European Journal of Obstetrics & Gynecology and Reproductive Biology 156 (2011) 181–185

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Phenotypic expression, body mass index and insulin resistance in relation to LH levels in women with polycystic ovary syndrome

Ilias Katsikis [a], Artemis Karkanaki [a,*], Georgios Misichronis [a], Dimitrios Delkos [b], Eleni A. Kandaraki [c], Dimitrios Panidis [a]

[a] Division of Endocrinology and Human Reproduction, Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece
[b] Third Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece
[c] Division of Endocrinology, First Department of Medicine, Laiko Hospital, Medical School, University of Athens, Athens, Greece

ARTICLE INFO

Article history:
Received 12 May 2010
Received in revised form 6 January 2011
Accepted 25 January 2011

Key words:
LH
LH/FSH
PCOS
Phenotypes
1990 criteria
2003 criteria
BMI
Insulin resistance

ABSTRACT

Objective: To evaluate LH levels in women with the classic (1990 criteria) and the newer (2003 criteria) PCOS phenotypes, and to examine the impact of BMI and insulin resistance indices on hormone levels.
Study design: In this controlled clinical study 936 women with PCOS, classified as classic ($n = 729$) and newer ($n = 207$), and 204 controls were included. All women were divided into normal-weight (BMI < 25 kg/m^2) and overweight plus obese (BMI ≥ 25 kg/m^2). Serum LH, FSH, anthropometrics, androgens, fasting insulin and glucose, HoMA-IR, number of follicles, and ovarian volume were assessed.
Results: Women with classic PCOS presented significantly higher LH and LH/FSH ratios, and lower glucose/insulin levels than those with the newer phenotype and controls. Overweight plus obese women of all groups had lower LH levels than normal-weight women. Independent positive correlations between LH and androgens and negative correlation between LH and BMI were found.
Conclusions: The higher LH concentrations of the classic phenotypes of PCOS could be attributed to the higher androgen levels, which desensitize the hypothalamus to the negative feedback regulation by progesterone. Moreover, the lower LH levels of overweight plus obese women of all groups could be attributed to the increased peripheral aromatization of androgens to estrogens in adipose tissue leading to suppression of LH secretion.
Condensation: Both normal-weight and overweight women with classic PCOS phenotypes present higher LH levels and LH-to-FSH ratios than women with similar BMI but the newer phenotypes.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the outstanding matters of endocrinological and gynecological investigation due to its complex pathogenesis and its multiple clinical expressions. One of the most stable findings of clinical research on the syndrome is the higher luteinizing hormone (LH) levels and the higher values of the LH to follicle stimulating hormone (FSH) ratio. LH levels were found to be influenced by weight and, specifically, it has been repeatedly reported that normal-weight women with PCOS present significantly higher concentrations of LH compared to overweight and obese women with the syndrome [1,2].

Diagnosis of PCOS characterizes a mosaic cohort of women with different clinical features. In fact, this heterogeneity of the syndrome triggers divergent opinions about the importance of every feature and the characterization of women with the diagnosis of PCOS, since the newer phenotypes seem to present differentiation of the classic syndrome, as initially diagnosed. Today, four possible phenotypes of PCOS women arise through distinct combinations of the three key features of the syndrome [3] (Table 1).

The first two phenotypes are considered the "classic" PCOS, as their diagnosis is based upon the old diagnostic criteria of 1990 [4]. The last two phenotypes, called "non-classic" or "newer" PCOS, are based on the Rotterdam Consensus Diagnostic criteria of 2003 [5,6]. According to the latter, diagnosis of the syndrome is made when at least two of the three criteria are present. Criteria include (i) oligo- and/or anovulation (ANOV), (ii) hyperandrogenemia (HA) and/or hyperandrogenism, and (iii) polycystic ovarian morphology on ultrasonography (PCO).

The dispute concerning the uniformity of PCOS phenotypes was amplified by the publication of data demonstrating differences in the metabolic and hormonal profile between the distinct phenotypes of PCOS. The Androgen Excess Society, in recent guidelines, argued that PCOS should be considered, basically, as an

* Corresponding author at: Ioanninon Str. 30, 54639 Thessaloniki, Greece. Tel.: +30 6932315022.
E-mail address: kartemis2004@hotmail.com (A. Karkanaki).

0301-2115/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejogrb.2011.01.023

Table 1
PCOS phenotypes.

PHENOTYPES		Oligo-anovulation	Hyperandrogenism	Polycystic morphology
Classic PCOS	1	+	+	+
	2	+	+	–
Newer PCOS	3	–	+	+
	4	+	–	+

excess disturbance in biosynthesis, metabolism or use of androgens [7]. Thus, ovulating women with HA and PCO present a mild type of the syndrome [8]. On the other hand, women with ANOV and PCO, despite the initial indications, manifest mild endocrinologic and metabolic disorders, and their metabolic profile is not related to increased metabolic risk characteristic of women with PCOS [9,10].

In a study of 32 women with PCOS, 16 normal-weight and 16 obese, it was found that LH levels were not significantly different between the two groups and increased values of the LH-to-FSH ratio were not correlated to insulin resistance [11]. On the contrary, other studies with greater numbers of participants showed that normal-weight women with PCOS have higher LH concentrations than overweight plus obese women with the syndrome [1,2]. There is, however, no evidence concerning the impact of phenotypic expression of PCOS on LH levels. Considering that anovulation in PCOS is caused by the persistent, rapid frequency of GnRH stimulation of the pituitary, resulting in increased LH and testosterone concentrations, low levels of FSH, and failure of follicular maturation, the aim of the present study was the evaluation of LH levels and LH-to-FSH ratio in women with the "classic" and the "newer" phenotypes of the syndrome as well as the impact of BMI and insulin resistance on LH levels.

2. Materials and methods

Nine hundred and thirty six (936) women with PCOS and two hundred and four (204) healthy women with normal ovulating cycles (controls) (28 ± 2 days, blood progesterone levels >10ng/mL in the luteal phase of two consecutive cycles), without hyperandrogenism (clinical or biochemical) or polycystic ovarian morphology on ultrasound examination participated voluntarily. All women with PCOS were outpatients at the Gynecological Endocrinology Infirmary of the Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki.

Women with PCOS were divided in two groups according to their phenotype, namely 'classic' (oligo-/anovulation and hyperandrogenemia irrespective of polycystic ovaries on ultrasonographic evaluation) (group A, $n = 729$), and 'newer' (polycystic ovaries and either hyperandrogenemia or oligo-/anovulation) (group B, $n = 207$). Additionally, all women were divided into two groups according to their BMI, namely normal-weight (BMI < 25 kg/m^2) (group A: $n = 381$; group B: $n = 118$; controls: $n = 123$) and overweight plus obese (BMI ≥ 25 kg/m^2) (group A: $n = 348$; group B: $n = 89$; controls: $n = 81$).

Diagnosis of PCOS was based on the revised Rotterdam criteria of (2003) [5,6]. None of the participants had galactorrhea or any systemic disease that could possibly affect their reproductive physiology. No woman reported use of any lipid-modulating medication or other substance that could interfere with the normal function of the hypothalamic-pituitary-gonadal axis. The protocol and procedures were approved by the local institutional review board and all patients consented after being fully informed.

Baseline blood samples were collected and transvaginal ultrasound ovary scanning was performed between days 3 and 7 of the menstrual cycle in the control group and after a spontaneous bleeding episode in the PCOS group, following an overnight fast. The Free Androgen Index (FAI), the homeostasis model for insulin resistance (HoMA-IR), and glucose-to-insulin ratio (GIR) were calculated as previously described [12].

Plasma glucose, insulin, LH, FSH, PRL, testosterone, Δ_4-androstendione, DHEA-S, 17-OH-progesterone and SHBG levels were measured exactly as previously described [12]. LH concentration was measured with an enzyme-linked immunoassay (EIA), using commercial kits (Nichols Institute Diagnostics, CA, USA). The intra-assay coefficient of variation was 0.7% and the inter-assay coefficient of variation was 1.7%.

Normality of the distribution was checked by Kolmogorov–Smirnov test. Kruskal–Wallis test was used for the comparison of mean values of continuous variables measurements. The Spearman correlation coefficient was calculated for the assessment of pairwise correlations. After log transformation, for normal distribution, Factorial ANOVA (GLM 3) was used to examine the effects of PCOS groups and BMI and the interactions between the two independent variables. Results are reported as mean $\pm$ SD. $p < 0.05$ was considered statistically significant. SPSS software v.16.0 was used for data analysis. The power of the study is 100% for alpha = 0.05 (GPower v.2.0) [13].

3. Results

When comparing all women with PCOS to controls, without classifying them according to their BMI, PCOS patients presented significantly lower FSH, SHBG, and GIR than controls (all $p < 0.001$). Conversely, LH levels, LH to FSH ratio values, androgens, insulin, 17OH-progesterone, and HoMA-IR levels were significantly higher in women with PCOS than controls (all $p < 0.001$). Importantly, there was no statistical difference in the BMI between the three study groups.

The comparison of the three study groups, before classification according to BMI, showed that women of group A presented significantly higher LH levels and LH-to-FSH ratio values than women of group B and controls (all $p < 0.001$) (Fig. 1). Furthermore, women of group B had higher LH concentrations and LH-to-FSH ratio values than controls but the difference did not reach statistical significance. Similarly, androgens (testosterone, Δ_4-androstendione and DHEAS) and 17OH-progesterone levels were significantly higher in women of group A than in women of group B and controls (all $p < 0.001$), though the same androgen levels were

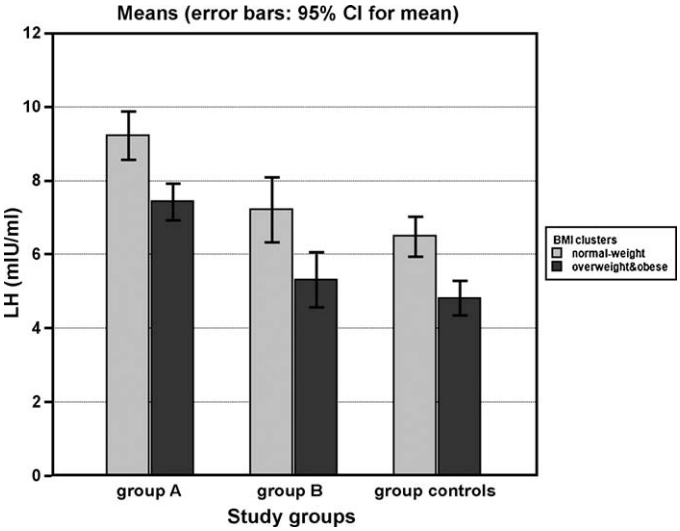

Fig. 1. LH levels in both normal-weight and overweight plus obese women with the classic and the newer PCOS phenotypes and the controls.

Table 2
Anthropometrics, hormonal and ultrasound characteristics of women in the study groups before classification according to BMI.

	Classic PCOS	Newer PCOS	Controls	*p* values
Age (years)	23.3 ± 5.2^{a}	25.1 ± 6.2^{a}	31.1 ± 5.7^{a}	≤0.001
BMI (kg/m^2)	26.7 ± 6.8	26.3 ± 6.9	25.7 ± 6.6	NS
Waist (cm)	83.7 ± 15.4	81.5 ± 14.8	82.0 ± 13.4	NS
Hip (cm)	106.2 ± 12.9	105.0 ± 14.8	105.3 ± 13.0	NS
Waist/hip	0.8 ± 0.1	0.8 ± 0.4	0.8 ± 0.1	NS
FSH (IU/l)	5.7 ± 1.7^{a}	6.1 ± 1.9^{a}	7.1 ± 2.4^{a}	≤0.02
LH (IU/l)	$8.4 \pm 5.8^{a,b}$	6.4 ± 4.5^{a}	5.8 ± 2.8^{b}	≤0.001
LH/FSH	$1.5 \pm 1.0^{a,b}$	1.1 ± 0.7^{a}	1.0 ± 1.2^{b}	≤0.001
PRL (ng/ml)	14.4 ± 7.4^{a}	13.9 ± 8.0	13.0 ± 5.8^{a}	0.048
T (ng/dl)	89.2 ± 26.2^{a}	60.6 ± 27.9^{a}	38.0 ± 13.1^{a}	<0.001
Δ_4-A (ng/dl)	3.1 ± 1.0^{a}	2.4 ± 1.0^{a}	1.7 ± 0.5^{a}	<0.001
DHEAS (ng/ml)	3228 ± 1257^{a}	2597 ± 1302^{a}	1887 ± 789^{a}	<0.001
17-OH-P (ng/ml)	1.2 ± 0.6^{a}	1.1 ± 0.6^{b}	$0.8 \pm 0.4^{a,b}$	<0.001
SHBG (nmol/l)	38.3 ± 21.8^{a}	49.6 ± 29.0^{a}	66.4 ± 36.0^{a}	<0.001
Insulin (μIU/ml)	13.1 ± 13.4^{a}	11.4 ± 10.2	9.3 ± 6.9^{a}	<0.001
Glucose (mg/dl)	96.6 ± 15.8	99.3 ± 12.5	96.9 ± 12.0	NS
HoMA-IR	3.2 ± 3.6^{a}	2.9 ± 3.0	2.3 ± 1.9^{a}	0.001
FAI	10.9 ± 7.9^{a}	5.9 ± 4.5^{a}	2.6 ± 1.8^{a}	0.001
Follicles number	22.0 ± 9.7^{a}	24.4 ± 8.6^{a}	12.7 ± 3.7^{a}	≤0.001
Ovarian volume (cm^3)	8.0 ± 3.6^{a}	8.5 ± 4.1^{b}	$5.3 \pm 1.9^{a,b}$	<0.001

Values are referred as mean ± S.D.
[a,b]Statistically important difference between means with the same index letter.

significantly higher in women of group B than controls (all $p < 0.001$) (Table 2).

When women in the three groups, namely classic PCOS, newer PCOS and controls, were divided according to BMI into normal-weight (BMI < 25 kg/m^2) and overweight plus obese (BMI > 25 kg/m^2), it was found that LH concentrations and LH-to-FSH ratio values were significantly higher in normal-weight women than in overweight plus obese women in all study groups (all $p < 0.001$) (Table 3, Fig. 2).

HoMA-IR values were significantly higher in women of group A than in women of group B and controls ($p < 0.001$). However, the difference in HoMA-IR values between women of group B and controls was not significant.

Again, when women in the three groups were divided according to the BMI limit of 25 kg/m^2, GIR values in normal-weight as well as in overweight plus obese women were lower in group A than group B and controls (all $p < 0.001$) (Table 3). Furthermore, the differences in GIR values, irrespective of BMI, between women of group B and controls did not reach statistical significance. Regarding HoMA-IR, significant differences were detected only between normal-weight women of group A and group B ($p < 0.001$), and between normal-weight women of group A and controls ($p < 0.05$). LH concentrations were positively correlated to Δ_4-androstendione levels ($r = 0.327$, $p < 0.001$), to 17OH-progesterone levels ($r = 0.256$, $p < 0.001$), and to testosterone ($r = 0.233$, $p < 0.001$).

Finally, there is a significant main effect of the grouping of women with 'classic' and 'newer' PCOS and controls ($F = 29.056$, $p < 0.001$) and BMI ($F = 24.832$, $p < 0.001$) on LH levels. Post hoc tests revealed that women with 'classic' PCOS presented significantly higher LH levels than both women with 'newer' PCOS and controls ($p < 0.001$). However, there was no significant interaction effect between LH concentrations and BMI values.

Table 3
Anthropometrics, hormonal and ultrasound characteristics of women in the study groups after classification according to BMI.

	Classic PCOS normal-weight	Classic PCOS overweight + obese	Newer PCOS normal-weight	Newer PCOS overweight + obese	Controls normal-weight	Controls overweight + obese	*p* values
Age (years)	22.6 ± 4.5	24.1 ± 5.8^{a}	24.7 ± 5.9^{a}	25.7 ± 6.4^{a}	30.6 ± 5.6^{b}	31.9 ± 5.7^{b}	≤0.003
BMI (kg/m^2)	21.6 ± 2.0^{a}	32.3 ± 5.8^{b}	21.9 ± 1.9^{a}	32.3 ± 6.5^{b}	21.8 ± 2.0^{a}	31.7 ± 6.6^{b}	<0.001
Waist (cm)	72.3 ± 5.8^{a}	96.2 ± 12.7^{b}	72.4 ± 5.6^{a}	93.6 ± 14.5^{b}	73.9 ± 6.1^{a}	92.7 ± 12.7^{b}	<0.001
Hip (cm)	96.9 ± 5.5^{a}	116.3 ± 10.8^{b}	96.9 ± 9.8^{a}	116.0 ± 13.1^{b}	97.7 ± 6.3^{a}	115.3 ± 12.9^{b}	<0.001
Waist/hip	0.8 ± 0.3^{a}	0.8 ± 0.1^{b}	$0.8 \pm 0.6^{a,b}$	$0.8 \pm 0.1^{a,b}$	0.7 ± 0.1^{a}	$0.8 \pm 0.1^{a,b}$	≤0.026
FSH (IU/l)	5.9 ± 1.7^{a}	5.6 ± 1.7^{a}	6.5 ± 2.0^{b}	5.6 ± 1.7^{a}	7.2 ± 2.3^{b}	7.0 ± 2.5^{b}	≤0.0016
LH (IU/l)	9.2 ± 6.5	7.4 ± 4.5^{a}	$7.2 \pm 4.9^{a,b}$	$5.3 \pm 3.6^{b,c}$	$6.5 \pm 3.0^{a,b,c}$	4.8 ± 2.1^{c}	≤0.015
LH/FSH	1.6 ± 1.2	1.4 ± 0.9^{a}	$1.1 \pm 0.7^{a,b}$	1.0 ± 0.6^{b}	1.0 ± 0.9^{b}	0.9 ± 1.5^{b}	≤0.023
PRL (ng/ml)	15.0 ± 7.6^{a}	$13.7 \pm 7.1^{a,b}$	$14.1 \pm 7.4^{a,b}$	$13.6 \pm 8.7^{a,b}$	$13.5 \pm 6.1^{a,b}$	12.3 ± 5.2^{b}	≤0.031
T (ng/dl)	87.3 ± 24.7^{a}	91.2 ± 27.7^{a}	59.1 ± 27.8^{b}	62.7 ± 28.0^{b}	37.9 ± 13.0^{c}	38.1 ± 13.4^{c}	<0.001
Δ_4-A (ng/dl)	3.2 ± 1.0^{a}	3.0 ± 1.1^{a}	2.4 ± 0.9^{b}	2.4 ± 1.0^{b}	1.7 ± 0.4^{c}	1.6 ± 0.5^{c}	<0.001
DHEAS (ng/ml)	3160 ± 1169^{a}	3303 ± 1345^{a}	2492 ± 1192^{b}	2737 ± 1430^{b}	1882 ± 756^{c}	1895 ± 843^{c}	≤0.041
17-OH-P (ng/ml)	1.2 ± 0.6^{a}	1.2 ± 0.6^{a}	1.1 ± 0.6^{a}	1.1 ± 0.6^{a}	0.7 ± 0.4^{b}	0.8 ± 0.4^{b}	≤0.004
SHBG (nmol/l)	47.0 ± 23.8^{a}	28.8 ± 14.5^{b}	59.4 ± 31.3^{c}	36.6 ± 19.3^{b}	76.5 ± 33.9	$51.5 \pm 33.9^{a,c}$	≤0.004
Insulin (μIU/ml)	$9.8 \pm 0.7^{a,c}$	16.7 ± 0.6^{b}	7.6 ± 4.3^{a}	16.4 ± 1.4^{b}	7.0 ± 0.4^{a}	$12.6 \pm 1.0^{b,c}$	≤0.039
Glucose (mg/dl)	94.5 ± 12.2^{a}	99.0 ± 18.7^{b}	$97.7 \pm 11.1^{a,b}$	101.5 ± 13.9^{b}	$94.7 \pm 11.1^{a,c}$	$100.4 \pm 12.6^{b,c}$	≤0.011
HoMA-IR	$2.3 \pm 3.4^{a,c}$	4.2 ± 3.6^{b}	1.9 ± 1.1^{a}	4.3 ± 4.0^{b}	1.7 ± 1.1^{a}	$3.2 \pm 2.4^{b,c}$	≤0.040
FAI	8.3 ± 0.3^{a}	13.9 ± 0.5	4.8 ± 0.3^{b}	7.5 ± 0.5^{a}	2.0 ± 0.1^{c}	$3.5 \pm 0.3^{b,c}$	≤0.010
Follicles number	21.5 ± 9.3^{a}	$22.6 \pm 10.1^{a,b}$	24.7 ± 8.8^{b}	$24.0 \pm 8.4^{a,b}$	12.4 ± 3.7^{c}	13.1 ± 3.7^{c}	≤0.007
Ovarian volume (cm^3)	6.9 ± 4.5^{a}	6.9 ± 4.2^{a}	7.7 ± 4.2^{a}	8.5 ± 4.6^{a}	4.9 ± 2.1^{b}	5.2 ± 2.2^{b}	<0.001

Values are referred as mean ± S.D.
[a,b,c]No statistically important difference between means with the same index letter.

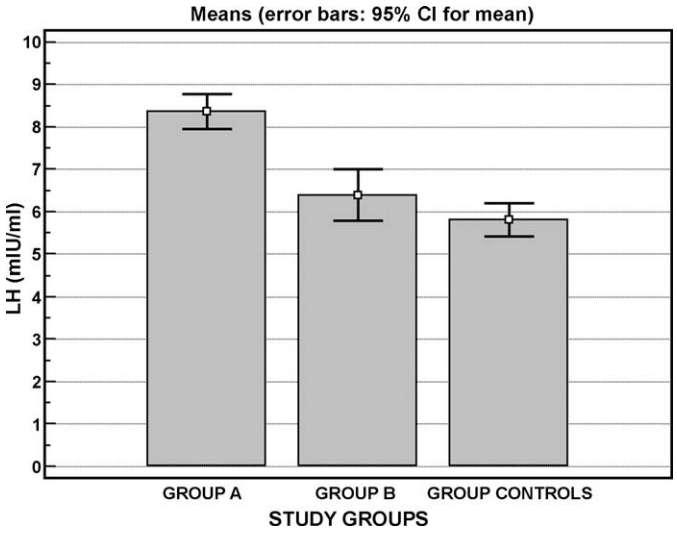

Fig. 2. LH concentrations in women with the classic and the newer PCOS phenotypes and the controls, clustered according to BMI into normal-weight and overweight plus obese women. Light color bars represent LH in normal-weight women, while dark color bars represent LH levels in overweight plus obese women of the three groups.

4. Comments

The etiopathogenesis of the polycystic ovary syndrome has not yet been entirely elucidated [14,15]. The heterogeneity between the different phenotypes of the syndrome has raised several theories for the explanation of the causes and the pathways of the syndrome. The most prevalent theories are three: (i) the theory of disturbed ovarian steroidogenesis, (ii) the theory of insulin resistance, and (iii) the theory of the hypothalamo-pituitary axis. It is presumed that every hypothesis should simultaneously explain the pathogenesis of all the three main characteristics of the syndrome, namely oligo- or anovulation, hyperandrogenism and polycystic ovarian morphology.

The neuroendocrine alterations in the function of the hypothalamo-pituitary axis seem to participate in the androgens' excessive production in polycystic ovary syndrome. In PCOS, the episodes of GnRH secretion are more frequent and higher (24 instead of 12 per day) than in normal women [16]. Frequent secretory episodes activate the gene of the LH β-subunit, thus leading to increased secretion of LH, whereas sparse episodes activate the gene of the FSH β-subunit resulting to augmented secretion of FSH. This pattern of secretion leads to the increased values of the LH-to-FSH ratio in some women with PCOS, mainly in normal-weight women [2,17]. This dysfunction in gonadotropin secretion is further accentuated during the test of stimulation with GnRH [18]. All the above findings are supportive of aberration in hypothalamo-pituitary axis function in polycystic ovary syndrome, which is enhanced by increased pituitary sensitivity to stimulation with corticotropin releasing hormone (CRH), thus leading to excessive secretion of adrenal corticotrophin hormone (ACTH) and, finally, increased cortisol response in women with this dysfunction [19].

In the present study, there was no significant difference in the BMI of the women of the three groups. Women diagnosed with PCOS according to 1990 criteria (group A), in total, presented higher LH levels than women diagnosed according to the additional criteria of 2003 (group B) ($p < 0.001$) and controls ($p < 0.001$) (Fig. 1). Moreover, women of group A had higher LH-to-FSH ratio values than women of group B ($p < 0.001$) and controls ($p < 0.001$). No significant differences, however, were found between LH concentrations and LH-to-FSH ratio values between women of group B and controls. Certainly, women of group A had higher testosterone, Δ_4-androstendione and DHEAS levels than women of group B (all $p < 0.001$) and controls (all $p < 0.001$). It has been found that excessive androgen concentrations cause desensitization of the hypothalamus to the negative feedback regulation by progesterone [20]. The latter finding suggests that gonadotropin secretion aberrations in PCOS are consequences of the existing pathologic ovarian or adrenal steroidogenesis.

It is well established that plasma LH levels are elevated in a great number of women with PCOS [21] and the fact that the frequency and the amplitude of LH pulses is increased is suggestive of a persistent rapid frequency of endogenous GnRH secretion [22]. Although a significant correlation between LH and androgens does not prove a direct relation between cause and effect, the high LH levels seem to reflect the hyperandrogenemia of PCOS, given that the administration of the anti-androgen, flutamide, for 1 month, restores the normal GnRH inhibition caused by the low progesterone concentrations [23]. In conclusion, the anovulation in women with PCOS is due to the persistent, rapid frequency of GnRH stimulation of the pituitary that results in elevated LH and testosterone concentrations, low FSH levels and aberrant follicular maturation. Actually, this disorder of the inhibitory progesterone action on GnRH secretion seems to involve the effects of the increased plasma androgens [24].

When women of the three groups, namely groups A, B and controls, were divided according to BMI into normal-weight (BMI < 25 kg/m^2) and overweight plus obese (BMI > 25 kg/m^2), it was found that LH concentrations and LH-to-FSH ratios were significantly higher in normal-weight women than in overweight plus obese women of all study groups (all $p < 0.001$) (Table 3, Fig. 2). This has already been reported, but in smaller cohorts [1,2]. It is well known that adipose tissue contains the enzyme aromatase which catalyzes the conversion of androgens to estrogens [25,26]. The explanation for the lower LH levels in overweight plus obese women with PCOS and controls could be attributed to the extra-ovarian estrogen production that takes place in adipose tissue and suppresses LH secretion.

At the same time, in the present study, glucose-to-insulin ratio values were significant lower, while HoMA-IR values were significantly higher, in women of group A compared to those of group B and controls (all $p < 0.001$). However, there was no significant difference in glucose-to-insulin ratio and HoMA-IR between women of group B and controls. When women of all groups were divided according to BMI, the only significant difference found was that of normal-weight women of group A compared to normal-weight women of group B and controls (all $p < 0.001$) (Table 3). There was no difference, however, between normal-weight women of group B and controls. Regarding the overweight plus obese women, the only significant difference detected was between group A and controls ($p < 0.001$) (Table 3).

No significant correlation was observed between insulin levels, glucose-to-insulin ratio or HoMA-IR, and LH concentrations or LH-to-FSH ratio values. Insulin resistance has been widely considered as the key element of the syndrome [27]. It has been reported that the disturbance in gonadotropin secretion is amplified by hyperinsulinemia [14]. The results of the present study provide evidence supportive of the hypothesis that gonadotropin secretion aberrations are not related with insulin resistance.

In the study of Moran et al. [28], no difference in LH levels was observed between normal-weight and obese women with PCOS. It was also implied that insulin resistance can promote high serum LH levels in obese patients with PCOS, since in vitro studies have demonstrated an insulin-induced secretion of gonadotropins [29]. Nevertheless, the number of women studied was relatively small and the results are contradictory to previous reports [2,30], which have shown significantly greater serum circulating LH levels in normal-weight than in overweight and obese women with PCOS.

A case in point is the absence of a significant difference in glucose-to-insulin ratio and HoMA-IR values between normal-weight and overweight plus obese women of group B and controls. This finding confirms the hypothesis that newer phenotypes are milder forms of the syndrome. Particularly, ovulating women with hyperandrogenism and polycystic ovarian morphology (phenotype 3, Table 1) manifest a milder form of PCOS [8]. Otherwise, in women with chronic oligo- or anovulation and polycystic ovarian morphology (phenotype 4, Table 1), despite the fact that initial evidence showed that they have mild endocrinologic and metabolic disturbances, compatible with mild forms of PCOS [8], their metabolic profile is considered too mild or not related to increase risk of serious metabolic dysfunction characteristic of the polycystic ovary syndrome [9,10].

In conclusion, the results of the present study show that high LH levels are not directly correlated to insulin resistance. The higher LH concentrations observed in "classic" PCOS in relation to the "newer" phenotypes could be attributed to higher androgen levels that desensitize the hypothalamus to the progesterone negative feedback regulation mechanism. On the other hand, the lower LH levels found in overweight plus obese women of all three study groups are possibly attributed to the increased peripheral aromatization of androgens to estrogens in adipose tissue, which leads to the suppression of LH secretion.

References

[1] Lobo RA, Kletzky OA, Campeau JD, di Zerega GS. Elevated bioactive luteinizing hormone in women with polycystic ovary syndrome. Fertil Steril 1983;39:674–8.

[2] Panidis D, Farmakiotis D, Rousso D, Katsikis I, Kourtis A, Diamanti-Kandarakis E. Serum luteinizing hormone levels are markedly increased and significantly correlated with Δ_4-androstenedione levels in lean women with polycystic ovary syndrome. Fertil Steril 2005;84:538–40.

[3] Diamanti-Kandarakis E, Panidis D. Unraveling the phenotypic map of polycystic ovary syndrome. Clin Endocrinol (Oxf) 2007;67:735–42.

[4] Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GE, editors. Hershman SM, series editor. Polycystic ovary syndrome. Current issues in endocrinology and metabolism. Boston: Blackwell Scientific Publications; 1992. p. 377–84.

[5] The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.

[6] The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Fertil Steril 2004;81:19–25.

[7] Azziz R, Carmina E, Dewailly D, et al. Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006;91:4237–45.

[8] Carmina E, Lobo RA. Do hyperandrogenic women with normal menses have polycystic ovary syndrome? Fertil Steril 1999;71:319–22.

[9] Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. Br J Obstet Gynecol 2006;113:1210–7.

[10] Welt CK, Gudmundsson JA, Arason G, Adams J, Palsdottir H, Gudlaugsdottir G. Characterizing discrete subsets of polycystic ovary syndrome as defined by the Rotterdam criteria: the impact of weight on phenotype and metabolic features. J Clin Endocrinol Metab 2006;91:4842–8.

[11] Moran C, Garcia-Hernandez E, Barahona E, Gonzalez S, Bermudez J. Relationship between gonadotropin dissociation in obese and non-obese women with polycystic ovary syndrome. Fertil Steril 2003;80:1466–72.

[12] Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D. Anti-Mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. Am J Physiol Endocrinol Metab 2009;269:E238–43.

[13] Faul F, Erdfelder E. GPower: a priori, post hoc, and compromise power analyses for MS-DOS (computer program). Bonn, FRG: Bonn University, Department of Psychology, 1992.

[14] Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med 2008;358:47–54.

[15] Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007;370:685–97.

[16] Ehrmann RA. Polycystic ovary syndrome. N Engl J Med 2005;352:323–36.

[17] DeVane GW, Czekala NM, Judd HL, Yen SS. Circulating gonadotropins, estrogens, and androgens in polycystic ovarian disease. Am J Obstet Gynecol 1975;121:496–500.

[18] Ehrmann DA, Rosenfield RL, Barnes RB, Brigell DF, Sheikh Z. Detection of functional ovarian hyperandrogenism in women with androgen excess. N Engl J Med 1992;327:157–62.

[19] Lanzone A, Petraglia F, Fulghesu AM, Ciampelli M, Caruso A, Mancuso S. Corticotropin-releasing hormone induces an exaggerated response of adrenocorticotropic hormone and cortisol in polycystic ovary syndrome. Fertil Steril 1995;63:1195–9.

[20] Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. Hum Reprod Update 2006;12:351–61.

[21] Taylor AE, McCourt B, Martin KA, et al. Determinants of abnormal gonadotropins secretion in clinically defined women with polycystic ovary syndrome. J Clin Endocrinol Metab 1997;82:2248–56.

[22] Waldstreicher J, Santoro NF, Hall JE, Filicori M, Crowley Jr WF. Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1988;66:165–72.

[23] Eagleson CA, Gingrich MB, Pastor CL, et al. Polycystic ovarian syndrome: evidence that flutamide restores sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone. J Clin Endocrinol Metab 2000;85:4047–52.

[24] Marshall JC, Eagleson CA, McCartney CR. Hypothalamic dysfunction. Mol Cell Endocrinol 2001;183:29–32.

[25] Edman CD, MacDonald PC. Effect of obesity on conversion of plasma androstendione to estrone in ovulatory and anovulatory young women. Am J Obstet Gynecol 1978;130:456–61.

[26] Dunaif A, Mandeli J, Fluhr H, Dobrjansky A. The impact of obesity and chronic hyperinsulinemia on gonadotropin release and gonadal steroid secretion in the polycystic ovary syndrome. J Clin Endocrinol Metab 1988;66:131–9.

[27] Diamanti-Kandarakis E, Dunaif A. New perspectives in polycystic ovary syndrome. Trends Endocrinol Metab 1996;267–71.

[28] Moran C, Garcia-Hernandez E, Barahona E, Gonzalez S, Bermudez J. Relationship between gonadotropin dissociation in obese and obese and non-obese women with polycystic ovary syndrome. Fertil Steril 2003;80:1466–72.

[29] Adashi EY, Hsuech AJW, Yen SSC. Insulin enhancement of luteinizing hormone and follicle-stimulating hormone release by cultured pituitary cells. Endocrinol 1981;108:1441–9.

[30] Lobo RA, Kletzky OA, Campeau JD, di Zerega GS. Elevated bioactive luteinizing hormone in women with the polycystic ovary syndrome. Fertil Steril 1983;39:674–8.