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Characteristics of Different Phenotypes of Polycystic Ovary Syndrome Based on the Rotterdam Criteria in the Croatian Population

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A B S T R A C T

The aim of this study was to calculate the relative prevalence of all phenotypes of polycystic ovary syndrome (PCOS) and to compare them for anthropometrical, hormonal and metabolic differences according to the Rotterdam Criteria. A total of 300 women with PCOS aged 26.7±5.6 years (mean±SD) and 100 women aged 28.3±4.1 years (mean±SD) were included in a control group. Anthropometrical, hormonal and metabolic parameters were compared between the groups. The most prevalent phenotype in our population was the most severe, phenotype A (56.7%), followed by phenotype D (26.7%) and phenotype C (14.3%). Phenotype B was present in only 2.3% of patients. The four main phenotypes did not differ in age, BMI and WHR. Women with phenotypes A and C had increased levels of LH and an increased LH/FSH ratio along with elevated androgen levels compared to the other groups. Serum glucose levels did not differ between the groups studied, however, higher levels of insulin, GIR and HOMA-IR were found between phenotype A and the control group. Phenotype C PCOS or ovulatory PCOS have the same characteristics as classic PCOS, however in a more mild form, which represents a transition between the classic form and the control group. Compared to the control group, phenotype D had higher mean levels of serum testosterone (still within normal range) along with elevated LH levels and LH/FSH ratio, similar to classic PCOS. However, compared with women diagnosed with PCOS based on hyperandrogenism, oligo-ovulation and polycystic ovaries, these patients demonstrated milder endocrine and metabolic abnormalities. Therefore, from an endocrine point of view, our study supports the inclusion of a normoandrogenic anovulatory phenotype in PCOS diagnostic criteria.

Key words: *polycystic ovary syndrome, Rotterdam Criteria, phenotypes*

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder with an unclear etiology and an underlying pathogenic mechanism.

The endocrine abnormalities in PCOS include hyperandrogenism of ovarian and/or adrenal origin, which varies in clinical presentation, leading to arrested follicular development and consequently anovulation and polycystic ovarian morphology. The majority of women with PCOS have increased luteinizing hormone (LH) secretion further worsening the hyperandrogenemia. Metabolic characteristics of PCOS include central adiposity and hyperinsulinemia with consequential insulin resistance further exacerbating hyperandrogenism. Endocrine and metabolic abnormalities seen in PCOS range in clinical manifestation and may vary among affected women, thus creating a heterogeneous biochemical and clinical phenotype and ultimately producing difficulties in establishing a detailed diagnosis of the syndrome.

With an uncertain etiology, causal mechanisms and varying symptom presentation, PCOS is defined by con-

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sensual criteria. For many years only the classic phenotype, characterized by anovulation and hyperandrogenism/hyperandrogenemia was included in the diagnosis of PCOS[1]. The ESHRE/ASRM or Rotterdam Criteria broadened the phenotypic spectrum by including two additional phenotypes[2]. The four central phenotypes defined by these guidelines include: A) hyperandrogenism, chronic anovulation and polycystic ovaries (classic PCOS); B) hyperandrogenism and chronic anovulation with normal ovaries (classic PCOS); C) hyperandrogenism and polycystic ovaries with ovulatory cycles (ovulatory hyperandrogenic PCOS); and D) chronic anovulation and polycystic ovaries without clinical or biochemical hyperandrogenism (anovulatory normoandrogenic PCOS). Expansion of diagnostic criteria doubled the number of women diagnosed by PCOS. Since PCOS is a genetic disorder with a likelihood of developing serious reproductive and metabolic consequences, such women may have life-long implications, affecting her health, health insurance, and possibly that of her relatives and offspring. In addition, PCOS may result in a significant economic burden to the health care system, consequently having implications on health insurance in such patients. Therefore, it is imperative to accentuate the importance of a correct identification of specific phenotypes in women diagnosed with PCOS[3].

Currently there is a limited amount of data on the clinical characteristics and the endocrine-metabolic features in women belonging to the novel PCOS phenotypes as defined by the Rotterdam Criteria. Moreover, with significant variations in PCOS presentation seen in different ethnic populations, additional studies are needed. However, it is important to note that an attempt to generalize data obtained from any single ethnic group to other population groups should be approached with caution. As a result, the aim of this study was to report the relative prevalence of all four Rotterdam PCOS phenotypes in a medical setting and compare all phenotypes for anthropometrical, hormonal, and metabolic differences. Although a true prevalence study would survey a community, our clinic represents a reference center for women with all types of menstrual irregularities and clinical signs of androgen excess, thus we could assume that this study could present a representative sample within the Croatian population.

Subjects and Methods

Subjects

Between April 2010 and October 2012, 300 women with PCOS aged 26.7±5.6 years (mean±SD) and 100 women in a control group, aged 28.3±4.1 years (mean± SD) were enrolled in the study. They were included in the study during their treatment at the Human Reproduction Unit of the Department of Obstetrics and Gynecology, at the University Medical Centre in Zagreb.

The diagnosis of PCOS was based on the Rotterdam Consensus Criteria[2]. Clinical hyperandrogenism was defined by the presence of hirsutism (assessed by Ferriman-Gallwey-Lorenzo score, with patients having scores ≥8 considered as hirsute)[4]. Biochemical hyperandrogenemia was defined by a serum level of total testosterone (TT) more than 2.0 nmol/L, a free testosterone (FT) level greater than 26 pmol/L, an androstendione (A) level greater than 12 nmol/L or dehydroepiandrosterone sulphate (DHEAS) greater than 10 μmol/L. Menstrual irregularities were defined by the presence of amenorrhea/ oligomenorrhea or anovulation determined by progesterone less than 9.54 nmol/L levels on day 21 of two consecutive menstrual cycle. The diagnosis of polycystic ovaries (PCO) by ultrasonography was based on the established criteria[5]. In order to avoid inter-observer variations, the same examiner performed the ultrasound. Other endocrinopathies and related disorders were excluded by measuring basal serum 17-hydroxyprogesterone (17-OHP), prolactin (PRL), thyroid stimulating hormone (TSH), and cortisol levels. The control group consisted of 100 healthy volunteers preparing for in vitro fertilization cycles due to male factor infertility. They had no menstrual cycle abnormalities, nor clinical or biochemical evidence of hyperandrogenism or PCO findings on ultrasound.

The patients registered in our study had not taken any medications that could affect these values for at least six months prior to enrollment. They were enrolled at the early follicular phase of the spontaneous or progesterone induced menstrual cycle (day 3–5) when blood samples for hormonal and biochemical analysis were drawn, transvaginal ultrasound (TV – US) was performed and body mass index (BMI, calculated as a weight (kg) / height (m^2) and waist to hip ratio (WHR) were calculated. At enrollment, informed consent was obtained from all participants. The University of Zagreb Medical School Ethics Committee approved the study, protocol No. 04–1116–2006.

Biochemical analysis

Serum luteinizing hormone (LH), follicle–stimulating hormone (FSH), and total testosterone (TT) concentrations were determined by chemiluminescent immunometric assays using LH – Vitros, FSH – Vitors and Testosterone – Vitros (Ortho Clinical Diagnostics, Johnson & Johnson, Rochester, NY, USA). Serum sex hormone binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEAS) and androstendione (A) were measured using chemiluminescent immunometric assays using SHBG – Immulite, DHS – Immulite and Androstendion – Immulite (Siemens Healthcare Diagnostic Inc, Deerfield, Il USA). The intra – assay and inter – assay coefficient of variation were 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 (Siemens Healthcare Diagnostics Inc, Deerfield, IL, USA). Insulin resistance (IR) was quantified by calculating homeostatic model assessment of IR (HOMA IR) (fasting Ins mIU/L x fasting Glc mmol/L/22.5)[6] and by calculating fasting glucose to insulin ratio (GIR). Insulin resistance was defined by a HOMA-IR of 2.5 or

higher based on original HOMA research[6]. Free testosterone (FT) was calculated from TT and SHBG as previously described[7] using a web-based calculator (http://www.issam.ch/freetesto.htm).

Women with PCOS were divided into four groups, based on phenotype, according to their clinical characteristics: oligo/anovulation (OA), clinical and/or biochemical hyperandrogenism (HA) and polycystic ovaries on ultrasound (PCO). Phenotype A: OA+HA+PCO; phenotype B: OA+HA; phenotype C: HA+PCO (ovulatory hyperandrogenic); and phenotype D: OA+PCO (anovulatory normoandrogenic).

Statistical analysis

Frequency of different phenotypes is described by percentages. The hormonal and clinical data are presented as mean±standard deviation. Comparisons of continuous variables across the four groups were performed using analysis of variance (ANOVA). Tukey HSD post hoc test was used to determine significant differences between the groups. All statistical analyses were completed using the SPSS for Windows (version 15.0, SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

The most prevalent phenotype in our population was the most severe, phenotype A (56.7%), followed by phenotype D (26.7%) and phenotype C (14.3%) as presented in Table 1. Phenotype B was present in only 7/300 PCOS patients (2.3%) and was therefore excluded from further analysis (Table 1).

TABLE 1
CLINICAL PRESENTATION AND FREQUENCY OF THE DIFFERENT PCOS PHENOTYPES

	Phenotype			
Characteristic	A (N=170)	B (N=7)	C (N=43)	D (N=80)
OA	+	+	–	+
HA	+	+	+	–
PCO	+	–	+	+
Frequency (%)	56.7	2.3	14.3	26.7

Abbreviations: OA – oligo/anovulation; HA – Clinical and/or biochemical hyperandrogenism; PCO – polycystic ovaries

The clinical and hormonal parameters in the different PCOS and control groups of patients are presented in Table 2. Mean age, BMI and WHR was similar in all phenotypes of PCOS, and did not differ compared to the control group (Table 2.). As expected, patients in all three PCOS groups had significantly higher levels of LH, serum TT, FT, GIR and HOMA-IR, whereas serum SHBG and FSH were significantly lower compared to control group (Table 2). There were no statistical differences in BMI between the three study groups. Patients with PCOS, phenotype A, presented with a statistically significant higher LH level and LH/FSH ratio compared to the other two phenotypes and the control group (p<0.001, Table 2).

TABLE 2
CLINICAL AND HORMONAL CHARACTERISTICS OF DIFFERENT PCOS PHENOTYPES AND CONTROL GROUP

	Phenotype A	Phenotype C	Phenotype D	Control	p-values*
Age (years)	27.7±5.8	27.5±5.6	26.9±5.4	28.3±4.1	ns
BMI (kg/m^2)	24.5±5.3	24.3±4.2	25.5±4.7	23.3±4.1	ns
WHR	0.79±0.08	0.77±0.07	0.82±0.1	0.79±0.07	ns
FSH (IU/L)	3.9±1.2^{d}	4.8±1.4^{d}	3.7±1.0^{d}	5.5±1.6 ^{a,b,c}	<0.001
LH (IU/L)	10.0±4.3^{b,c,d}	8.1±1.9^{a,d}	7.3±0.9^{a,d}	3.7±0.9 ^{a,b,c}	<0.001
LH/FSH	2.8±1.6^{b,c,d}	2.0±1.1^{a,d}	2.3±0.9^{a,d}	0.7±0.8 ^{a,b,c}	<0.001
TT (nmol/L)	2.7 ±0.6^{B,c,d}	2.3±0.7^{A,c,d}	1.4±0.3^{a,b}	1.3±0.5 ^{a,b}	<0.001
FT (pmol/L)	53.1±21.7^{c,d}	44.8±26.8^{c,d}	25.3±12.9^{a,b,d}	14.2±6.6 ^{a,b,c}	<0.001
A (nmol/L)	11.6±4.7^{d}	12.2± 5.9^{d}	10.0±6.3^{d}	7.6±2.5 ^{a,b,c}	<0.001
DHEAS (μmol/L)	7.6±3.1^{d}	7.1±2.9 ^{d}	6.7±3.2	5.0±1.9 ^{a,b}	<0.001
SHBG (nmol/L)	35.3±16.7^{c,d}	37.6±19.5^{c,d}	62.3±20.4^{a,b,d}	71.2±22.2 ^{a,b,c}	<0.001
Fasting glucose (mmol/L)	4.5±0.5	4.4±0.4	4.4±0.4	4.4±0.5	Ns
Fasting insulin (mIU/L)	14.4±7.9^{d}	12.0±9.8	9.6±5.5	6.5±2.6 ^{a}	<0.001
HOMA-IR	2.9±1.4^{d}	2.4±2.0	1.9±1.1	1.3±0.6 ^{a}	<0.001
GIR	10.7±4.1^{d}	9.0±4.6	12.5±6.0	14.8±7.2 ^{a}	<0.001

Abbreviations: BMI – body mass index, WHR – waist to hip ratio, 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, GIR – glucose to insulin ratio

* ANOVA test; ^{a}p<0.001 compared with phenotype A, ^{b}p<0.001 compared with phenotype C, ^{c}p<0.001 compared with phenotype D; ^{d}p<0.001 compared with controls; ^{A}p<0.01 compared with phenotype A, ^{B}p<0.01 compared with phenotype C

Both new Rotterdam phenotype C and D have statistically significant higher levels of LH than the control group ($p<0.001$, Table 2). The phenotype A group also presented with significantly higher levels of total testosterone levels compared to the other two phenotypes and controls ($p<0.01$ and $p<0.001$, respectively, Table 2). Serum levels of other androgens (androstendione and DHEAS), as well as serum SHBG levels, were found to be similar between the different PCOS phenotypes (Table 2). Serum levels of glucose were not found to be different between groups studied but higher levels of insulin, GIR and HOMA-IR were found between phenotype A and the control group ($p<0.001$, Table 2).

Discussion and Conclusion

The Rotterdam Criteria[2] added two phenotypes of women with PCOS: women with normal menstrual periods and normal fertility, but who have androgen excess and polycystic ovaries on ultrasound (phenotype C), and women with oligomenorrhea and polycystic ovaries on ultrasound, but normal androgen excess (phenotype D). The names given to these phenotypes in this study are arbitrary and not accepted by all experts. In the recently published Consensus on Women's Health, it is noted that geographic location, ethnic origin and even cultural and social practices are contributing factors to the different phenotypes of PCOS[8]. Therefore, in our study, information on relative prevalence of the main phenotypes of PCOS in the Croatian population was given.

The most common phenotype in our study was phenotype A (56.7%), characterized by oligo/anovulation, clinical and/or biochemical hyperandrogenism and a polycystic appearance of the ovaries. All published studies reported this phenotype to be the most prevalent[9–14]. This phenotype is included in all three-consensus criteria[1,2,15] and certainly represents the basis of PCOS diagnosis. The prevalence of the other three groups differs between published studies[9–14].

In our population, the less frequent phenotype is phenotype B (2.3%), characterized by oligo/anovulation, clinical and/or biochemical hyperandrogenism with normal appearing ovaries on the ultrasound exam. Although this finding is in accordance with the studies for other population groups[9–14], other authors reported a higher frequency of phenotype B (22.8–7.6%) compared to those found in our study. This difference can be explained by the fact that American gynecologists traditionally do not perform ultrasound, while European gynecologists prefer to view polycystic ovaries on ultrasound as a means of diagnosing PCOS. The other reason for differences in frequency of diagnosing this phenotype is that endocrinologists, who do not use ultrasound, diagnose many cases of PCOS. In our study, an experienced gynecologist performed a complete ultrasound exam.

Phenotype C, characterized by hyperandrogenism and a polycystic appearance of the ovaries was represented by 14.3% in our study groups. This is in accordance with studies from Bulgaria[10], and Poland[13]. We expected to have similar results to the Italian population[14] who reported the prevalence of this phenotype in 28.8% of the PCOS population, attributing to the fact that women from Mediterranean ancestry tend to have more body hair than women of other ethnicities. Phenotype D is the second most frequent phenotype in our study group, represented by 26.7%. Other studies reported the prevalence of this unusual and most controversial phenotype as having a 19.9–8.4% incidence[9–14]. Again, the reason for these differences could lie in the variances of examining PCOS patients between American and European gynecologists and endocrinologists. Endocrinologists treat many PCOS patients without doing ultrasounds in the office. Additionally, many gynecologists in the US send patients to radiology, where reports are usually less informative. Furthermore, normal androgen levels and abnormal menstrual cycles characterize this phenotype; therefore it is more logical to be referred to a gynecologist rather than an endocrinologist. The elevated level of LH, distinguishing this group of patients from the control groups, is currently not considered to be a diagnostic feature of PCOS[2]. Nevertheless, evidence attributing to the unusual PCOS phenotype D is scarce, and therefore, new and additional studies are needed. As a result, the Androgen Excess and PCOS Society have suggested excluding patients with normal androgen levels among the PCOS phenotypes until more data becomes available[15].

In our study, we provided the difference in anthropometrical, hormonal, and metabolic characteristics between the main PCOS phenotypes, according to the Rotterdam Criteria and the control groups. The four main phenotypes studied did not differ in age, BMI and WHR. The majority of studies demonstrated elevated BMI, WHR, glucose, IR, GIR and HOMA-IR in the classic PCOS phenotypes (A and B) compared to Rotterdam phenotype (C and D)[16–18]. Previously, we reported that there is a low prevalence of obesity in the Croatian population with PCOS, for this reason, the difference between our study and other studies can be explained by such a finding[19]. As there is evidence of an increasing rate of obesity[20–23], especially in childhood[24], we can expect more pronounced metabolic differences between the phenotypes in years to come.

Type A or classic PCOS represents the most common form of PCOS, characterized by increased levels of LH and an increased LH/FSH ratio, with increased androgen levels. Although serum levels of insulin and HOMA-IR were not found to be different between the groups studied, higher levels of these parameters were found between phenotype A and the control group representing the elevated risk for diabetes type 2, a feature of PCOS.

Type C PCOS or ovulatory PCOS have the same characteristics as classic PCOS but in a milder form and represents the transition between the classic form and the controls. Despite the proven ovulatory cycles, patients have elevated levels of LH and an increased LH/FSH ratio compared to control group.

Type D or normoandrogenic anovulatory PCOS represents the conflicting group. Compared to the control

group, these women have higher mean levels of serum testosterone (still within normal range) and elevated LH levels and an increased LH/FSH ratio similar to classic PCOS. However, compared with women diagnosed with PCOS based on hyperandrogenism, oligo-ovulation and polycystic ovaries, these patients demonstrated milder endocrine and metabolic abnormalities. Therefore, from an endocrine point of view, our study supports the inclusion of a normoandrogenic anovulatory phenotype in PCOS diagnostic criteria. In the long run, it will be interesting to note, if these women will progress to a more severe phenotype, and how pronounced their cardiac risk factors will progress with age. The majority of studies reported less adverse metabolic profiles for the newly introduced Rotterdam phenotypes[11,24,25]. However, in these studies, due to a lack of weight matching, it is not possible to determine whether a worsened metabolic profile is due to differences in adiposity or other factors. In our study, all groups have similar BMI and WHR profiles.

In conclusion, four phenotypes of PCOS share the abnormalities in LH, LH/FSH ratio and androgen parameters, but vary in severity. With an abnormal secretion of gonadotropins, characteristic of PCOS, new phenotypes merit inclusion in the PCOS spectrum. Only the most severe phenotype showed abnormalities in insulin resistance in comparison to women in the control group. Whether these newly introduced phenotypes have the intrinsic predisposition to an adverse metabolic profile independent of obesity, other molecular genetic studies will be demonstrative. Certainty with regards to PCOS diagnostic criteria and the inclusion of various phenotypes and their endocrine-metabolic risks will be not be explained until research shows the underlying cause. An accurate definition of PCOS will be reached when genetic analyses of the population are completed to determine the genetic–pathophysiologic phenotypes.

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OSOBINE RAZLIČITIH FENOTIPOVA POLICISTIČNIH JAJNIKA U HRVATSKOJ DIJAGNOSTICIRANIH PO ROTTEDRAMSKIM KRITERIJIMA

S A Ž E T A K

Cilj ovog istraživanja bio je izračunati relativnu zastupljenost svih fenotipova sindroma policističnih jajnika (PCOS), dijagnosticiranih po Rotterdamskom kriteriju i usporediti njihove antropometrijske, hormonske i metaboličke razlike. Analizirano je ukupno 300 žena s PCOS-om u dobi od 26,7±5,6 godina (srednja vrijednost ± SD) i 100 žena iz kontrolne skupine u dobi od 28,3±4,1 godina (srednja vrijednost ± SD). Antropometrijski, hormonalni i metabolički parametri uspoređeni su između navedenih skupina. Najučestaliji fenotip u našoj populaciji je onaj najteži – fenotip A (56,7%), slijede ga fenotip D (26,7%) i fenotip C (14,3%). Fenotip B je bio prisutan samo u 2,3% ispitanica. Četiri glavna fenotipova nisu se razlikovala u dobi, BMI i WHR. U fenotipovima A i C nađene su povišene razine LH te omjer između LH i FSH kao i povišene vrijednosti androgena u odnosu na ostale skupine. Serumske razine glukoze nisu se značajno razlikovale između ispitivanih skupina, ali su pronađene više serumske razine inzulina, GIR i HOMA-IR između fenotipa A i kontrolne skupine. Fenotip C PCOS imao je iste karakteristike kao klasični PCOS, ali u blažem obliku i predstavlja prijelaz između klasične forme i kontrole. U usporedbi s kontrolnom skupinom, fenotip D ima višu razinu serumskog testosterona (iako u granicama normalnih vrijednosti) te povišen LH i LH / FSH omjer slično kao u klasičnom PCOS. Međutim, u usporedbi sa ženama s PCOS dijagnosticiranim na temelju hiperandrogenizma, oligoovulacije i policističnih jajnika, ove ispitanice pokazuju blaze endokrinološke i metaboličke abnormalnosti. Stoga s endokrinološkog gledišta naša studija podupire uključivanje normoandrogenog anovulatornog fenotipa PCOS-a u dijagnostičke kriterije.