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OBESIDADE E ALTERAÇÕES METABÓLICAS EM MULHERES COM A SÍNDROME DOS OVÁRIOS POLICÍSTICOS: DISTRIBUIÇÃO NA AMÉRICA LATINA E ENSAIO CLÍNICO RANDOMIZADO COM METFORMINA E TOPIRAMATO

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Obesidade e alterações metabólicas em mulheres com a síndrome dos ovários policísticos: distribuição na América Latina e ensaio clínico randomizado com metformina e topiramato

Tese apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de doutor em Endocrinologia.

Orientadora: Profª Dra Poli Mara Spritzer

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LISTA DE ABREVIATURAS E SIGLAS

- PCOS **-** Polycystic ovary syndrome; Síndrome dos Ovários Policísticos
- DM2 – Diabetes Mellitus tipo 2
- DMG – Diabetes Mellitus Gestacional
- MASLD - Metabolic dysfunction-associated steatotic liver disease; Doença hepática esteatótica associada à disfunção metabólica
- HDL - High Density Lipoprotein
- LDL - Low Density Lipoprotein
- IMC – Índice de massa corporal
- SM – Síndrome Metabólica
- MTF – Metformina
- TPM – Topiramato

SUMÁRIO

RESUMO

A Síndrome dos Ovários Policísticos (PCOS) é uma endocrinopatia comum em mulheres em idade fértil e está associada a distúrbio ovulatório, hiperandrogenismo e morfologia ovariana policística, sendo frequentemente acompanhada de alterações cardiometabólicas. Entre essas alterações, destaca-se a obesidade, resistência insulínica, alterações do metabolismo de lipídios e glicose, entre outras. Os diferentes fenótipos da PCOS têm prevalência e expressão variáveis de acordo com a região estudada e se provindos de estudos com populações selecionadas ou de base-populacional. Neste sentido, existem poucos dados sobre a prevalência de obesidade e gravidade das alterações cardiometabólicas associadas à PCOS em mulheres na América Latina e a maioria desses dados encontra-se em pequenos estudos de alguns países desta região. A obesidade, presente em 70-80% das pacientes com PCOS mundialmente, exacerba as alterações cardiometabólicas e contribui para a infertilidade, ansiedade e depressão. Assim sendo, a sua abordagem é um dos pilares fundamentais no manejo da PCOS, melhorando desfechos metabólicos, de fertilidade e de qualidade de vida. No estudo 1 foram compilados, através de uma revisão sistemática, dados de 41 estudos da América Latina, com tamanhos das amostras variando de 10 a 288 no grupo PCOS e 10 a 1500 no grupo controle. A prevalência dos fenótipos A e B (PCOS clássica) variou de 65,8% a 87,5%, conforme relatado em estudos da Argentina, Brasil e Chile. A prevalência de síndrome metabólica variou de 33,3% a 44,0% para o fenótipo A, de 15,0% a 58,0% para o fenótipo B, de 11,9% a 36,0% para o fenótipo C e de 14,2% a 66,0% para o fenótipo D. As mulheres com PCOS apresentaram maior índice de massa corporal (IMC), circunferência da cintura, pressão arterial, glicose e maior resistência insulínica (HOMA-IR), bem como um perfil lipídico mais adverso do que aquelas sem PCOS. A obesidade esteve associada ao diagnóstico de PCOS na maioria dos estudos, reforçando sua importância na expressão fenotípica na região. No estudo 2, realizamos um ensaio clínico randomizado duplo-cego, controlado por placebo, com o objetivo de verificar o efeito de adicionar topiramato à metformina, em conjunto com uma dieta hipocalórica, em mulheres com PCOS e obesidade ou sobrepeso acompanhado de alterações metabólicas. Neste estudo, foram incluídas 31 participantes no grupo metformina (MTF) + placebo (P) e 30 no grupo MTF+ topiramato (TPM). O grupo MTF+TPM apresentou maior perda de peso média em 3 meses (-3,4% vs. -1,6%, p=0,03) e 6 meses (-4,5% vs. -1,4%, p=0,03). Ambos os grupos melhoraram androgênios, lipídios e escores psicossociais. As participantes com perda de peso ≥3% aos 6 meses melhoraram o escore de Ferriman modificado (mFGS), (8,4 para 6,5, p=0,026). Parestesia, geralmente leve e transitória, foi mais comum no grupo MTF+TPM (23,3% vs. 3,2%, p=0,026). Portanto, os dados do primeiro estudo indicam um pior perfil cardiometabólico nas mulheres com PCOS na América Latina em relação a mulheres sem PCOS e enfatizam o impacto negativo da obesidade na modulação desse perfil. Também evidenciam uma carência de estudos em várias regiões da América Latina, onde dados de prevalência e do perfil cardiometabólico ainda não estão disponíveis. No segundo estudo, observou-se a importância da perda de peso na melhora do perfil cardiometabólico e hiperandrogênico das mulheres com PCOS. Em uma era onde novas medicações efetivas para o tratamento da obesidade têm surgido, o uso da metformina associada ao topiramato e uma dieta hipocalórica, mostrou-se uma opção efetiva, bem tolerada e de baixo custo para essas pacientes.

Palavras-chave: Síndrome dos Ovários Policísticos; América Latina; obesidade; alterações cardiometabólicas.

ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of childbearing age and is associated with ovulatory disorders, hyperandrogenism and polycystic ovarian morphology, and is often accompanied by cardiometabolic alterations. These changes include obesity, insulin resistance, changes in lipid and glucose metabolism, among others. The different phenotypes of PCOS vary in prevalence and expression according to the region studied and whether they come from studies of selected populations or population-based studies. In this sense, there are few data on the prevalence of obesity and the severity of cardiometabolic alterations associated with PCOS in Latin American women and most of these data are found in small studies from a few countries in this region. Obesity, present in 70-80% of PCOS patients worldwide, exacerbates cardiometabolic alterations and contributes to infertility, anxiety and depression. Therefore, its approach is one of the fundamental pillars in the management of PCOS, improving metabolic outcomes, fertility and quality of life. In study 1, data from 41 Latin American studies were compiled through a systematic review, with sample sizes ranging from 10 to 288 in the PCOS group and 10 to 1500 in the control group. 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. The prevalence of 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 a higher body mass index (BMI), waist circumference, blood pressure, glucose and higher insulin resistance (HOMA-IR), as well as a more adverse lipid profile than those without PCOS. Obesity was associated with the diagnosis of PCOS in most studies, reinforcing its importance in phenotypic expression in the region. In study 2, we conducted a randomized, double-blind, placebo-controlled clinical trial with the aim of verifying the effect of adding topiramate to metformin, in conjunction with a low-calorie diet, in women with PCOS and obesity or overweight accompanied by metabolic alterations. In this study, 31 participants were included in the metformin (MTF) + placebo (P) group and 30 in the MTF+ topiramate (TPM) group. The MTF+TPM group showed greater mean weight loss at 3 months (-3.4% vs. -1.6%, p=0.03) and 6 months (-4.5% vs. -1.4%, p=0.03). Both groups improved androgen, lipid and psychosocial scores. Participants with weight loss ≥3% at 6 months improved their modified Ferriman score (mFGS), (8.4 to 6.5, p=0.026). Paresthesia, generally mild and transient, was more common in the MTF+TPM group (23.3% vs. 3.2%, p=0.026). Therefore, the data from the first study indicate a worse cardiometabolic profile in women with PCOS in Latin America compared to women without PCOS and emphasize the negative impact of obesity in modulating this profile. They also highlight the lack of studies in various regions of Latin America, where data on prevalence and cardiometabolic profile are not yet available. The second study showed the importance of weight loss in improving the cardiometabolic and hyperandrogenic profile of women with PCOS. In an era where new effective medications for the treatment of obesity

have emerged, the use of metformin combined with topiramate and a low-calorie diet has proved to be an effective, well-tolerated and low-cost option for these patients.
Keywords: Polycystic ovary syndrome; Latin America; obesity; cardiometabolic changes.

INTRODUÇÃO

A Síndrome dos Ovários Policísticos (PCOS) é uma condição endócrina comum em mulheres em idade fértil, com prevalência estimada em 10 a 13% entre as diferentes etnias e regiões do mundo, utilizando-se os critérios de Rotterdam(1).

Os critérios de Rotterdam definem o diagnóstico pela presença de pelo menos dois dos três seguintes achados, após exclusão de outras causas que cursem com hiperandrogenismo ou demais achados da síndrome: disfunção menstrual, hiperandrogenismo clínico e/ou laboratorial e morfologia ovariana policística. Este último, refere-se a um ou mais dos seguintes achados: presença de 20 ou mais microfolículos com 2 a 9 mm de diâmetro; número de folículos por seção (FNPS) ≥ 10 em qualquer ovário; volume ovariano maior ou igual a 10cm³ em pelo menos um dos ovários; (avaliados por ecografia, preferencialmente, transvaginal); ou ainda um aumento do hormônio anti-mulleriano acima do valor de referência definido pelo método laboratorial empregado. A avaliação da morfología policística ovariana não é necessária, se a paciente preenche os outros dois critérios (1).

Um maior risco para alterações cardiometabólicas, como obesidade, resistência insulínica, diabetes mellitus tipo 2 (DM2) e diabetes gestacional (DMG), hipertensão arterial sistêmica, dislipidemia e doença hepática esteatótica associada a disfunção metabólica (MASLD), tem sido associado com a PCOS, sendo maior esse risco naquelas definidas pelos critérios anovulatório e hiperandrogênico (fenótipos A e B de Rotterdam)(2-6).

Fatores étnicos e sociodemográficos podem modular a expressão da síndrome e sua prevalência(7-9). Estudos com mulheres com PCOS em algumas regiões da Ásia, por exemplo, evidenciaram uma população com menor prevalência de obesidade, hiperandrogenismo e também menor risco cardiometabólico quando comparado a mulheres com PCOS de outras regiões (10, 11). No entanto, a prevalência de PCOS e o perfil metabólico ainda não foram descritos em vários grupos étnicos, especialmente em populações latino-americanas (12-15), exceto por uma recente metanálise de distúrbios metabólicos em mulheres brasileiras com PCOS

(16). No Brasil, a composição étnica populacional foi descrita como 0,62 europeus, 0,21 africanos e 0,17 ameríndios (17), enquanto os países da América Latina do Pacífico são predominantemente ameríndios. Argentina e Chile têm ascendência europeia e ameríndia semelhantes e menor contribuição de ascendência africana em comparação ao Brasil (17, 18). É esperado que essas diferenças étnicas possam influenciar a expressão fenotípica da PCOS, incluindo a prevalência de obesidade.

Principais alterações cardiometabólicas em mulheres com PCOS

Perfil lipídico aterogênico

Estima-se que cerca de 70% das mulheres com PCOS tenham seus níveis lipídicos aumentados ou em valores limítrofes (19). Fatores como resistência insulínica, obesidade central e hiperandrogenismo podem estar associados a essas alterações (19, 20). A combinação de hipertrigliceridemia, redução do HDL e aumento das partículas de LDL de alta densidade é conhecida como tríade aterogênica (21) e está frequentemente presente em mulheres com PCOS(22). Uma metanálise que avaliou o perfil lipídico em mulheres com PCOS comparado a controles, demonstrou que as mulheres com PCOS tinham triglicerídeos 26 mg/dL (95% IC 17-35) mais alto e HDL 6 mg/dL (IC 95% 4-9) mais baixo em relação a controles. Além disso, as concentrações de colesterol LDL e colesterol não-HDL foram maiores nas mulheres com PCOS: 12 mg/dL (IC 95% 10-16) e 19 mg/dL (IC 95% 16-22), respectivamente. Nos estudos pareados pelo índice de massa corporal (IMC), o LDL-colesterol e o colesterol não-HDL ainda eram mais altos nas mulheres com PCOS: 9 mg/dL (IC 95% 6-12) e 16 mg/dL (IC 95% 14-19), respectivamente(23).

Hipertensão arterial sistêmica em mulheres com PCOS

Estudos apontam uma maior prevalência de hipertensão em mulheres com PCOS quando comparado às controles (24-26). A hipertensão na PCOS tem sido associada a diferentes mecanismos fisiopatológicos, como à hiperfunção do sistema renina-angiotensina, resistência insulínica, hiperandrogenismo, ativação do sistema nervoso simpático e redução na produção de óxido nítrico(27). A hipertensão está

frequentemente associada a outras alterações clínicas e metabólicas, como a obesidade e a dislipidemia. Em um estudo com mulheres com PCOS atendidas no Hospital de Clínicas de Porto Alegre (HCPA), verificamos que os limiares para o diagnóstico de hipertensão definidos pelos critérios atualizados na diretriz de 2017 da American College of Cardiology/American Heart Association (≥130/80mmHg) , incluíram um maior número de mulheres definidas como hipertensas que também possuíam outras alterações cardiometabólicas quando comparado aos limiares diagnósticos previamente estabelecidos (≥140/90mmHg), onde um grande número de mulheres que foram definidas como normotensas apresentavam um perfil metabólico desfavorável. Isso sugere que anormalidades precoces da pressão arterial possam estar associadas com disfunção metabólica nas mulheres com PCOS, embora outros estudos sejam necessários. (3).

Síndrome metabólica em mulheres com PCOS

Existe uma prevalência aumentada de síndrome metabólica (SM) nas diferentes fases da vida de mulheres com PCOS(28). Assim como seus componentes isolados, a prevalência varia nas diferentes regiões do mundo, conforme o arcabouço genético e as particularidades sociodemográficas de cada local (29-32). Em geral, em diferentes populações estudadas, a presença de SM está associada à doença cardiovascular e à ocorrência de eventos cardiovasculares e morte(33, 34), além de poder agravar os desfechos de doenças cardiovasculares estabelecidas(35). Desta forma, mulheres com PCOS devem ser consideradas um grupo com risco aumentado para doenças cardiovasculares, mesmo que dados em relação a aumento de eventos cardiovasculares sejam escassos na população com PCOS e, a maioria da evidência disponível, seja proveniente de estudos observacionais (1).

Diabetes mellitus tipo 2 e diabetes gestacional

A resistência insulínica, junto com a disfunção ovulatória e o hiperandrogenismo, são os marcos da PCOS. A resistência insulínica precede o desenvolvimento de DM2. Além disso, o aumento de androgênios nas mulheres predispõe à deposição de gordura ectópica e visceral, contribuindo com a resistência

insulínica (36, 37). Estudos iniciais indicavam que a PCOS está associada à piora da sensibilidade insulínica, mesmo na ausência de obesidade(38). Outros estudos colocam o excesso de peso como o principal componente que predispõe essas mulheres à ocorrência de DM2 (39).

Além disso, a ocorrência de diabetes na gestação também se mostrou elevada nas mulheres com PCOS. Em um estudo canadense de base populacional recentemente publicado, mulheres com PCOS tiveram prevalência aumentada de DMG quando comparado a mulheres sem PCOS. A obesidade foi a principal mediadora desta associação(40). Outro estudo encontrou aumento da prevalência de DMG em mulheres com PCOS de forma independente da obesidade, porém a obesidade foi um importante fator de risco materno associado a desfechos desfavoráveis, tanto maternos como neonatais, em mulheres com e sem PCOS(41).

A obesidade como um fator agravante das alterações clínicas e cardiometabólicas e o impacto favorável do seu manejo

A PCOS é frequentemente associada com a obesidade(2). Embora mesmo mulheres eutróficas com PCOS tenham aumento do risco de alterações cardiometabólicas(42), a obesidade tem impacto negativo sobre a ocorrência e gravidade dessas alterações(43, 44). Na PCOS, o aumento da adiposidade e um tecido adiposo disfuncional potencializam um estado de inflamação crônica de baixo grau (45-47) que contribui para a disfunção metabólica e risco cardiovascular. Estudos sugerem que mulheres com PCOS têm um aumento de adipocinas circulantes quando comparadas a controles saudáveis(48, 49).

A obesidade também impacta a fertilidade(43, 50) e mulheres com PCOS e obesidade podem ter pior resposta aos tratamentos para infertilidade, como indução de ovulação (51) e tratamentos de reprodução assistida(52, 53).

A MASLD também está intimamente associada à obesidade. Sua prevalência estimada em adultos é de 25% a 30%, mas pode ser o dobro em mulheres com PCOS(4, 54). Nas mulheres com PCOS, especialmente se com obesidade associada, a resistência insulínica e o hiperandrogenismo podem acelerar a progressão da MASLD, como sugerido em alguns estudos(55, 56). A perda de peso, neste contexto,

ameniza as consequências deletérias da MASLD, tanto do ponto de vista hepático como extra-hepático(54).

É importante destacar que, além das alterações cardiometabólicas anteriormente descritas, tanto a PCOS como a obesidade podem aumentar o risco de câncer endometrial, o qual é especialmente associado a uma maior exposição ao estrogênio (parte proveniente da conversão dos androgênios via enzima aromatase no tecido adiposo) sem oposição da progesterona, nos estados anovulatórios e amenorreicos (57-59).

Por fim, PCOS e obesidade aumentam a prevalência de ansiedade e depressão e reduzem a qualidade de vida(60, 61), o que pode ser amenizado com estratégias de redução de peso e do hiperandrogenismo (62). Uma perda de peso modesta, em torno de 5% do peso, pode oferecer amplos benefícios metabólicos, reprodutivos e psicológicos(1). Neste sentido, modificações do estilo de vida, incluindo uma dieta saudável, hipocalórica para os estados de sobrepeso e obesidade, além da recomendação de atividade física regular, devem ser incentivadas. Adicionado a essas medidas, o uso da metformina, amplamente recomendada na abordagem do DM2, apresenta baixo custo e perfil de segurança conhecido, sendo também indicada (*off-label*) no manejo das alterações cardiometabólicas associadas à PCOS e obesidade (1, 63, 64). Reconhecendo-se a dificuldade de manter modificações do estilo de vida a longo prazo, o tratamento farmacológico da obesidade, pode representar uma estratégia adjuvante efetiva. Preferencialmente, as medicações empregadas devem demonstrar eficácia, segurança, perfil de tolerabilidade aceitável, fácil uso e, a depender da população estudada, custo acessível.

Com base nos tópicos descritos acima, este trabalho busca avaliar o perfil metabólico e obesidade em mulheres com PCOS na América Latina, de acordo com a literatura disponível e, em paralelo, verificar a eficácia e segurança de uma intervenção farmacológica para a redução de peso em mulheres com PCOS, através de um ensaio clínico randomizado, combinando uma dieta hipocalórica associada ao uso de metformina e topiramato, ambas drogas com longa experiência de uso e custo acessível.

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ARTIGOS CIENTÍFICOS

ARTIGO 1:

METABOLIC FEATURES OF WOMEN WITH POLYCYSTIC OVARY SYNDROME IN LATIN AMERICA: A SYSTEMATIC REVIEW

Lucas Bandeira Marchesan, Ramon Bossardi Ramos and Poli Mara Spritzer

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Metabolic features of women with Polycystic Ovary Syndrome in Latin America: a systematic review

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Running head: PCOS-related metabolic features in Latin America

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Keywords: PCOS; South America; obesity; metabolic syndrome; insulin resistance.

Abstract

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 produce invaluable information for primary and secondary prevention of PCOS in the region. This systematic review was registered with PROSPERO under number CRD42016038537.

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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) (25, 54-60), Venezuela (n=2) (61, 62), and Mexico (n=1) (63). Most studies used the Rotterdam criteria to diagnose PCOS, except for one study conducted in Argentina (26), one in Brazil (47), and three in Chile (54, 56, 58), all of which used the National Institutes of Health (NIH) criteria. The two studies from Venezuela (61, 62) used criteria defined by the authors. Sixteen studies had no control group for comparison (24, 25, 31, 32, 36, 46-51, 53, 59, 60, 62), and six had BMI-matched controls without PCOS for comparison (29, 35, 39, 40, 45, 57). 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 (26-28, 33, 37, 41-44, 52, 54-56, 58). 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, 33, 37, 38, 41, 58) and the others with overweight women (26, 28, 29, 36, 39, 42, 45, 52, 60, 61). In six studies HOMA-IR was ≤ 2.5 (31, 34, 35, 51, 56, 63), 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 (26, 28, 33, 34, 37, 41, 42, 52, 58, 61) and 3 BMI-matched (29, 39, 45). 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 (63) (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 (26-29, 35, 37, 38, 41-44, 56-58, 61) (Figure 4). In nine of these studies, women with PCOS had higher systolic (SBP) and/or diastolic blood pressure (DBP) than controls (27-29, 37, 41-44, 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) (44). Another study found higher SBP and DBP only in late reproductive-age (35–40 years) women with PCOS (56). 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 (26-29, 31-42, 44-49, 51, 52, 54, 56-61). Glucose levels ranged from 79 to 125.2 mg/dL in women with PCOS. In six of 21 studies (26-28, 37, 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 (34, 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 (26-28, 34, 37, 41, 45, 52, 56, 58, 61). One BMI-matched study (45) 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, 60) and one from Venezuela (61) 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 (26-29, 34, 35, 37-39, 41-45, 56-58, 61). In 10 of these studies, HDL-C was significantly lower in women with PCOS than in controls (26-29, 37, 39, 42-44, 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 (27-29, 31, 32, 35, 37, 39, 41, 42, 46-49, 52, 56-58, 60-62). One study of women with PCOS conducted in Argentina reported HDL-C > 50 mg/dL (26), and studies of Brazilian women with PCOS showed variable HDL-C results, but mostly below the cutoff point of 50 mg/dL (27-29, 31, 32, 35, 37, 39, 41, 42, 46-49, 52). Studies from Chile and Venezuela reported mean HDL-C levels below this cutoff point (56-58, 60-62) (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 (29, 35, 43, 45, 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 (26, 28, 35, 43, 45, 52, 58, 61) (supplementary Table 2).

The prevalence of PCOS was estimated in only two studies. One study was conducted in Mexico (63) 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 (30), 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 (25, 37, 41, 53, 60) 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 countries are needed, which could positively impact the prevention and management strategies for PCOS.

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Not applicable

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

LBM contributed to study design, was involved with data collection and analysis, drafted the article and final review. RBR contributed to study design, was involved with data collection and analysis, drafted the article and final review. PMS was involved in the conception and design of the study, data collection and analysis, drafted the article and final review.

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Figure Captions

Figure 1. PRISMA flow diagram of the study selection process.

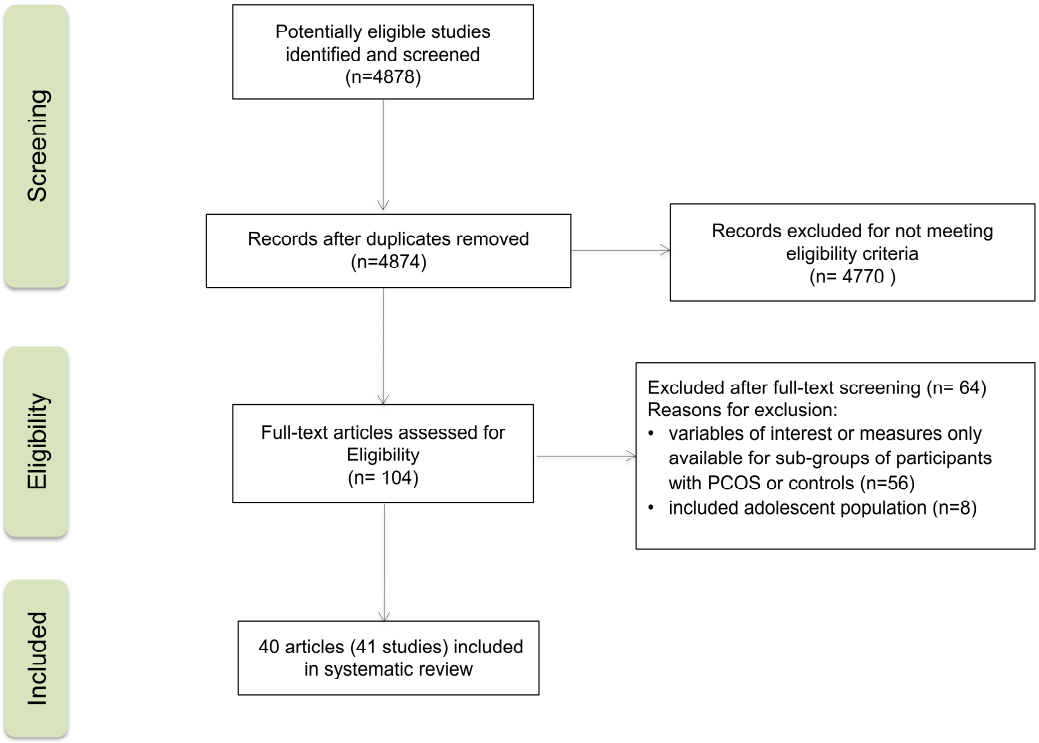
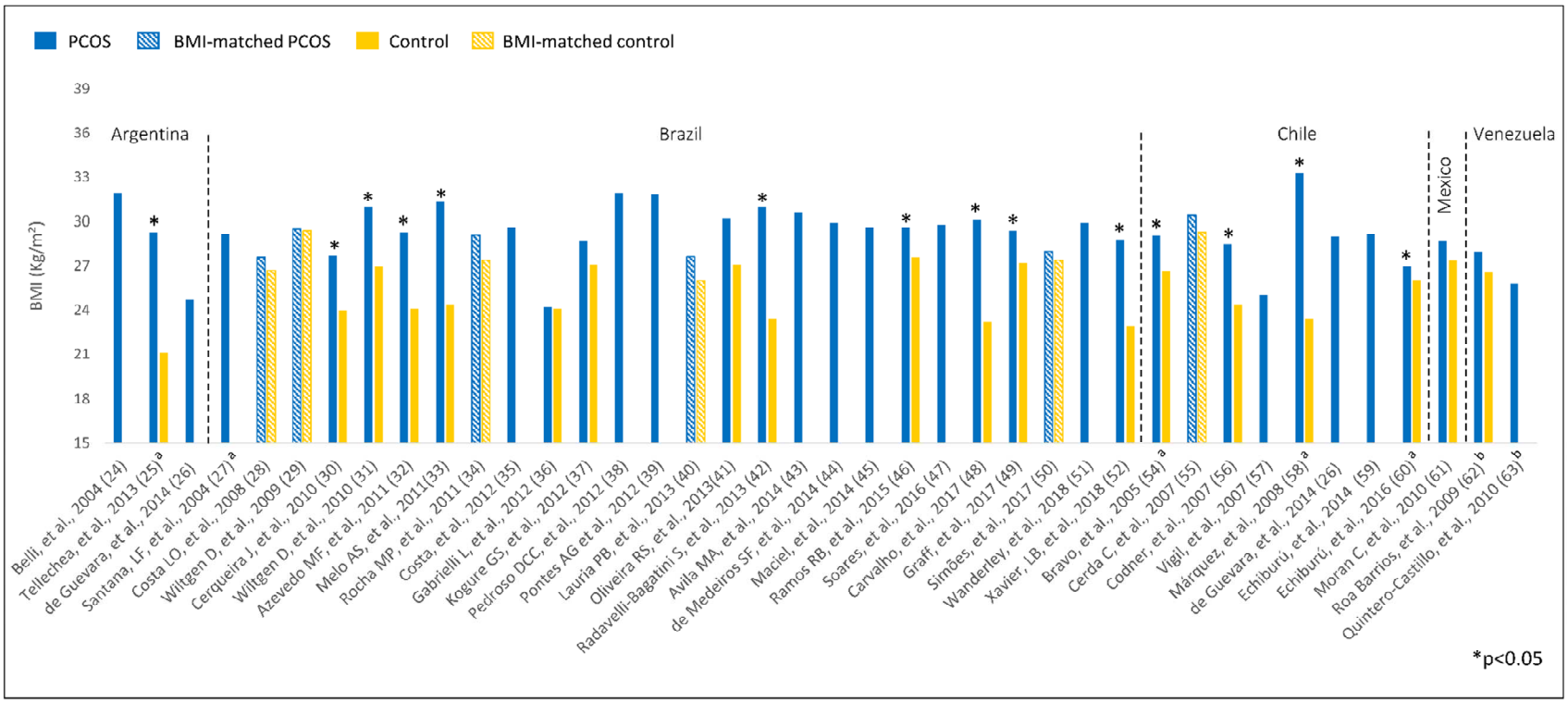


Figure 2. BMI (kg/m²) among Latin American women with PCOS and controls. Mean values. The "x" axis shows the name of studies and reference numbers (refer to the text). [a] PCOS diagnosis according to NIH criteria; [b] PCOS diagnosis defined by the authors.


PCOS
BMI-matched PCOS
Control
BMI-matched control
BMI (Kg/m²)
39
36
33
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24
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Argentina
Brazil
Chile
Mexico
Venezuela
Belli, et al., 2004 (24)
Tellechea, et al., 2013 (25)a
de Guevara, et al., 2014 (26)
Santana, LF, et al., 2004 (27)a
Costa LO, et al., 2008 (28)
Wiltgen D, et al., 2009 (29)
Cerqueira J, et al., 2010 (30)
Wiltgen D, et al., 2010 (31)
Azevedo MF, et al., 2011 (32)
Melo AS, et al., 2011(33)
Rocha MP, et al., 2011 (34)
Costa, et al., 2012 (35)
Gabrielli L, et al., 2012 (36)
Kogure GS, et al., 2012 (37)
Pedroso DCC, et al., 2012 (38)
Pontes AG et al., 2012 (39)
Lauria PB, et al., 2013 (40)
Oliveira RS, et al., 2013(41)
Radavelli-Bagatini S, et al., 2013 (42)
Avila MA, et al., 2014 (43)
de Medeiros SF, et al., 2014 (44)
Maciel, et al., 2014 (45)
Ramos RB, et al., 2015 (46)
Soares, et al., 2016 (47)
Carvalho, et al., 2017 (48)
Graff, et al., 2017 (49)
Simões, et al., 2017 (50)
Wanderley, et al., 2018 (51)
Xavier, LB, et al., 2018 (52)
Bravo, et al., 2005 (54)a
Cerda C, et al., 2007 (55)
Codner, et al., 2007 (56)
Vigil, et al., 2007 (57)
Márquez, et al., 2008 (58)a
de Guevara, et al., 2014 (26)
Echiburú, et al., 2014 (59)
Echiburú, et al., 2016 (60)a
Moran C, et al., 2010 (61)
Roa Barrios, et al., 2009 (62)b
Quintero-Castillo, et al., 2010 (63)b
*p<0.05

1

Figure 3. HOMA-IR among Latin American women with PCOS and controls. Mean values. The "x" axis shows the name of studies and reference numbers (refer to the text). [a] PCOS diagnosis according to NIH criteria; [b] PCOS diagnosis defined by the authors.

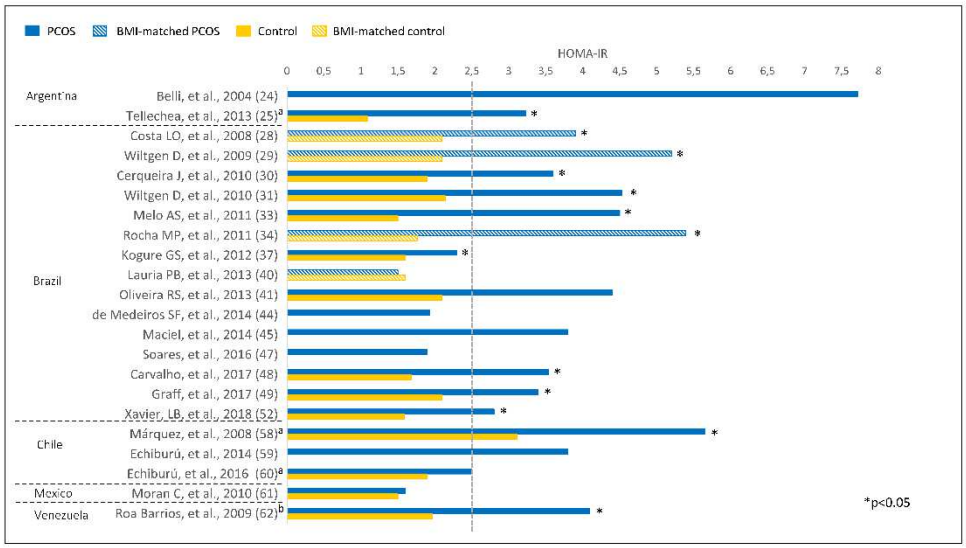

Figure 4. Risk factors composing the metabolic syndrome in Latin American women with PCOS. **(A)** Waist circumference (cm); **(B)** systolic and diastolic blood pressure (mm Hg); **(C)** fasting glucose (mg/dL); **(D)** triglycerides (mg/dL); **(E)** HDL-cholesterol (mg/dL). Values are expressed as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

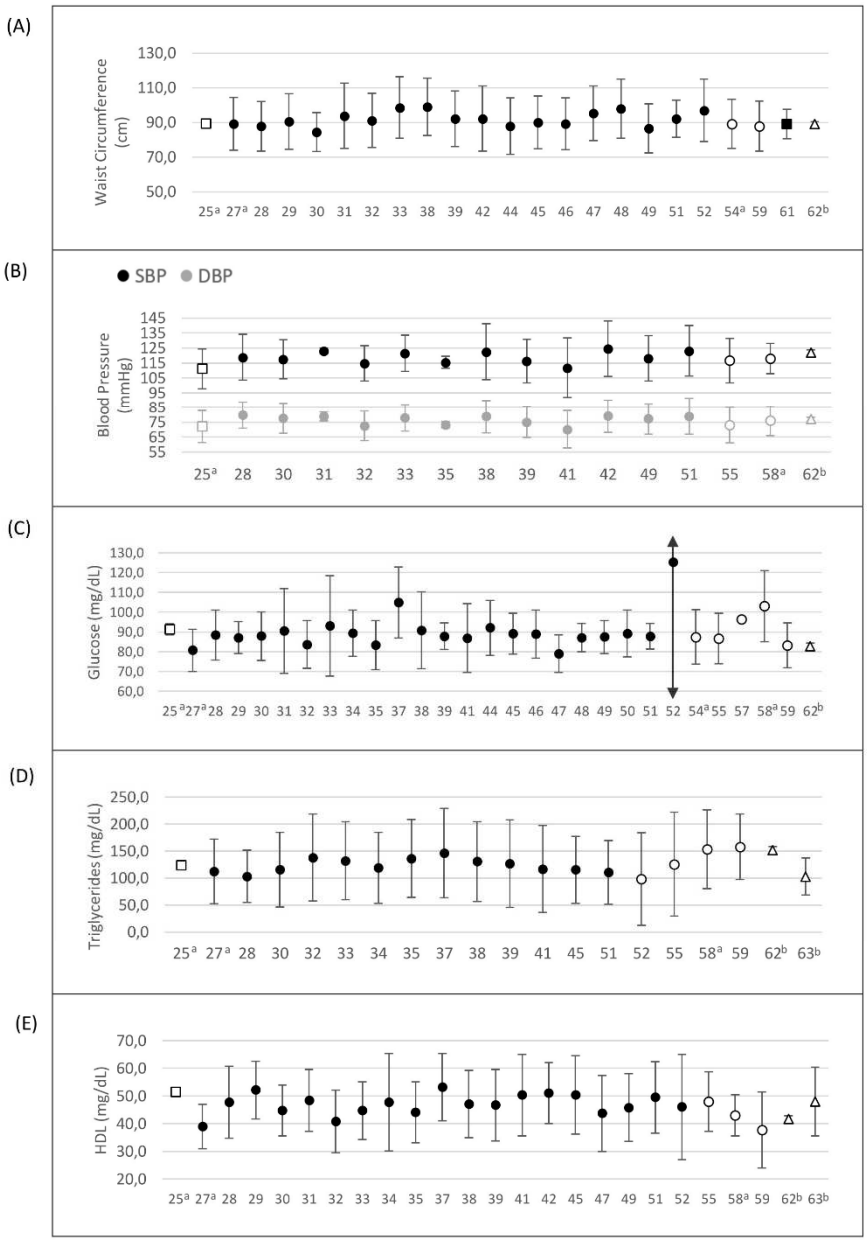
(A)
Waist Circumference (cm)
130,0
110,0
90,0
70,0
50,0
25ª 27ª 28 29 30 31 32 33 38 39 42 44 45 46 47 48 49 51 52 54ª 59 61 62ᵇ
(B)
SBP DBP
Blood Pressure (mmHg)
145 135 125 115 105 95 85 75 65 55
25ª 28 30 31 32 33 35 38 39 41 42 49 51 55 58ª 62ᵇ
(C)
Glucose (mg/dL)
130,0 120,0 110,0 100,0 90,0 80,0 70,0 60,0
25ª 27ª 28 29 30 31 32 33 34 35 37 38 39 41 44 45 46 47 48 49 50 51 52 54ª 55 57 58ª 59 62ᵇ
(D)
Triglycerides (mg/dL)
250,0 200,0 150,0 100,0 50,0 0,0
25ª 27ª 28 30 32 33 34 35 37 38 39 41 45 51 52 55 58ª 59 62ᵇ 63ᵇ
(E)
HDL (mg/dL)
70,0 60,0 50,0 40,0 30,0 20,0
25ª 27ª 28 29 30 31 32 33 34 35 37 38 39 41 42 45 47 49 51 52 55 58ª 59 62ᵇ 63ᵇ

Table 1. Characteristics of the studies from Latin America included in the systematic review about women with PCOS

Country	Study, Year	PCOS criteria	Type of studies	PCOS		Control group		BMI-matched
				N	Age	N	Age	
Argentina	Belli, et al., 2004 (24)	Rotterdam	Cross-sectional	24	23.7±6.4	-	-	
	Tellechea, et al., 2013 (26)	NIH	Case-control	165	26.4±0.5	121	30.7±0.78	
	de Guevara, et al ., 2014 (25)	Rotterdam	Cross-sectional	206	26.0 (18-39)	-	-	
Brazil	Santana, LF, et al., 2004 (47)	NIH	Cohort	21	27.2±5.02	-	-	
	Costa LO, et al., 2008 (29)	Rotterdam	Cross-sectional	57	25.5±5.3	37	26.6±5.4	yes
	Wiltgen D, et al., 2009 (45)	Rotterdam	Case-control	51	20.6±5.1	44	28.9±5.6*	yes
	Cerqueira J, et al., 2010 (28)	Rotterdam	Cross-sectional	56	26.2±6.0	54	27.7±6.1	
	Wiltgen D, et al., 2010[a] (41)	Rotterdam	Case-control	195	22.3±6.7	25	29.7±4.29*	
	Azevedo MF, et al., 2011 (27)	Rotterdam	Cross-sectional	113	26.2±4.3	242	26.8±5.0	
	Melo AS, et al., 2011[b] (37)	Rotterdam	Cross-sectional	132	26.6±5.1	146	28.9±0.5	
	Rocha MP, et al., 2011 (39)	Rotterdam	Case-control	142	25.1±5.4	31	27.5±4	yes
	Costa, et al., 2012 (32)	Rotterdam	Cross-sectional	113	27.2±4.5	-	-	
	Gabrielli L, et al., 2012 (30)	Rotterdam	Cross-sectional	73	28.4±6.5	725	31.0±7.3*	
	Kogure GS, et al., 2012 (34)	Rotterdam	Case-control	20	27.8±5.0	19	27.9±5.2	
	Pedroso DCC, et al., 2012 (48)	Rotterdam	Cross-sectional	105	29±4.4	-	-	
	Pontes AG et al., 2012 (49)	Rotterdam	Cross-sectional	189	24.9±5.2	-	-	

	Lauria PB, et al., 2013 (35)	Rotterdam	Case-control	40	29(25-34)	36	30(15-43)	yes
	Oliveira RS, et al., 2013[c] (38)	Rotterdam	Case-control	42	27.4±5.5	18	31.4±6.1	
	Radavelli-Bagatini S, et al., 2013 (43)	Rotterdam	Case-control	80	21.3±0.6	1500	22.7±0.4	
	Avila MA, et al., 2014 (50)	Rotterdam	Cross-sectional	100	25.7±4.9	-	-	
	de Medeiros SF, et al., 2014 (51)	Rotterdam	Cross-sectional	288	26.9±5.5	-	-	
	Maciel, et al., 2014 (36)	Rotterdam	Cross-sectional	97	24.9±5.1	-	-	
	Ramos RB, et al., 2015 (44)	Rotterdam	Case-control	199	22 ± 6	99	25 ± 7	
	Soares, et al., 2016 (31)	Rotterdam	Cross-sectional	22	26±6.0	-	-	
	Carvalho, et al., 2017 (33)	Rotterdam	Case-control	86	31.1±4.92	86	29.0±7.04	
	Graff, et al., 2017 (42)	Rotterdam	Case-control	84	23.5±6.3	54	26.2±6.5	
	Simões, et al., 2017 (40)	Rotterdam	Case-control	10	29.6±1.2	10	28.6±2.0	yes
	Wanderley, et al, 2018 (46)	Rotterdam	Cross-sectional	83	28.79 ±5.85	-	-	
	Xavier, LB, et al., 2018 (52)	Rotterdam	Case-control	97	30.5±5.1	99	29.8±7.1	
	Tavares A, et al., 2019 (53)	Rotterdam	Cross-sectional	111	18-39	-	-	
Chile	Bravo, et al., 2005 (54)	NIH	Case-control	106	23.5± 5.19	82	25.1± 5.64	
	Cerda C, et al., 2007 (57)	Rotterdam	Case-control	41	24.6± 7.2	31	27.9± 6.9	yes
	Codner, et al., 2007 (55)	Rotterdam	Cross-sectional	20	24.5±5	35	26.4±7.2	
	Vigil, et al., 2007 (59)	Rotterdam	Cross-sectional	69	26.01±0.76	-	-	
	Márquez, et al., 2008 (58)	NIH	Cross-sectional	50	28.8±8.2	70	28.6±8.6	
	de Guevara, et al ., 2014 (25)	Rotterdam	Cross-sectional	220	26.0 (18-39)	-	-	

	Echiburú, et al., 2014[d] (60)	Rotterdam	Cross-sectional	60	22.3±5.3	-	-
	Echiburú, et al., 2016[e] (56)	NIH	Cross-sectional	43	27 (23–30)	38	29 (20–30)
Mexico	Moran C, et al., 2010 (63)	Rotterdam	Cross-sectional	10	28.9±2	140	34.5±7
Venezuela	Roa Barrios, et al., 2009 (61)	Other[f]	Case-control	62	23.9±0.6	48	25.4±0.7
	Quintero-Castillo, et al., 2010 (62)	Other[f]	Cross-sectional	65	23.2±4.92	-	-

[a] data are from A plus B PCOS phenotypes *vs* controls; [b] data are from A PCOS phenotype *vs* controls; [c] women included in the control group had similar complaints as the ones from the PCOS group, but did not meet the diagnostic criteria; [d] data are from baseline and regarding the phenotype A only; [e] data shown from the early reproductive age group (18–34 years); [f]PCOS diagnosis defined by the authors; * $p < 0.05$ between the groups.

Author	Year	Selection	Comparability	Exposure/Outcome
Belli, et al.	2004	****	*	**
Tellechea, et al.	2013	****	**	***
de Guevara, et al.	2014	****	**	***
Santana, LF, et al.	2004	***	*	**
Costa LO, et al.	2008	***	*	***
Wiltgen D, et al.	2009	****	**	***
Cerqueira J, et al	2010	**	*	***
Wiltgen D, et al.	2010	****	**	***
Azevedo MF, et al.	2011	****	**	***
Melo AS, et al.	2011	****	**	***
Rocha MP, et al.	2011	****	**	***
Costa, et al.	2012	***	*	**
Gabrielli L, et al.	2012	***	**	***
Kogure GS, et al.	2012	****	**	***
Pedroso 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	****	**	***

Vigil, et al.	2007	**	*	*
Márquez, 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	****	*	***

Table 2. Newcastle-Ottawa quality (NOS) assessment scale for studies included in the systematic review

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).

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 (ys) phenotypes	Prevalence PCOS phenotypes (%)	Prevalence Met S (%)
de Guevara, et al., 2014 (25)	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
Wiltgen D, et al., 2010 (41)	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 (37)	Southeastern Brazil	Rotterdam	Cross-sectional	150/25/51	A: 26.6 ± 5.1 B: 26.2 ±5.7 C: 27 ± 4.5 D: 25.9 ±5.3	A+B:66.4 C:11 D:22.6	A: 45 B:39 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: 36.4
de Guevara, et al., 2014 (25)	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

Echiburú B, et al., 2014 [a] (60)	Chile	Rotterdam	Cross-sectional	77/9/2	A: 22.3 ± 5.3 B: 24.9 ± 7.3 C: 25.7 ± 5.7 D:24.5 ± 14.8	A+B: 87.5 C: 10.2 D: 2.3	A+B: NA C: NA D: NA

[a] Data from baseline.

ARTIGO 2:

TOPIRAMATE ADDED TO METFORMIN FOR OBESITY CONTROL IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: A RANDOMIZED CLINICAL TRIAL

Lucas Bandeira Marchesan, Thais Rasia da Silva and Poli Mara Spritzer

Submetido para publicação - 2024

CONSIDERAÇÕES FINAIS

Este trabalho buscou: 1-avaliar e compilar os dados disponíveis em países da América Latina, publicados na literatura, em relação à obesidade e o perfil cardiometabólico de mulheres com PCOS vivendo nesta região e 2- avaliar a efetividade de uma abordagem farmacológica da obesidade e alterações cardiometabólicas, em mulheres com PCOS com obesidade ou sobrepeso, através de medicações de uso simples, longa experiência de uso e perfil de segurança conhecido, além de custo acessível para uma população de menor renda, como é a realidade da maioria dos países da América Latina.

No primeiro artigo, podemos verificar de forma abrangente os dados publicados em relação aos diferentes países da América Latina, verificando-se um pior perfil cardiometabólico nas mulheres com PCOS em relação aos seus pares, sem PCOS. Observou-se uma alta prevalência de obesidade, síndrome metabólica e seus componentes e resistência insulínica. Embora a diferença na ancestralidade pudesse sugerir uma expressão variável da PCOS nos diferentes países da região, o que se observou foram traços comuns de expressão fenotípica. Estes dados podem ser úteis para estratégias públicas de saúde, especialmente com ênfase em programas de prevenção. Devido à grande heterogeneidade dos estudos incluídos, não foi possível realizar uma meta-análise, optando-se por uma revisão sistemática.

No segundo artigo, a estratégia para manejo clínico da obesidade em mulheres com PCOS, através da combinação de metformina e topiramato associados a uma dieta hipocalórica, mostrou-se efetiva e segura para redução do peso e melhora de parâmetros hormonais e metabólicos. Neste trabalho, tendo em vista o desenho de um ensaio clínico randomizado, obtivemos um grupo de mulheres semelhantes em relação às suas características basais nos grupos metformina-placebo e metformina-

topiramato, incluindo taxa metabólica em repouso, nível de atividade física e em relação ao uso prévio de metformina. Também houve uma alta taxa de adesão às medicações em estudo, o que é importante para a interpretação dos resultados. Apesar de uma perda considerável de seguimento (26,2%), esta perda foi próxima à estimada previamente ao início do estudo e inferior a muitos estudos com desenho semelhante disponíveis na literatura. Embora esta perda de seguimento e o pequeno tamanho amostral tenha nos impossibilitado de análises estratificadas por subgrupos, o estudo foi consistente no seu objetivo primário e logrou êxito em responder à questão à qual se propôs.

Em conclusão, os dados obtidos sobre o perfil cardiometabólico desfavorável em relação às controles, com alta prevalência de obesidade e resistência insulínica em mulheres com PCOS na América Latina, referem-se a alguns países da região. São ainda escassas estas informações em outros países da América Latina e, portanto, novos estudos devem ser incentivados para essas populações. Considerando que a obesidade é um fator significativo na modulação da expressão fenotípica da PCOS e que frequentemente a terapia farmacológica se torna necessária para seu manejo, a combinação de metformina e topiramato demonstrou ser eficaz e segura na redução de peso e na melhora do perfil metabólico e hormonal em mulheres com PCOS e excesso de peso. Novos medicamentos para o tratamento da obesidade estão surgindo, com diferentes mecanismos de ação, perfis de segurança, tolerabilidade e custos. Estudos com essas drogas serão de grande valor para a abordagem farmacológica da obesidade em mulheres com e sem PCOS.