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Clinical, Hormonal and Metabolic Characteristics of Polycystic Ovary Syndrome among Obese and Nonobese Women in the Croatian Population

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A B S T R A C T

Obesity has a deteriorating impact on women with PCOS, although prevalence and the impact of specific traits of PCOS remain inconstant in different populations. Therefore, the aim of this study was to explore the differences in clinical, hormonal and metabolic features between obese and nonobese Croatian women diagnosed as having PCOS according to Rotterdam consensus criteria. The study included 74 obese and 208 nonobese women with PCOS. Clinical, biochemical and metabolic variables were compared among those PCOS subgroups. Obese subjects with PCOS had a higher risk of developing oligo-amenorrhea (OR 3.7; 95% CI, 1.1–12.5) and lower risk for developing hirsutism and acne (OR 0.2; 95% CI, 0.1–0.3 and OR 0.8; 95% CI 0.5–1.4, respectively). Obese PCOS subjects also had a higher risk of developing hyperandrogenemia (OR 2.5; CI 95% 0.9–6.7), insulin resistance (OR 4.5; CI 95%, 2.6–7.9), hypercholesterolemia (OR 5.0, CI 95% 2.5–10.2), hypertriglyceridemia (OR 5.2; 95% CI, 2.9–9.2) as well as elevated serum CRP levels (OR 4.1; 95% CI 1.4–12.2) compared to nonobese PCOS women. In conclusion, nonobese Croatian women with PCOS are more inclined to cosmetic problems associated with PCOS then metabolic ones. This is the first study to report the impact of obesity on acne and irregular menses as a study outcome. Obesity deteriorates menstrual regularity, insulin sensitivity and lipid profile in Croatian women with PCOS; therefore one of the fundamental treatment strategies of PCOS should be obesity prevention.

***Key words**: PCOS, obesity, hyperandrogenism, insulin resistance, dyslipidemia*

Introduction

The polycystic ovary syndrome (PCOS) was first recognized by Stein and Leventhal in 1935 as a triad of amenorrhea, obesity and hirsutism[1]. Since then, the PCOS has gained clinical and public health importance as it is very common, affecting up to one in five women of reproductive age[2]. The importance of the PCOS is not only in its numerosity, but also in its substantial and diverse clinical consequences including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life)[3], which make this syndrome a major health risk in reproductive age women[4]. It is estimated that the economic burden of the PCOS in the USA is about 4 billion dollars per year, making the PCOS not only a health, but also a significant economic burden[5].

Obesity and insulin resistance often accompany PCOS, although those parameters are not considered necessary to perform diagnosis. Unitly recently health care providers concentrated on skin and reproductive complications of the PCOS, not beening much aware of obesity and its profound effect on clinical, hormonal and metabolic features of PCOS. There are great ethnic differences in the frequency of obesity among women with the PCOS that can be explained with diverse gene-gene and gene-environmental interaction in distinct population[6]. However, the exact prevalence of obesity in PCOS patients is not known due to the lack of representative

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population data. The US study reported that the prevalence of obesity in women with PCOS has increased from 51% in 1987–1990 to 74% in 2000–2002[7]. Controversy, a study in Italy reported that only 14% of women with PCOS were obese[8]. We recently published that 23.8% of Croatian PCOS have excess weight[9]. The effect of being obese on clinical, hormonal, and metabolic aspects of PCOS is inconsistent from the existing literature, and differ among various ethnical groups.

Therefore, the aim of the study was to explore the difference in clinical, hormonal and metabolic features between obese and nonobese Croatian women diagnosed as having PCOS.

Subjects and Methods

Subjects

In total, 282 women fulfilling the criteria for PCOS (average age, 27.0±5.8 years; range, 18–38 years) were enrolled in the study. The adolescent girls were not included because there is no agreement concerning how to diagnose PCOS in adolescence considering that many features characteristic to PCOS may be the result of normal evolution from girls to adulthood[10]. Women older than age 38 were also excluded considering the well-known decline of androgens with age[11]. All studied subjects were enrolled during their treatment at the Division of Human Reproduction and Gynecologic Endocrinology of the Department of Obstetrics and Gynecology, Clinic for Women's diseases, Zagreb University Hospital Centre, Croatia between October 2007 and January 2012. None of the patients had diabetes, hypertension and cardiovascular disease. Any medications known to affect sex hormones or carbohydrate metabolism were discontinued at least six months prior to enrolment.

The diagnosis of PCOS was based on the Rotterdam consensus criteria[2]. Menstrual cycles were defined as: a) regular (menstrual interval of 21 to 35 days with normal progesterone levels >22.5 nmol/L on 21.–24. day of the cycle, determined in two consecutive menstrual cycles); b) irregular – oligomenorrhea or amenorrhea (intermenstrual interval of 36 day – 6 months or 6 months or longer, respectively). Hirsutism was assessed by a single investigator and defined by a Ferriman-Gallwey index score >8 (FG>8)[12]. Hyperandrogenemia was defined as a serum level of total testosterone (TT) higher than 2.0 nmol/L or free testosterone (FT) greater than 26 pmol/L or androstendione (A) greater than 12 nmol/L or dehydroepiandrosterone sulphate (DHEAS) greater than 10 μmol/L. Polycystic ovaries (PCO) were defined by the presence of 12 or more follicles measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL) by transvaginal ultrasound (TVUS)[13]. To avoid the inter-observational variations the same examiner performed all the ultrasonographic exams. Body mass index was calculated as weight in kilograms divided by square of height in meters. Obesity was defined as BMI >25 kg/m^2. Other endocrinopaties and related disorders were excluded by measuring basal serum 17-hydroxyprogesterone (17-OHP), prolactin (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulated hormone (TSH) levels. All the patients were recruited in the early follicular phase of the spontaneous or progesterone induced menstrual cycle (day 3–5) when blood samples for biochemical and hormonal analysis was drawn and TVUS was performed.

The University of Zagreb Medical School Ethics Committee approved the study protocol No. 04–1116–2006. Informed written consent was obtained from all women enrolled in the study.

Biochemical analysis

Serum LH, FSH, TSH, PRL, and TT concentrations were determined by chemiluminescent immunometric assays using LH-Vitros, FSH-Vitros, TSH-Vitros, Prolactine-Vitros and Testosterone-Vitros, respectively (Ortho Clinical Diagnostics, Johnson&Johnson, Rochester, NY, USA). Serum SHBG, DHEAS and A levels were measured using chemiluminescent immunometric assays (SHBG-Immulite, DHEAS-Immulite and Androstendione-Immulite, respectively) (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). The concentration of 17-OHP was determined by a solid phase enzyme-linked immunosorbent assay (ELISA) based on the principle of the competitive binding (DRG-diagnostics, Marburg, Germany). The intra–assay and inter-assay coefficients of variation ranged between 1.5 and 7.9 %. The plasma glucose level (Glc) was determined by the UV-photometric hexokinase method and the serum insulin (Ins) level by chemiluminescent immunometric assay using Insulin – Immulite, respectively (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). Total cholesterol and triglycerides were measured by standard routine enzymatic photometric assay. HDL cholesterol was determined after precipitation of VLDL and LDL with dextran sulphate and $MgCl_2$. C-reactive protein (CRP) was determined by a particle enhanced turbidimetric immunoassay (PETIA) technique with sensitivity of the test 0.1 mg/L. Free testosterone (FT) was calculated from TT and SHBG as previously described[14] using a web-based calculator (http://www.issam.ch/freetesto.htm). Insulin resistance (IR) was quantified using the homeostatic model assessment of IR (HOMA–IR) (fasting insulin (mU/L) x fasting glucose (mmol/L)) / 22.5)[15]. Insulin resistance was defined by HOMA-IR of 2.5 or higher based on original HOMA research[15]. The LDL cholesterol concentration was calculated mathematically from the total cholesterol, triglyceride and HDL cholesterol concentrations using the Friedewald's formula[16]: LDL cholesterol (mmol/L) = total cholesterol (mmol/L) – HDL cholesterol (mmol/L) – triglycerides (mmol/L) / 2.2. All the laboratory analysis was performed at the Department of Clinical Biochemistry of Clinical Hospital Center Zagreb, Croatia.

Statistical analysis

Data are presented as $\overline{X}$±SD or percentage unless otherwise indicated. We used the independent Student's T-test to compare the values of the means between obese

and nonobese PCOS patients. Differences in categorical characteristics between obese and nonobese PCOS patients were assessed using χ^2-test. Logistic regression analyses were used to estimate the odds ratios (ORs) and 95% confidence intervals (95%CIs). All statistical analyses were done using the SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

The comparison of clinical, hormonal and metabolic features between obese and nonobese PCOS subjects are summarized in Tables 1 and 2.

Obese subjects with PCOS had a higher risk of developing oligo-amenorrhea (95.9% *vs.* 86.5%; OR 3.7; 95% CI, 1.1–12.5, p<0.026) while the risk for developing hirsutism was lower than in nonobese subjects (44.6% *vs.* 80.8%; OR 0.2; 95% CI, 0.1–0.3. p<0.01). Obese subjects also presented with lower incidence of acne than nonobese PCOS patients (48.6% *vs.* 53.8%; OR 0.8; 95% CI 0.5–1.4, p<0.442) although the difference was not significant. There was no difference in the prevalence of PCO appearance on ultrasound between both examined groups (Table 1). OR for the incidence of some clinical and biochemical manifestations in obese versus nonobese women with PCOS are presented on Figure 1.

Obese women with PCOS had significantly higher serum levels of free T (50.2±19.1 *vs.* 39.8±14.4, p<0.001) and significantly lower levels of SHBG (32.7±15.1 *vs.* 43.4±19.7, p<0.001) than nonobese women with PCOS (Table 2). Moreover, obese PCOS subjects had a higher risk of developing hyperandrogenemia (93.2% *vs.* 84.6%; OR 2.5; CI 95% 0.9–6.7) as it is presented on Figure 1.

The overall prevalence of insulin resistance was observed in 31.6%. of PCOS patients. Elevated serum levels of total cholesterol was found in 14.2% of PCOS patients while 37.6% of patients had elevated serum levels of triglycerides. Decreased serum levels of HDL were found in only 2.5 % and elevated serum levels of LDL and CRP in 12.4% and 5%, respectively.

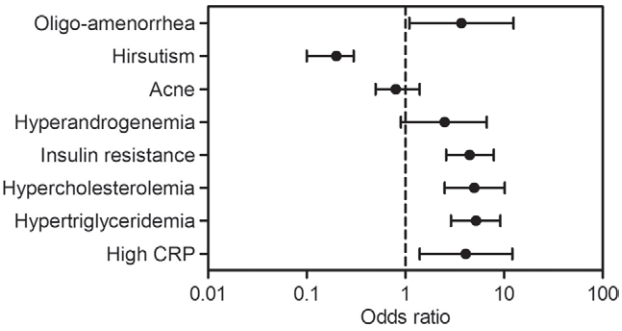

Fig. 1. Odds ratio for the incidence of some clinical manifestations in obese versus nonobese women with PCOS. CRP – C-reactive protein.

Obese PCOS patients had significantly higher serum levels of HOMA-IR compared to nonobese PCOS (3.4± 2.1 *vs.* 2.0±1.2, p<0.001) as well as elevated serum levels of total cholesterol (4.8±0.3 *vs.* 4.5±0.4, p<0.001), triglycerides (1.8±0.3 *vs.* 1.3±0.4, p<0.001), LDL cholesterol (2.6±0.4 *vs.* 2.4±0.5, p<0.001) and CRP (2.3±0.6 *vs.* 2.1±0.6, p<0.002) (Table 2.). Moreover, obese women with PCOS had a higher risk of developing insulin resistance (56.8% *vs.* 22.6%; OR 4.5; CI 95%, 2.6–7.9), hypercholesterolemia (31.1% *vs.* 8.2%; OR 5.0, CI 95% 2.5–10.2), hypertriglyceridemia (66.2% *vs.* 27.4%; OR 5.2; 95% CI, 2.9–9.2) as well as elevated serum CRP levels (10.8% *vs.* 2.9%; OR 4.1; 95% CI 1.4–12.2) (Figure 1).

Discussion and Conclusion

In Stein and Leventhal's original description[1], obesity, together with hirsutism and infertility, represents one of the characteristics of the PCOS. Since then, although obesity has an important pathophysiological impact on PCOS, and obese PCOS women are described by aggravated endocrine and metabolic profiles and poorer fertility, the specific obesity-PCOS phenotype has not been acknowledged. As the obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility it is not suprising that its prevalence of obesity in PCOS patients vary in distinct population. Futhermore, published

TABLE 1
CLINICAL CHARACTERISTICS OF PCOS PATIENTS

	Total	Nonobese	Obese	p value[1]
No. of cases	282	208	74	
Age (years)	27.0±5.8	27.0±5.8	27.1±5.9	0.900
BMI (kg/m^2)	24.6±4.9	22.4±1.8	31.0±5.4	<0.001
Oligo-amenorrhea (%)	89.0	86.5	95.9	0.026
Hirsutism (%)	71.3	80.8	44.6	<0.001
Acne (%)	52.5	53.8	48.6	0.442
US findings of PCO (%)	96.5	97.1	94.6	0.314

BMI: body mass index, US: ultrasound, PCO: polycystic ovaries.
[1] Students' t-test was used for continuous and χ^2-test for categorical variables

TABLE 2
HORMONAL AND METABOLIC CHARACTERISTICS OF PCOS PATIENTS

	Total	Nonobese	Obese	p value[1]
No. of cases (%)	282	208	74	
FSH (IU/L)	3.6±1.2	3.7±1.2	3.4±1.1	0.067
LH (IU/L)	8.9±4.4	9.9±4.7	6.3±2.2	<0.001
TT (nmol/L)	2.4±0.5	2.3±0.4	2.5±0.8	0.067
FT (pmol/L)	42.5±16.4	39.8±14.4	50.2±19.1	<0.001
FT >26.0 (pmol/L) (%)	86.9	84.6	93.2	0.059
A (nmol/L)	11.4±4.9	11.6±5.1	10.8±4.2	0.180
DHEA-S (μmol/L)	6.7±2.8	6.6±2.7	7.1±3.0	0.239
SHBG (nmol/L)	40.6±19.1	43.4±19.7	32.7±15.1	<0.001
Glucose (mmol/L)	4.4±0.5	4.4±0.5	4.5±0.5	0.010
Insulin (mIU/L)	11.8±7.8	10.1±6.0	16.9±9.8	<0.001
HOMA-IR	2.4±1.6	2.0±1.2	3.4±2.1	<0.001
HOMA-IR >2.5 (%)	31.6	22.6	56.8	<0.001
Total cholesterol (mmol/L)	4.6±0.4	4.5±0.4	4.8±0.3	<0.001
Total cholesterol >5 mmol/L (%)	14.2	8.2	31.1	<0.001
HDL cholesterol (mmol/L)	1.5±0.2	1.5±0.2	1.4±0.2	<0.001
HDL cholesterol <1.2 mmol/L (%)	2.5	1.9	4.1	0.312
LDL cholesterol (mmol/L)	2.5±0.4	2.4±0.5	2.6±0.4	<0.001
LDL cholesterol >3 mmol/L (%)	12.4	11.1	16.2	0.248
Triglycerides (mmol/L)	1.4±0.3	1.3±0.4	1.8±0.3	<0.001
Triglycerides >1.7 mmol/L (%)	37.6	27.4	66.2	<0.001
CRP (mg/L)	2.1±0.6	2.1±0.6	2.3±0.6	0.002
CRP >3 mg/L (%)	5	2.9	10.8	0.007

FSH: follicle stimulating hormone, LH: luteinizing hormone, TT: total testosterone, FT: free testosterone, DHEAS: dehydroepiandrosterone sulphate, SHBG: sex hormone binding globulin, HOMA-IR: homeostatic model assessment of insulin resistance, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CRP: C-reactive protein

[1] Students' t-test was used for continuous and χ^2-test for categorical variables

studies have not been in consensus on whether excess BMI would have a significant impact on reproductive and metabolic features of PCOS.

In the present study we evaluated the difference in the clinical, hormonal and metabolic features between obese and nonobese women with PCOS. To our knowledge this is the first study to examine the impact of obesity on clinical and metabolic traits in the Croatian population with PCOS.

It has been proposed that obesity is associated with a greater prevalence of menstrual irregularities[10], although no studies reported irregular menses as outcomes. We found that obese women have a higher risk of developing oligo-amenorrhea (OR 3.7; 95% CI, 1.1–12.5). This is possibly the consequence of additional disturbance of endocrine and metabolic profile associated with obesity in PCOS patients[17], which was also observed in our study.

Only a few studies investigated the effect of body weight on the prevalence of hirsutism using Ferriman-Gallwey scores but found no significant association[6,18–20] Obese PCOS patients present with lower serum SHBG levels and therefore higher free T levels in contrast to nonobese PCOS patients[17]. This was also observed in our study. Consequently, it would be expected to find more severe clinical signs of hyperandrogenism in obese women with PCOS. In contrast, we found that hirsutism occurred less frequently in obese than in nonobese PCOS group (44.6% *vs.* 80.8%, p<0.001). This finding could be explained by the fact that adipose tissue increases the aromatase activity, the enzyme that converts testosterone to estradiol. Aromatase is also present in the sebaceous glands so it may play a »detoxifying« role by removing excess androgens[21]. No previous studies reported acne as study outcome. We found that obese PCOS patients tend to have lower frequency of acne than nonobese but this finding was not significantly different between the groups studied (48.6% *vs.* 53.8%, p=0.442). This is consistent with the agreement that acne is not commonly associated with hyperandrogenism[17]. Moreover, the presence of acne is known to be associated with the number of androgens receptors within the pilosebaceous unit as well as on 5α-reductase activity, the enzyme that converts testosterone to dihydrotestosterone (DHT)[22].

It is well established that obese PCOS women present with greater insulin resistance[23,24] which is in agreement with our findings. The overall incidence of insulin resistance observed in our study was lower than previously reported in other populations of PCOS patients[23,24]. This could be related to genetic factors that modulate sensitivity to insulin as well as environmental factors[25]. Ranilovic et al. reported that Croatian adults have a high level of similarity of eating habits with Italians, practicing cardio- protective Mediterranean diet, which could contribute to lower insulin resistance observed[26].

We found that the obese women with PCOS present with higher levels of LDL, triglyceride and total cholesterol as well as lower levels of HDL than nonobese which is concurrent with the conclusions of the Amsterdam ESHRE /ASRM 3rd consensus and recently published meta analysis that obesity is associated with poorer metabolic health in PCOS[17,27]. Additionally it is recognized that insuline resistance exaggerates dislypidemia[28,29]. Although the overall incidence of insulin resistance was low in our group of PCOS patients (31.6%) we found high incidence of hypertriglyceridemia in both studied groups (overall 37.6%, obese 66.2% and nonobese 27.4%). Elevated serum levels of triglycerides that we observed are most likely the result of concurrent hyperandrogenemia since androgens stimulate the release of free fatty acids into circulation[29]. Moreover, increased free fatty acids in the liver stimulate the secretion of VLDL thus increasing serum triglyceride levels[29]. Chapman et al. reported increased early risk for cardiovascular disease in patients experiencing remote hypertriglyceridemia[29].

Further more, PCOS is belived to be a proinflamatory state aggravated with inflammatory factors produced from the fat tissue[30]. The recently published metaanalysis by Escobar Moreale et al. indicated that elevated CRP is a circulating marker of the proinflammatory state in PCOS independently of obesity although the degree of elevation in CRP levels was much greater when obesity is present[31]. Concurrent with their findings obese PCOS patients in our studied group presented with higher serum CRP levels compared to nonobese PCOS (2.3 ± 0.6 *vs.* 2.1 ± 0.6 $p= 0.002$). It has been proposed that CRP levels of <1, 1 to 3, and >3 mg/l correspond to low-, moderate-, and high-risk groups for future cardiovascular events[32]. Although overall incidence of elevated serum CRP levels above 3 mg/l was low in our study, obese women with PCOS had a higher risk for eleveated serum CRP compared to nonobese PCOS therefore they may represent a high risk group for future adverse cardiovascular events.

In conclusion we can state that nonobese Croatian women with PCOS are more inclined to cosmetic problems associated with PCOS than metabolic ones. This study observed that obesity deteriorates menstrual regularity, insulin sensitivity and lipid profile therefore one of the fundamental treatment strategies of PCOS should be obesity prevention. Considering there is growing prevalence of obesity in Croatia[33–37] as well as rising in childhood obesity[38] we could expect more pronounced metabolic consequences of PCOS in following years.

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KLINIČKE, HORMONSKE I METABOLIČKE KARAKTERISTIKE PCOS PACIJENTICA U HRVATSKOJ U OVISNOSTI O TJELESNOJ TEŽINI

S A Ž E T A K

Pretilost ima negativan utjecaj na žene s PCOS-om. Istraživanja o učestalost i utjecaju pretilosti na specifične simptome PCOS daju nedosljedne rezultate. Do sada nisu objavljene studije kojima je utjecaj debljine kod pacijentica s PCOS na redovitost menstruacija i akne bio krajni ishod. Cilj ovog rada bio je istražiti razlike u kliničkim, metaboličkim i hormonskim značajkama između pacijentica sa sindromom policističnih jajnika (PCOS) pretjerane i normalne tjelesne mase kod kojih je dijagnoza postavljena prema Rotterdamskim kriterijima. U istraživanje je uključeno 74 PCOS pacijentice pretjerane i 208 PCOS pacijentice normalne tjelesne mase. Uspoređivane su njihove kliničke, metaboličke i hormonske značajke. Zabilježili smo da PCOS pacijentice sa pretjeranom tjelesnom masom imaju viši rizik za razvoj oligo-amenoreje (OR 3,7; 95% CI, 1,1–12,5) te niži rizik za pojavu hirzutizma i akni (OR 0,2; 95% CI, 0,1–0,3 i OR 0,8; 95% CI 0,5–1,4). U skupini PCOS pacijentica sa pretjeranom tjelesnom masom također je zabilježen viši rizik za nastanak hiperandrogenemije (OR 2,5; CI 95% 0,9–6,7), inzulinske rezistencije (OR 4,5; CI 95%, 2,6–7,9), hiperkolesterolemije (OR 5,0, CI 95% 2,5–10,2), hipertriglicidemije (OR 5,2; 95% CI, 2,9–9,2) kao i povišenih vrijednosti C-reaktivnog proteina (CRP) u serumu (OR 4,1; 95% CI 1,4–12,2), u usporedbi s PCOS pacijenticama normalne tjelesne mase. U zaključku, PCOS pacijentice normalne tjelesne mase u Hrvatskoj sklonije su kozmetičkim značajkama PCOS-a u odnosu na metaboličke. Ovo istraživanje potvrđuje da pretjerana tjelesna masa pogoršava poremećaje ciklusa, osjetljivost na inzulin i lipidni profil kod PCOS pacijentica stoga prevencija pretjerane tjelesne mase mora biti jedna od temeljnih strategija liječenja PCOS-a.