.0001$), and elevated androstenedione (OR 4.8 [95% CI; 2.6-8.9]; $p < 0.0001$) compared to controls (Table 4).

Discussion

A total of 119 PCOS women were compared to 118 non-PCOS controls in this prospective study to determine the androgens elevated and diagnostic for PCOS.

The BMI was significantly high in the studied PCOS compared to the controls ($p = 0.001$), and the number of over-weight and obese women was significantly high in the studied PCOS group compared to controls ($p = 0.0001$ and 0.0002, respectively). 41.2% of the studied PCOS had waist circumference > 35 inches compared to 12.7% of controls ($p = 0.0001$). The studied PCOS group had significantly higher RR and OR of overweight, obesity, and waist circumference > 35 inches compared to controls.

Ibrahim and Walid found that the BMI and the waist-hip ratio were significantly high in PCOS patients with metabolic syndrome (MS) than in those without MS [1].

Abufaza *et al.* found that 10-40% of PCOS women are obese and 40-90% are overweight [2]. In addition; Abufaza *et al.* concluded that the obesity of the PCOS women was characterised by BMI > 26 kg/m^2 and waist circumference > 35 inches [2].

Although, Cho *et al.* found that the LH/FSH ratio has little use in diagnosing PCOS [9]. The LH and the LH/FSH were significantly high in the studied PCOS group compared to controls.

Banaszewska *et al.* reported abnormally elevated LH/FSH ratio in 45.4% of PCOS women, and they also

found that the elevated LH in PCOS women constituteed a subgroup of PCOS with increased adrenal androgenic activity [10]. In addition, Nath *et al.* found that 70% of PCOS women have LH/FSH ratio > 2 [11].

The testosterone (both free and total testosterone) and the androstenedione were significantly high in the studied PCOS group compared to controls, while there was no significant difference between the two studied groups regarding the DHEA. The studied PCOS group had higher RR and OR of elevated testosterone (both free and total testosterone) and elevated androstenedione compared to controls.

Similarly, Lerchbaum *et al.* found that free testosterone and androstenedione are the main androgens elevated in PCOS. Lerchbaum *et al.* concluded that PCOS women with high free testosterone have an adverse metabolic profile, and PCOS women with high androstenedione/free testosterone ratio have a beneficial metabolic profile [8].

Mostafa *et al.* reported manifestation of hyperandrogenism in 70% of PCOS women [5]. Mostafa *et al.* in another study reported excess ovarian androgen in 50% of PCOS women and excess adrenal androgen (detected by DHEAs) in 30% of PCOS women [12].

Mostafa *et al.* suggested measurement of free and total testosterone to detect the ovarian source of hyperandrogenism and measurement of DHEAs to detect the adrenal source of hyperandrogenism in PCOS women [12].

In addition, Azziz *et al.* reported excess adrenal androgen (detected by elevated DHEA-s) in 20-30% of PCOS women [13].

This study concluded that testosterone (both total and free) and androstenedione were the main elevated androgens and were diagnostic for excess ovarian androgen in the studied PCOS women, while DHEA was not elevated and/or diagnostic for excess ovarian androgen in the studied PCOS women.

To the best of our knowledge, this is the first prospective multicentre study conducted to determine the androgens elevated and diagnostic for PCOS. Women lost during follow-up and women who refused to participate in this study were the limitations faced during the conduction of this study. Larger studies are needed to confirm the androgens elevated and diagnostic for PCOS.

Conclusions

Testosterone (both total and free testosterone) and androstenedione were the main elevated androgens and were diagnostic for excess ovarian androgen in the studied PCOS women, while DHEA was not elevated and/or diagnostic for excess ovarian androgen in the studied PCOS women.

Acknowledgments

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Disclosure

The authors report no conflict of interest.

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