Metabolic profile of the different phenotypes of polycystic ovary syndrome in two Latin American populations

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Objective: To evaluate the metabolic profile of Chilean and Argentinian women with polycystic ovary syndrome (PCOS) according to the Rotterdam criteria.

Design: Observational cross-sectional study.

Setting: Academic centers.

Patient(s): Women with PCOS, aged 18–39 years: 220 Chilean (PCOS$_{Ch}$) and 206 Argentinian (PCOS$_{Ar}$).

Intervention(s): Physical examination, fasting blood samples for androgens, gonadotropins, metabolic parameters, and a transvaginal ultrasound.

Main Outcome Measure(s): Comparative analysis of the metabolic profile in both populations divided into four phenotypes.

Result(s): The distribution of the different phenotypes was different in both populations. PCOS$_{Ch}$ women showed a higher body mass index and a higher percentage of metabolic syndrome in all phenotypes compared with the PCOS$_{Ar}$ women. The PCOS$_{Ar}$ women exhibited a statistically significantly higher diastolic blood pressure in phenotypes A, B, and C and a higher percentage of hypertension in phenotypes A and D compared with the PCOS$_{Ch}$ women.

Conclusion(s): The data show differences in the metabolic profile of both populations. PCOS$_{Ch}$ women presented with greater metabolic alterations such as dysglycemia and dyslipidemia and a higher prevalence of metabolic syndrome, independent of the phenotype. The PCOS$_{Ar}$ patients showed more elevated blood pressure. Ethnic diversity associated with environmental factors are fundamental elements in the analysis of the PCOS phenotypes. (Fertil Steril® 2014;101:1732–9. ©2014 by American Society for Reproductive Medicine.)

Key Words: Argentina, Chile, metabolic syndrome, polycystic ovary syndrome, Rotterdam phenotypes

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Polycystic ovary syndrome (PCOS) is a hyperandrogenic disorder associated with chronic oligo-ovulation and polycystic ovary morphology. It is the most common cause of hyperandrogenism, with a prevalence reaching up to 15% when using the Rotterdam criteria described in 2003 (1). Hyperandrogenism and chronic anovulation are the main elements of this definition; the ultrasound pattern of polycystic ovaries is the third

element incorporated in the 2003 consensus (1). According to this definition, the diagnosis of PCOS may be established with two of the three criteria described, generating four different phenotypes:

> Phenotype A: hyperandrogenic women with oligoanovulation and transvaginal ultrasound with polycystic ovarian morphology (H/O/PCOM).

> Phenotype B: women with hyperandrogenism, oligoanovulation, and without PCOM (H/O).

> Phenotype C: hyperandrogenic women with ovulatory cycles and PCOM (H/PCOM).

> Phenotype D: normoandrogenic women with oligoanovulation and PCOM (O/PCOM).

Recently, it has been observed that each PCOS phenotype is associated with a different metabolic risk. Most studies have shown that hyperandrogenism is the main factor for the development of metabolic and cardiovascular alterations, with phenotypes A and B having a higher metabolic risk than phenotype D, whose risk is comparable to that of control women (2, 3). However, these phenotypes may vary in individuals and may be modified by changes in weight, treatment, and/or healthy lifestyle factors (4).

It has been proposed that the development of PCOS and its phenotypic expressions may be influenced by genetic and environmental factors that can affect a woman from her intrauterine life until the reproductive stage (4, 5). In this regard, racial and ethnic characteristics are a very important genetic aspect to be considered in PCOS and its phenotypic expressions (6). This background may influence the clinical manifestations of PCOS. For instance, Middle Eastern women have a greater prevalence of hirsutism (2) whereas among East Asian women hirsutism is less common (7, 8). In Indian women, acne has been described as the most prevalent clinical expression of hyperandrogenism (9).

The presence of the metabolic syndrome has been associated with PCOS with variable frequency; its prevalence is lower in East Asian women (7, 8) and higher in women of African, South Asian, and Hispanic descent (2, 10). A northern California study of women with PCOS found that, compared with white patients, black and Hispanic patients were more likely and Asian patients less likely to be obese, the Asian and Hispanic women were more likely to have diabetes, and the black women were more likely and Hispanic women less likely to have hypertension (10).

The phenotypic distribution of PCOS in Latin American populations is only partially known. Thus, our study compares the metabolic profile of women with PCOS from two neighboring countries with different ethnic compositions. Argentina, and especially the city of Córdoba, has been influenced by a large, mainly European immigration wave composed primarily of Italians and secondarily of Spaniards (11). In contrast, in Chile over 65% of the population is of Spanish descent, with the phenotypic characteristics of a mostly white population: the average proportion is 60% Hispanic and 40% Amerindian (12, 13). Our study compares the metabolic profile, classified into the four phenotypes

described according to the Rotterdam criteria, of 220 women with PCOS from Santiago de Chile (PCOS$_{Ch}$) and 206 women with PCOS from the province of Córdoba, Argentina (PCOS$_{Ar}$), who have a different ethnic background.

MATERIALS AND METHODS
Patients

We studied 220 PCOS$_{Ch}$ women who were treated at the polyclinic of the Department of Endocrinology and Metabolism of Universidad de Chile in Santiago (Chile) and 206 PCOS$_{Ar}$ women who were treated at the Department of Endocrinology and Diabetes of Universidad de Córdoba (Argentina), both academic health centers serving patients from a socioeconomically middle-class area. All the women were between 18 and 39 years old and had a body mass index (BMI) between 18 and 35. The study was approved by the institutional review boards of both academic centers, and all participants gave their written informed consent.

An analysis of the ethnic background in both countries was conducted. All women belonged to the white race. The PCOS$_{Ch}$ group was composed of women who were 90% Hispanic-Amerindian mixture, 7% Amerindian, and 3% other races. The PCOS$_{Ar}$ group was composed of 87% of European, predominantly Italian, descent; 10% Hispanic-Amerindian mixture; and 3% other ethnicities. The differences in the distribution pattern of ethnicities between the two groups was statistically significant (P<.001). Comparisons were made only between the Chilean and Argentinean country groups. We did not make comparisons between the various ethnic groups because it would have meant combining only 10% of the Argentinean group with 90% of the Chilean group; this would have left other two groups too small for analysis and ignored the potential lifestyle differences between the country groups.

The diagnosis of PCOS was established according to the Rotterdam criteria (1), including at least two of the following elements:

> Hyperandrogenism (H): modified Ferriman-Gallwey score ≥8 and/or total serum testosterone (T) ≥80 ng/dL (≥2.77 nmol/L).

> Ovulatory dysfunction (O): oligomenorrhea (cycles >35 days) or amenorrhea (no menses in the last 6 months), negative pregnancy test, and progesterone level <4 ng/mL (12.72 nmol/L) before beginning of the study.

> Polycystic ovaries at transvaginal ultrasound (PCOM): ≥12 follicles measuring 2–9 mm in diameter and/or increased ovarian volume (>10 mL) in at least one ovary.

The exclusion criteria were other causes of hyperandrogenism (Cushing syndrome, congenital adrenal hyperplasia, or androgen-secreting tumors), a previous diagnosis of type 2 diabetes mellitus and/or treatment with insulin-sensitizing drugs, or use of contraceptives, antiandrogens, or glucocorticoids 6 months before the beginning of the study. Moreover, all participants had normal thyroid function, normal prolactin levels, and a follicle-stimulating hormone (FSH) level in the

premenopausal range. All patients signed a written informed consent before entering the study, which was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of each health center.

Study Protocol

A complete clinical history was obtained for all participants, including their family and ethnic background. The estimation of their ethnic background was based on the two surnames of each family member. After the interview, a complete physical examination was performed with anthropometric measurements, including weight, height, waist circumference, waist-to-hip ratio, waist-to-height ratio, body mass index (BMI), systolic blood pressure, and diastolic blood pressure. The degree of hirsutism was determined according to the modified Ferriman-Gallwey score (14).

The studies were conducted during the early follicular phase (days 3 to 7) of a spontaneous cycle. Patients were admitted at 8:00 AM to the corresponding health center after a 12-hour fast, at which point an oral glucose tolerance test was performed (75-g glucose in 250 mL water), with glucose and insulin measurements in the basal sample and 120 minutes after the glucose load. Additionally in the basal sample, concentrations were determined of luteinizing hormone (LH), FSH, T, androstenedione ($\Delta 4$), dehydroepiandrosterone sulphate (DHEAS), 17-hydroxyprogesterone (17-OHP), and sex hormone-binding globulin (SHBG) as well as a lipid profile: total cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDL-C).

Glucose tolerance was evaluated using the criteria of the American Diabetes Association (ADA) (15). Impaired fasting glucose was defined as fasting glycemia >100 mg/dL and <126 mg/dL, and impaired glucose tolerance as a 2-hour glucose, after the glucose load, between 140 and 200 mg/dL. Insulin resistance was calculated through the homeostatic model assessment for insulin resistance (HOMA-IR) (16).

A transvaginal ultrasound examination was performed with a transducer of 3.8–7.5 MHz (SSD-4000; Aloka) in the $PCOS_{Ch}$ group, and with a transvaginal transducer of 5–9 MHz (Voluson 730 Expert; General Electric) in the $PCOS_{Ar}$ women. We identified PCOM according to the Rotterdam consensus as the presence of either ≥ 12 follicles measuring 2–9 mm in diameter and/or an ovarian volume >10 mL in one or more ovaries (1). In each group, the same operator performed all the ultrasound examinations. For comparisons between groups regarding ovarian volume, the average volume was considered.

Assays

Serum glucose was determined by the glucose oxidase method. The intra-assay coefficient of variation (CV) was <2.0%. Lipid profile was determined by standard colorimetric assay (Photometric Instrument 4010; Roche). For both groups, the intra-assay and interassay CVs were less than 10%. The low-density lipoprotein cholesterol (LDL-C) concentration was calculated by Friedewald's formula: LDL-C = TC − (HDL + Tg/5).

The insulin concentration was measured by radioimmunoassay (RIA) (Diagnostic Systems Laboratories) in the $PCOS_{Ch}$ patients (intra-assay and interassay CV: 5% and 8%, respectively), and by electrochemiluminescence in $PCOS_{Ar}$ patients (intra-assay and interassay CV: <10%). The HOMA-IR was calculated by the formula: (Basal glycemia × Basal insulin)/405. The presence of the metabolic syndrome was defined according to the criteria described in the National Cholesterol Education Program Adult Treatment Panel III guidelines (ATP III) (17).

In both populations, LH, FSH, and DHEAS were determined by electrochemiluminescence assays (Roche). Serum $\Delta 4$ and 17-OHP were analyzed by RIA. We determined SHBG by radioimmunometric assay (Diagnostic Products Corp.) in the $PCOS_{Ch}$ patients and by electrochemiluminescence in the $PCOS_{Ar}$ patients. Serum T was determined by RIA (Diagnostic Systems Laboratories) in the $PCOS_{Ch}$ patients and by electrochemiluminescence in $PCOS_{Ar}$ patients. All assays conducted in both PCOS populations had an intra-assay and interassay CV of <10%. The free androgen index (FAI) was calculated using the following formula: FAI= [T (nmol/L)/SHBG (nmol/L)] × 100 (18).

Statistical Analysis

Distribution was assessed using the Shapiro-Wilk test. Results are expressed as median and range. The Kruskal-Wallis test was used for comparisons between groups. The chi-square test was used for percentage comparisons. To establish relationships between dichotomous variables, the odds ratio (OR) with a 95% confidence interval (CI) was calculated by logistic regression analysis. All data were analyzed in the STATA 10.0 program (StataCorp). $P < .05$ was considered statistically significant.

RESULTS

Both the $PCOS_{Ch}$ and $PCOS_{Ar}$ groups were classified into the following four phenotypes: A: $PCOS_{Ch}$ n = 158, and $PCOS_{Ar}$ n = 104; B: $PCOS_{Ch}$ n = 23, and $PCOS_{Ar}$ n = 40; C: $PCOS_{Ch}$ n = 36, and $PCOS_{Ar}$ n = 41; D: $PCOS_{Ch}$ n = 3, and $PCOS_{Ar}$ n = 21. The percentage of distribution of the different PCOS phenotypes was as follows: for $PCOS_{Ch}$, A 72%; B 10.5%; C 16.5%, and D 1%; and for $PCOS_{Ar}$, A 50.4%; B 19.4%; C 20%, and D 10% (chi-square = 14.5, $P < .002$).

Regarding the anthropometric variables, BMI was statistically significantly higher in the total $PCOS_{Ch}$ group, but the waist circumference, waist-to-hip ratio, and waist-to-height ratio were comparable between both groups. Diastolic blood pressure was statistically significantly higher in the $PCOS_{Ar}$ group. Family background was established considering both the paternal and maternal first- and second-degree relatives. Regarding family background, 64.5% of $PCOS_{Ch}$ women had a family history of diabetes, and 30% a family history of hypertension. In $PCOS_{Ar}$ women, 27% had a family background of diabetes and 46.3% of hypertension (Supplemental Table 1, available online).

Age was comparable between the $PCOS_{Ch}$ and $PCOS_{Ar}$ women in each phenotype. Figure 1 shows the clinical parameters of the statistically significant differences between the

FIGURE 1
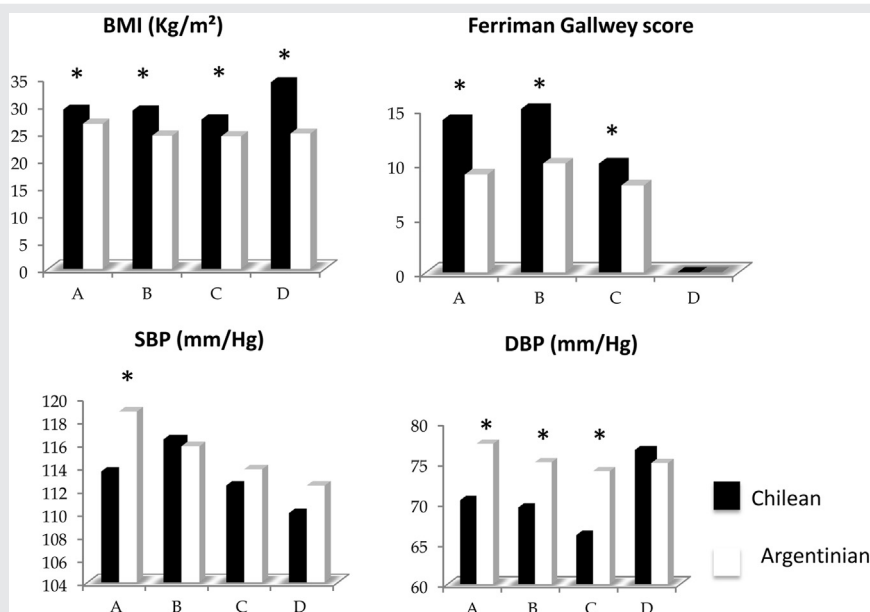
Clinical features in Chilean and Argentinian women with polycystic ovary syndrome according to the different phenotypes. *P<.05.

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$PCOS_{Ch}$ and $PCOS_{Ar}$ women in each of the four phenotypes. The $PCOS_{Ch}$ women showed a statistically significantly higher BMI in all of the phenotypes and a statistically significantly higher Ferriman-Gallwey score in phenotypes A, B, and C, than the $PCOS_{Ar}$ women.

Among the $PCOS_{Ar}$ women with phenotype A, a statistically significantly higher systolic blood pressure was found than in $PCOS_{Ch}$ women. For diastolic blood pressure, $PCOS_{Ar}$ women exhibited statistically significantly higher blood pressure in phenotypes A, B, and C compared with the $PCOS_{Ch}$ women.

Table 1 shows the hormone profile and ovarian volume in the $PCOS_{Ch}$ and $PCOS_{Ar}$ groups according to the different phenotypes. The concentrations of LH and FSH were similar in the A, B, and C phenotypes for both populations, and the LH/FSH ratio was comparable in the four phenotypes between both populations. Different assays were used to assess T and SHBG, so these measurements and the FAI calculation were not compared between the $PCOS_{Ch}$ and $PCOS_{Ar}$ groups. When analyzing the two populations separately, both exhibited a statistically significant difference in T concentration between phenotypes A, B, and C with respect to D. The same occurred with the FAI. Nevertheless, this information has to be taken carefully in the $PCOS_{Ch}$ group as the size of the D phenotype was very small.

Regarding SHBG concentrations, in the $PCOS_{Ar}$ patients there was a statistically significant difference between phenotypes A and D, whereas in the $PCOS_{Ch}$ patients there was no statistically significant difference when comparing the four phenotypes. The Δ4 concentration was higher in the $PCOS_{Ar}$ group and reached statistical significance in phenotypes B and C in comparison with the $PCOS_{Ch}$ group. The DHEAS con-

centration tended to be higher in the $PCOS_{Ar}$ group, reaching statistical significance only in phenotype C.

The 17-OHP concentration and the average ovarian volumes were discretely higher in phenotype A for $PCOS_{Ar}$. This difference reached statistical significance.

Metabolic Profile

Table 2 shows the metabolic profile of both populations divided into phenotypes. The 2-hour glucose levels tended to be higher in the $PCOS_{Ch}$ group, and were statistically significantly higher in phenotypes C and D with respect to $PCOS_{Ar}$ (this latter comparison has to be taken carefully as the $PCOS_{Ch}$ D group was very small).

In the $PCOS_{Ch}$ patients, insulin concentration and HOMA-IR were comparable between the four phenotypes. In the $PCOS_{Ar}$ patients, insulin concentration and HOMA-IR were statistically significantly higher in phenotype A compared with C. The finding of type 2 diabetes was generally very low and comparable between both PCOS populations.

The triglyceride concentration was higher in the $PCOS_{Ch}$ group for all phenotypes, and was statistically significant in phenotypes A and B. The same occurred with LDL-C, which was statistically significantly higher in the $PCOS_{Ch}$ group for the A, B, and C phenotypes compared with $PCOS_{Ar}$. The HDL-C level was lower in all the phenotypes of $PCOS_{Ch}$, which was statistically significant for the A, B, and C phenotypes compared with the $PCOS_{Ar}$ group. The triglycerides concentration was statistically significantly higher in the $PCOS_{Ch}$ group for all phenotypes compared with $PCOS_{Ar}$.

Supplemental Table 2 (available online) shows the prevalence of the metabolic syndrome for both total groups

TABLE 1

Hormone profile and ovarian volume in Chilean and Argentinian women with PCOS according to the different phenotypes.

	A		B		C		D	
	PCOS_Ch (n = 158)	PCOS_Ar (n = 104)	PCOS_Ch (n = 23)	PCOS_Ar (n = 40)	PCOS_Ch (n = 36)	PCOS_Ar (n = 41)	PCOS_Ch (n = 3)	PCOS_Ar (n = 21)
LH (IU/L)	8.7 (1–31.4)	9.1 (3.1–24)	8 (2.2–16.4)	8.6 (3.2–12.8)	3.9 (1–14.7)	7 (4.7–12.7)	6 (5.3–8.1)[a]	9.8 (6.1–19.5)
FSH (IU/L)	5.4 (0.9–14)	5.4 (3–11)	4.6 (1.8–8.3)	5.2 (2.1–9.9)	4.8 (1.6–13.7)	5.1 (3.2–7.3)	4.1 (3.2–4.3)[a]	6.8 (3.2–9.3)
LH/FSH	1.7 (0.3–6.2)	1.6 (0.7–3.5)	1.4 (0.4–3.9)	1.7 (0.6–3.6)	0.99 (0.3–8.3)	1.5 (0.6–2.4)	1.9 (1.2–1.9)	1.7 (0.9–2.5)
T (ng/mL)	0.94 (0.24–2.05)	0.89 (0.76–1.76)	0.93 (0.38–1.41)	0.9 (0.8–1.8)	0.85 (0.34–2.27)	0.87 (0.8–1.3)	0.5 (0.44–0.52)[b]	0.29 (0.21–0.65)[b]
SHBG (nmol/L)	25.4 (9.8–128.6)	39.6 (16–161)	27 (6.61–76)	46.7 (16–100)	37.7 (4.6–137.4)	51.1 (14.3–100)	24 (17–27)	59.2 (29.2–105.1)[c]
FAI	12.17 (1.41–48.82)	8.72 (1.72–25.04)	10.4 (2.6–38.29)	7.3 (3.3–21.8)	8.6 (3.1–49.3)	6.1 (2.8–19.0)	3.7 (3.3–6.7)[b]	1.98 (0.78–5.22)[b]
Δ4 (ng/mL)	3.1 (0.8–7.1)	4.6 (2.3–8)	2.9 (1–5.4)[a] n = 16	4.2 (2.2–6.8)	3.2 (0.9–7.4)[a]	4.1 (2.7–7)	2 (1.7–2.3)	2.5 (1–7.1)
DHEAS (μg/dL)	247.1 (194–1,970) n = 88	343 (30–607)	248 (167–1,800) n = 11	375 (178–557)	272 (181–580)[a] n = 25	350 (170–570)	186.6 (172–201)	206.1 (124–301)
17-OHP (ng/mL)	1.5 (0.2–4.6)[a]	1.8 (0.8–3.6)	1.4 (0.1–3.3)	1.7 (0.8–2.3)	1.5 (0.5–3.5)	1.7 (0.9–2.7)	1.2 (1–1.3)	0.89 (0.5–1.7)
Ovarian volume (mL)[d]	10 (2.5–32.9)[a]	11.5 (4.3–25)	6.4 (2.6–8.7)	5.5 (3.6–8.3)	9.8 (4.9–26.3)	10.9 (6–19.5)	8.7 (8.3–15.6)	10.5 (8–30.9)

Note: Comparisons regarding phenotype D of the Chilean PCOS (PCOS_Ch) group have to be taken carefully as the size of the group is very small. Testosterone and SHBG levels were measured by radioimmunoassay in PCOS_Ch patients and by electrochemiluminescence in Argentinian PCOS (PCOS_Ar) patients. Thus, they cannot be directly compared. Δ4 = androstenedione; DHEAS = dehydroepiandrosterone sulfate; FAI = free androgen index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; 17-OHP = 17-hydroxiprogesterone; PCOS = polycystic ovary syndrome; SHBG = Sex hormone-binding globulin; T = total testosterone.
[a] P<.05 compared with PCOS_Ar from the same phenotype.
[b] P<.05 compared with A, B, and C from the same phenotype.
[c] P<.05 compared with A from the same PCOS group.
[d] Average ovarian volume.

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(PCOS_Ch= 52.9 % vs. PCOS_Ar = 36.5 %; P<.05). Analyzing the metabolic syndrome by each phenotype, the PCOS_Ch women showed a higher prevalence of the metabolic syndrome in all phenotypes; this was statistically significant in the B and D phenotypes with respect to PCOS_Ar (Table 3).

The percentage of 2-hour glucose >140 mg/dL in PCOS_Ch was statistically significantly higher in phenotypes B, C, and D compared with PCOS_Ar. For the percentage of women with increased waist circumference (>88 cm), both populations were comparable between the different phenotypes, except for phenotype D in whom it was higher in PCOS_Ch compared with PCOS_Ar. The percentage of elevated blood pressure (≥130/85) was higher in the PCOS_Ar women in the A and D phenotypes. For lipid alterations, the PCOS_Ch group showed a statistically significantly higher percentage of HDL-C <50 mg/dL in the A, B, and C phenotypes; similarly, the percentage of triglycerides >150 mg/dL was statistically significantly higher in the B, C, and D phenotypes in comparison with the PCOS_Ar group.

Multivariate Analysis

In each PCOS group, we evaluated the odds ratio (OR) for the metabolic syndrome according to the phenotype. Multivariate analysis by logistic regression showed that in the PCOS_Ar group there is a statistically significant reduction in the OR for the metabolic syndrome in phenotypes B (OR 0.36; 95% CI, 0.14–0.91; P=.03), C (OR 0.24; 95% CI, 0.08–0.66; P=.006), and D (OR 0.28; 95% CI, 0.08–1.04; P=.06) when compared with phenotype A. In the PCOS_Ch group, the OR for the metabolic syndrome was not different between phenotype A versus B (OR 1.77; 95% CI, 0.5–6; P=.36), C (OR 0.56; 95% CI, 0.5–1.98; P=.37), or D (OR 2.5; 95% CI, 0.21–29.1; P=.45).

Note that all comparisons regarding the PCOS_Ch D group, although statistically significant, are susceptible to bias: this group was composed of only three patients.

DISCUSSION

In the present study, we analyzed two groups of women with PCOS from two academic centers in the cities of Santiago de Chile and Córdoba, Argentina. It should be highlighted that this is the first study comparing two groups of Latin American women in whom the same criteria for the diagnosis of PCOS were used, whose ages were similar but ethnic conformation was different. The distribution of the PCOS phenotypes was different in the two groups studied (Chilean and Argentinian). Both groups showed a higher prevalence of the classic phenotypes (A and B), as has been described in many studies of Western women with PCOS (2). The D phenotype was more prevalent in PCOS_Ar (10%), similar to what has been described in the women with PCOS of southern Europe (19). Classification of PCOS into different Rotterdam phenotypes has allowed the identification of the groups who have a greater cardiometabolic risk (20–23). The presence of hyperandrogenism seems to be strongly related to the development of metabolic alterations, with phenotypes A and B having the highest cardiovascular risk whereas

TABLE 2

Metabolic profile in Chilean and Argentinian women with PCOS according to the different phenotypes.

	A		B		C		D	
	$PCOS_{Ch}$ (n = 158)	$PCOS_{Ar}$ (n = 104)	$PCOS_{Ch}$ (n = 23)	$PCOS_{Ar}$ (n = 40)	$PCOS_{Ch}$ (n = 36)	$PCOS_{Ar}$ (n = 41)	$PCOS_{Ch}$ (n = 3)	$PCOS_{Ar}$ (n = 21)
Fasting glucose (mg/dL)	83 (57–134)	87 (64–121)	84 (67–107)	83 (70–110)	83 (67–126)	82 (64–103)	78 (66–99)	82 (70–106)
2-h glucose (mg/dL)	98 (42–210)	89 (50–196)	92 (45–148)	88 (60–170)	94 (60–229)[a]	83 (63–119)	128[a] (86–149)	81 (68–140)
Fasting insulin (µIU/mL)	16 (2.5–99)	12 (3–34)	14 (4.7–78)	8.5 (3.2–30)	15.7 (3.7–34)	7.7 (2.1–16)[b]	17 (10–21)	10 (3–22)
2-h insulin (µIU/mL)	77.4 (8.2–868)	42.4 (7.3–136)	129.9 (24.7–159)	41.7 (17.6–127)	71.9 (18.6–300)	ND	51 (20–91)	ND
HOMA-IR	3.5 (1.5–21.2)	2.6 (0.5–9.5)	2.4 (0.98–20.6)	1.8 (0.55–7.4)	3 (0.7–8.7)	1.5 (0.3–4)[b]	4.1 (1.6–4.16)	2.1 (0.5–5.6)
Type 2 diabetes (%)	1.3	0	4.3	0	0	0	0	0
Cholesterol (mg/dL)	195 (118–316)[a]	179 (108–261)	202 (8,149–256)[a]	175 (117–260)	185 (130–273)	172 (96–217)	177 (141–235)	171 (110–216)
LDL-C (mg/dL)	130.6 (57.1–218)[a]	106 (34–185)	130 (44–194)[a]	103 (48–176)	111 (63–186)[a]	99 (47–155)	108 (65–136)	100 (60–145)
Triglycerides (mg/dL)	135 (55–388)[a]	109.5 (45–324)	131 (64–230)[a]	80 (44–247)	108 (62–283)[a]	77 (36–170)	167 (74–215)[a]	79 (42–200)
HDL-C (mg/dL)	37.6 (11–74)[a]	50 (26–77)	40.6 (28.7–56.7)[a]	55.5 (30–81)	38 (30–76)[a]	54 (26–86)	43 (36–54)	50 (30–82)

Note: Comparisons regarding phenotype D of the Chilean PCOS ($PCOS_{Ch}$) group have to be taken carefully as the size of the group is very small. Insulin levels were measured by radioimmunoassay in the $PCOS_{Ch}$ patients and by electrochemiluminescence in Argentinean PCOS ($PCOS_{Ar}$) patients. Thus, they cannot be directly compared. ND = no data; PCOS = polycystic ovary syndrome.
[a] $P < .05$ compared with $PCOS_{Ar}$ from the same phenotype.
[b] $P < .05$ compared with A from the same PCOS group.

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phenotype D (normoandrogenic) is comparable to the control women in terms of metabolic profile (3, 23).

Previous studies in which different ethnic groups have been assessed have shown evidence of the profound impact that ethnicity may have on the metabolic parameters of the PCOS phenotypes (9, 23–28). In our study, $PCOS_{Ch}$ women had a higher BMI in all phenotypes compared with the $PCOS_{Ar}$ women; the latter had higher blood pressure with a higher prevalence of hypertension accordingly compared with the $PCOS_{Ch}$ women.

In the $PCOS_{Ar}$ group, the surrogate parameters of insulin resistance and dysglycemia improved from phenotypes A to C. In contrast, this phenomenon was not observed in the $PCOS_{Ch}$ group, in whom these disturbances were found throughout the phenotypes. When comparing the lipid profile between both groups, we observed that the $PCOS_{Ch}$ women showed greater alterations in LDL-C, triglycerides, and HDL-C in all phenotypes, constituting a more atherogenic profile than found in the $PCOS_{Ar}$ women. All these findings described in the $PCOS_{Ch}$ group could constitute a worse metabolic profile independent of the degree of hyperandrogenism.

Regarding type 2 diabetes, its prevalence was generally low, probably because the women in the groups analyzed were under 40 years old. Additionally, after patients who had previously received diagnoses of diabetes or glucose intolerance were specifically excluded from the study, only in the $PCOS_{Ch}$ patients were cases of type 2 diabetes diagnosed through the OGTT. These early alterations in glucose metabolism are comparable with what has been described in other groups, such as the Hispanic and South Asian PCOS patients living in California (10).

When comparing the metabolic syndrome in the $PCOS_{Ar}$ group, we found that the A phenotype exhibited a higher prevalence than the B, C, and D phenotypes. In these last three phenotypes, there was a significant decrease in the OR for the metabolic syndrome, comparable with the group of healthy Argentinian women (14%) (29). In $PCOS_{Ch}$, the prevalence of the metabolic syndrome in all the phenotypes was slightly higher than that described in healthy women of the same age (41.7%) (30). We found that the OR for the metabolic syndrome was independent of the phenotype evaluated. This observation differs from the findings of Wiltgen and Spritzer (31) in Brazilian women with PCOS.

The characteristics of the D phenotype in the $PCOS_{Ch}$ group are difficult to interpret because the sample was very small (n = 3) and thus susceptible to bias. Even so, the D phenotype of both groups showed a higher BMI and greater metabolic alterations than the D phenotype of other groups who have been studied (2, 3).

To explain the findings regarding the metabolic profile of these two groups of women with PCOS, one must consider the ethnic composition of each group. As previously mentioned, the population of the city of Córdoba has been influenced by a large, mainly Italian and secondarily Spanish immigration wave (11). If we analyze the metabolic characteristics of European women, especially Italians, we can see that they show fewer alterations in glucose metabolism, the metabolic syndrome becomes apparent at older ages, and

TABLE 3

Metabolic syndrome and its components in Chilean and Argentinian women with PCOS according to the different phenotypes.

	A		B		C		D	
	SOP_{Ch} (n = 158)	SOP_{Ar} (n = 104)	SOP_{Ch} (n = 23)	SOP_{Ar} (n = 40)	SOP_{Ch} (n = 36)	SOP_{Ar} (n = 41)	SOP_{Ch} (n = 3)	SOP_{Ar} (n = 21)
MS (%)[a]	44	36.2	58[b]	15	30	12.2	66[b]	14.2
Fasting glucose >100 mg/dL (%)	12	19	5.2	2.5	8.1[b]	2.4	66[b]	9.5
2-h glucose >140 mg/dL (%)	20	19	15.7[b]	2.5	16.2[b]	0	66[b]	4.7
Waist circumference >88 cm (%)	59.4	71.2	50	41.9	50	39	100[b]	52.1
Hypertension (%) ≥ 130/85 mm Hg	8.8[b]	25	10	10	5.4	14.6	0[b]	14.2
HDL 50 mg/dL (%)	82.9[b]	52.2	85[b]	32.6	85.7[b]	29.3	66.6	52.2
Triglycerides ≥ 150 mg/dL (%)	40	31.8	45.5[b]	21	35.7[b]	4.9	66.6[b]	13

Note: Comparisons regarding phenotype D of the $PCOS_{Ch}$ group have to be taken carefully as the size of the group is very small. HDL = high density lipoprotein; MS = metabolic syndrome; PCOS = polycystic ovary syndrome.
[a] Metabolic syndrome according to ATP III (14).
[b] $P < .05$ compared to $PCOS_{Ar}$ from the same phenotype.

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there is a higher percentage of hypertension than found in Hispanic women of comparable ages (2, 6, 19). As mentioned earlier, 65% of the Chilean population is of Spanish descent, with an average proportion of 60% Hispanic and 40% Amerindian. When we analyze the metabolic profile of Spanish women, we can see that they have a higher trend toward obesity with higher risk of the metabolic syndrome at an early age (<40 years old) and type 2 diabetes, which is similar to the metabolic profile of the $PCOS_{Ch}$ group (2, 10).

It is important to mention that in Hispanic patients the antecedent of a first-degree-relative family member with diabetes is a better predictor for the metabolic syndrome than hyperandrogenemia (10). Regarding the Amerindian component of the $PCOS_{Ch}$ group, the most prevalent Amerindian group in Chile are the Mapuches. Some studies have shown that when the Mapuche people migrate to the urban environment they have a higher risk for developing the metabolic syndrome (32).

During the last decades, people from Latin America have undergone a transition to a less healthy lifestyle (33). The prevalence of obesity is 25% in Chile (34) and 19.4 % in Argentina (35). According to the Food and Agriculture Organization (FAO), the food balance sheets of both countries have some differences in terms of calorie consumption. In this regard, in Argentina animal product consumption is 929 kcal/capita/day and in Chile is 717 kcal/capita/day, but consumption of products such as butter and sugar is very similar. The total calorie intake in Chile is 2,920 kcal/capita/day, and in Argentina is 3,000 kcal/capita/day. Nevertheless, the macronutrient distribution is a little different: for Chile, with 61% carbohydrates, 12% protein, and 27% fat; and for Argentina, with 55% carbohydrates, 13% protein, and 32% fat (www.fao.org). There has been no specific study comparing lifestyle in more detail between the two countries, factors that could explain part of the differences we have observed between our patients.

Ethnic diversity associated to the sociocultural habits of different countries are elements of capital importance in the analysis of the PCOS phenotypes (2, 4). Considered to be a multifactorial disorder, PCOS develops through a combination of genetic risk factors and triggering environmental factors. The importance of knowing the genetic background resides in adopting lifestyles that may delay the appearance of the pathology and its possible complications. For this reason, it is important to know the local phenotypic characteristics of women with PCOS so that a correct therapeutic and preventive approach may be devised toward the prevalent metabolic aspects.

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SUPPLEMENTAL TABLE 1

Anthropometric variables and family background in Chilean and Argentinian total PCOS groups.

	Chilean (n = 220)	Argentinian (n = 206)	*P* value
Age (y)	26 (18–39)	26 (18–39)	NS
BMI (kg/m^2)	29 (18.2–35)	24.7 (18–35)	<.05
Waist circumference (cm)	90 (59–126)	88 (68–120)	NS
WHR	0.86 (0.68–1.1)	0.87 (0.74–1.5)	NS
WHtR	0.56 (0.38–0.75)	0.54 (0.42–0.64)	NS
SBP (mm/Hg)	112 (100–160)	120 (100–150)	NS
DBP (mm/Hg)	70 (50–100)	80 (60–95)	<.05
Family history of diabetes	64.5%	27%	<.05
Family history of hypertension	30%	46.3%	<.05

Note: Values are median and range. Comparisons assessed with Mann-Whitney test for continuous variables and chi-square test for percentages. BMI = body mass index; DBP = diastolic blood pressure; NS = not statistically significant; PCOS = polycystic ovary syndrome; SBP = systolic blood pressure; WHR = waist to hip ratio; WHtR = waist to height ratio.

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SUPPLEMENTAL TABLE 2

Percentage of metabolic syndrome and its components in the total Chilean and Argentinian PCOS groups.

	Chilean (n = 220)	Argentinian (n = 206)	*P* value
MS (%)[a]	52.9	36.5	<.05
Fasting glucose >100 mg/dL (%)	11.43	11.65	NS
Glucose 120 min >140 mg/dL (%)	14.35	5.83	<.05
Waist circumference >88 cm (%)	56.8	52.9	NS
Hypertension ≥130/85(%)	11.28	15.05	NS
HDL <50 mg/dL (%)	81.08	41.26	<.05
Tg >150 mg/dL(%)	41.44	20.87	<.05

Note: Differences assessed using the chi-square test. HDL = high density lipoprotein; MS = metabolic syndrome; PCOS = polycystic ovary syndrome; Tg = triglycerides.
[a] Metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III guidelines (ATP III) (17).

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