Prevalence of Metabolic Syndrome in Reproductive-Aged Polycystic Ovary Syndrome Thai Women

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Objective: To determine the prevalence of metabolic syndrome (MS) in reproductive-aged polycystic ovary syndrome (PCOS) Thai women.

Material and Method: A Cross sectional study was done at the Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital of 250 PCOS Thai women who were diagnosed using Revised Rotterdam 2003 criteria, and who did not take medications affecting sex hormones or lipid metabolism, and attended the Gynecologic Endocrinology Unit between May 2007 and January 2009. Patents were interviewed and examined for weight, height, waist circumference, and blood pressure. Venous blood sample of each patient was drawn after 12-hour fasting. Prevalence of MS determined using the definitions of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), International Diabetes Federation (IDF), and National Heart Lung and Blood Institutes/American Heart Association (NHLBI/ AHA).

Results: $Mean \pm SD$ of age, body mass index (BMI), and waist circumference (WC) were 25.4 ± 5.8 years, 26.2 ± 7.6 kg/M², and 82.3 ± 16.3 cm, respectively. Prevalence of MS by the definitions of NCEP ATP III, IDF, and NHLBI/AHA was 18.0%, 21.2%, and 21.2%, respectively. Of non-MS women, > 40% already had one to two criteria of IDF definition. Among MS women, 100% had central obesity, 50.9% had high blood pressure, 28.3% had impaired fasting blood glucose, 62.3% had hypertriglyceridemia, and 92.5% had high-density lipoprotein cholesterol < 50 mg/dL. The prevalence of MS increased from 10.3% in women aged < 20 years to 50.0% in those aged ≥ 40 years (p of trend = 0.003), and from 0.0% in women with BMI < 23 kg/M² to 54.5% in those with BMI ≥ 30 kg/M² (p of trend < 0.001).

Conclusion: The prevalence of MS in reproductive-aged PCOS Thai women was 18.0% by NCEP ATP III and 21.2% by IDF and NHLBI/AHA. The prevalence varies only little with definitions of diagnostic criteria. The prevalence increases with age and body mass index. Slightly more than 40% of the non-MS PCOS Thai women already had one to two criteria of MS.

Keywords: Metabolic syndrome, PCOS, Polycystic ovary syndrome, Thai

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Metabolic syndrome (MS) is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes⁽¹⁻³⁾. The diagnosis of MS requires clinical and laboratory information, which are grouped into criteria. Many definitions of diagnostic criteria have been introduced⁽⁴⁾ but the three definitions currently in use are those of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), International Diabetes Federation (IDF), and National Heart Lung and Blood Institute/ American Heart Association (NHLBI/AHA). The criteria that these three definitions have in common are central obesity, hypertension, dyslipidemia, and insulin resistance^(2,3). However, each institute defines cutoff for each criterion differently. Such difference would affect the prevalence of MS even in the same population. Moreover, the prevalence varies among various populations, which are influenced by the variation in age, sex, genetic factors, lifestyle characteristics, culture, and dietary composition^(2,5).

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Polycystic ovary syndrome (PCOS) is a common female endocrinopathy. The syndrome encompasses a broad spectrum of signs and symptoms. Its common clinical manifestations include menstruation irregularities, signs of androgen excess, and infertility. Most PCOS women are overweight or obese with a special feature so called central obesity. The women with central obesity have accumulation of visceral fat, *i.e.* android fat, which increases the risk to develop insulin resistance and metabolic derangement⁽⁶⁾. Since the anthropometric and metabolic abnormalities found in PCOS overlap with components of metabolic syndrome⁽⁷⁻⁹⁾, the issue regarding MS in PCOS women are gaining interest. Recent studies found that the prevalence of MS was much higher in the women with PCOS than in those without PCOS^(7,10,11). The studies that recently surveyed the prevalence of MS in PCOS women are summarized in Table 1^(7,8,10-19).

The present study aimed to determine the prevalence of MS in reproductive-aged PCOS Thai women using the definitions of NCEPATP III, IDF, and NHLBI/AHA.

Material and Method

The present study was a part of Siriraj PCOS project that was established in the Gynecologic Endocrinology clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University in 2007. The present study was conducted in accordance with the ethical principles stated in the latest version of the Declaration of Helsinki and the present study protocol was approved by the Siriraj Institutional Review Board.

Participants

Participants were 250 reproductive-aged PCOS Thai women who registered in the Siriraj PCOS project between May 2007 and January 2009. Women who had previous surgery of at least one ovary, took hormonal treatment or any medication for dyslipidemia within 3 months, or took steroid medication within 6 months before participation in the present study were excluded. The participants underwent complete physical examination and anthropometric measurement including body weight, height, and waist circumference (WC). Body mass index (BMI) was then calculated. Venous blood sample was drawn after 12 hours fasting. Blood tests were used for ruling out diseases with clinical mimicking PCOS, and for determining baseline glucose and lipid profiles (Wongwananuruk T et al, 2009 submitted).

Diagnostic criteria

PCOS was diagnosed using the Revised Rotterdam 2003 criteria⁽²⁰⁾. Briefly, the diagnosis is made in the patient who did not have diseases with clinical mimicking PCOS, and must have at least two in three of the following: 1) oligomenorrhea and/or amenorrhea, 2) hyperandrogenemia and/or hyperandrogenism, or 3) polycystic ovary. MS was diagnosed using the definitions of NCEP ATP III⁽²¹⁾, IDF⁽⁵⁾, and NHLBI/ AHA⁽³⁾. Briefly, the NCEP ATP III definition requires the presence of at least three in five of the following criteria: WC > 88 cm for women, blood pressure (BP) \geq 130/85 mmHg, fasting glucose \geq 110 mg/dL, triglyceride levels > 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 50 mg/dL. The IDF definition requires WC \geq 80 cm for Southeast Asian women plus any two in four of the following criteria: systolic BP \geq 130 mmHg or diastolic BP \ge 85 mmHg or treatment of previously diagnosed hypertension, triglyceride $\geq 150 \text{ mg/dL}$, HDL-C < 50 mg/dL in females, fasting blood glucose \geq 100 mg/dL or previously diagnosed type 2 diabetes. The NHLBI/AHA definition is similar to the IDF definition, except that it does not require WC as the essential criterion.

Laboratory assays

All laboratory assays were performed at the laboratory unit of the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, the central laboratory certified by ISO 15189. All assays were done using automatic analyzers, i.e. Modular P800, Roche for total cholesterol, HDL-C, low density lipoprotein cholesterol (LDL-C), triglycerides, and glucose; and Modular E170, Roche for thyroid stimulating hormone (TSH), prolactin, and cortisol. Plasma glucose levels were assayed using glucose hexokinase method. Plasma total cholesterol, HDL-C, LDL-C, and triglycerides were assayed using enzymatic method. TSH and prolactin were measured using chemiluminometric assay technique. All techniques had intra-and inter-assay coefficients of variation (CV) < 5%.

Statistical analysis

Sample size was calculated using the formula for descriptive study. When the estimated prevalence of MS in PCOS Thai women (p) = $35\%^{(19)}$, precision error of estimation (d) = 0.07 (or 20% of p), and alpha = 0.05, a sample size of at least 180 cases is needed to estimate the prevalence. Statistical analysis was performed using SPSS version 13 (SPSS Inc). Data

Authors	Year of publication	Prevalence of MS (%)	Diagnostic criteria for MS	Study design	Sample size	Ethnic	Age (yr)	BMI (kg/M ²)	Waist parameters
Glueck CJ, et al Apridonidze T, et al	2003 2005	46 43 72000 47 2	NCEP ATP III NCEP ATP III NCEP ATP III	Prospective Retrospective	138 106 62221120	American American	31.0 ± 9.0 20-40	$\frac{1}{25}$	WC 116 ± 15 cm NA
DOKTAS A, EL AL	C007	Case: 47.3 Control: 4.3	NUEF ALF III	Case-control	Case: 129 Control: 177	American	Case 29-34 Control 40-47	W	NA
Vural B, et al	2005	Case: 11.6 control: 0	NCEP ATP III	Case-control	Case: 43 Control: 43	Turkish	21.4 ± 1.8	23.4 ± 4.7	W/H ratio 0.77 ± 0.05
Park HR, et al	2007	14.5	NCEP ATP III	Cross sectional	117	Korean	26.0 ± 5.0	23.6 ± 4.5	WC 92.4 ± 7.3 cm
Carmina E, et al	2006	Case - NCEP ATP III:	NCEP ATP III WHO	Case-control	Case: 282 Control: 85	Italian	Case 24.9 ± 0.1	Case 27.2 ± 0.3	Case 89.0 ± 0.1
		8.2 - WHO: 16.0					Control	Control	Control
		Control - NCEP ATP III:					25.2 ± 0.2	23.3 ± 0.6	85.0 ± 0.1
		8.2 - WHO: 16.0							
Weerakiet S, et al	2007	35.3	IDF	Cross sectional	170	Thai	28.8 ± 5.9	27.1 ± 7.0	W/H ratio 0.85 ± 0.06
Bhattacharya SM, et al	2008	46.2	IDF	Cross sectional	117	Indian	21.8 ± 4.3	25.0 ± 4.1	NA
Cheung LP, et al	2008	Case: 24.9 Control: 3.1	NCEP ATP III	Case-control	Case: 295 Control: 98	Hong Kong Chinese	30.2 ± 6.4	25.8 ± 5.9	WC 82.3 \pm 13.1 cm
Rossi B, et al	2008	Case: 26.0 Control: 29.0	IDF for adolescence NHLBI/AHA for adult	Case-control	Case: 43 Control: 41	American	Case 15.6 ± 1.5 Control 14.8 + 1.8	Case 36.6 ± 6.9 Control 34.0 + 5.2	Case 108 <u>+</u> 15 Control 105 + 10
Soares EM, et al	2008	28.4	NCEP ATP III	Cross sectional	102 Case: 29 Control: 73	Brazilian	26.4 ± 5.3	Case 34.2 ± 5.3 Control 27.5 + 6.2	Case 101.2 ± 12.3 Control 86.8 + 15.6
Ni R, et al	2009	Case: 16.8	IDF	Case-control	Case: 578 Control: 281	Chinese		I	I

Table 1. Summary of studies surveying prevalence of metabolic syndrome in PCOS women

BMI = body mass index; IDF = International Diabetes Federation; MS = metabolic syndrome; NA = data not available; NCEP APT III = National Cholesterol Education Program Adult Treatment Panel III; NHLBI/ AHA = National Heart Lung and Blood Institutes/American Heart Association; WC = waist circumference; W/H ratio = waist/hip ratio; WHO = World Health Organization

were presented in mean \pm standard deviation (SD), number (%) with or without 95% confidence interval (CI), or bar graph. Chi-square test was used to compare prevalence among categories. All tests were two-sided, and had a significant level at a p-value of <0.05.

Results

Characteristics of 250 reproductive-aged PCOS Thai women are shown in Table 2. Mean \pm SD of age, BMI, and WC were 25.4 ± 5.8 years, 26.2 ± 7.6 kg/M², and 82.3 ± 16.3 cm, respectively. Of all participants, 46.0% were overweight to obese, 48.8% had WC \geq 80 cm, 14.0% and 8.0% had high systolic and diastolic blood pressure, respectively, 6.8% had impaired fasting glucose, and 39.6% had low HDL-C.

The prevalence of MS determined by the definitions of NCEPATP III, IDF, and NHLBI/AHA were 18.0% (45/250), 21.2% (53/250), and 21.2% (53/250),

respectively (Table 3). Among women with MS by the IDF definition, 100% had WC \geq 80 cm, 50.9% had blood pressure \geq 130/85 mmHg, 28.3% had fasting blood glucose \geq 100 mg/dL, 62.3% had hypertriglyceridemia, and 92.5% had HDL-C < 50 mg/dL. Approximately 70% of patients with MS had three criteria, and only 3.8% had five criteria. More than 40% of non-MS women had one to two criteria of metabolic syndrome.

The prevalence of MS increased with age and BMI (Fig. 1). The prevalence increased from 10.3% in women aged < 20.0 years to 50.0% in those aged \geq 40 years (p of trend = 0.003), and from 0.0% in women with BMI < 23 kg/M² to 54.5% in those with BMI \geq 30 kg/M² (p of trend < 0.001).

Discussion

Prevalence of MS in a certain population varies with the definitions of diagnostic criteria. A

Table 2. Characteristics of 250 reproductive-aged polycystic ovary syndrome Thai women
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Characteristics	Mean ± SD or n (%, 95% CI)	
Age (yr)	25.4 ± 5.8	
Body mass index (kg/M ²)	26.2 ± 7.6	
Waist circumference (cm)	82.3 ± 16.3	
≥ 80	122 (48.8, 42.6-55.0)	
> 88	87 (34.8, 28.9-40.7)	
Systolic blood pressure (mmHg)	112.5 ± 12.5	
\geq 130	35 (14.0, 9.7-18.3)	
Diastolic blood pressure (mmHg)	70.3 + 9.1	
> 85	20 (8.0, 4.6-11.4)	
Rotterdam criteria components*		
Oligomenorrhea and/or amenorrhea	246 (98.4, 96.8-100)	
Hyperandrogenism and/or hyperandrogenemia	123 (49.2, 43.0-55.4)	
Ultrasonographic PCO ⁺	242 (97.2, 95.1-99.2)	
Fasting blood glucose (mg/dL)	85.4 + 22.9	
> 100	17 (6.8, 3.7-9.9)	
_ > 110	12 (4.8, 2.2-7.5)	
Lipid profiles		
Cholesterol (mg/dL)	189.2 + 37.6	
Triglyceride (mg/dL)	103.2 + 66.2	
> 150	43 (17.2, 12.5-21.9)	
High density lipoprotein cholesterol (mg/dL)	55.4 + 14.6	
<50	99 (39.6, 33.5-45.7)	
Low density lipoprotein cholesterol (mg/dL)	112.0 + 32.5	

PCO = polycystic ovary

* Rotterdam criteria components: oligomenorrhea defines as menstrual cycle length > 35 days or menstruation less than 10 cycles per year, amenorrhea defines as no menstruation > 6 months or 3 cycles, hyperandrogenemia defines as serum androgen (total testosterone, free testosterone, or dehydroepiandrosterone) level higher than recommended cutoff, hyperandrogenism defines as a modified Ferriman-Gallwey score \geq 8, ultrasonographic PCO defines as ultrasonogram of at least one ovary showing 12 or more follicles with 2-9 mm in diameter

⁺ One woman did not receive ultrasonography

Components	NCEP APT III		IDF or NHLBI/AHA	
	MS (n = 45)	Non-MS (n = 205)	MS (n = 53)	Non-MS (n = 197)
Prevalence of metabolic syndrome, % [95% CI]	18.0 [13.2-22.8]	NA	21.2 [16.1-26.3]	NA
Waist circumference				
$\geq 80 \text{ cm}$	NA	NA	53 (100.0)	69 (35.0)
> 88 cm	45 (100)	42 (20.5)	NA	NA
Blood pressure $\geq 130/85$ mmHg	25 (55.6)	12 (7.3)	27 (50.9)	10 (5.1)
Fasting blood glucose				
$\geq 100 \text{ mg/dL}$	NA	NA	15 (28.3)	2 (1.0)
$\geq 110 \text{ mg/dL}$	11 (24.4)	1 (0.5)	NA	NA
Triglyceride $\geq 150 \text{ mg/dL}$	27 (60.0)	16 (7.8)	33 (62.3)	10 (5.1)
HDL-C < 50 mg/dL	42 (93.3)	57 (27.8)	49 (92.5)	50 (25.4)
Number of metabolic syndrome criteria				
- 1	NA	48 (23.4)	NA	45 (22.8)
- 2	NA	40 (19.5)	NA	48 (24.4)
- 3	32 (71.1)	NA	37 (69.8)	NA
- 4	11 (24.4)	NA	14 (26.4)	NA
- 5	2 (4.5)	NA	2 (3.8)	NA

 Table 3. Prevalence and abnormal components of metabolic syndrome criteria in 250 reproductive-aged polycystic ovary syndrome Thai women

Data are n (%), otherwise indicated

CI = confidence interval; HDL-C = high density lipoprotein cholesterol; IDF = International Diabetes Federation; NA = not applicable; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; NHLBI/AHA = Nation Heart Lung and Blood Institute/American Heart Association



Fig. 1 Prevalence of metabolic syndrome (MS) in polycystic ovary syndrome Thai women classify by age (a), and body mass index (b). Bar graph and whisker represent prevalence and 95% confidence interval

survey in a European population showed that the IDF definition was more sensitive than the NCEP ATP III to diagnosed metabolic syndrome, but the NCEP ATP III was more specific to predict insulin resistant metabolic syndrome⁽²²⁾. The IDF definition differs from the NCEP ATP III one in that the IDF needs WC as the essential criterion for diagnosis; this criterion is classified per gender and ethnic group, and it has lower cutoff for Asian women (\geq 80 vs. > 88 cm). Moreover, the IDF

has lower cutoff for fasting blood glucose (≥ 100 vs. \geq 110 mg/dL). Such differences make the IDF more sensitive than the NCEP ATP III to define MS especially in Asian women whose body-build is smaller than the Caucasian women. The NHLBI/AHA definition is more sensitive than the former two definitions as it is similar to the IDF but does not require WC as the essential criterion. In the presented reproductive-aged PCOS Thai women, there was trivial variation in the prevalence of MS when different definitions were applied, *i.e.* 18.0% by the NECP ATP III and 21.2% by the IDF or NHLBI/ ASA. This implied that the MS in the PCOS might be different from the MS in general, as all of these women had large waist circumferences that made them fit to all definitions of metabolic syndrome. The authors' finding was well suited with the hypothesis that central obesity is the key pathophysiology of MS in PCOS women^(6,23).

The prevalence of MS in the PCOS women varies from 11.6% to 46.2%, according to previous reports shown in Table 1. The prevalence of approximately 20% in the presented population was not out of this range. Compared with the population that had a higher prevalence, the presented patients were younger, thinner, and had smaller waist circumference; opposite

characteristics were found when compared with the population that had a lower prevalence. The authors could demonstrate that the prevalence of MS in the presented population increased with age and BMI. Interestingly, the prevalence in each age or BMI category was comparable with the relevant prevalence reported from other ethnic groups. An exception existed in an Indian study⁽¹³⁾ that reported a much higher prevalence than the authors' even though its population was younger and had BMI comparable with the authors'. In this case, the difference in genetic factor might be the best explanation for such a finding.

An increasing number of MS criteria associates with increasing mortality from cardiovascular diseases, as shown in the National Health and Nutrition Examination Survey (NHANES) II Mortality Study⁽²⁴⁾. In the present study, although approximately 20% of all participants had MS, more than 40% of those without MS already had one to two criteria by the time of recruitment into the present study. Despite the fact that these participants were not diagnosed with MS by that time, they already had a risk of cardiovascular diseases. Moreover, without any intervention, they might develop full-blown MS in the future, as the authors found that the prevalence of MS in this population increased with age.

The present study reported a prevalence of MS in PCOS Thai women that were averagely younger than the women in a previous Thai study⁽¹⁹⁾. The lower prevalence in the younger population and the increasing prevalence with increasing age and BMI would be valuable information for a management plan for PCOS Thai women. Universal screening for MS remains inconclusive due to lack of evidence in cost effectiveness. However, the authors' findings suggest that screening for MS in obese PCOS Thai women in order to provide early intervention with preventive measures might be beneficial to this high health-risk population.

Conclusion

The prevalence of MS in reproductive-aged PCOS Thai women was approximately 20%. The prevalence varied only little with definitions of diagnostic criteria. The prevalence increases with age and body mass index.

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ความชุกของกลุ่มอาการทางเมตาบอลิกในสตรีไทยวัยเจริญพันธุ์ที่เป็นโรคกลุ่มอาการถุงน้ำรังไข่

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วัตถุประสงค์: เพื่อศึกษาความซุกของกลุ่มอาการทางเมตาบอลิกในหญิงไทยวัยเจริญพันธุ์ ที่เป็นโรคกลุ่มอาการ ถุงน้ำรังไข่

วัสดุและวิธีการ: การศึกษาแบบตัดขวางในสตรีไทยจำนวน 250 ราย ที่เป็นโรคกลุ่มอาการถุงน้ำรังไข่ ตามเกณฑ์การวินิจฉัยของ Rotterdam 2003 ที่มารับการตรวจ ณ คลินิกต่อมไร้ท่อทางนรีเวช โรงพยาบาลศิริราช ระหว่างเดือนพฤษภาคม พ.ศ. 2550 ถึง เดือนมกราคม พ.ศ. 2552 ผู้ที่กำลังได้รับการรักษาด้วยยาที่มีผลต่อ ฮอร์โมนเพศ หรือ ต่อเมตาบอลิซึมของไขมันจะถูกคัดออกจากการวิจัย ผู้ร่วมวิจัยจะได้รับการซักประวัติ การตรวจ ร่างกาย ซั่งน้ำหนัก วัดส่วนสูง วัดเส้นรอบเอว วัดความดันโลหิต และตรวจเลือดหลังจากอดอาหาร 12 ชั่วโมง การประเมินความซุก ของกลุ่มอาการเมตาบอลิกใช้เกณฑ์วินิจฉัยของ National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), International Diabetes Federation (IDF) และ National Heart Lung and Blood Institutes/American Heart Association (NHLBI/AHA)

ผลการศึกษา: ค่าเฉลี่ย <u>+</u> ส่วนเบี่ยงเบนมาตรฐาน ของอายุ ดัชนีมวลกาย และเส้นรอบเอว คือ 25.4 <u>+</u> 5.8 ปี 26.2 <u>+</u> 7.6 กก./ม.² และ 82.3 <u>+</u> 16.3 ซม. ตามลำดับ พบความชุกของกลุ่มอาการเมตาบอลิกตามเกณฑ์วินิจฉัยของ NCEP ATP III, IDF และ NHLIB/AHA คือ ร้อยละ 18.0, 21.2 และ 21.2 ตามลำดับ ในกลุ่มผู้หญิงที่มีกลุ่มอาการ ทางเมตาบอลิกตามเกณฑ์ของ IDF ร้อยละ 100 มีภาวะอ้วนลงพุง ร้อยละ 50.9 มีความดันโลหิตสูง ร้อยละ 28.3 มีภาวะ impaired fasting glucose ร้อยละ 62.3 มีไตรกลีเซอไรด์สูง, และร้อยละ 92.5 มี high density lipoprotein cholesterol อยู่ในระดับต่ำกว่า 50 มก./ดล. พบความชุกของกลุ่มอาการทางเมตาบอลิกเพิ่มขึ้นตามอายุ และ ดัชนีมวลกาย โดยเพิ่มจากร้อยละ 10.3 ในผู้ที่อายุน้อยกว่า 20 ปี ไปเป็นร้อยละ 50.0 ในผู้ที่อายุมากกว่าหรือเท่ากับ 40 ปี (p of trend = 0.003) และเพิ่มจากร้อยละ 0.0 ในผู้หญิงที่มีดัชนีมวลกายน้อยกว่า 23 กก./ม.² ไปเป็นร้อยละ 54.5 ในกลุ่มที่มีดัชนีมวลกายมากกว่าหรือเท่ากับ 30 กก./ม.² (p of trend < 0.001)

สรุป: หญิงไทยวัยเจริญพันธุ์ที่เป็นโรคกลุ่มอาการถุงน้ำรังไข่ มีกลุ่มอาการเมตาบอลิก ร้อยละ 18.0 ตามเกณฑ์ของ NCEP ATP III และร้อยละ21.2 ตามเกณฑ์ของ IDF และ NHLIB/AHA โดยความชุกมีความแตกต่างกันเพียงเล็กน้อย เมื่อใช้เกณฑ์วินิจฉัยที่แตกต่างกัน ความชุกของกลุ่มอาการเมตาบอลิกเพิ่มขึ้นตามอายุและดัชนีมวลกาย พบว่าร้อยละ 40 ของสตรีไทยที่เป็นโรคกลุ่มอาการถุงน้ำรังไข่ และไม่มีกลุ่มอาการเมตาบอลิกมีความผิดปกติขององค์ประกอบ ในเกณฑ์วินิจฉัยกลุ่มอาการเมตาบอลิกแล้วหนึ่งถึงสองข้อ