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ความชุกและอาการแสดงทางคลินิกของภาวะถุงน้ำรังไข่หลายใบในสตรีวัยรุ่น

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Prevalence and Clinical Features of Polycystic Ovary Syndrome in Thai Adolescents

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วัตถุประสงค์: เพื่อศึกษาความชุกของภาวะถุงน้ำรังไข่หลายใบในสตรีวัยรุ่นในระดับมัธยมปลายในจังหวัดขอนแก่น และอาการแสดงทางคลินิกของสตรีวัยรุ่นที่ได้รับการวินิจฉัยภาวะถุงน้ำรังไข่หลายใบ

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาเชิงพรรณนาไปข้างหน้าในนักเรียนหญิงระดับมัธยมปลายในจังหวัดขอนแก่น อายุระหว่าง 15-18 ปี จำนวน 385 ราย โดยวินิจฉัยภาวะถุงน้ำรังไข่หลายใบตามเกณฑ์ของ The International Consortium of Pediatric Endocrinology (ICPE)

ผลการศึกษา: พบความชุกของภาวะถุงน้ำรังไข่หลายใบในสตรีวัยรุ่นร้อยละ 1.81 ความผิดปกติของประจำเดือนที่พบมากที่สุดคือ รอบประจำเดือนห่างผิดปกติ (Oligomenorrhea), สตรี 5 รายมีลักษณะทางคลินิกของฮอร์โมนเพศชายสูง เมื่อใช้การประเมินขนตามเกณฑ์ของ modified Ferriman-Gallwey scores และประเมินสิวที่ใบหน้า, สตรี 5 รายมีระดับฮอร์โมนเพศชายในเลือดสูง

สรุป: ความชุกของภาวะถุงน้ำรังไข่หลายใบในสตรีวัยรุ่นของการศึกษานี้ คือร้อยละ 1.81 โดยพบลักษณะประจำเดือนผิดปกติที่มากที่สุดคือ Oligomenorrhea และลักษณะทางคลินิกของฮอร์โมนเพศชายสูงพบได้เกือบทั้งหมดของผู้ที่ได้รับการวินิจฉัยภาวะถุงน้ำรังไข่หลายใบ

Background and objective: This study was conducted to assess the prevalence and clinical features of polycystic ovary syndrome (PCOS) among high school-age Thai adolescents in Khon Kaen.

Materials and Methods: This was a cross sectional study in which 385 adolescents aged 15 to 18 years were enrolled. The diagnosis of PCOS was made according to the criteria issued by the International Consortium of Pediatric Endocrinology (ICPE).

Results: The prevalence of PCOS among participants was 1.81%. Oligomenorrhea was the most common form of abnormal menstruation among participants with PCOS. Of the seven participants with PCOS, five had evidence of clinical hyperandrogenism according to their modified Ferriman-Gallwey scores, and two were noted as having clinical hyperandrogenism based on the presence of moderate acne vulgaris. Five of the seven participants with PCOS were found to have biochemical hyperandrogenism.

Conclusion: The prevalence of PCOS in the present study was 1.81%. The most common abnormal menstruation pattern among the patients with PCOS was oligomenorrhea. Clinical hyperandrogenism was

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คำสำคัญ: ภาวะถุงน้ำรังไข่หลายใบ; ความชุก; วัยรุ่น; ฮอร์โมนเพศชายสูง; ประจำเดือนมาน้อย

Keywords: Polycystic ovary syndrome, prevalence, adolescent, hyperandrogenism, oligomenorrhea

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in reproductive-age women[1]. PCOS is a complex disorder characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology[2, 3]. Clinical presentations of PCOS consist of hirsutism, alopecia, acne, menstrual irregularity, and infertility. Over the long-term, women with PCOS carry higher risks of various metabolic disorders, i.e., diabetes mellitus, dyslipidemia, and cardiovascular disease. Mood disorders and depression, which can adversely affect quality of life, have also frequently been noted among women with PCOS[4]. Early diagnosis of PCOS is, therefore, necessary in order to provide appropriate management in a timely fashion.

Traditionally, there are three sets of criteria commonly used to diagnose PCOS. The first are the National Institute of Health (NIH) diagnostic criteria, which are based on ovulatory dysfunction and clinical or biochemical hyperandrogenism[5]. The Rotterdam criteria proposed in 2003 are based on the NIH criteria but also incorporate polycystic ovarian morphology noted on ultrasound findings[6]. Finally, the criteria proposed by the Androgen Excess Society focuses on clinical or biochemical hyperandrogenism[7]. The prevalence of PCOS among adolescents according to the NIH and Rotterdam diagnostic criteria varies between 3.0% to 7.3% and 5.3% to 9.1%, respectively. However, all three of these criteria may be problematic if applied to adolescents, as they potentially overlap with normal physiological changes that can occur during pubertal development.

Consequently, the International Consortium of Pediatric Endocrinology (ICPE) has issued a consensus regarding the specific PCOS diagnostic criteria for adolescents. According to these criteria, diagnosis of PCOS requires a combination of abnormal uterine bleeding and evidence of hyperandrogenism[8, 9]. This study was accordingly undertaken to determine the prevalence of PCOS among high school-age Thai adolescents using the ICPE diagnostic criteria.

Materials and methods

This prospective cross-sectional study was approved by the Khon Kaen University Ethics Committee in Human Research (Reference No. HE611213). Our inclusion criteria included girls 15 to 18 years of age who have undergone menarche at least 2 years prior to the study. We excluded those who had history of hormonal contraceptive use within 3 months prior to the study. Written informed consent was obtained from either participants or their guardians before enrollment. The adolescents were defined as individuals in the 10-19 years age group as per the World Health Organization classification[10]. We recruited a total of 385 high school adolescent girls, aged between 15 to 18 years from two Khon Kaen University secondary schools in Khon Kaen, Thailand. Data collection was conducted from September 2018 to February 2019.

This study used the ICPE diagnostic criteria for PCOS[8], consisting of a combination of an abnormal uterine bleeding (AUB) pattern and evidence of hyperandrogenism. The AUB pattern must be abnormal for the patient's age or gynecologic age and the symptoms must persist for at least 2 years. Evidence of hyperandrogenism can be established either clinically or biochemically. Clinical hyperandrogenism is diagnosed by the presence of moderate to severe hirsutism based on a modified Ferriman-Gallwey (mF-G) score of ≥5[11, 12]. Moderate to severe acne vulgaris (defined as 11–25 comedonal or inflammatory lesions and >25 comedonal or inflammatory lesions, respectively) is an indication to test for hyperandrogenemia. Biochemical hyperandrogenism was defined as serum total testosterone level > 55 ng/dL[13].

Data collection

After learning of the study and its purpose, the adolescents and parents of adolescents who agreed to participate signed informed consent forms. First, data were collected via a questionnaire regarding patients' baseline characteristics (age at menarche, body weight, height, menstrual history, AUB if any, underlying disease, history of any hormonal use, and

self-reported degree of hirsutism and acne). The degree of hirsutism was assessed according to mF-G scoring method. The participants were asked to compare the amount of body hair they had to a pictorial chart. Data, including waist and hip circumference and blood pressure, were obtained by physical examination. Thereafter, we made an appointment to re-examine participants in whom hirsutism and acne were suspected (i.e., those who reported having hirsutism and/or moderate to severe acne vulgaris).

Participants who experienced abnormal menstruation were invited to undergo blood collection to test follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), Prolactin, 17-hydroxyprogesterone (17-OHP), and total testosterone levels, as well as for a 75-gm oral glucose tolerance test (OGTT) and lipid study. FSH, TSH, Prolactin, and 17-OHP were assessed in order to exclude other endocrinopathies that can mimic PCOS. Lipid studies and OGTT were evaluated to identify any metabolic disturbances.

Laboratory assays

The 75 gm OGTT was performed using enzymatic reference method with hexokinase (Roche/Hitachi cobas c system analyzer), and lipid profiles were ascertained using enzymatic colorimetric assay (Roche/Hitachi cobas c system analyzer). Serum prolactin, testosterone, TSH, FSH were also measured using ECLIA (Cobas e801, e601, e602 immunoassay analyzer, Roche Diagnostics, Mannheim, Germany). Serum 17-OHP was measured using a radioimmunoassay (RIA) for direct determination of 17α-OHP (Wizard 2470 automatic gamma counter, PerkinElmer, Massachusetts, USA).

Statistical analyses

Statistical analyses were performed using STATA version 10.1. Descriptive statistics were presented as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the distribution of the continuous variables. Numbers and percentages were used to represent categorical variables.

Results

Of the 483 girls were invited to participate in the study, 385 accepted. Participants' baseline characteristics are summarized in Table 1. Their ages ranged from 15 to 18 years, with a mean age of 16.36 years. Two hundred thirty-two (60.3%) reported having hirsutism. Moderate to severe acne was noted in 27 (7.0%).

Ten (2.6%) participants reported abnormal menstruation. Of these, all agreed to undergo blood testing according to the study protocol. Seven of the girls met the ICPE diagnostic criteria for PCOS in adolescents, making the prevalence of PCOS 1.81%. Three participants did not meet the ICPE diagnostic criteria due to the presence of hyperprolactinemia (1) and no evidence of hyperandrogenism (2). None of participants diagnosed with PCOS had been previously diagnosed or treated for this condition.

Participants diagnosed with PCOS were more likely to have hirsutism (71.4% versus 60.1%) and moderate to severe acne (28.6% versus 6.6%) than those who were not. Body composition measurements, including weight, height, waist circumference, hip circumference, and BMI, of the adolescents with PCOS were roughly similar to those without (Table 1).

The most common abnormal menstruation pattern among participants who met the ICPE criteria was oligomenorrhea (5 cases). One of the remaining two participants reported experiencing secondary amenorrhea and the other reported frequent menstruation.

Of the seven participants with PCOS, five had evidence of clinical hyperandrogenism according to their mF-G scores, and two were noted as having clinical hyperandrogenism based on the presence of moderate acne vulgaris. Five were found to have biochemical hyperandrogenism.

Table 2 shows the hormonal and metabolic profiles of the participants with PCOS. All had normal FSH, TSH, PRL, and 17OHP, meaning that other causes of abnormal menstruation and hyperandrogenism could be excluded. None of participants with PCOS were found to have impaired glucose tolerance or abnormal lipid profiles.

Discussion

Based on the ICPE diagnostic criteria developed specifically for adolescents, the prevalence of PCOS in this study was 1.81%. Oligomenorrhea was the most common abnormal menstruation pattern among participants with PCOS. Evidence of hyperandrogenism was revealed by clinical examination in 6 cases and by biochemical evaluation in 5 cases. To our

Table 1 Baseline characteristics of participants (N= 385)

Characteristics	Total (N=385)	PCOS (N=7)	Non-PCOS (N=378)
Age (years), mean (SD)	16.36 (0.93)	16.57 (0.98)	16.36 (0.93)
Age Menarche (years),			
median (IQR)	12 (12-13)	13 (12-13)	12 (12-13)
Height (cm), mean (SD)	160.17 (5.28)	161.29 (5.09)	160.15 (5.29)
Weight (kg), median (IQR)	51 (46-58)	53 (40-55)	51 (46-58)
Waist circumference (cm), median (IQR)	69 (65-74)	67 (64-74)	69 (65-75)
Hip circumference (cm), median (IQR)	89 (84-95)	86 (81-95)	89 (84-95)
Waist-hip ratio, median (IQR)	0.78 (0.74-0.81)	0.79 (0.74-0.82)	0.78 (0.74-0.81)
BMI (Kg/m2), median (IQR)	19.96 (18.36-22.07)	18.34 (16.02-22.03)	19.97 (18.37-22.10)
Classification of BMI[a], n (%)			
Underweight	101 (26.2)	4 (57.1)	97 (25.7)
Normal	208 (54.0)	3 (42.9)	205 (54.2)
Overweight	35 (9.1)	0 (0.0)	35 (9.3)
Obesity	41 (10.7)	0 (0.0)	41 (10.8)
mFG score, median (IQR)	6 (3-9)	6 (3-11)	6 (3-9)
Abnormal menstruation, n (%)			
No	375 (97.4)	0 (0)	375 (99.2)
Yes	10 (2.6)	7 (100)	3 (0.8)
Hirsutism[b], n (%)			
No	153 (39.7)	2 (28.6)	151 (40.0)
Yes	232 (60.3)	5 (71.4)	227 (60.1)
Acne[c], n (%)			
No	72 (18.7)	2 (28.6)	70 (18.5)
Mild	286 (74.3)	3 (42.9)	283 (74.9)
Moderate	25 (6.5)	2 (28.6)	23 (6.1)
Severe	2 (0.5)	0 (0.0)	2 (0.5)

PCOS, polycystic ovarian syndrome; SD, standard deviation; IQR, interquartile range: BMI, body mass index; mFG, modified Ferriman-Gallwey

[a] Classification of BMI; Underweight < 18.5 kg/ m2, Normal 18.5-22.9 kg/m2, Overweight 23-24.9 kg/m2, Obesity >=25 kg/m2

[b] Hirsutism; Modified Ferriman-Gallwey score ≥ 5

[c] Acne; No = 0 point, Mild = 1-10 points, Moderate = 11-25 points, Severe ≥ 25 points

knowledge, this is the first study conducted to determine the prevalence of PCOS in adolescents based on the diagnostic criteria proposed by the ICPE.

Despite the fact that PCOS can affect women of all ages, there are limited data regarding the prevalence and impact of PCOS among adolescents. The prevalence of PCOS among adolescents according to the NIH diagnostic criteria varies from 3.0% to 7.3%, depending on the age of the patients[14, 15]. Musmar et al. reported the prevalence of PCOS to be 7.3% among 137 Palestine female university students, which is relatively high compared to the present study[14]. Hashemipour et al. reported the prevalence of PCOS to be 3% among 14 to 18 year-old high school girls in Iran[15]. By using the Rotterdam criteria, the prevalence of PCOS among adolescents in Iran, India, and Thailand based on the Rotterdam criteria were was found to be 8.30%, 9.13% and 5.29%,

Table 2 Hormonal and metabolic features of the seven adolescents with PCOS

Results	Number (%)
Total testosterone level (ng/dl)	
≤ 55	2 (28.6)
> 55	5(71.4)
75 gm oral glucose tolerance test, median (IQR)	86 (82-96)
Fasting blood sugar (mg/dl)	
55-99	7 (100)
100-125	0 (0)
≥ 126	0 (0)
2hr blood sugar (mg/dl)	
< 140	7 (100)
140-199	0 (0)
≥ 200	0 (0)
Lipid profile	
Total cholesterol (mg/dl)	
< 200	4 (57.1)
≥ 200	3 (42.9)
Triglyceride (mg/dl)	
< 150	6 (85.7)
≥ 150	1 (14.3)
Low density lipoprotein (mg/dl)	
< 130	4 (57.1)
≥ 130	3 (42.9)
High density lipoprotein (mg/dl)	
< 35	0 (0)
≥ 35	7 (100)
Hormonal profile, mean (SD)	
Follicular stimulating hormone (FSH)	7.16 (2.05)
Thyroid stimulating hormone (TSH)	2.08 (0.91)
Prolactin	16.7 (5.9)
17-Hydroxyprogesterone (17-OHP)	0.93 (0.52)

PCOS, polycystic ovarian syndrome
Data are presented as numbers (percentages) unless state otherwise

respectively[16-18]. Differences in the diagnostic criteria applied in each study preclude any meaningful cross-study comparisons. However, the prevalence of PCOS appears to be highest when the Rotterdam criteria are used. A study by Yildiz et al.[19] found that the prevalence of PCOS was three times higher when using the Rotterdam criteria compared with the NIH criteria in the same population.

This study used the ICPE criteria, which have been proposed as a diagnostic tool specifically for adolescents and have never been used in any previous studies. These criteria consist of a combination of AUB and evidence of hyperandrogenism. More specifically, AUB must persist for 2 years after menarche to ensure that it is not a normal pubertal transition. Polycystic ovarian morphology is excluded from the ICPE criteria because this information can only be accurately obtained via transvaginal ultrasound and is, thus, not clinically feasible for adolescents. In addition, there is no standard criteria for diagnosis of abnormal ovarian volume parameters among adolescents[20].

Oligomenorrhea was the most common pattern of abnormal menstruation among adolescents with PCOS in this study, which is in line with the findings of previous reports[18]. The prevalence of clinical hirsutism varies widely across the studies. The rate of 71.4% observed among adolescents with PCOS in this study appears to be consistent with the findings of some previous reports[14-16]. However, this is much higher than the 4.7% and 17.2% noted in previous studies conducted in India and Thailand, respectively[17, 18]. The wide variation in reported prevalence of clinical hirsutism among adolescents with PCOS in the literature is likely due to differences in population characteristics, particularly ethnicity, and patients' age and the mF-G score cutoff point used for diagnosis of hirsutism, which has yet to be established for adolescents. In this study, we applied a cutoff score of ≥ 5 according to that which has been proposed for Chinese women[12].

In this study, all patients with PCOS had normal BMI (median 18.34; IQR 16.02-22.03) according to the Asian criteria guideline[21]. However, both obese and non-obese adolescents with PCOS carry higher risks of metabolic disorders[22]. The Endocrine Society recommends that all patients with PCOS be screened for obesity, cardiovascular risk factors including dyslipidemia, and type 2 diabetes mellitus[23]. Although none of the adolescents with PCOS in this study had

impaired glucose tolerance or abnormal lipid studies, these cases require regular follow-up.

The main strength of this study is the use the ICPE diagnostic criteria, which are updated criteria developed specifically to diagnose PCOS in adolescents. Other causes that may mimic the features of PCOS were excluded by means of hormonal profile evaluation. However, the low prevalence of PCOS and relatively small sample size in this study precluded the analysis of associations between clinical variables and diagnosis of PCOS. Finally, there is not yet established mF-G score cutoff point for adolescents. This may lead to high percentage of hirsutism in our study when using cutoff point of adults because hyperandrogenic state can be seen in adolescents due to physiologic hyperandrogenism of puberty[24].

In conclusion, the prevalence of PCOS among adolescents who participated in this study was 1.81% according to the ICPE criteria. Oligomenorrhea was the most common abnormal menstrual pattern among the participants with PCOS. More than half of the patients with PCOS had clinical hirsutism.

Conflicts of Interest

None to declare

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