Metabolic Features of Women With Polycystic Ovary Syndrome in Latin America: A Systematic Review

Lucas Bandeira Marchesan1,2, Ramon Bossardi Ramos2† and Poli Mara Spritzer1,2,3*

1 Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, 2 Post-graduate Program in Endocrinology, Medicine School, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, 3 Department of Physiology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Background: Polycystic ovary syndrome (PCOS) is an endocrine disorder that commonly affects women of childbearing age and has been associated with metabolic and reproductive abnormalities. Only a few studies have investigated metabolic traits in women with PCOS in Latin America. Therefore, we conducted a systematic review to provide an overview of the available evidence on the metabolic profile of Latin American women with PCOS.

Methods: We searched PubMed, Cochrane Central Register of Controlled Trials, and Embase databases for cross-sectional, case-control, or cohort studies focusing on populations of countries in South and Central America and Mexico, published until October 31, 2019. We selected studies that reported the diagnostic criteria for PCOS. In the absence of a control group, we included studies if they reported relevant metabolic data.

Results: The initial search yielded 4878 records, of which 41 studies were included in the systematic review. Sample sizes ranged from 10 to 288 in PCOS groups and from 10 to 1500 in control groups. The prevalence of phenotypes A and B (classic PCOS) ranged from 65.8% to 87.5% as reported in studies from Argentina, Brazil, and Chile. Metabolic syndrome ranged from 33.3% to 44.0% for phenotype A, from 15.0% to 58.0% for phenotype B, from 11.9% to 36.0% for phenotype C, and from 14.2% to 66.0% for phenotype D. Women with PCOS had higher body mass index, waist circumference, blood pressure, glucose, and homeostasis model assessment index as well as a more adverse lipid profile than those without PCOS.

Conclusions: Evidence from the present systematic review suggests that anthropometric and metabolic profiles are worse in women with PCOS who live in different Latin American countries than in women without PCOS living in the same region. Additional studies assessing metabolic comorbidities, such as diabetes, and distinct PCOS phenotypes in different Latin American countries are warranted and may
INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine condition that commonly affects women of childbearing age. The etiology of PCOS is uncertain, but the available evidence strongly suggests that its onset is triggered by environmental, genetic, and behavioral factors that interact in a complex manner (1–3).

Obesity affects the majority of women with PCOS, placing them at increased risk for impaired glucose tolerance, metabolic abnormalities, and type 2 diabetes (4–7), and possibly for cardiovascular and cerebrovascular events and venous thromboembolism (2, 8–11). Insulin resistance with compensatory hyperinsulinemia affects approximately 65% to 70% of women with PCOS (12). An estimated 30%–40% of patients with PCOS have impaired glucose tolerance, and 7.5%–10% have type 2 diabetes (13–15). While the prevalence of insulin resistance is high in both lean and obese women with PCOS (16), the presence of obesity may exacerbate the development of metabolic comorbidities and cardiovascular risk factors (17–19).

Many studies have investigated the prevalence of PCOS and related metabolic abnormalities in different continents. A recent meta-analysis showed a lower prevalence of PCOS in Chinese women than in white (Caucasian), Middle Eastern (Iranian and Turkish), and black (African American and Afro-Brazilian) women (20). However, the prevalence of PCOS and metabolic profile has not yet been described in several ethnic groups, especially in Latin American populations (6, 17, 21, 22), except for a recent meta-analysis of metabolic disturbances in Brazilian women with PCOS (23). Therefore, we conducted the present systematic review to provide an overview of the available evidence on the metabolic profile of Latin American women with PCOS, as well as the frequency of different PCOS phenotypes in this population.

METHODS

Search Strategy and Study Selection

A systematic review was designed and described in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. This systematic review was registered with PROSPERO under number CRD42016038537. We searched PubMed, Cochrane Central Register of Controlled Trials, and Embase databases for cohort, case-control, cross-sectional, and prevalence studies with populations of South and Central America and Mexico, published until October 31, 2019. We set no language or publication date restrictions. To identify eligible studies, we used medical subject headings (MeSH) for PubMed and Ovid Tree terms for Embase. We used the following search strategy for PubMed, with equivalent terms being used in the other databases: “Polycystic Ovary Syndrome” [MeSH] OR “Ovary Syndrome, Polycystic” OR “Syndrome, Polycystic Ovary” OR “PCOS” OR “Polycystic Ovarian Syndrome” OR “Ovarian Syndrome, Polycystic” OR “Polycystic Ovary Syndrome 1” AND “Body Mass Index” [MeSH] OR “Metabolic Syndrome” OR “Glucose Intolerance” [MeSH] OR “Intolerance, Glucose” OR “Intolerances, Glucose” OR “Diabetes Mellitus, Type 2” [MeSH]. We performed additional searches in review articles and research articles focusing on PCOS.

We selected only studies that clearly defined the diagnostic criteria for PCOS and that included at least one of the following variables in the analysis: waist circumference (WC), body mass index (BMI), glucose levels, lipid profile, homeostasis model assessment of insulin resistance (HOMA-IR), blood pressure, diabetes mellitus, metabolic syndrome (MetS), PCOS prevalence, and milder PCOS phenotypes. Eligibility assessment was done by screening the titles and abstracts of all articles selected, and when abstracts did not provide the necessary information, the full text of the article was reviewed. This was performed independently, in a standardized manner, by two investigators (RBR and LBM). Disagreements between reviewers were resolved with discussion. If a consensus was not reached, a third investigator (PMS) was consulted. When articles had missing information, we contacted the authors for further information. In the case of duplicate data that had been published more than once, we opted to include the most complete study. In addition, the reference lists of all articles fulfilling the eligibility criteria were hand searched to identify other essential citations.

Data Extraction and Quality Control Assessment

Data were individually extracted by two researchers (LBM and RBR), and agreement was pursued in all extracted items. When an agreement could not be achieved, data extraction discrepancies were resolved by referring to the original publication or by consulting a third reviewer (PMS). Data extracted from each study included: name of the authors, country, publication year, type of study, characteristics of the population, diagnostic criteria, total sample size, and outcomes of interest in the PCOS and control groups. We assessed the quality of observational studies included in this systematic review using the Newcastle-Ottawa Scale (NOS). The NOS uses a “star
system” to judge the quality of the studies in three broad perspectives: selection of the study groups, comparability of the groups, and ascertainment of the outcome of interest. Each item contains a sequence of alternative questions to be answered by the investigators. Then, a star rating system allows the semi-quantitative analysis of article quality. No statistical quantitative meta-analysis was performed due to study heterogeneity.

RESULTS

Flowchart of Study Selection

Figure 1 provides a flowchart summarizing the study selection process. The initial search yielded 4878 records. Of these, 41 studies from 40 reports were included in the systematic review. All of them were observational studies: 24 cross-sectional studies, 16 case-control studies, and one cohort study. Publication years ranged from 2004 to 2019. PCOS group size ranged from 10 to 288 participants, and control group size ranged from 10 to 1500 participants. Age ranged from 20.6 to 31.1 years for women with PCOS and from 22.7 to 34.5 years for non-PCOS controls.

Characteristics of Included Studies

Table 1 presents the characteristics of studies, which included populations from Argentina (n=3) (24–26), Brazil (n=27) (27–53), Chile (n=8) (26, 54–60), Venezuela (n=2) (62, 63), and Mexico (n=1) (61). Most studies used the Rotterdam criteria to diagnose PCOS, except for one study conducted in Argentina (25), one in Brazil (27), and three in Chile (54, 58, 60), all of which used the National Institutes of Health (NIH) criteria. The two studies from Venezuela (62, 63) used criteria defined by the authors. Sixteen studies had no control group for comparison (24, 26, 27, 35, 38, 39, 43–45, 47, 51, 53, 57, 59, 63), and six had BMI-matched controls without PCOS for comparison (28, 29, 34, 40, 50, 55). NOS score was 7-9 in 33 studies and ≤ 6 in 7 (Table 2).

Qualitative Data

Overweight (BMI 25-29.9 kg/m²) or obesity (BMI ≥ 30 kg/m²) was prevalent among Latin American women with PCOS (Figure 2). BMI ranged from 24.2 to 33.3 kg/m² in women with PCOS. Most studies comparing women with PCOS versus BMI-unmatched controls showed higher BMI in PCOS groups.
(25, 30–33, 42, 46, 48, 49, 52, 54, 56, 58, 60). Several studies also assessed HOMA-IR, a marker of insulin resistance, in women with PCOS (Figure 3). HOMA-IR was > 2.5 in women with PCOS in 16 studies, six of them with obese participants (24, 31, 33, 41, 48, 58) and the others with overweight women (25, 28–30, 34, 45, 49, 52, 59, 62). In six studies HOMA-IR was ≤ 2.5 (37, 40, 44, 47, 60, 61), all of them with overweight participants. Seventeen studies compared HOMA-IR between women with PCOS and non-PCOS controls. HOMA-IR was higher in women with PCOS than in controls in 13 studies, 10 BMI-unmatched (25, 30, 31, 33, 37, 48, 49, 52, 58, 62) and 3 BMI-matched (28, 29, 34). While HOMA-IR was > 2.5 in most studies from Argentina, Brazil, Chile, and Venezuela, it was < 2.5 in the only included study from Mexico (61) (Figure 3).

Figure 4 summarizes the variation of MetS components among studies of women with PCOS in Latin American countries. Central obesity (WC ≥ 88 cm) was prevalent among women with PCOS, who had higher WC values than controls in 13 of the 20 studies that reported this information (Supplementary Table 1).

Fifteen studies reported blood pressure data for PCOS and control groups (25, 28, 30–33, 40–42, 46, 49, 55, 58, 60, 62) (Figure 4). In nine of these studies, women with PCOS had higher systolic (SBP) and/or diastolic blood pressure (DBP) than controls (28, 30–33, 42, 46, 49, 58). One study evaluated blood pressure as a MetS component and found a higher prevalence of this criterion in the PCOS group, considering a 130/85 mm Hg cutoff point (35.1% vs. 7.1%, p = 0.005, PCOS vs. controls) (46).
TABLE 2 | Newcastle-Ottawa quality (NOS) assessment scale for studies included in the systematic review.

| Author           | Year | Selection | Comparability | Exposure/Outcome |
|------------------|------|-----------|---------------|-----------------|
| Belli, et al.    | 2004 | ***       | ***           | **              |
| Tellechea, et al.| 2013 | ***       | ***           | **              |
| de Quevara, et al.|2014  | ***       | ***           | **              |
| Santana, LF, et al.|2004  | ***       | ***           | **              |
| Costa LO, et al. | 2008 | ***       | ***           | **              |
| Wilgten D, et al.| 2009 | ***       | ***           | **              |
| Cerqueira J, et al.| 2010 | **       | ***           | **              |
| Wilgten D, et al.| 2010 | ***       | ***           | **              |
| Azevedo MF, et al.|2011  | ***       | ***           | **              |
| Melo AS, et al.  | 2011 | ***       | ***           | **              |
| Rocha MP, et al. | 2011 | ***       | ***           | **              |
| Costa, et al.    | 2012 | ***       | ***           | **              |
| Galbiatti L, et al.|2012  | ***       | ***           | **              |
| Kogure GS, et al.| 2012 | ***       | ***           | **              |
| Pedrosa DCC, et al.|2012  | ***       | ***           | **              |
| Pontes AG et al. | 2012 | ***       | ***           | **              |
| Lauria PB, et al.| 2013 | ***       | ***           | **              |
| Oliveira RS, et al.| 2013 | ***       | ***           | **              |
| Radavelli-Bagatini S, et al.|2013  | ***       | ***           | **              |
| Avila MA, et al. | 2014 | ***       | ***           | **              |
| de Medeiros SF, et al.|2014  | ***       | ***           | **              |
| Maciel, et al.   | 2014 | ***       | ***           | **              |
| Ramos RB, et al. | 2015 | ***       | ***           | **              |
| Soares, et al.   | 2016 | ***       | ***           | **              |
| Carvalho, et al. | 2017 | ***       | ***           | **              |
| Graff, et al.    | 2017 | ***       | ***           | **              |
| Simões, et al.   | 2017 | ***       | ***           | **              |
| Wanderley, et al.| 2018 | ***       | ***           | **              |
| Xavier, LB, et al.|2018  | ***       | ***           | **              |
| Tavares A, et al.| 2019 | ***       | ***           | **              |
| Bravo, et al.    | 2005 | ***       | ***           | **              |
| Cerda C, et al.  | 2007 | ***       | ***           | **              |
| Codner, et al.   | 2007 | ***       | ***           | **              |
| Vigli, et al.    | 2007 | ***       | ***           | **              |
| Marques, et al.  | 2008 | ***       | ***           | **              |
| Echiburú, et al.| 2014 | ***       | ***           | **              |
| Echiburú, et al.| 2016 | ***       | ***           | **              |
| Moran C, et al.  | 2010 | ***       | ***           | **              |
| Roa Barrios, et al.|2009  | ***       | ***           | **              |
| Quintero-Castillo, et al.|2010  | ***       | ***           | **              |

Quality of selection for case/control (minimum 1 – maximum 4 stars); Comparability (minimum 0 – maximum 2 stars); Exposure (minimum 1 – maximum 3 stars).

Quality of selection adapted for cross-sectional/cohort studies (minimum 0 – maximum 5 stars); Comparability (minimum 0 – maximum 2 stars); outcome (minimum 0 – maximum 3 stars).

Another study found higher SBP and DBP only in late reproductive-age (35–40 years) women with PCOS (60). Blood pressure levels were homogeneously distributed across countries. However, in all four studies from Chile, where these data were available, the mean SBP and DBP would be classified as “normal” according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) definition of high blood pressure (64) (Supplementary Table 1).

Fasting glucose was measured in 31 studies (25, 27–35, 37–41, 44–52, 54, 55, 57–60, 62). Glucose levels ranged from 79 to 125.2 mg/dL in women with PCOS. In six of 21 studies (25, 30, 32, 33, 54, 58), women with PCOS had higher glucose levels than controls (Supplementary Table 2). Mean fasting glucose was homogeneously distributed across countries, and in most of them mean glucose levels were within the reference range. However, in two studies from Brazil (37, 52) and in one from Chile (58), mean fasting glucose was within the prediabetes range in patients with PCOS (Figure 4).

Regarding lipid profile, 26 studies showed triglyceride levels ranging from 81 to 157.8 mg/dL (Supplementary Table 2). Triglyceride levels were higher in women with PCOS than in controls in 11 of 17 studies (25, 29–33, 37, 52, 58, 60, 62). One BMI-matched study (29) also found higher triglyceride levels in the PCOS group. Whereas Brazilian and Argentinian studies showed mean triglyceride levels within the reference range, two studies from Chile (58, 59) and one from Venezuela (62) reported mean triglyceride levels > 150 mg/dL in patients with PCOS (Figure 4).

Twenty-seven studies assessed high-density lipoprotein cholesterol (HDL-C), and 18 of them compared HDL-C levels between PCOS and control groups (25, 28–34, 37, 40–42, 46, 49, 55, 58, 60, 62). In 10 of these studies, HDL-C was significantly lower in women with PCOS than in controls (25, 28, 30, 32–34, 42, 46, 49, 58). In the remaining studies, HDL-C levels did not differ between PCOS and control groups (Supplementary Table 2). In most studies, patients with PCOS had HDL-C < 50 mg/dL (27, 28, 30–35, 38–40, 47, 49, 51, 52, 55, 58–60, 62, 63). One study of women with PCOS conducted in Argentina reported HDL-C > 50 mg/dL (25), and studies of Brazilian women with PCOS showed variable HDL-C results, but mostly below the cutoff point of 50 mg/dL (27, 28, 30–35, 38–40, 47, 49, 51, 52). Studies from Chile and Venezuela reported mean HDL-C levels below this cutoff point (55, 58–60, 62, 63) (Figure 4).

Low-density lipoprotein cholesterol (LDL-C) levels ranged from 88.6 to 127.3 mg/dL in women with PCOS in 24 studies. Six of 15 studies comparing data between women with PCOS and controls reported higher LDL-C levels for PCOS (28, 29, 40, 42, 52, 58). LDL-C was within the reference range in control groups (Supplementary Table 2).

In 25 studies, mean total cholesterol levels ranged from 167 to 209.7 mg/dL in PCOS groups. Eight of 17 studies showed higher total cholesterol levels for women with PCOS than controls (25, 29, 30, 40, 42, 52, 58, 62) (Supplementary Table 2).

The prevalence of PCOS was estimated in only two studies. One study was conducted in Mexico (61) with a convenience sample of 150 female Mexican volunteers aged 20 to 45 years, and the authors found a prevalence of 6.6% (95% confidence interval, 2.3%–10.9%) according to the Rotterdam criteria. The other study was conducted in the city of Salvador, Brazil (36), and estimated a prevalence of 8.5% using the Rotterdam criteria in a probability sample of 859 women aged 18 to 45 years.

Six studies reported prevalence data on PCOS phenotypes and on MetS stratified by phenotype (26, 31, 33, 53, 59) for Brazilian, Chilean, and Argentinian populations. Phenotypes A+B were more prevalent in all studies, with rates ranging from 65.8% to 87.5%. The prevalence of MetS ranged from 33.3% to
44.0% for phenotype A, from 15.0% to 58.0% for phenotype B, from 11.9% to 36.0% for phenotype C, and from 14.2% to 66.0% for phenotype D (Table 3).

DISCUSSION

PCOS is a complex disorder affecting metabolic and reproductive functions. This systematic review, which included 24 cross-sectional studies, 16 case-control studies, and one cohort study conducted in Latin America, found that women with PCOS had a more adverse metabolic profile than non-PCOS controls across different countries. In most studies, BMI was within the overweight or obesity range for women with PCOS, reinforcing its contribution to the disease phenotype. In addition, MetS components, such as central obesity (measured by WC), low HDL-C, and hypertension, were prevalent in women with PCOS from different Latin American countries.

Although efforts have long been made to assess the impact of different sociocultural and ethnic backgrounds on PCOS-related metabolic abnormalities, few data are available for Latin America. This region is known to have populations of different ancestry. In Brazil, pooled ancestry contributions have been listed as 0.62 European, 0.21 African, and 0.17 Amerindian (65), whereas Pacific Latin American countries are predominantly Amerindian. Argentina and Chile are particular cases that show similar European and Amerindian ancestry contributions but lower African ancestry contribution compared with Brazil (65, 66). It is reasonable to assume that different genetic backgrounds may influence the phenotypic heterogeneity of PCOS, but evidence from the present systematic review rather suggests that Latin American countries are similar in terms of metabolic traits. This information may be potentially useful to public health systems in developing PCOS prevention programs and policies.

Metabolic abnormalities are considered common in women with PCOS, especially those linked to the MetS cluster, as shown in this study. However, controversy exists as to whether these features are directly related to PCOS itself or dependent on obesity—mainly on abdominal adiposity, a well-known cardiometabolic risk factor (7, 67, 68). In this respect, the finding of decreased insulin sensitivity in Latin American women with PCOS, as opposed to controls, is in line with current evidence from other regions (6, 15) and has been associated with low-grade chronic inflammation, linked to increasing BMI (68, 69). Besides, in meta-analyses of different populations, women with PCOS were more likely to have MetS (4, 17, 70). However, these studies provide relatively few data from Latin American populations. Insulin resistance may actually drive most of the alterations observed in PCOS, even in nonobese women. While not universally present in patients with PCOS, the presence of insulin resistance has been considered an intrinsic factor independent of obesity (71, 72). Recently, we have also observed an association of insulin resistance with hypertension, regardless of BMI, in Brazilian women with PCOS, with hypertension being associated with other MetS components (18). Data from the present systematic review add support to this notion by showing that Latin American women with PCOS had higher HOMA-IR than controls in most studies.

Although patients with PCOS consistently show a more unfavorable metabolic profile than controls in different regions of the world, there are discrepancies between PCOS populations. In China, the prevalence of MetS in PCOS ranged from 18.2% in community-dwelling patients in one study (73) to 53.3% in women older than 40 years in another study (74). In a
prospective cohort of 479 women with PCOS from Vietnam (Southeast Asia), patients were lean, had no increase in metabolic disease and Rotterdam phenotype D was the most prevalent (67.6%) (75). Current evidence also indicates a lower prevalence of hyperandrogenemia in women with PCOS from Asian countries (76). In Latin America, we found a predominance of Rotterdam phenotypes A and B, similar to what has been reported in most of the available studies across the world (76). A recent meta-analysis reported that, compared with controls, patients with PCOS from North America had a higher risk of MetS than those from Asia and Europe (17). Likewise, in the present systematic review, we also found a high prevalence of MetS in Latin American women with PCOS. In addition to the ethnic composition of the population, dietary habits may also influence the expression of metabolic traits in different populations. Indeed, adherence to the Mediterranean diet (77) or a low-glycemic-index diet (78) has been associated with a better metabolic profile in PCOS. Regarding the dietary pattern in Latin America, the Latin American Study of Nutrition and Health (ELANS) (79) reported low consumption of vegetables, nuts, whole grains, fish, and yogurt according to the recommendations of the World Health Organization. This may explain, at least in part, the similarities in the adverse metabolic profile between Latin American countries and other countries with high consumption of processed foods (80).

Despite the paucity of research undertaken to date, the results of the present systematic review provide a broad overview of the evidence on metabolic and anthropometric parameters in women with PCOS living in Latin American countries. The comprehensive search strategy can be seen as a strength of this study, as it covered the major electronic databases in order not to miss any relevant articles and included an active search for publications without language restrictions. Limitations include the relatively few studies found despite the vast size of the region, possible heterogeneity between studies, small sample sizes, and a lack of studies in some countries of the region, which hindered a proper comparison between women with PCOS from different Latin American countries. Nevertheless, no similar analysis has yet been undertaken. The present study is the first to provide evidence that allows us to characterize the metabolic profile of women with PCOS from an array of sociocultural and ethnic backgrounds in Latin American countries.

**CONCLUSIONS**

The results of the present systematic review suggest that anthropometric and metabolic profiles are worse in women with PCOS who live in different Latin American countries than in women without PCOS living in the same region. These findings are similar to those from North America but differ from the milder phenotype seen in Asia and Europe. Further studies assessing the prevalence of cardiometabolic comorbidities, such as diabetes and hypertension, in Latin American women with PCOS should be encouraged.
American countries are needed, which could positively impact the prevention and management strategies for PCOS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

FIGURE 4 | Risk factors composing the metabolic syndrome in Latin American women with PCOS. (A) Waist circumference (cm); (B) systolic and diastolic blood pressure (mm Hg); (C) fasting glucose (mg/dL); (D) triglycerides (mg/dL); (E) HDL-cholesterol (mg/dL). Values are expressed as mean and standard deviation. The “x” axis shows the reference number of studies (refer to the text). □ Argentina; ● Brazil; ○ Chile; △ Venezuela. a PCOS diagnosis according to NIH criteria; b PCOS diagnosis defined by the authors.

AUTHOR CONTRIBUTIONS

LM contributed to study design, was involved with data collection and analysis, drafted the article and final review. RR contributed to study design, was involved with data collection and analysis, drafted the article and final review. PS was involved in the conception and design of the study, data collection and analysis, drafted the article and final review. All authors contributed to the article and approved the submitted version.
TABLE 3 | Prevalence of PCOS phenotypes and of Metabolic syndrome in the studies included in the systematic review.

| Study, year | Country | PCOS criteria | Type of study | N PCOS phenotypes A+B/C/D | Age range PCOS (%) | Prevalence PCOS (%) | Prevalence Met S (%) |
|-------------|---------|---------------|---------------|---------------------------|-------------------|---------------------|---------------------|
| de Guevara, et al., 2014 (26) | Argentina | Rotterdam | Cross-sectional | 144/41/21 | 18 - 39 | A+B: 69.9 | C: 19.9 | D: 10.2 | A: 36.2 | B: 15 | C: 12.2 | D: 14.2 |
| Wilten D, et al., 2010 (31) | Southern Brazil | Rotterdam | Cross-sectional | 195/45/- | A+B:22.3 ± 6.7 | C: 25.89-7.56 | D:- | A:B:81 | C: 19 | A:B:31.3 | C:11.9 | D:- |
| Melo AS, et al., 2011 (33) | Southeastern Brazil | Rotterdam | Cross-sectional | 150/25/51 | A: 26.6 ± 5.1 | B: 25.2 ± 5.7 | C: 27 ± 4.5 | D: 25.9 ± 5.3 | A+B:66.4 | C:11 | D:22.6 | C:36 | D:33 |
| Tavares A, et al., 2019 (53) | Northeast Brazil | Rotterdam | Cross-sectional | 73/16/22 | 18-39 | A+B: 65.8 | C: 14.4 | D: 19.8 | A:33.3 | B:30.8 | C:12.5 | D:38.4 |
| de Guevara, et al., 2014 (26) | Chile | Rotterdam | Cross-sectional | 181/36/3 | 18 - 39 | A+B:82.5 | C:16.5 | D:1 | A:44 | B:58 | C:30 | D:66 |
| Echiburu B, et al., 2014* (59) | Chile | Rotterdam | Cross-sectional | 77/9/2 | A: 22.3 ± 5.3 B: 24.9 ± 7.3 | A+B: 87.5 | C: 10.2 | D: 2.3 | A:B: NA | C: NA | D: NA |

*Data from baseline.

FUNDING
This work was funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (grant number INCT/CNPq 465482/2014–7) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (grant number INCT/FAPERGS: 17/2551–0000519-8). The funding source had no role in the collection, analysis, interpretation of data

and in the writing of the report or in the decision to submit the article for publication.

SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.759835/full#supplementary-material

REFERENCES
1. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. *Endocr Rev* (2016) 37(5):467–520. doi: 10.1210/er.2015-1104
2. Aziz R, Carmina E, Chen Z, Dunai A, Laven J, Legro RS, et al. Polycystic Ovary Syndrome. *Nat Rev Dis Primers* (2016) 2:16057. doi: 10.1038/nrdp.2016.57
3. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The Prevalence of Polycystic Ovary Syndrome in a Community Sample Assessed Under Contrasting Diagnostic Criteria. *Hum Reprod* (2010) 25(2):544–51. doi: 10.1093/humrep/dep399
4. Moran LJ, Misso ML, Phillips DI, Norman RJ, Davies MJ. The Incidence of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. *Hum Reprod Update* (2010) 16 (4):347–63. doi: 10.1093/humupd/dmp001
5. Rubin KH, Glinthor N, Duby M, Abrahamsen B, Andersen M, Development and Risk Factors of Type 2 Diabetes in a Nationwide Population of Women With Polycystic Ovary Syndrome. *J Clin Endocrinol Metab* (2017) 102 (10):3848–57. doi: 10.1210/jc.2017-01354
6. Kakoly NS, Earnest A, Teede HJ, Moran LJ, Joham AE. The Impact of Obesity on the Incidence of Type 2 Diabetes Among Women With Polycystic Ovary Syndrome. *Diabetes Care* (2019) 42(4):560–7. doi: 10.2337/dc18-1738
7. Diamanti-Kandarakis E, Spritzer FM, Sir-Petermann T, Mota AB. Insulin Resistance and Polycystic Ovary Syndrome Through Life. *Curr Pharm Des* (2012) 18(34):5569–76. doi: 10.2174/13816121280307590
8. Osibogun O, Ogunmoroti O, Michos ED. Polycystic Ovary Syndrome and Cardiometabolic Risk: Opportunities for Cardiovascular Disease Prevention. *Trends Cardiovasc Med* (2019) 30(7):399–404. doi: 10.1016/j.tcm.2019.08.010
9. Zhao L, Zhu Z, Lou H, Zhu G, Huang W, Zhang S, et al. Polycystic Ovary Syndrome (PCOS) and the Risk of Coronary Heart Disease (CHD): A Meta-Analysis. *Oncotarget* (2016) 7(23):33715–21. doi: 10.18632/oncotarget.9553
10. de Groot PC, Dukker OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, Coronary Heart Disease, Stroke and the Influence of Obesity: A Systematic Review and Meta-Analysis. *Hum Reprod Update* (2011) 17(4):495–500. doi: 10.1093/humupd/dmr001
11. Cooney LG, Dokras A. Cardiometabolic Risk in Polycystic Ovary Syndrome: Current Guidelines. *Endocrinol Metab Clin North Am* (2021) 50(1):83–95. doi: 10.1016/j.ecl.2020.11.001
12. DeUgarte CM, Bartolucci AA, Aziz R. Prevalence of Insulin Resistance in the Polycystic Ovary Syndrome Using the Homeostasis Model Assessment. *Fertil Steril* (2005) 83(5):1454–60. doi: 10.1016/j.fertnstert.2004.11.070
13. Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose Intolerance in Polycystic Ovary Syndrome—A Position Statement of the Androgen Excess Society. *J Clin Endocrinol Metab* (2007) 92(12):4546–56. doi: 10.1210/jc.2007-1549
14. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of Impaired Glucose Tolerance and Diabetes in Women With Polycystic Ovary Syndrome. *Diabetes Care* (1999) 22(1):141–6. doi: 10.2337/ diacare.22.1.141
15. Ollila MM, West S, Keinanen-Kiukaanniemi S, Jokelainen J, Auvinen J, Puukka K, et al. Overweight and Obese But Not Normal Weight Women With PCOS
are at Increased Risk of Type 2 Diabetes Mellitus: A Prospective Population-Based Cohort Study. *Hum Reprod* (2017) 32(4):968. doi: 10.1093/humrep/dex030.

16. Diamanti-Kandarakis E, Dunaf A. Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications. *Endocr Rev* (2012) 33(6):981–1030. doi: 10.1210/er.2011-11034.

17. Lima SS, Kakoly N, Tan JW, Fitzgerald G, Bahri Khamami M, Joham AE, et al. Metabolic Syndrome in Polycystic Ovary Syndrome: A Systematic Review, Meta-Analysis and Meta-Regression. *Obes Rev* (2019) 20(2):339–52. doi: 10.1111/obr.12762.

18. Marchesan LB, Spritzer PM. ACC/AHA 2017 Definition of High Blood Pressure: Implications for Women With Polycystic Ovary Syndrome. *Fertil Steril* (2019) 111(3):579–87.e1. doi: 10.1016/j.fertnstert.2018.11.034.

19. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid Levels in Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. *Fertil Steril* (2011) 95 (3):1073–9.e1. doi: 10.1016/j.fertnstert.2010.12.027.

20. Ding T, Hardiman PJ, Petersen I, Wang FF, Qu F, Bai G. The Prevalence of Polycystic Ovary Syndrome in Reproductive-Aged Women of Different Ethnicity: A Systematic Review and Meta-Analysis. *Oncotarget* (2017) 8 (56):96351–8. doi: 10.18632/oncotarget.19180.

21. Diamanti-Kandarakis E, Papavasiliou AG, Kandarakis SA, Chrousos GP. Pathophysiology and Types of Dyslipidemia in PCOS. *Trends Endocrinol Metab* (2007) 18(7):280–5. doi: 10.1016/j.tem.2007.07.004.

22. Carmina E, Novoa MC, Romano LM, Lobo RA. Characterization of Metabolic Changes in the Phenotypes of Women With Polycystic Ovary Syndrome in a Large Mediterranean Population From Sicily. *Clin Endocrinol (Oxf)* (2019) 91(4):553–60. doi: 10.1111/cen.14063.

23. Spritzer PM, Ramos RB, Marchesan LB, de Oliveira M, Carmina E. Metabolic Profile of Women With PCOS in Brazil: A Systematic Review and Meta-Analysis. *Diabetol Metab Syndr* (2021) 13(1):18. doi: 10.1186/s13098-021-00636-5.

24. Belfi SH, Graffigna MN, Oneto A, Otero P, Schurman L, Lavelle OA. Effect of Rosiglitazone on Insulin Resistance, Growth Factors, and Reproductive Disturbances in Women With Polycystic Ovary Syndrome. *Fertil Steril* (2004) 81(3):624–9. doi: 10.1016/j.fertnstert.2003.08.024.

25. Tellechea ML, Muzzio DO, Iglesias Molli AE, Belfi SH, Graffigna MN, Lavelle OA, et al. Association Between Beta2-Adrenoceptor (ADRB2) Haplotypes and Insulin Resistance in PCOS. *Clin Endocrinol (Oxf)* (2013) 78(4):600–6. doi: 10.1111/cen.12019.

26. Ladron de Guevara A, Fux-Orta C, Crisofio N, Szafryk de Mereshian P, Marchesan et al. PCOS-Related Metabolic Features in Latin America.
