Original Report

Metabolic Syndrome in Adolescents with Polycystic Ovary Syndrome: Prevalence on the Basis of Different Diagnostic Criteria

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A B S T R A C T

Study Objective: Existing literature on the prevalence of metabolic syndrome (MBS) in adolescents with polycystic ovary syndrome (PCOS) is inconsistent, likely because of the application of differing diagnostic criteria. The objective was to assess the prevalence of MBS in adolescents with PCOS depending on the PCOS diagnostic criteria used.
Design, Setting, and Participants: A retrospective chart review of female patients (N = 37), ages 11-22 years, diagnosed with PCOS between January 2013 and December 2017. Patients were included only if they had received screening allowing comparison across all PCOS diagnostic criteria: National Institutes of Health, Rotterdam, Androgen Excess Society, Amsterdam, Endocrine Society, and the Pediatric Endocrine Society (PES). The presence of MBS was established using the International Diabetes Federation criteria. The proportion of patients having MBS was then calculated for each PCOS diagnostic criteria subgroup.
Interventions and Main Outcome Measures: For the entire study cohort, MBS was present in 17/37 patients (45.9%). The highest prevalence of MBS was among the subgroup of patients meeting the PES PCOS diagnostic criteria (13/25; 52.0%), whereas the lowest prevalence was in the subgroup meeting the Amsterdam PCOS criteria (6/15; 40.0%). Those diagnosed using the PES criteria also had the highest percentage of patients with 3 or more risk factors for MBS.
Results and Conclusion: The prevalence of MBS varied according to the specific PCOS diagnostic criteria and was highest when PES guidelines were used. The PES criteria are adolescent-specific and have thus refined the diagnosis of PCOS for this population. Our results highlight the importance of validated adolescent-specific PCOS diagnostic criteria.
Key Words: Metabolic syndrome, Polycystic ovary syndrome, Diagnostic criteria

Introduction

There is ample evidence that increased risk of metabolic dysfunction is present in women with polycystic ovary syndrome (PCOS). Cardiovascular problems, obesity, and insulin resistance are among the factors that determine long-term life expectancy and quality of life.[1] Metabolic dysfunction can start as early as puberty; thus, correctly diagnosing adolescent girls with PCOS is extremely important.[2]

Existing literature on the prevalence of metabolic syndrome (MBS) in the adolescent population with PCOS is inconsistent. A recently conducted meta-analysis showed that the prevalence of MBS ranged from 4.9% to 43.6% in adolescent girls with PCOS.[3] Although most studies have shown an increased risk compared with a healthy population,[2,4–6] some studies have not.[7–9] The discrepancy in the prevalence of MBS in adolescents is likely partly because of application of differing PCOS diagnostic criteria.

Currently, there are multiple criteria proposed for the diagnosis of PCOS.[10] The first 3 published guidelines (ie, National Institutes of Health [NIH],[11] Rotterdam,[12] and Androgen Excess Society (AES),[13] were developed for adults and then applied to adolescents. Newer recommendations, such as the Amsterdam,[14] Endocrine Society (ES),[15] and Pediatric Endocrine Society (PES),[16] have worked to develop adolescent-specific criteria.

Although all criteria require the exclusion of other causes of hyperandrogenism, subtle and important differences exist (Table 1). Although the NIH,[11] ES,[15] and PES[16] guidelines require chronic anovulation and biochemical or clinical hyperandrogenism for a PCOS diagnosis, they do not require polycystic ovarian morphology (PCOM) on ultrasound. These criteria differ, however, with regard to their specific definition of clinical hyperandrogenism and ovulatory dysfunction. The Rotterdam guidelines[12] require 2 of 3 criteria (oligo-anovulation, clinical/biochemical hyperandrogenism, and/or PCOM), whereas the AES[13] requires the presence of hyperandrogenism with either menstrual irregularity and/or PCOM. The most strict criteria are the Amsterdam, which require all 3 findings (oligo-anovulation, clinical/biochemical hyperandrogenism, and PCOM) for a PCOS diagnosis.[14]

The effect of the specific PCOS diagnostic criteria used on the prevalence of MBS in adolescents has not yet been evaluated. As such, the objective of the current study was to assess the prevalence of MBS in adolescents with PCOS depending on the PCOS diagnostic criteria used.

The authors indicate no conflicts of interest.
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Table 1
Diagnostic Criteria for PCOS According to Different Published Guidelines

Diagnostic Guideline	Criteria for Diagnosis	HA	OD	PCOM
Adult guidelines applied to adolescents				
NIH 1990[11]	HA and OD	Clinical and/or biochemical HA (clinical HA defined as hirsutism, acne, and/or alopecia)	Oligo- or anovulation	–
Rotterdam 2003[14]	At least 2 of 3: HA, OD, or PCOM	Clinical and/or biochemical HA (clinical HA defined as hirsutism and/or acne)	Oligo- or anovulation	Presence of 12 or more follicles measuring 2-9 mm in diameter and/or ovarian volume greater than 10 mL
AES 2006[15]	HA with either OD or PCOM	Clinical and/or biochemical HA (clinical HA defined as hirsutism)	Oligo- or anovulation	Presence of 12 or more follicles measuring 2-9 mm in diameter and/or ovarian volume greater than 10 mL
Adolescent-specific guidelines				
Amsterdam 2012[16]	HA, OD, and PCOM	Clinical and/or biochemical HA (clinical HA defined as progressive hirsutism)	Chronic anovulation (must be present for ≥2 years)	If diagnosed using abdominal ultrasound must include ovarian volume greater than 10 mL
Endocrine Society 2013[12]	HA and OD	Clinical and/or biochemical HA (acne in isolation is not evidence of clinical HA; alopecia should be used cautiously)	Persistent oligomenorrhea (persistent not defined, but menstrual irregularity ≥2 years is noteworthy)	PCOM criteria not validated for adolescents
Pediatric Endocrine Society 2015[13]	HA and OD	Clinical and/or biochemical HA (moderate-severe hirsutism evidence of clinical HA; persistent acne unresponsive to topical therapy suggestive)	OD evidenced by: • Consecutive menstrual intervals greater than 90 days even in the first year postmenarche • Menstrual intervals persistently less than 21 days or greater than 45 days for 2 or more years postmenarche • No menses by 15 or 2-3 years after thelarche	PCOM criteria not validated for adolescents

AES, Androgen Excess Society; HA, hyperandrogenism; OD, ovulatory dysfunction; NIH, National Institutes of Health; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome.

Materials and Methods

A retrospective chart review was conducted on female patients, ages 11-22 years, with PCOS who were seen at Nationwide Children's Hospital between January 2013 and December 2017. The study protocol was approved by the institutional review board before data collection.

Potential study subjects were first identified by 1 of the following post visit diagnoses according to International Classification of Diseases, 9th and 10th revision codes: PCOS, polycystic ovary, PCOM (256.4/E28.2); amenorrhea (626.0/N91.2); oligomenorrhea (626.1/N91.5); irregular menses (626.4/N92.6); dysfunctional uterine bleeding, abnormal uterine bleeding (626.8/N93.8); androgen excess, hyperandrogenism (259.8/E34.8); hirsutism (704.1/L68.0); and elevated testosterone (259.8/E34.8). This resulted in 5226 potential study subjects (Fig. 1).

To allow comparisons across all diagnostic criteria, subjects needed to have all of the following for inclusion in the current analysis: (1) received screening for biochemical hyperandrogenism; (2) documentation concerning clinical hyperandrogenism in the medical record; (3) had undergone pelvic ultrasonography; (4) had metabolic screening laboratory studies; and (5) have at least 2 of the following: ovulatory dysfunction, clinical and/or biochemical hyperandrogenism, or PCOM. Additional exclusion criteria included presence of other endocrine diseases (eg, thyroid dysfunction, congenital adrenal hyperplasia, androgen secreting adrenal tumor, hyperprolactinemia) and receipt of specific medications at time of evaluation (eg, oral contraceptives, steroids, metformin, or other insulin sensitizer, and antilipidemic medication). Application of these requirements resulted in a final sample of 37 patients (Fig. 1). Lack of pelvic ultrasonography accounted for the largest reduction in sample size, resulting in the exclusion of 4996 individuals.

Information extracted from medical records included demographic, clinical, and laboratory data from the first visit and first follow-up visit. Medical records were evaluated for the presence the following menstrual findings: menstrual interval greater than 45 days, menstrual interval less than 20 days, lack of menses by 15 years, or lack of menses 2-3 years after thelarche. Ovulatory dysfunction was defined depending on the specific PCOS diagnostic criteria (Table 1). Biochemical hyperandrogenism was defined as total testosterone greater than 55 ng/mL and/or free testosterone greater than 6.3 pg/mL. Presence of mild, moderate, or severe hirsutism, acne, and/or alopecia was noted. Clinical hyperandrogenism was defined according to the specific PCOS diagnostic criteria (Table 1). Ultrasonographic findings of PCOM were having 12 or more follicles measuring between 2 and 9 mm and/or an ovarian volume greater than 10 cm^3 depending on the diagnostic criteria applied.

The presence of MBS was established using the International Diabetes Federation (IDF) criteria (Table 2).[17] According to these criteria the MBS diagnosis is met if a patient has altered abdominal circumference and 2 or more additional factors. Waist circumference was not recorded in any patient files in the current study. As such, obesity,

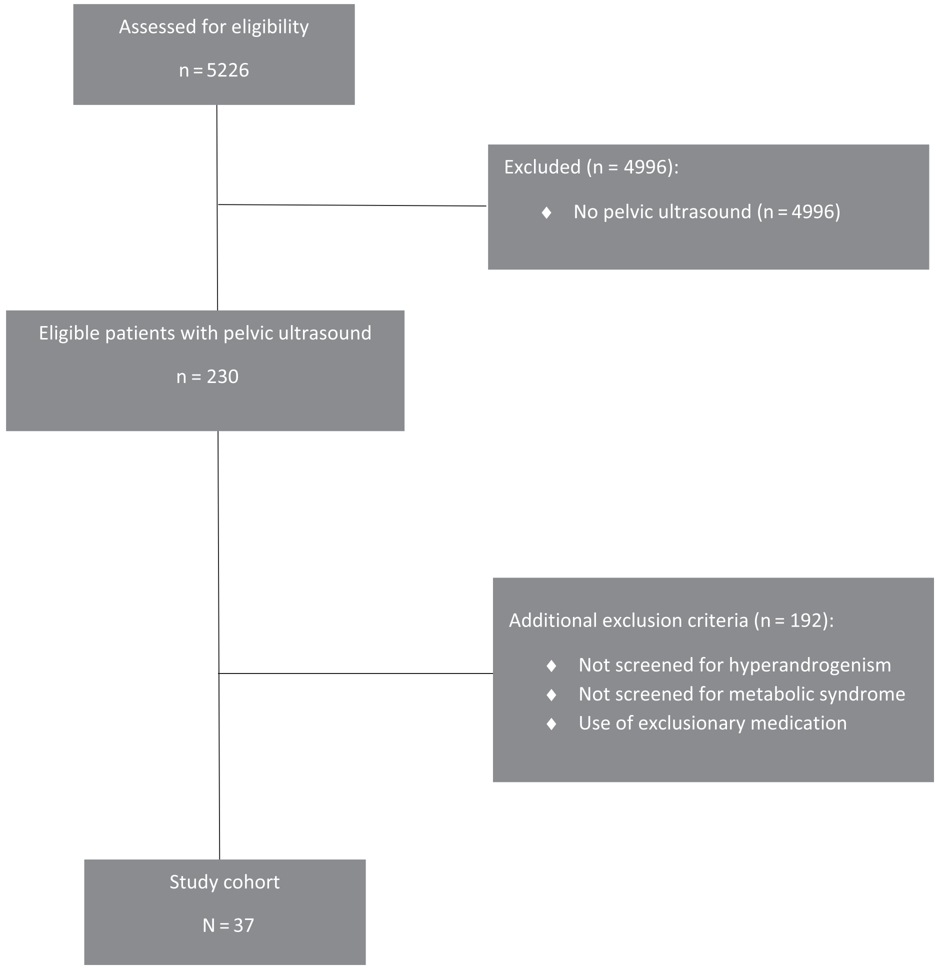

Fig. 1. Participant flow diagram.

defined as a body mass index (BMI) at the 95th percentile or higher, was used as a surrogate for central obesity. BMI was calculated by using the body weight (in kilograms) divided by the height (in meters squared) formula. A high correlation between waist circumference and BMI has been reported in previous studies in adolescent populations.[18]

Statistical Analyses

Descriptive statistics of the study sample included means and SDs for continuous variables and frequencies and percent for categorical variables. The main outcome measure was the presence of MBS as defined using the IDF criteria. All patients were categorized as to whether or not they met each of the 6 PCOS diagnostic criteria (Table 1) and also as to whether or not they met the definition of MBS. The proportion of patients having MBS was then calculated for each PCOS diagnostic criteria subgroup as well as the proportion having individual risk factors for MBS.

Results

A total of 37 patients met all eligibility requirements for inclusion in the study. The mean age of the study population

Table 2
International Diabetes Federation Criteria for Metabolic Syndrome in Female Adolescents

Criteria*	Age	
	10 to 16 years	Older than 16 years
Central obesity†	WC at the 90th percentile or greater	WC 80 cm or more
Impaired glucose metabolism	Fasting BG 100 mg/dL or greater	Fasting BG 100 mg/dL or greater or type 2 DM
Dyslipidemia: TG	TG 150 mg/dL or higher	TG 150 mg/dL or more or taking LLD
Dyslipidemia: HDL	HDL 40 mg/dL or less	HDL 50 mg/dL or less or taking LLD
Arterial hypertension	SBP 130 mm Hg or higher or DBP 85 mm Hg or higher or taking AHD	SBP 130 mm Hg or higher or DBP 85 mm Hg or higher or taking AHD

AHD, antihypertensive drug; BG, blood glucose; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; LLD, lipid-lowering drug; SBP, systolic blood pressure; TG, triglyceride level; WC, waist circumference.
* Must have central obesity with at least 2 additional criteria to meet the diagnosis.
† BMI at the 95th percentile or greater was used as a surrogate for central obesity in the current study.

Table 3
Baseline Characteristics of the Study Population (N = 37)

Characteristic	Statistic
Mean age ± SD, years	15.4 ± 1.66
Mean BMI ± SD	35.9 ± 7.42
Weight Status, n (%)	
Normal weight	1 (2.7)
Overweight	4 (10.8)
Obese	32 (86.5)
Race, n (%)	
White	22 (59.5)
African American	11 (29.7)
Multiracial	4 (10.8)
Ethnicity, n (%)	
Hispanic	4 (10.8)
Non-Hispanic	33 (89.2)
Ovulatory dysfunction, n (%)	
Menstrual interval greater than 45 days	33 (89.2)
Menstrual interval less than 20 days	0 (0.0)
No menses by age 15 years	1 (2.7)
No menses 2-3 years after thelarche	0 (0.0)
Normal menses	3 (8.1)
Biochemical hyperandrogenism, n (%)	
Elevated total testosterone only	7 (18.9)
Elevated free testosterone only	3 (8.11)
Elevated total and free testosterone	15 (40.5)
Normal total and free testosterone	12 (32.4)
Clinical hyperandrogenism, n (%)	
Mild hirsutism only	9 (24.3)
Moderate-severe hirsutism only	8 (21.6)
Mild acne only	4 (10.8)
Moderate-severe acne only	1 (2.7)
Alopecia only	1 (2.7)
Moderate-severe hirsutism and moderate acne	7 (18.9)
None	7 (18.9)
Polycystic ovarian morphology on ultrasound, n (%)	
12 or more follicles measuring between 2 and 9 mm	2 (5.4)
Ovarian volume greater than 10 cm^3	14 (37.8)
Both	4 (10.8)
Neither	17 (45.9)

BMI, body mass index.

was 15.4 ± 1.66 (range, 11.5-20.4) years, and patients were predominantly white, non-Hispanic (Table 3). Thirty-six of 37 patients (97.3%) were either overweight or obese.

Menstrual interval greater than 45 days was the most common menstrual finding (89.2%); however, 3/37 (8.1%) had regular menstrual cycles. Biochemical hyperandrogenism was detected in 25/37 patients (67.6%), and 30/37 (81.1%) of patients had documented signs of clinical hyperandrogenism. On ultrasound, 20/37 patients (54.1%) had PCOM, defined by follicular number, ovarian size, or both (Table 3).

All patients met the diagnosis of PCOS using the Rotterdam criteria; whereas only 15/37 (40.5%) met the diagnosis using the Amsterdam criteria. The prevalence of a PCOS diagnosis among the other diagnostic guidelines was 30/37 (81.1%) NIH, 32/37 (86.5%) AES, 29/37 (78.4%) ES, and 25/37 (67.6%) with the PES criteria (Table 4).

For the entire study cohort, MBS was present in 17/37 patients (45.9%). Arterial hypertension was evident in 10/37 (27.0%), and no patients were receiving antihypertensive medication. Low high-density lipoprotein cholesterol was observed in 28/37 (75.7%), high triglyceride level in 12/37 (32.4%), and no patients were receiving lipid-lowering medication. Elevated blood glucose was found in 9/37 (24.3%), and no patients had type 2 diabetes mellitus (Table 4).

The highest prevalence of MBS was found among the subgroup of patients who met the PES PCOS diagnostic criteria (13/25; 52.0%), whereas the lowest prevalence of MBS was in the subgroup who met the Amsterdam PCOS criteria (6/15; 40.0%). Those diagnosed using the PES criteria also had the highest percentage of patients with 3 or more risk factors for MBS (Table 4).

Discussion

Early identification of MBS or predisposing factors leads to early intervention in adolescents with PCOS. In this study of adolescents evaluated for PCOS we found that the prevalence of MBS varied according to the specific PCOS diagnostic criteria used. The MBS prevalence ranged from 40% to 52% in the same patient population. Hart et al[4] similarly reported that risk of MBS was 35.3% in adolescents diagnosed using NIH criteria and 26.2% in those diagnosed using the Rotterdam criteria. Unlike previous studies, we included all current diagnostic criteria, including those specific to adolescents.

In the present study, use of the Amsterdam criteria, also endorsed by Carmina et al,[19] resulted in the lowest prevalence of MBS. Using the Amsterdam criteria, ovulatory dysfunction, hyperandrogenism, and PCOM are all required for a PCOS diagnosis.[19] Arguments in favor of using these diagnostic guidelines point to the possibility of inaccurate diagnosis in adolescents when less strict criteria are used. Patients with less than 3 criteria are described as having a

Table 4
Prevalence of Metabolic Risk Factors According to PCOS Diagnostic Criteria

Risk Factor	Rotterdam 2003[14] (n = 37)	NIH 1990[11] (n = 30)	AES 2006[15] (n = 32)	Amsterdam 2012[16] (n = 15)	ES 2013[12] (n = 29)	PES 2015[13] (n = 25)
Central obesity, n (%)*	32 (86.5)	26 (86.7)	27 (84.4)	12 (80.0)	25 (86.2)	22 (88.0)
Arterial hypertension, n (%)	10 (27.0)	10 (33.3)	9 (28.1)	3 (20.0)	9 (31.0)	10 (40.0)
Elevated TG, n (%)	12 (32.4)	11 (36.7)	10 (31.3)	5 (33.3)	10 (34.5)	10 (40.0)
Low HDL, n (%)	28 (75.7)	23 (76.6)	25 (78.1)	11 (73.3)	22 (75.9)	18 (72.0)
Elevated fasting glucose, n (%)	9 (24.3)	6 (20.0)	8 (25.0)	4 (26.7)	6 (20.7)	6 (24.0)
One risk factor, n (%)†	17 (46.0)	14 (46.7)	15 (46.8)	6 (40.0)	14 (48.3)	10 (40.0)
Two risk factors, n (%)†	10 (27.0)	7 (23.3)	9 (28.1)	2 (13.3)	7 (24.1)	6 (24.0)
Three or more risk factors, n (%)†	7 (18.9)	7 (23.3)	6 (18.7)	4 (26.7)	6 (20.7)	7 (28.0)
Metabolic syndrome, n (%)	17 (46.0)	14 (46.7)	15 (46.8)	6 (40.0)	13 (44.8)	13 (52.0)

AES, Androgen Excess Society; ES, Endocrine Society; HDL, high-density lipoprotein cholesterol; NIH, National Institutes of Health; PCOS, polycystic ovary syndrome; PES, Pediatric Endocrine Society; TG, triglyceride level.
* BMI at the 95th percentile or higher was used as a surrogate for central obesity.
† Risk factors in addition to central obesity.

milder PCOS phenotype with lower cardiovascular and metabolic risk profiles. The current findings are not supportive of this concept.

Prevalence of MBS was highest when PES PCOS guidelines were used. PES requires hyperandrogenism and anovulation.[16] This phenotype has been associated with a more adverse metabolic profile in adults with PCOS.[20] Studies in women with PCOS have shown that androgen excess plays a significant role in the exacerbation of central adiposity and insulin resistance.[21] Similarly, Sıklar et al reported that hyperandrogenism was associated with more metabolic abnormalities in adolescents with PCOS.[22]

The PES criteria are adolescent-specific, and thus have refined the definition of clinical hyperandrogenism and ovulatory dysfunction for this population.[16] For example, PES criteria require moderate-severe hirsutism because isolated mild hirsutism might be developmentally normal in adolescents. Similarly, persistent acne unresponsive to topical therapy is specified as suggestive of clinical hyperandrogenism, whereas milder forms of acne are not. PES guidelines also highlight that most adolescent menstrual cycles fall within certain parameters and allow for diagnosis even in the first year post menarche if consecutive menstrual intervals are greater than 90 days. The increased prevalence of MBS observed with the use of the PES guidelines might reflect appropriate refinement for adolescents. Our results highlight the importance of validated adolescent-specific PCOS diagnostic criteria.

Limitations of our study include the high prevalence of obesity in study subjects. Obesity prevalence in PCOS patients is reported to be 60% and was 86% in the current study.[23] Rossi et al[8] examined the prevalence of MBS in obese adolescents with PCOS and concluded that the metabolic effect of obesity was more significant than the presence of PCOS. Other studies have also shown MBS risk to be higher in obese PCOS patients compared with their nonobese counterparts.[5,7] Patients were only included in the current study if they had received MBS screening, which might have resulted in selection bias. Physicians might be more prone to screening obese PCOS patients for metabolic complications.

We opted to use the most recent IDF criteria for diagnosing MBS. Previous studies have shown that use of different criteria for MBS results in variation in prevalence.[24] Our study was further limited by small sample size. Most potentially eligible patients were excluded because of lack of pelvic ultrasonography. Because the first statements regarding lack of validation of PCOM criteria in adolescents were released in 2013,[15] this could have affected physician use of pelvic ultrasound in our study population.

In conclusion, our study showed that in the same group of adolescents, choice of PCOS diagnostic criteria resulted in varying prevalence of MBS. The most recent PES guidelines most reliably identified adolescents with PCOS at risk for MBS. These results highlight the importance of validated adolescent-specific PCOS diagnostic criteria.

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