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Polycystic Ovary Syndrome: Correlation between Phenotypes and Metabolic Syndrome

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Abstract

The polycystic ovary syndrome (PCOS) is an endocrine metabolic disorder affecting 7% to 10% of women during reproductive age. The metabolic syndrome is understood as a set of clinical factors related to the potential increase in the risk of cardiovascular disease, type II diabetes mellitus, and early mortality. The hyperandrogenism and insulin resistance related to PCOS will result in increased cardiovascular risk and extending throughout the patient's lifetime.

Objectives: To identify the prevalence of metabolic syndrome in each of the polycystic ovary syndrome (PCOS) phenotypes and the factors linked with metabolic risk.

Methods: Observational study of 566 women between 14 and 39 years with PCOS according to the Rotterdam criteria. The metabolic risk was assessed by descriptive analysis with a confidence interval of 95%. Quantitative variables were tested using the Shapiro-Wilk test and nonparametric Mann-Whitney test. For the multivariate analysis was used the prevalence ratio between several independent variables and the outcome metabolic risk. Identify factors associated with metabolic risk using Cox regression with robust variance.

Results: The mean age was 26.4 ± 5.9 years. Metabolic risk was found in 21%, with a predominance of phenotypes E (28.4%), which is characterized by hirsutism, oligoanovulation, polycystic ovaries; B (25%), defined as biochemical hyperandrogenism, hirsutism, oligoanovulation; and A (22%) described biochemical hyperandrogenism, hirsutism, oligoanovulation and polycystic ovaries. A one-year increase in age raised the risk by 5%. Every one-unit increase in body mass index (BMI) added 8%. Presence of hirsutism tripled the risk. Patients with at least one child ran twice the risk than the nulliparous.

Conclusions: Our data suggested the important factors of metabolic syndrome in women with PCOS are age, obesity, hirsutism, and parity.

Keywords: Polycystic ovary syndrome; Metabolic syndrome

Introduction

The polycystic ovary syndrome (PCOS) is an endocrine metabolic disorder affecting 7% to 10% of women during reproductive age [1]. It is considered not only a systemic disorder with reproductive, psychological, cosmetic, and oncologic consequences, but also a metabolic disorder, such as hyperglycemia and insulin resistance, resulting in increased cardiovascular risk and type II diabetes mellitus and extending throughout the patient's lifetime with potential financial burden to public health [2].

The definition of PCOS is based on the consensus of several groups. The 2003 Rotterdam consensus workshop provided a wider definition than had been proposed until then, encompassing a larger number of phenotypes. It was established that the diagnosis of the syndrome should include the presence of two out of the following three features: 1) oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, or 3) polycystic ovaries (presence of 12 or more follicles with a diameter of 2 mm-9 mm in one or both of the ovaries or ovarian volume ≥ 10 cm^3) [3]. Later, in 2006, Azziz et al. proposed the incorporation of several different metabolic-syndrome-related phenotypes in order to encompass the clinical diversity of PCOS [2]. It is necessary to exclude the diseases with similar clinical aspects to PCOS (congenital adrenal hyperplasia, Cushing's syndrome, tumors secreting ovarian and adrenal androgens, hyperprolactinemia, and thyroid dysfunctions) and conditions requiring the use of exogenous androgens [3]. It is noted that some androgen-producing tumors occur with increased insulin resistance and increased risk of cardiovascular disease in women [4]. It is questionable that elevated androgen levels increases the metabolic syndrome, which justifies the importance of recognizing the different phenotypes of PCOS.

Metabolic syndrome (MetS) has been the subject of many studies in recent years [5,6]. It was defined by ATP III (2004) [7] as a group of interrelated risk factors of metabolic origin that contribute directly to the development of cardiovascular disease (CVD) and/or type II diabetes mellitus [7].

The prevalence of MetS in PCOS patients is almost twice as great as in the general population of women, raising the risk of cardiovascular

disease by seven times [8]. However, the metabolic syndrome study of each PCOS phenotype reveals phenotypic groups with a worse metabolic profile and a larger number of harmful results to one's health [8,9]. Because of the high incidence of the association between PCOS and MetS, we sought to identify the frequency of metabolic syndrome in each PCOS phenotype and the factors associated with metabolic risk in the population of the city of Sao Paulo, Brazil.

Patients and Methods

This was an observational study which used data extracted from the medical records of 1408 women with chronic anovulation. The women came for their first consultation at the Sector of Endocrine Gynecology and Menopause, Clinics Hospital, University of São Paulo between June 1964 and November 2011. The research protocol was approved by the Ethics Committee for Analysis of Research Projects (CAPPesq) of the Clinics Hospital and the School of Medicine of Sao Paulo, under number 0746/10.

Inclusion criteria: patients aged 14-39 years and diagnosed with PCOS according to the 2003 Rotterdam consensus and whose medical records had the date of the anamnesis and showed that the physical examination and the medical tests were suitable for PCOS.

Exclusion criteria: use of hormonal contraception (in the previous 6 months) or of psychiatric medications, hyperprolactinemia, thyroid dysfunction, and other causes of hyperandrogenism, such as congenital adrenal hyperplasia, Cushing's syndrome, adrenal neoplasia, or virilizing ovarian tumors.

According to the eligibility criteria, 566 patients were included in the study (Figure 1).

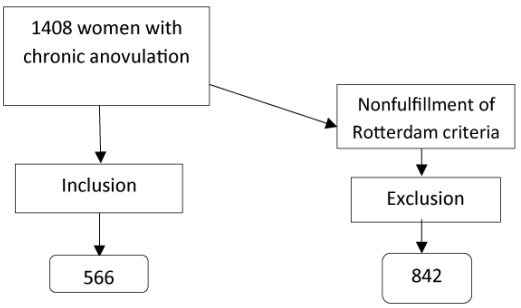

Figure 1: Algorithm showing patients included after application of eligibility criteria

Clinical hyperandrogenism was considered when the presence of hirsutism was indicated by a score of 7 or more on the Ferriman and Gallwey scale [10-11]. Oligoanovulation was evidenced by either amenorrhea or oligomenorrhea (less than six menstrual periods in the previous year) [9].

The suprapubic pelvic ultrasound or transvaginal ultrasound evaluated the presence of 12 or more follicles with a diameter between 2 mm and 9 mm in one or both ovaries or ovarian volume greater than 10 cm^3.

Anthropometric data: BMI was obtained by dividing weight (kg) by height (meters) squared. Waist circumference (cm) was measured with a tape measure both flexible and inextensible which was positioned at the lower curvature located between the last rib and the iliac crest with the patient in supine position and in expiration. Blood pressure was measured using a sphygmomanometer with a mercury column or aneroid manometer [10-13].

In order to determine metabolic measures of triglycerides and HDL-C, blood samples were collected after a 12-hour fast and analyzed using automated enzymatic methods (Roche Laboratories). The plasma glucose concentration was established by the hemoxynase method. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, androstenedione, dehydroepiandrosterone sulfate (DHEAS), and total and free testosterone were evaluated. Total testosterone was measured by fluoroimmunoassay (Wallac, Finland) and free testosterone was calculated based on total testosterone and on sex hormone-binding globulin (SHBG) measured by fluorimetry. Biochemical hyperandrogenism was defined as a testosterone level greater than or equal to 98 nmol/l and a free testosterone concentration of 45 nmol/l. Samples were drawn in the first phase of the cycle from patients with menstrual regularity or anytime from patients in amenorrhea.

The phenotypes proposed by Azziz et al. (2006) for patients meeting the Rotterdam criteria demonstrate the clinical diversity of PCOS and manifest as biochemical hyperandrogenism, hirsutism, oligoanovulation, and polycystic ovaries [2,3] (Table 1).

Phenotypes	Characteristics
A	Biochemical Hyperandrogenism, Hirsutism, Oligoanovulation and Polycystic Ovaries
B	Biochemical hyperandrogenism, Hirsutism and Oligoanovulation
C	Biochemical hyperandrogenism, Oligoanovulation and Polycystic ovaries
D	Biochemical hyperandrogenism and Oligoanovulation
E	Hirsutism, Oligoanovulation and Polycystic ovaries
F	Hirsutism and Oligoanovulation
G	Biochemical hyperandrogenism, Hirsutism and Polycystic ovaries
H	Hirsutism and Polycystic ovaries
I	Biochemical hyperandrogenism and Polycystic ovaries
J	Oligoanovulation and Polycystic ovaries

Table 1: Pcos phenotypes according to rotterdam criteria

Metabolic syndrome was defined according to the third report of the National Cholesterol Education Project Adult Treatment Panel (NCEP-ATPIII) and thus considered present when the patient had three or more of the following five values changed: waist circumference >88 cm, triglycerides ≥ 150 mg/dl; HDL-C<50 mg/dl, systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg or when taking antihypertensive drugs; fasting glucose of 12 hours between 100 to 126 mg/dl [7].

In the search for factors correlating with metabolic risk in PCOS patients, the following variables were analyzed: age, parity, hirsutism, oligoanovulation, oligoanovulation time, infertility, menarche, BMI, biochemical hyperandrogenism, polycystic ovaries, family history of

type 2 diabetes mellitus, hypertension, gynecological cancer, nongynecological cancer.

Statistical analysis

The data were organized and the average standard deviation (SD), prevalence ratio, and confidence interval of 95% (95% CI) were calculated and displayed in the text, tables, and graphs. Quantitative variables were assessed by the Shapiro-Wilk test and then by the nonparametric Mann-Whitney test [14-16]. Initially, a descriptive analysis of the study variables was performed. Qualitative variables were shown in tables of frequency, whereas quantitative variables were estimated according to the measures of central tendency and dispersion. The prevalence of metabolic risk and its respective interval were calculated using a 95% CI. In order to identify possible factors associated with metabolic risk, the relationship between metabolic syndrome and all study variables was tested. The variables with a p value below 0.20 were the starting point in univariate analysis. The model used was the Cox regression with variance [16,17]. In this study, a significance level of 5% was adopted. The data were plotted into Excel and analyzed using the STATA statistical software version 12.0 (StataCorp LP, College Station, Texas, USA).

Results

Of the total of 566 patients in the study, 478 were of African descent, 86 were white, and 2 were Asian. The age range was 14-39 years and mean age was 26.4 ± 5.9 years. The analysis of menstruation type showed that 518 (90.6%) patients had menstrual irregularity. A total of 396 women reported having an active sexual life, and 89 of them had one or more children. Hirsutism was present in 520 (91.8%) patients, acne in 310 (54.9%), and *acanthosis nigricans* in 109 (54.9%). Biochemical hyperandrogenism was observed in 294 (51.9%) patients and polycystic ovary in 440 (77.7%).

Waist circumference greater than 88 cm was observed in 51% of the 566 patients, overweight in 28.5%, and obesity in 38%. Systolic blood pressure ≥ 130 mmHg was found in 220 women (38.9%) and diastolic blood pressure ≥ 85 mmHg at 20% in 113. Patients with glucose intolerance added up to 231 (40.8%), with low HDL-cholesterol to 242 (43%), and with high triglycerides to 51 (9%).

Analysis of the phenotypes [2] showed that A and J predominated and were present in 204 women and in 90, respectively. Of the 566 women, 119 (21%) were at metabolic risk (95% CI, 17.7 to 24.6). Phenotypes that showed a higher incidence of metabolic syndrome were E, found in 23 patients (28.4%), followed by B, in 9 (25%), and A, in 45 (22.1%) (Table 2).

Phenotypes				**Metabolic Risk**			**BMI ≥ 25 kg/m2**
(Groups)	(N)	(%)		(N)	(%)		(%)
A	204	36		45	22.1		67.4
B	36	6.4		9	25		71
C	12	2.1		1	8.3		66
D	2	0.3		0	0		100
E	81	14.3		23	28.4		65.4
F	88	15.6		18	20.5		50
G	39	6.9		8	20.5		55.9
H	13	2.3		2	15.4		40
I	1	0.2		0	0		100
J	90	15.9		13	14.4		67.9
TOTAL	566	100		21	119		100

Table 2: phenotypes in metabolic risk and in BMI

We researched epidemiological and clinical characteristics such as ethnicity, parity, presence of menstrual irregularities, signs of hyperandrogenism, polycystic ovaries in patients with PCOS to assess the metabolic risk. The data on family history, including diabetes (p=0.394), hypertension (p=0.639), gynecological cancer (p=0.329), and nongynecological cancers (p=0.704) failed to explain the increased risk or to show metabolic protection. In order to identify the variables independently associated with metabolic risk, two models were chosen from the multivariate analysis of the data. It was found that metabolic risk was independently associated with age (p=0.006), BMI (p<0.001), parity (p=0.002), and the occurrence of hirsutism (p=0.029) (Tables 3 and 4).

Variables	Total	Metabolic syndrome no (Prevalence)	PR	95% CI (PR)	p
Ethnicity					0.191
white or Asian	88	23 (26.1)	1		
biracial or black	478	96 (20.1)	0.77	0.52 - 1.14	
Parity					0.020
not applicable (virgins)	84	11 (13.1)	1		
without children	393	80 (20.6)	1.57	0.88 - 2.82	
with children	89	27 (30,3)	2.32	1.22 - 4.37	
Menstrual Irregularity and amenorrhea					0.640

no	59	11 (18.6)	1		
yes	507	108 (21.3+A1:F33)	1.14	0.653 - 2.00	
Hirsutism					0.029
no	46	3 (6.5)	1		
yes	520	116 (22.3)	3.42	1.13 - 10.35	
Hyperandrogenemia					0.807
no	272	56 (20.6)	1		
yes	294	63 (21.4)	1.04	0.76 - 1.43	
Polycystic ovaries					0.900
no	126	27 (21.4)	1		
yes	440	92 (20.9)	0.98	0.67 - 1.43	
Family history of diabetes					0.394
no	38	10 (26.3)	1		
yes	528	109 (20.6)	0.78	0.45 - 1.37	
Family history of hypertension					0.639
no	506	105 (20.7)	1		
yes	60	14 (23.3)	1.12	0.69 - 1.83	
Family history of gynecological cancer					0.329
no	554	118 (21.3)	1		
yes	12	1 (8.3)	0.39	0.06 - 2.58	
Family history of nongynecological cancer					0.704
no	541	113 (20.9)	1		
yes	25	6 (24.0)	1.15	0.56 - 2.35	

Quantitative	without Metabolic Risk	with Metabolic Risk	p*
Variables	mean (SD); median (min-max)	mean (SD); median (min-max)	
Age	26.1 (5.8); 25.0 (14 - 39)	27.7 (6.1); 28.0 (14 - 39)	0.006
BMI (n=308)	27.5 (6.9); 26.9 (16.8 - 59.0)	36.1 (7.8); 34.9 (25.1 - 56.9)	<0.001
Menarche	13.0 (1.8); 13 (9 - 18)	12.8 (1.9); 13 (9 - 18)	0.619
Time period (years) of reproductive desire (years)	1.3 (2.2); 0 (0 - 14)	1.9 (3.2); 0 (0 - 16)	0.195
Time period (years) of irregularity (n=437)	6.3 (5.8); 5 (0 - 28)	7.6 (6.3); 5 (0 - 24)	0.101

Table 3: Relationship between family comorbidities, clinical and gynecological characteristics and metabolic syndrome. *Mann-Whitney test

PR: Prevalence Ratio; SD: standard Deviation

As can be seen, for every one-year increase in age, the risk of a metabolic event increased by 5%, regardless of BMI. The results also show that for every one-unit increase in BMI, there was an increase of 8% in the occurrence of the event, regardless of the patient's age.

Likewise, metabolic risk grew in parallel with increasing age (p=0.047), irrespective of BMI, parity, and occurrence of hirsutism. In addition, it has been estimated that the risk of a metabolic event for patients of any age with children, independently of hirsutism, is twice as large as that for women without children.

Variables	PRcr	RPadj (95% CI)	p
Model 1			
Age	1.04	1.05 (1.01 - 1.09)	0.006
BMI	1.08	1.08 (1.05 - 1.10)	<0.001
Model 2			
Age	1.04	1.03 (1.00 - 1.06)	0.047
Parity			
not applicable (virgins)	1		0.015
without children	1.57	1.43 (0.80 - 2.56)	
with children	2.32	2.03 (1.08 - 3.82)	
Hirsutism			0.036
no	1		
yes	3.42	3.31 (1.08 - 10.17)	
PRcr: Crude Prevalence Ratio; PRadj: Adjusted Prevalence Ratio			

Table 4: Estimates of the prevalence ratio by multiple regression model for metabolic syndrome

The analysis of patients with hirsutism, no matter what their age and parity, showed a threefold increase in metabolic risk against those without hirsutism (p=0.036).

Discussion

The metabolic syndrome is understood as a set of clinical factors related to the potential increase in the risk of cardiovascular disease, type 2 diabetes mellitus, and early mortality [7,5].

Considering the high prevalence of metabolic risk, the prevalence ratios (PRs) and their CIs were estimated using univariate analysis for the relationship between several independent variables and the outcome metabolic risk variable. Estimation of the relative risk by the odds ratio was prevented by the possibility that it would be overestimated because the prevalence of metabolic alterations exceeded 20%. Therefore, this was a cohort study with cross-sectional characteristics, where the association between exposure and outcome was estimated by PR [14-16].

Although differences between ethnicity, environment, and diet can alter the frequency of PCOS-related metabolic abnormalities, the incidence of obesity and the impact of age seem to be the main determinants of the prevalence of metabolic syndrome in different populations [18]. Hence, a comparison of adult women diagnosed with PCOS by the Rotterdam criteria led to the finding that the rate of metabolic syndrome is 47.3% in the U.S. [19,20], while in southeast China it is 25.6% [21], 23.8% in Sweden [22], 19.9% in Greece [23], 12.5% in Turkey [24] and 1.6% in the Czech Republic [25]. The prevalence of metabolic syndrome ranges from 33% to 45% in Brazilian women with PCOS [26,27].

This study revealed a prevalence of 21% in the association between PCOS and metabolic syndrome-related prevalence of more hyperandrogenic phenotypes, as oligoanovulation and hirsutism. This result corroborates the results found in the literature, which indicates a higher incidence of metabolic diseases early phenotypes, groups A to F, characterized by the presence of oligoanovulation [2].

The occurrence of MetS was observed in these three phenotypes, concomitant with an increase in BMI, which rose to 65.4% in E, 71% in B, and 67.4% in A. Besides weight gain, excess androgens were also the source of the numbers obtained in this study, because biochemical hyperandrogenism is a characteristic in the clinical phenotypic classification of groups A and B, totaling 42.4% of the 566 women in our sample [6,28].

As expected, the incidence of metabolic dysfunction in PCOS was significantly increased by the concurrent presence of obesity, which exacerbates the PCOS unfavorable metabolic outcomes from insulin resistance, promoting deterioration in the form of hyperandrogenism, hirsutism, and infertility [29]. In our study, the prevalence of overweight was 28.5%, of obesity, 38%, and of waist circumference greater than 88, 51%.

March et al. while investigating obesity in PCOS patients, observed a prevalence of 28% of PCOS in obese women and an association of 5% between PCOS and thin women [30].

Legro reported that obesity and age progression substantially increase the metabolic risk, although PCOS itself is responsible for the higher incidence of carbohydrate intolerance and diabetes among young and not obese patients. According to our survey, hirsutism is notably the dermatological complaint motivating the search for more medical attention and it was found in 91.8% (N=520) of the cases. The presence of hirsutism tripled the metabolic risk when compared to patients without hirsutism (p=0.036), regardless of age and parity [31].

Paoletti et al. and Cebeci et al. [32,33] suggested that the peripheral activity of androgens is related to hyperinsulinemia, based on studies where the antiandrogen treatment improved insulin resistance. Other studies suggested that insulin is one of the factors which interact with androgen to regulate the development of the pilosebaceous unit [34-36]. The same authors also concluded that insulin resistance is closely related to hirsutism, much more so than excess body weight in women with PCOS [34-36]. The relationship between the presence of hirsutism and an increased risk of a metabolic event is still an unresolved issue deserving further studies.

Although there are no reports in the literature associating parity and the occurrence of MetS after a gestational event, there is often additional body mass gain as well as worsening metabolism in PCOS patients. It's important to remember that patients have a higher incidence of undesirable vascular and hyperinsulinemic events during pregnancy and the postpartum period. Further research into these two issues might corroborate our findings and strengthen the case for prevention of metabolic disorders in PCOS patients [37-39].

Advancing age and BMI in patients with PCOS are well-known factors related to metabolic risk. However, further studies showing other statistical relationships between MetS and clinical manifestations of PCOS, similar to those between parity and hirsutism, are necessary in order to predict the simultaneous occurrence of these two syndromes.

The prevalence of metabolic syndrome in PCOS was 21%, and was more common in phenotypes E, B and A. In our search for predictors of metabolic risk, we focused on age, parity, and the presence of obesity and hirsutism among women with PCOS. Age and obesity have been extensively studied in the literature, and our work confirms their value as indicators. However, hirsutism and parity are new

factors demanding further investigation of their potential as predictors of metabolic risk in women with PCOS.

Our data suggested the important factors of metabolic syndrome in women with PCOS are age, obesity, hirsutism and parity.

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