CLINICAL STUDY

Obesity is the major factor determining an insulin sensitivity and androgen production in women with anovulary cycles

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Abstract

Aim of this study was to test the hypothesis that obesity promotes the insulin-sensitivity and ovarian hyperandrogenism in anovulating women independently of the polycystic ovary syndrome (PCOS).
We examined 80 women of reproductive age (19–38 years, mean 28.5±0.6 years) with anovulary cycles. 45 subjects had PCOS and 35 had chronic anovulation without hormonal and ultrasound criteria of PCOS. The control group consisted of 12 healthy females with normal ovulary menstrual cycle (age 26.4±0.6 years). We evaluated plasma insulin level baselines (I_0); 120 min after oral administration of 75g of glucose (I_{120}), we examined FSH, LH, prolactin, testosterone, 17 OH progesterone and DHEAS and calculated indexes of insulin sensitivity, i.e. FIRI and G/I.
Women with anovulary cycles yielded a significant increase in I_0 ($p<0.01$), I_{120} ($p<0.01$), FIRI ($p<0.01$), FSH, LH (both $p<0.05$) and testosterone ($p<0.01$), and a significantly decrease in G/I ($p<0.01$) in comparison to controls with normal weight. There was a significant correlation between BMI and insulin levels, BMI and FIRI, and between WHR or waist circumference and FIRI, or G/I. The highest levels of insulinemia and the highest degree of insulin resistance were found in obese women (BMI>30 kg/m^2). In the group of obese anovulating women we found a positive correlation between I_0 and testosterone ($p<0.01$). In PCOS group, we found a negative correlation between I_0 and LH ($p<0.01$), and FIRI and LH ($p<0.01$). In the group of obese PCOS women there were significantly higher levels of plasma insulin, and lower insulin sensitivity as compared to lean PCOS patients. However, lean PCOS women were more hyperinsulinemic and insulin resistant than the control group of lean women.
Our results indicate, that obesity is the important factor determinating the insulin sensitivity and hyperinsulinemia in PCOS women. Moreover, the body weight is the major determinant of insulinemia, insulin sensitivity and ovarian hyperandrogenism, independently of PCOS. ***(Tab. 5, Fig. 4, Ref. 23.)***
Key words: obesity, polycystic ovary syndrome, insulin sensitivity, anovulation, menstrual cycle.

The polycystic ovary syndrome (PCOS) and/or obesity are the most common causes of chronic anovulation and menstrual cycle abnormalities. PCOS affects approximately 6 % of women of the reproductive age, and is characterized by chronic anovulation and hyperandrogenism (1, 2). Hyperinsulinemia and/or insulin resistance is a frequent feature of PCOS, and the evidence suggests that it plays a pathogenic role in the development of hyperandrogenism promoting an increase in ovarian androgen production (3).

Obesity has long been recognized as one of the features of PCOS and approximately 33–60 % of PCOS women are obese (4, 5). In addition, overweight and obesity are frequently associated with anovulary cycles and/or amenorrhoea independently of PCOS (6). Obesity appears to increase the circulating androgens production by suppressing the secretion of serum SHBG and gonadotropins. Moreover, its association with hyperinsulinemia and decreased insulin sensitivity has been well estab-

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lished in the past 20 years. Thus, the asssessment of relative contributions of obesity and PCOS to neuroendocrine-metabolic aberrations and their impact on ovarian hyperandrogenism and chronic anovulation are pivotal in the understanding of this complex syndrome.

Several studies have reported hyperandrogenemia and hyperinsulinemia with relatively normal LH in obese women with PCOS, whereas higher LH levels with normal insulinemia are more likely in lean PCOS women (7).

Some authors demostrated that obesity, rather than menstrual cycle pattern determinates insulinemia, lipid profile and blood pressure in aging women with PCOS (8).

However the results in PCOS females in reproductive age are different. According to some authors hyperinsulinemia is a prominent feature of the syndrome which is not solely related to obesity (9), while others demonstrated that obesity is an important factor which has a pathogenetic role in the development of PCOS and hyperinsulinemia leading to hyperandrogenism and anovulation (4, 10).

The aim of this study was to test one of these hypotheses that obesity promotes the insulin resistance development resulting in ovarian hyperandrogenism independently of PCOS, and to establish the most important factor in the development of insulin resistance in chronically anovulating women.

Material and methods

We examined 80 women at the reproductive age (19–38 years, mean 28.5±0.6 years). All of them suffered from anovulary cycles – oligomenorrhoea, amenorrhoea or anovulary sterility. All endocrinopathies potentially causing anovulation (hyperprolactinemia, thyroid diseases, adrenal steroid enzymopaties and ovarian failure) were ruled out by carefull endocrinological evaluation.

45 women had PCOS according to hormonal and/or ultrasound criteria. Other 35 patients had anovulary cycles without clinical, endocrinological and ultrasound signs of PCOS. 60 % of PCOS subjects were hirsute, none had acanthosis nigricans.

Endocrinological features of PCOS included the increased LH levels, normal FSH, LH:FSH ratio >2, and increased testosterone concentration.

Vaginal ultrasonography was performed in all subjects, and PCO was diagnosed in cases with enlarged ovaries with a thickened stroma or with more than 10 cysts of 2–8 mm in diameter.

The control group consisted of 12 healthy females with normal menstrual cycle (age 26.4±0.6 years). Each woman had regular menstrual cycle, and normal ovaries according to ultrasonographic examinations. All of them were lean and had normal progesterone levels indicating the ovulary cycle.

According to BMI, all subjects were divided into three groups: lean (BMI<25 kg/m^2), overweight (BMI 25–30 kg/m^2) and obese (BMI>30 kg/m^2).

Characteristics of the study group depending on BMI are demonstrated in Figure 1.

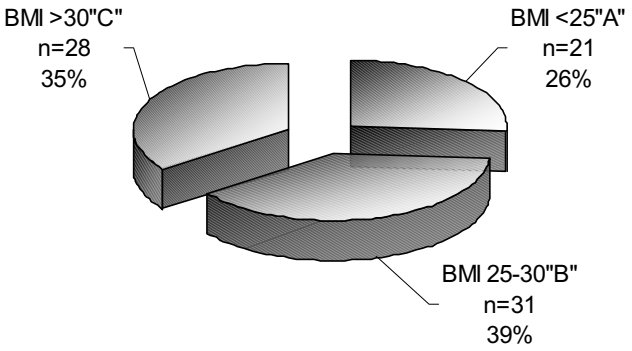

Fig. 1. Distribution of the group of anovulating women (n=80) according to body weight.

Methods

Women were studied in the morning after an overnight fasting. The hormonal evaluation was performed in the follicular phase of the anovulary cycle. Venous blood was collected for measurement of plasma estradiol, FSH, LH, testosterone, glucose and insulin levels.

We performed the standard oral glucose tolerance test i.e. blood samples for evaluation of glucose and plasma insulin were collected 2 hours after oral administration of 75 g of glucose.

Indexes of insulin sensitivity such as FIRI (fasting index of insulin resistance) and G/I (glucose:fasting insulin ratio) were calculated in all women.

FIRI was calculated as plasma glucose x plasma insulin/25 and G/I as fasting glucose/fasting insulin.

Insuline resistance was confirmed when the value of FIRI was higher than 1.0, and G/I was lower than 0.25.

Hormones, such as estradiol, FSH, LH, testosterone, progesterone and prolactin were investigated by routine methods (immunoanalysis), and plasma insulin was evaluated by immunoassay kits.

Statistics

The data are presented as mean±SEM. A statistical analysis was performed using linear regression analysis to assess the correlation between variables, Student's unpaired test and the analysis of variance (ANOVA) to compare the differences between groups.

Results

The values of measured parameters of body weight and fat distribution together with serum hormones are presented in Table 1.

There were significant differences in BMI, WHR and waist circumference in the studied group compared to normal women.

The women with anovulary cycles yielded a significant increase in plasma insulin levels (I_0, I_{120}) when compared to the control group. Moreover, the levels of FSH, LH and testosterone were significantly higher in the group of patients compared to normal subjects. The group of anovulating women had a higher degree of insulin resistance (FIRI and G/I). There were no sig-

Tab. 1. Mean values of evaluated parameters in lean control group (n=12) and group of patients with anovulary cycles (n=80).

Measured parameters	Controls n=12	Anovulating pts n=80	Statistical significance
Age (years)	26.4 ± 5.0	28.5 ± 0.6	NS
BMI (kg/m^2)	20.5 ± 2.6	28.8 ± 0.7	p<0.01
WHR	0.7 ± 0.04	0.79 ± 0.01	p<0.05
Waist circumference (cm)	68 ± 4.4	88.8 ± 2.7	p<0.01
I_0 (μIU/ml)	5.5 ± 2.8	11.1 ± 0.7	p<0.01
I_{120} (μIU/ml)	17.4 ± 13	51.8 ± 5.6	p<0.01
FSH (U/l)	3.3 ± 1.2	5.0 ± 0.4	p<0.05
LH (U/l)	6.1 ± 2.2	10.1 ± 0.7	p<0.05
Testosterone (ngl/ml)	0.44 ± 0.12	1.6 ± 0.3	p<0.01
PRL (ng/ml)	9.6 ± 1.3	14.6 ± 2.8	NS
DHEAS (μg/dl)	198 ± 23	256 ± 17	NS
17 OHP (nmol/l)	1.3 ± 0.2	2.05 ± 0.2	NS
FIRI	0.8 ± 0.3	2.1 ± 0.16	p<0.01
G/I	1.08 ± 0.46	0.65 ± 0.05	p<0.01

BMI — body mass index, WHR — waist to hip ratio, I_0 — basal insulin, I_{120} — stimulated insulin (post 75 g glucose load), DHEAS — dehydroepiandrosterone - sulphate, 17 OHP — 17-hydroxprogesterone, FIRI — fasting index of insulin resistance, G/I — serum glucose during fasting to serum insulin during fasting ratio

nificant differences in levels of prolactin, dehydroepiandrosterone sulphate (DHEAS) and 17 hydroxyprogesterone (17 OHP) between the two studied groups.

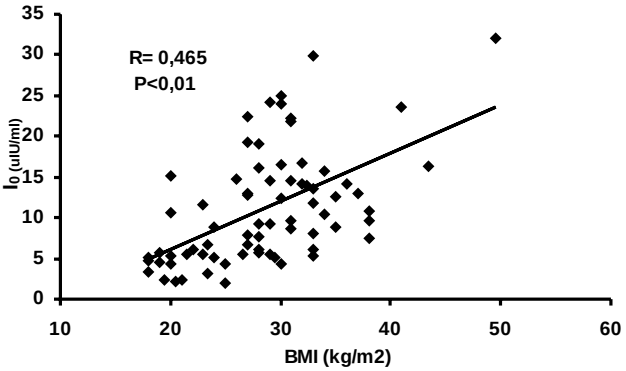

Fig. 2. Correlation between I0 and BMI in anovulating women (n=80).

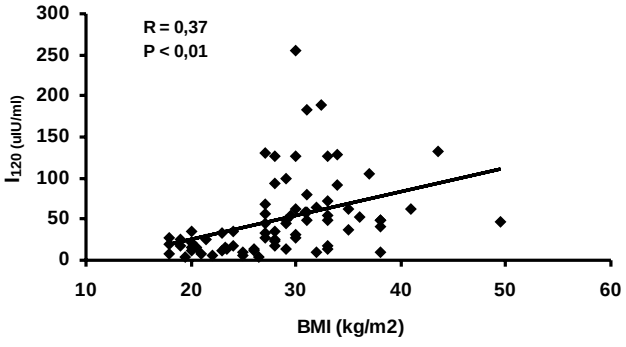

Fig. 3. Correlation between I120 and BMI in anovulating women (n=80).

There was a significant correlation between I_0 and BMI (Fig. 2), I_{120} and BMI (Fig. 3), but no correlation between LH or testosterone and BMI in the group of patients. Moreover, we found a positive correlation between BMI and FIRI (r=0.466, p<0.01), and WHR and FIRI (r=0.425, p<0.05). Both indexes of insulin sensitivity, i.e. FIRI (r=0.502, p<0.01) and G/I (r=-0.509, p<0.01) were in significant correlation with waist circumference.

The mean values of measured parameters in the studied group are presented according to BMI in Table 2.

A significant increase in insulinemia and insulin resistance were found in correlation with the body weight i.e. obese women had highest levels of I_0 and I_{120} and highest degree of insulin resistance. The highest values of LH and testosterone were observed in patients with normal weight, however the differences between the three groups were not significant.

There was a positive correlation between insulinemia and testosterone (r=0.67, p<0.01) in obese women (BMI>30 kg/m^2).

The mean values of measured parameters in women with and without PCO are demonstrated in Table 3.

BMI was mildly but significantly increased in the group without PCOS. However, we were not able to demonstrate the differences in I_0 and I_{120}, and insulin sensitivity between non PCOS and PCOS groups. We only found a significantly increased LH and testosterone levels in PCOS women.

There was a positive correlation between BMI and insulinemia (I_0 and I_{120}), negative correlation between insulinemia and LH (r=-0.429, p<0.01) in PCOS group. Moreover, LH was in negative correlation with FIRI (r=-0.467, p<0.01) (Fig. 4) and FSH with a mild but statistically significant correlation with FIRI (r=-0.322, p<0.05).

The Table 4 demonstrates the values of measured parameters in PCOS group with normal weight (BMI<27) and PCOS group overweight and obesity (BMI>27).

There was found a significant difference in basal and stimulated insulin levels i.e. insulin values, as well as FIRI and G/I

Tab.2. Mean values of evaluated parameters in three groups of anovulating women according to body weight.

BMI kg/m^2	<25 n=21	25-30 n=31	>30 n=28	Statistical sigficance
BMI (kg/m^2)	20.9 ± 0.5	27.9 ± 0.3	34.9 ± 0.81	p<0.01
WHR	0.75 ± 0.02	0.81 ± 0.02	0.82 ± 0.02	p<0.01
Waist (cm)	67.8 ± 2.6	92 ± 2.9	98.8 ± 2.9	p<0.01
I_0 (µIU/ml)	6.1 ± 0.8	12.0 ± 1.4	14.3 ± 1.3	p<0.01
I_{120} (µIU/ml)	18.6 ± 2.2	55 ± 10.6	69.9 ± 9.1	p<0.01
FSH (U/l)	5.1 ± 0.8	6.1 ± 1.0	4.3 ± 0.4	NS
LH (U/l)	12.4 ± 1.2	9.4 ± 1.1	9.1 ± 1.4	NS
Testosterone (ngl/ml)	2.5 ± 1.1	1.2 ± 0.2	1.4 ± 0.3	NS
PRL (ng/ml)	19.3 ± 6.6	12.6 ± 3.7	14.1 ± 5.7	NS
DHEAS (µg/dl)	241.5 ± 43	274.9 ± 26	221.8 ± 18.9	NS
17 OHP (nmol/l)	1.7 ± 0.5	1.9 ± 0.4	2.1 ± 0.7	NS
FIRI	1.4 ± 0.2	2.2 ± 0.3	2.8 ± 0.3	p<0.01
G/I	0.99 ± 0.1	0.6 ± 0.06	0.49 ± 0.08	p<0.01

Tab. 3. Mean values of evaluated parameters in group of anovulating women without PCOS (nPCOS, n=35) and group with PCOS (n=45).

Measured parameters	nPCOS n=35	PCOS n=45	Statistical significance
Age (years)	29.1 ± 1	28.1 ± 0.7	NS
BMI (kg/m^2)	30.1 ± 1.1	27.3 ± 0.9	p<0.5
WHR	0.8 ± 0.01	0.78 ± 0.02	NS
Waist (cm)	88.8 ± 3.6	88.8 ± 3.9	NS
I_0 (µIU/ml)	11.3 ± 1.4	10.9 ± 0.9	NS
I_{120} (µIU/ml)	46.2 ± 7.4	55.9 ± 8.2	NS
FSH (U/l)	5.8 ± 1.1	4.7 ± 0.4	NS
LH (U/l)	7.8 ± 1.2	11.2 ± 0.9	p<0.05
Testosterone (ngl/ml)	1.1 ± 0.2	1.8 ± 0.4	p<0.05
PRL (ng/ml)	15.1 ± 5.3	14.4 ± 3.4	NS
DHEAS (µg/dl)	258 ± 15.5	255 ± 25	NS
17 OHP (nmol/l)	1.8 ± 0.5	2.2 ± 0.4	NS
FIRI	2.1 ± 0.3	2.2 ± 0.2	NS
G/I	0.75 ± 0.1	0.59 ± 0.06	NS

were significantly lower in lean PCOS than in obese PCOS women. Obese PCOS women had a higher degree of insulin resistance than the lean group of PCOS females.

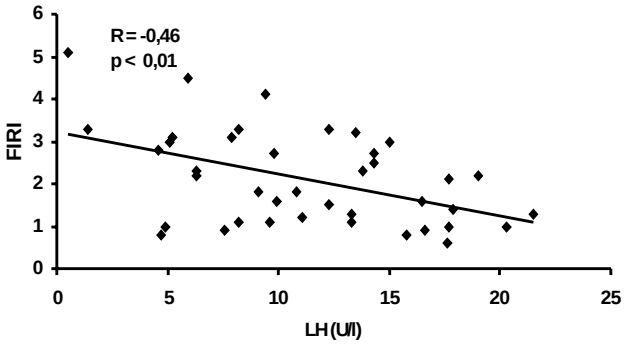

Fig. 4. Correlation between LH and FIRI in group of women with PCOS (n=45).

There were significantly lower insulin levels in healthy lean women and a significantly decreased insulin sensitivity in normal weight PCOS subjects (Tab. 5).

Discussion

In this study we looked for the differences between PCOS and non PCOS anovulating women and for the participation of body weight in insulin resistance and hyperandrogenemia in women with chronic anovulation.

In the group of 80 anovulating women we found a significant increase in BMI indicating a higher prevalence of overweight, and obesity in subjects with anovulary cycles. Only 26 % of women had normal weight. It is in agreement with previous studies demonstrating a 4-fold more frequent prevalence of obesity in females with menstrual cycle disturbances. In addition, amenorrhoic women have been found to have obesity in approximately 45 % (11, 12). On the contrary, menstrual irregularities were reported 3.1-fold more frequently in obese than in lean women (6).

Tab. 4. Mean values of measured parameters in lean PCOS group with BMI<27 kg/m² (n=21) and PCOS group with BMI>27 kg/m² (n=24).

Measured parameters	BMI<27kg/m² n=21	BMI>27kg/m² n=24	Statistical significance
Age (years)	26.9 ± 0.9	28.4 ± 0.9	NS
BMI (kg/m²)	22.3 ± 0.7	31.8 ± 0.7	p<0.01
WHR	0.75 ± 0.02	0.83 ± 0.02	p<0.05
Waist (cm)	74.9 ± 3.9	101.3 ± 3.3	p<0.01
I_0 (μIU/ml)	7.9 ± 1.1	13.3 ± 1.3	p<0.01
I_{120} (μIU/ml)	21.9 ± 3.4	83.9 ± 12	p<0.01
FSH (U/l)	4.9 ± 0.7	4.4 ± 0.4	NS
LH (U/l)	12.4 ± 1.1	10.3 ± 1.2	NS
Testosterone (ngl/ml)	2.2 ± 0.9	1.3 ± 0.2	NS
PRL (ng/ml)	17.9 ± 5.6	11.0 ± 3.6	p<0.05
DHEAS (μg/dl)	241.5 ± 43	262 ± 32	NS
17 OHP (nmol/l)	1.7 ± 0.5	2.6 ± 0.7	NS
FIRI	1.9 ± 0.3	2.4 ± 0.2	p<0.01
G/I	0.87 ± 0.12	0.43 ± 0.05	p<0.01

Tab. 5. Mean values of measured parameters in lean controls (n=12) and PCOS women with normal weight (n=21).

Measured parameters	Control group n=12	BMI<27kg/m² n=21	Statistical significance
Age (years)	26.4 ± 5.0	26.9 ± 0.9	NS
BMI (kg/m²)	20.5 ± 2.6	22.3 ± 0.7	NS
WHR	0.7 ± 0.04	0.75 ± 0.02	NS
Waist (cm)	68 ± 4.4	74.9 ± 3.9	p<0.01
I_0 (μIU/ml)	5.5 ± 2.8	7.9 ± 1.1	p<0.01
I_{120} (μIU/ml)	17.4 ± 13	21.9 ± 3.4	p<0.01
FSH (U/l)	3.3 ± 1.2	4.9 ± 0.7	NS
LH (U/l)	6.1 ± 2.2	12.4 ± 1.1	p<0.05
Testosterone (ngl/ml)	0.44 ± 0.12	2.2 ± 0.9	p<0.01
FIRI	0.8 ± 0.3	1.9 ± 0.3	p<0.01
G/I	1.08 ± 0.46	0.87 ± 0.12	p<0.01

None of our patients had diabetes mellitus, 8 i.e. 10 % had impaired glucose tolerance. In previous studies, 10–20 % of obese subjects with PCOS have been found to have diabetes mellitus (13, 14) and 35 % of obese subjects with PCOS have been shown to have impaired glucose tolerance (14). Recently it has been demonstrated that 82 % of premenopausal women with type 2 diabetes have polycystic ovaries revealed by ultrasound examination (15).

In consistency with previous studies, we found a positive correlation between BMI and insulinemia and a correlation between BMI and insulin sensitivity. However we did not show the relationship between insulinemia and testosterone levels which appears to be the result of heterogenity of the studied group. Similarly, the same results were reported by Kiddy et al but in a homogenous group of PCOS women (16). Our study group consisted of PCOS and non PCOS women. Therefore, these findings yield an explanation that hyperinsulinemia stimulates ovarian androgen production in both PCO and non PCO.

There were 57 % of patients with and 43 % of patients without PCOS in our study group. Non PCOS subjects had mildly but significantly higher BMI, lower LH and testosterone levels than those with PCOS.

There are some different reports about insulin sensitivity and PCOS. Some authors found significantly higher levels of insulinemia, while others demonstrated only decreased insulin sensitivity without the demonstration of hyperinsulinemia (3, 23, 17, 10). Marsden et al documented an impaired tissue insulin sensitivity in obese PCOS as well as in lean PCOS women and showed that the impaired insuline sensitivity appears to be independent of obesity (18). However any degree of obesity has a powerfull effect in decreasing insuline sensitivity.

This study showed an increase in the levels of insulinemia and a higher degree of insulin resistance in lean PCOS compared to lean controls. Moreover, Robinson et al demonstrated a lower insulin sensitivity in lean patients with oligo- or amenorrhoea compared to lean PCOS women with regular menstrual cycle or lean controls (19). Morales et al reffered that insulin sensitivity was reduced by 50 % in lean PCOS compared to that in lean controls. There was a further decrease in obese controls and a 2-fold greater reduction in obese PCOS than obese controls, sug-

gesting that insulin resistance is a common lesion in PCOS and that obesity contributes an additional component to hyperinsulinemia and insulin resistance in obese PCOS (4).

The highest degree of insulin resistance in this study was found in PCOS women with overweight or obesity. In non PCOS subjects, the body weight is the most important factor in determining the insulin sensitivity and androgen production, the fact of which was demonstrated in our group of obese non PCOS women.

Hyperinsulinemia is a prominent feature of the PCOS syndrome which is not solely related to obesity and appears to play a key role in the ovarian hyperandrogenism and glucose intolerance. The fact that obesity is related to the menstrual cycle pattern was proven by the restoration of ovulation and regular menstrual cycles by dietary treatment and weight loss in obese PCOS patients (20, 16). Recently, Huber-Buchholz et al reported that lifestyle modifications in 18 obese anovulary PCOS patients resulted in ovulation in approximately half of the patients (21).

Most important differences in the studied group appear to be weight-dependent. In this study a significant increase of insulinemia and decrease of insulin sensitivity were foud together with an elevation of BMI. However, we were not able to demonstrate the differences in FSH, LH and prolactinemia in three groups according to body weight. Dunaif et al demonstrated a negative correlation between BMI and LH in obese females. In our group of obese patients we found only mildly but insignificantly decreased LH levels. It may partially indicate a relative participation of hypothalamic dysfunction on chronic anovulation. The positive correlation between insulinemia and testosteronemia in obese women is in agreement with some authors indicating that obesity itself is a disease entity with hyperinsulinemia and insulin resistance, and it appears to have independent effects on androgen ovarian secretion (13, 4).

Although this study demonstrates an insulin resistance in lean PCOS women, obesity is an important factor, which potentiates or modifies insulin sensitivity in patients with anovulary cycles independently of PCOS. According to Cibula et al, obesity determinates also the lipid profile and hyperlipoproteinemia as they did not show the lipid profile differencies in PCOS women and weight-matched control subjects (22).

There was found a negative correlation between basal insulinemia and LH. This finding is in agreement with previous studies demonstrating higher levels of LH in lean PCOS subjects (20, 18) although other workers demonstrated no difference in LH between lean and obese PCOS (13, 16). These differences between studies may reflect differences in the selection of patients. It is possible that lean patients in these studies had a more pronounced or more severe form of PCOS than the obese group. Additionally, the fact of pulsatile secretion of LH, is well known, thus a single level cannot reflect the real secretion of LH. Another possibility is that obese women had lower levels of SHBG resulting in increased free fractions of plasma ovarian hormones which have a more pronounced suppressing efect on gonadotropin secretion.

We did not detect any correlation between testosterone and insulinemia in the large studied group, however a positive correlation was demonstrated only in the group of obese females. This finding supports our previous hypothesis that obesity is more important factor for androgen ovarian production than PCOS itself.

In conclusion, we demonstrated that the body weight is the most important factor determining the insulin sensitivity and ovarian hyperandrogenism not only in PCOS women but also in anovulating women without PCOS.

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