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Prevalence and Predictive Factors for Being High-risk of Obstructive Sleep Apnea Using Berlin Questionnaire in Polycystic Ovary Syndrome: Age - and BMI-matched study

Natnicha Kangwolkij, M.D.*,
Areepan Sophonsritsuk, M.D., PhD**,
Visasiri Tantrakul, M.D.***,
Chuenkamon Charakorn, M.D., MSc****,
Siriluk Tantanavipas, M.D.**

** Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
*** Reproductive Endocrinology and Infertility Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
**** Division of Sleep Medicine, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
***** Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

ABSTRACT

Objectives: To evaluate prevalence and predictive factors for being high-risk of obstructive sleep apnea (OSA) in women with and without polycystic ovary syndrome (PCOS).

Materials and Methods: This age and body mass index matched cross-sectional study recruited 94 women with ages between 20 and 40 years. Risk of OSA was assessed by Berlin questionnaire in 47 women with PCOS diagnosed by the Rotterdam criteria and 47 women without PCOS.

Results: Women with PCOS had significantly greater waist circumference, waist-hip ratio, hyperandrogenism (HA), biochemical and clinical HA, and poorer metabolic parameters, that is, total cholesterol, low-density lipoprotein cholesterol and insulin, compared to women without PCOS. Women with PCOS revealed a statistically significantly higher prevalence in being high-risk of OSA than women without PCOS (27.7% vs 6.4%, p = 0.006). Impaired fasting glucose (IFG, fasting plasma glucose ≥ 100 mg/dL) was an independent predictor of high-risk for OSA using Berlin questionnaire with an odds ratio (95% confidence interval) of 29.19 (1.26-674.04).

Conclusion: The prevalence of being high-risk of OSA assessed by Berlin questionnaire was higher in women with PCOS than those without PCOS. IFG but not PCOS was a significant key predictive factor associated with the development of being high-risk of OSA. Consequently, we suggested OSA risk screening using Berlin questionnaire should be assessed in women with PCOS. Polysomnography should be offered to the patients who either are being high-risk of OSA identified by questionnaire screening tool or having insulin resistance.

Keywords: obstructive sleep apnea syndrome, questionnaire, polycystic ovary syndrome, impaired fasting glucose.

Correspondence to: *Siriluk Tantanavipas MD, Reproductive Endocrinology and Infertility Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand. Email: siriluk.tan@mahidol.ac.th*

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ความชุกและปัจจัยทำนายความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ โดยใช้แบบสอบถามเบอร์ลินในกลุ่มอาการถุงน้ำรังไข่หลายใบ: การศึกษาแบบเข้าคู่กันของอายุและค่าดัชนีมวลกาย

ณัฐณิชา กังวลกิจ, อารีย์พรรณ โสภณสฤษฏ์สุข, วิสาข์สิริ ตันตระกูลม, ชื่นกมล ชรากร, สิริลักษณ์ ตันธนาวิภาส

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความชุกและปัจจัยทำนายความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับในหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ และหญิงที่ไม่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ*

วัสดุและวิธีการ: *การศึกษาแบบตัดขวางแบบเข้าคู่กันของอายุและค่าดัชนีมวลกาย รวบรวมผู้เข้าร่วมวิจัย 94 ราย อายุระหว่าง 20 - 40 ปี 47 ราย เป็นหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบที่ได้รับการวินิจฉัยด้วเกณฑ์ Rotterdam และ 47 ราย เป็นหญิงที่ไม่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ ผู้เข้าร่วมวิจัยได้ทำแบบสอบถามเบอร์ลินเพื่อประเมินความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ*

ผลการศึกษา: *หญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบมีความความชุกของความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับสูงกว่าหญิงที่ไม่มีกลุ่มอาการถุงน้ำรังไข่หลายใบอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 27.7 เปรียบเทียบกับ ร้อยละ 6.4, p = 0.006) ระดับน้ำตาลในเลือดสูงกว่าปกติ (ระดับน้ำตาลในเลือดหลังอดอาหาร ≥ 100 มิลลิกรัม/เดซิลิตร) เป็นปัจจัยทำนายความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ โดยมีอัตราส่วนออด (ช่วงความเชื่อมั่น ร้อยละ 95) 29.19 (1.26-674.04)*

สรุป: *ความชุกของความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับสูงขึ้นอย่างมีนัยสำคัญทางสถิติในหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ ดังนั้นแนะนำให้ใช้แบบสอบถามเบอร์ลินในการคัดกรองความเสี่ยงของโรคหยุดหายใจขณะนอนหลับในหญิงที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ ในกรณีที่คัดกรองพบว่ามีความเสี่ยงสูงของโรคหยุดหายใจขณะนอนหลับ หรือมีระดับน้ำตาลในเลือดสูงกว่าปกติ แนะนำให้ส่งตรวจการนอนหลับเพื่อวินิจฉัยโรคหยุดหายใจขณะนอนหลับต่อไป*

คำสำคัญ: *โรคหยุดหายใจขณะนอนหลับ, แบบสอบถาม, กลุ่มอาการถุงน้ำรังไข่หลายใบ, ระดับน้ำตาลในเลือดสูงกว่าปกติ*

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in almost 10% of reproductive-age women[1, 2]. The characteristics of PCOS include anovulation, hyperandrogenism (HA), insulin resistance (IR), and polycystic ovarian morphology assessed by ultrasonography. Multiple comorbidities of PCOS include IR, diabetes mellitus (DM), metabolic syndrome (MetS), obesity, non-alcoholic fatty liver disease, cardiovascular disease, depression, and sleep disorder[3, 4].

The most common sleep-related breathing disorder is obstructive sleep apnea (OSA). It is characterized by repeated episodes of breathing cessation during sleep[5]. The diagnosis of OSA is done by monitoring breathing during sleep. In-laboratory polysomnography (PSG) is the gold standard for the OSA diagnosis. However, the high cost and lack of availability of PSG are the main problems for investigating the patients suspected of having OSA[6]. Using some questionnaires i.e. Berlin and the STOP-BANG were the effective screening tools to identification of OSA patients[7].

OSA is an obesity-related condition[8]. Women with PCOS are frequently associated with the development of obesity[9]. Hence, it is not surprising that the prevalence of OSA is increased in women with PCOS[10, 11]. It is questionable that an increase of OSA in women with PCOS was related to either obesity or other associated conditions. The common co-exist mechanisms of PCOS and OSA such as obesity, IR, and HA might play a role in its etiology and contribute to the comorbidities of the other[12]. Moreover, the similar consequences of OSA and PCOS including metabolic and hormonal abnormalities might lead to more severe phenotypes of PCOS among women with OSA[13].

A recent systematic review and meta-analysis revealed that 35% of women with PCOS had OSA (95% confidence interval (CI) 22.2-48.9%)[11]; however, no study was ever performed in Thai PCOS patients. In the present study, the Berlin questionnaire was used for early identification OSA in PCOS women. The prevalence and predictive factors for being high risk of OSA in women with PCOS were investigated. We hypothesized that Thai women with PCOS have an increased risk of OSA when compared to Thai women without PCOS.

Materials and Methods

Between September 2020 and October 2021, 94 women ages 20 - 40 years were recruited in this present age and BMI matched cross-sectional study after written informed consent. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital (MURA2020/1023).

Forty-seven women with PCOS were recruited from the Endocrine Clinic, Division of Reproductive Endocrinology & Infertility, Department of Obstetrics and Gynecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The inclusions criteria in PCOS group were: 1) women with PCOS diagnosed by Rotterdam criteria (which defined as two or more of the following three symptoms: anovulation, HA, or polycystic ovary[14]), and 2) no underlying disease associated with sleep disturbance such as depression, mood disorder, psychiatric disorder, severe chronic disease, malignancy, etc.

The control group was 47 women without PCOS who were recruited from local advertisements. The inclusion criteria for control women were: 1) having regular menstruation with menstrual duration between from 21 to 35 days, 2) no evidence of clinical or biochemical HA, and 3) no underlying disease associated with sleep disturbance such as depression, mood disorder, psychiatric disorder, severe chronic disease, malignancy, etc.

The exclusion criteria in both groups were other conditions related to sleep disorder including smoking, alcohol or caffeine drinking, sedative drug use, and receiving any medication with a side effect of drowsiness. None of the participants had received any hormonal contraceptive for at least 3 months.

The age of patients was categorized into 20 to 30 years and more than 30 to 40 years. The body mass index (BMI) was divided into less than 25 kg/m^2 and 25 kg/m^2 or more. After that, we matched the women with PCOS with the others in the control group one to one based on their ages and BMI.

All participants underwent a medical and past history interview, physical examination seeking for signs of HA and IR, laboratory investigation, and ultimately completing the

sleep disorder questionnaire.

Anthropometric Measurement

Weight, height, waist circumference (WC), and hip circumference were measured by the single investigator. WC was measured by a stretch-resistant tape at a midpoint between the lower margin of the lowest palpable rib and the iliac crest. Hip circumference was measured parallel to the floor around the widest part of the buttocks[15]. Waist-hip ratio (WHR) was defined as WC divided by the hip circumference. Weight in kilograms divided by the square of height on meters was considered for BMI.

Laboratory Methods

Blood was collected from all participants after fasting, at 8 o'clock, and evaluated for thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total testosterone (T), sex hormone-binding globulin (SHBG), fasting plasma glucose (FPG) and insulin. The second plasma samples for plasma glucose were assessed after 2 hours post- 75 g glucose-load (2h-PG). T and SHBG were performed by chemiluminescence assays (Immulite 2000 xpi, Siemens Healthineers Headquarters, Germany).

T (ng/mL) x 3.47 x 100 /SHBG (nmol/L) was the formula of the free androgen index (FAI) calculation. The homeostasis model assessment of IR (HOMA-IR) method was considered by the formula: HOMA-IR = insulin (μU/mL) × glucose (mg/dL)/405.

Sleep disorder questionnaire

All participants completed validated Thai versions of self-administered Berlin questionnaire (BQ)[16], Epworth sleepiness scale (ESS)[17], and Pittsburgh Sleep Quality Index (PSQI)[18] for assessing the risk of OSA, daytime sleepiness, and sleep disorder-breathing condition, respectively. All participants took the questionnaires in private room at the same visit when they recruited into this study. Five minutes were required for each questionnaire.

BQ was a survey screening the high risk of OSA with a sensitivity of 86% and specificity of 77% compared to apnea-hypopnea index (AHI) > 5 cut-off performed by polysomnography[19]. It consisted of 10 questions which were divided into 3 domains of sleep problems: 1) snoring behavior, 2) daytime sleepiness, and 3) hypertension or BMI > 30 kg/m^2. The positive score on the first and the second domain was considered when the symptoms occurred 3-4 times/week or more. The presence of hypertension or BMI > 30 kg/m^2 in the third domain was interpreted as the positive score. The positive score on 2 or more domains was diagnosed for being high-risk of OSA.

ESS was assessed for the degree of daytime sleepiness from 8 questions. The score ranged from 0-3 in each item. More than 10 scores were indicated for excessive daytime sleepiness.

PSQI was performed for overall sleep quality assessment over a 1-month time interval. It consisted of 7 aspects from 19 questions: 1) subjective sleep patients' quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbance, 6) use of sleep medication, and 7) daytime dysfunction. Each question yielded a score ranging from 0-3. More than 5 scores were considered as poor sleep quality.

Definition

A WC ≥ 80 cm and BMI ≥ 25.0 kg/m^2 were defined as abdominal obesity and obesity, respectively. MetS was diagnosed by 3 or more of the following criteria: 1) WC ≥ 80 cm, 2) TG ≥ 150 mg/dL, 3) HDL-C < 50 mg/dL, 4) Blood pressure ≥ 130/85 mmHg, and 5) FPG ≥ 100 mg/dL[20]. Biochemical HA was defined as FAI > 6.8[21] whereas clinical HA was characterized by acne, alopecia, and/or hirsutism[14]. HA was characterized by biochemical and/or clinical HA.

Level of FPG ≥ 100 mg/dL and 2-h PG during 75g-OGTT from 140 to 199 mg/dL were the criteria for the diagnoses of IFG and impaired glucose tolerance (IGT), respectively[22]. Homeostasis model assessment of IR (HOMA-IR) > 2.77 was defined as IR[23].

Sample size

Based on results from the study conducted by Babak et al, the prevalence of being high-risk of OSA was 47% and 15% in women with PCOS and without PCOS, respectively l[24]. These results were used for sample size calculation by two independent proportions at 95%CI (α =

0.05) and 90% power ($\beta = 0.1$). The sample size was 42 participants per group. The total sample size was 94 participants after adding 10% sample loss. There were 47 participants for each group.

Statistical Analysis

Statistical analyses were performed using SPSS program version 22 for Windows. T-test and chi-square test were analyzed for the normally distributed continuous and discrete data, respectively. Mann-Whitney U test was performed for non-normal distributed continuous data. Independent association of being high-risk of OSA was assessed by logistic regression. Univariate logistic regression was used for all participants. Mixed effects logistic regression model was performed for statistically significant factors in the univariate analyses. Odds ratio (OR) with 95%CI for the logistic regression was calculated. In all analyses, $p < 0.05$ was indicated statistically significant.

Results

There was no significant difference in several parameters between women with and without PCOS (median age 27 vs 27 years, $p = 0.423$ and median BMI 26.1 vs 25.1 kg/m^2, $p = 0.404$). WC and WHR were significantly increased in women with PCOS compared to women without PCOS; even though, the BMI was similar (WC 85 vs 74 cm, $p = 0.032$ and WHR 0.84 vs 0.79, $p < 0.001$). Women with PCOS had higher biochemical HA levels (T 42.0 vs 32.0 ng/ml, $p < 0.001$; SHBG 23.6 vs 45.2 nmol/L, $p = 0.012$ and FAI 5.95 vs 2.59, $p < 0.001$). More number of women had clinical HA and HA than those without PCOS, 29.8% vs 0%, $p < 0.001$ and 38.3% vs 4.3%, $p < 0.001$, respectively. Furthermore, metabolic parameters including circulatory TC, LDL, and insulin were higher in women with PCOS than those without PCOS, 207.0 vs 193.1 mg/dL $p = 0.030$, 138.5 vs 122.3 mg/dL $p = 0.024$, and 9.0 vs 7.7 µU/mL $p = 0.045$, respectively (Table 1).

Table 1. Baseline characteristics of PCOS and women without PCOS.

Characteristics	PCOS (n = 47)	without PCOS (n = 47)	p value
Age (years)	27.0 [24.0,30.0]	27.0 [24.0,32.0]	0.611
BMI (kg/m^2)	26.1 [20.9,31.2]	25.1 [19.5,27.8]	0.151
WC (cm)	85.0 [74.0,97.0]	74.0 [69.0,91.0]	0.019
HC (cm)	101.4 ± 11.5	100.1 ± 14.3	0.354
WHR	0.84 ± 0.06	0.79 ± 0.06	< 0.001
SBP (mmHg)	117.0 [111.0,121.0]	115.0 [108.0,125.0]	0.433
DBP (mmHg)	74.9 ± 9.2	75.7 ± 7.7	0.580
TSH (µU/mL)	1.39 [0.95,2.32[	1.86 [1.39,2.51]	0.052
FSH (µU/mL)	4.92 [3.97,5.63]	4.50 [2.93,5.73]	0.216
TG (mg/dL)	84.0 [63.0,125.0]	66.0 [52.0,103.0]	0.058
TC (mg/dL)	207.0 ± 33.2	193.1 ± 36.6	0.030
HDL-C (mg/dL)	54.3 ± 14.7	58.7 ± 14.3	0.142
LDL-C (mg/dL)	138.5 ± 35.6	122.3 ± 39.9	0.024
T (ng/mL)	42.0 [38.0,58.0]	32.0 [26.0,42.0]	< 0.001
SHBG (nmol/L)	23.6 [17.0,50.5]	45.2 [27.2,60.0]	0.001
FAI	5.95 [2.94,10.19]	2.59 [1.70,3.97]	< 0.001
Clinical HA	28 (29.8)	0 (0)	< 0.001
HA	36 (38.3)	4 (4.3)	< 0.001
FBG (mg/dL)	85.0 [78.0,89.0]	83.0 [78.0,88.0]	0.812
Insulin (µU/mL)	9.0 [7.6,14.3]	7.7 [5.8,10.1]	0.045
HOMA-IR	1.93 [1.33,3.10]	1.65 [1.25,2.34]	0.111
IR	15 (16)	8 (8.5)	0.093
MetS	10 (10.6)	8 (8.5)	0.600
ESS score	7.0 [6.0,11.0]	8.0 [5.0,10.0]	0.276
PSQI score	6.0 [4.0,9.0]	6.0 [4.0,7.0]	0.077

PCOS: polycystic ovary syndrome, BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, TSH: thyroid stimulating hormone, FSH: follicle-stimulating hormone, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, T: total testosterone, SHBG: sex hormone-binding globulin, FAI: free androgen index, HA: hyperandrogenism, FPG: fasting plasma glucose, 2hr-PP glucose: 2 hour postprandial glucose, HOMA-IR: homeostatic model assessment of insulin resistance, MetS: metabolic syndrome, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index. Data are presented as median [25th, 75th percentile] or mean ± SD or n (%) as appropriate.

The prevalence of being high-risk of OSA among women with PCOS was 27.7% compared to 6.4% in women without PCOS (p = 0.006). Nevertheless, there were no statistical differences in the number of participants with excessive daytime sleepiness assessed by ESS (PCOS vs without PCOS, 31.1 vs 21.3%, p = 0.243) and poor sleep quality assessed by PSQI (PCOS vs without PCOS, 59.6% vs 53.2%, p = 0.555), respectively (Table 2).

Baseline characteristics comparing between women with high- and low-risk of OSA were shown in Table 3.

Table 2. The prevalence of being high-risk of OSA based on Berlin questionnaire and sleep disorder assessment in women with PCOS comparing to women without PCOS.

Sleep disorder assessment	PCOS (n = 47) n (%)	Without PCOS (n = 47) n (%)	p value
Being high-risk OSA (Berlin questionnaire)	13 (27.7)	3 (6.7)	0.006
Excessive daytime sleepiness (ESS, score > 10)	15 (31.9)	10 (21.3)	0.243
Poor sleep quality (PSQI, score > 5)	28 (59.6)	25 (53.2)	0.533

PCOS: polycystic ovary syndrome, ESS: Epworth sleepiness scale, PSQI: Pittsburgh Sleep Quality Index

Table 3. Baseline characteristics of being high- and low-risk of OSA based on Berlin questionnaire.

Characteristics	Being high-risk OSA (n = 16)	Being low-risk OSA (n = 78)	p value
Age (years)	29.0 [24.8,33.0]	26.5 [24,30]	0.111
BMI (kg/m^2)	33.4 [28.4,36.2]	23.3 [19.8,28.0]	< 0.001
WC (cm)	98.5 [91.5,108.5]	74.0 [69.0,86.3]	< 0.001
HC (cm)	111.6 ± 9.9	98.5 ± 12.4	< 0.001
WHR	0.88 ± 0.06	0.80 ± 0.06	< 0.001
SBP (mmHg)	121.5 [111.8,126.0]	115.5 [110.0,121.3]	0.056
DBP (mmHg)	80.3 ± 8.3	74.3 ± 8.2	0.009
TSH (μU/mL)	1.39 [1.13,2.11]	1.69 [1.17,2.48]	0.457
FSH (μU/mL)	5.18 [4.27,5.51]	4.44 [3.31,5.74]	0.629
TG (mg/dL)	123.0 [70.8,199.8]	73.0 [54.0,98.5]	0.009
TC (mg/dL)	205.7 ± 22.4	198.9 ± 37.6	0.526
HDL-C (mg/dL)	47.8 ± 13.3	58.3 ± 14.2	0.009
LDL-C (mg/dL)	144.0 ±27.6	128.0 ±39.9	0.048
T (ng/mL)	39.0 [28.0,46.3]	39.5 [29.8,53.0]	0.710
SHBG (nmol/L)	20.2 [14.2,32.0]	41.0 [23.3,59.2]	0.001
FAI	6.52 [4.40,9.90]	3.08 [1.91,5.96]	0.009
Clinical HA	11 (11.7)	17 (18.1)	< 0.001
HA	12 (12.8)	28 (29.8)	0.004
FBG (mg/dL)	88.5 [85.0,100.8]	82.5 [78.0,87.3]	0.004
2hr-PP Glucose (mg/dL)	114.5 [102.8,169.8]	92.5 [77.0,113.0]	0.005
Insulin (μU/mL)	12.7 [9.0,19.8]	8.4 [6.0,10.3]	0.001
HOMA-IR	3.09 [2.02,4.29]	1.71 [1.23,2.33]	< 0.001
MetS	8 (8.5)	10 (10.6)	0.001
PCOS	13 (13.8)	34 (36.2)	0.006
ESS score	10.5 [6.0,12.0]	7.0 [5.8,10.0]	0.126
PSQI score	8.5 [6.0,10.8]	5.5 [4.0,7.0]	0.013

PCOS: polycystic ovary syndrome, BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, TSH: thyroid stimulating hormone, FSH: follicle-stimulating hormone, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, T: total testosterone, SHBG: sex hormone-binding globulin, FAI: free androgen index, HA: hyperandrogenism, FPG: fasting plasma glucose, 2hr-PP glucose: 2 hour postprandial glucose, HOMA-IR: homeostatic model assessment of insulin resistance, MetS: metabolic syndrome, PCOS: polycystic ovary syndrome, ESS: Epworth Sleepiness Scale, PSQI: Pittsburgh Sleep Quality Index.

BMI, WC, HC, WHR, DBP, TG, LDL-C, FAI, clinical HA, HA, FPG, 2hr-PP glucose, insulin, HOMA-IR, MetS, PCOS, and PSQI score were significantly higher while HDL-C and SHBG were lower in women with high risk of OSA than in women with low risk of OSA. Additionally, there were higher number of participants with excessive daytime sleepiness and poor sleep quality in high risk of OSA than low risk OSA groups, 50% vs 21.8%, p = 0.030 and 81.2% vs 51.5%, p = 0.030, respectively (Table 4).

Table 4. Score of Berlin questionnaire, Epworth sleepiness scale, and Pittsburgh Sleep Quality Index.

Sleep disorder assessment	PCOS (n = 47) median [25th, 75th percentile] or n (%)	Without PCOS (n = 47) median [25th, 75th percentile] or n (%)	p value	Being high-risk of OSA (n = 16) median [25th, 75th percentile] or n (%)	Being low-risk of OSA (n = 78) median [25th, 75th percentile] or n (%)	p value
BQ						
low-risk	34 (72.3)	44 (93.3)	-	-	-	-
high-risk	13 (27.7)	3 (6.7)	0.006	-	-	-
ESS						
Score	7.0 [6.0,11.0]	8.0 [5.0,10.0]	0.276	10.5 [6.0,12.0]	7.0 [5.8,10.0]	0.126
≤ 10	32 (68.1)	37 (78.7)	-	8 (50.0)	61 (78.2)	-
> 10	15 (31.9)	10 (21.3)	0.243	8 (50.0)	17 (21.8)	0.030
PSQI						
Score	6.0 [4.0,9.0]	6.0 [4.0,7.0]	0.077	8.5 [6.0,10.8]	5.5 [4.0,7.0]	0.013
≤ 5	21 (40.4)	22 (46.8)	-	3 (18.8)	38 (48.7)	-
> 5	28 (59.6)	25 (53.2)	0.533	13 (81.2)	40 (51.3)	0.030

PCOS: polycystic ovary syndrome, OSA: obstructive sleep apnea, BQ: berlin questionnaire, ESS: epworth sleepiness scale, PSQI: pittsburgh sleep quality index. Excessive daytime sleepiness defined as ESS > 10. Poor sleep quality defined as PSQI > 5

Univariate binary logistic regression showed that being high-risk of OSA was significantly associated with obesity (BMI ≥ 25 kg/m^2), central obesity (WC ≥ 80 cm), WHR ≥ 0.8, HDL-C < 50 mg/dL, clinical HA, HA, IFG (FPG ≥ 100 mg/dL), IR (HOMA-IR > 2.77), MetS, and PCOS. These factors were entered into mixed effects logistic regression model and demonstrated that the independent predictor of being high-risk of OSA using BQ was IFG with an odds ratio (95%CI) of 29.19 (1.26-674.04). Interestingly, we found no significant effects of PCOS on being high-risk of OSA. (Table 5)

Table 5. Risk factors associated with being high-risk of OSA based on Berlin questionnaire in women with and without PCOS.

Variables	Univariate			Multivariate		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
BMI ≥ 25 kg/m2	9.06	1.93-42.58	0.005			
WC ≥ 80 cm	10.06	2.14-47.35	0.003			
WHR ≥ 0.8	7.00	1.49-32.87	0.014			
HDL-C < 50 mg/dL	3.27	1.09-9.87	0.035			
Clinical HA	7.89	2.41-25.84	0.001			
HA	5.36	1.58-18.19	0.007			
FPG ≥ 100 mg/dL	11.36	2.38-54.35	0.002	29.19	1.26-674.04	0.035
HOMA-IR > 2.77	8.33	2.58-26.97	< 0.001			
MetS	6.80	2.08-22.21	0.002			
PCOS	5.61	1.48-21.26	0.011			

PCOS: polycystic ovary syndrome, OSA: obstructive sleep apnea, BQ: berlin questionnaire, ESS: epworth sleepiness scale, PSQI: pittsburgh sleep quality index. Excessive daytime sleepiness defined as ESS > 10. Poor sleep quality defined as PSQI > 5

Discussion

The present study demonstrated that the prevalence of being high-risk of OSA was statistically significantly increased among women with PCOS compared to women without PCOS (27.7% vs 6.4%, p = 0.006). PCOS was not the risk factor associated with the presence of being high-risk of OSA but the IFG, a comorbidity of PCOS, was a significant predictive factor of being high-risk of OSA assessed by BQ with an odds ratio (95%CI) of 29.19 (1.26-674.04). Women with high risk of OSA had poorer metabolic parameters and higher number of excessive daytime sleepiness and poor sleep quality than those with low risk of OSA.

Data from the present study confirmed that women with PCOS had the increased prevalence of being high-risk of OSA assessed by BQ compared to women without PCOS irrespective of obesity (27.7% vs 6.4%, p = 0.006). The results were compatible with the studies conducted by Mokhlesi et al[24], Hachul et al[25], and Melike Demir Çaltekin et al[26]. The increased development of OSA in women with PCOS was further supported by various studies diagnosed by polysomnography[10, 11].

The present study found that IFG was an important risk factor of being high-risk of OSA. The main pathophysiology of OSA includes intermittent hypoxia and sleep fragmentation. Patients with OSA were exposed to chronic intermittent hypoxia which led to down-regulation of insulin receptors and inhibition of the insulin signaling pathway. All of these alterations contributed to insulin resistance, hyperinsulinemia, and hyperglycemia[27]; therefore, this might explain why IFG was the important predictor of being high-risk of OSA. Likewise, previous studies from Seicean et al[28] and Kim et al[29] demonstrated that IFG was significantly associated with sleep-disorder breathing and OSA, respectively.

Although data from the present study suggested that surveillance for OSA should be offered to women with PCOS because of the higher number of OSA in women with PCOS than without PCOS, the high cost and the difficult accessibility of in-laboratory polysomnography would hinder OSA investigation for every PCOS women. Using screening tool to identify a high-risk patient for OSA or focusing on patients who have IR, a significant factor contributed to OSA, and then performed polysomnography in those women may be an alternative strategy to evaluate sleeping disorder. However, a comparison of OSA surveillance in every single PCOS women and women with a significant factor, IFG, or with high risk of OSA should be further studied.

Both excessive daytime sleepiness (EDS) and poor sleep quality (PSQ) are the detrimental clinical outcomes of OSA. EDS was serious risk factors of traffic accidents and decreased work performance. However, there was no significant difference of EDS between women with and without PCOS. These finding was compatible with Hachul et al's study[25]. Poor sleep quality using PSQI was demonstrated in 59.6% of women with PCOS that was paralleled with previous study from Melike Demir Çaltekin[26]. Nevertheless, the detection of poor sleep quality did not significantly different between women with and without PCOS in the present study. These finding was incompatible with study conducted by Hachul et al[25] and Melike Demir Çalteki et al[26]. Therefore, the present study revealed that PCOS was not only cause of EDS and PSQ. Poor sleep hygiene, sleep disorder, chronic health condition, and mental health condition might be the etiologies of EDS and PSQ. In contrast, there were higher number of participants with EDS and PSQ in high risk of OSA than low risk OSA groups. While only PCOS did not contribute to EDS and PSQ, being high-risk of OSA increased risk to EDS and PSQ. This result suggested the necessity of evaluation of OSA in women with PCOS.

The strength of the present study was that it was the first study in Thailand about being high-risk of OSA in women with PCOS. Additionally, we designed an age and BMI matched study to avoid confounding effects on OSA risk. Despite a cross-sectional study, the present study also had some limitations. Firstly, polysomnography was not performed. It is a gold standard for the diagnosis of OSA. Nevertheless, the

present study assessed OSA risk using a questionnaire that has a high positive and negative predictive value for the detection of OSA. Secondly, the small sample to evaluate the predictive factors for being high-risk of OSA might not show some significant factors.

Conclusion

The present study showed that the prevalence of being high-risk of OSA was significantly higher in women with PCOS than women without PCOS. PCOS was not a potential predictor of being high-risk of OSA but IFG, a comorbidity of PCOS, was the key predictive factor. Consequently, we suggested that OSA risk screening using Berlin questionnaire should be assessed in women with PCOS. Polysomnography should be evaluated in the patients who either are being high-risk of OSA identified by questionnaire screening tool or having IR. Women with high risk of OSA had poorer metabolic parameters and higher excessive daytime sleepiness and poor sleep quality than those with low risk OSA.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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