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Risk of obstructive sleep apnea in obese and non-obese women with polycystic ovary syndrome and healthy reproductively normal women

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Abstract

Objective—To study the risk for obstructive sleep apnea (OSA) in a group of non-obese and obese PCOS and control women. Women with polycystic ovary syndrome (PCOS) are at high risk for obstructive sleep apnea (OSA). Whether this risk is independent of obesity is not clear.

Design/Patients/Interventions/Main Outcome Measures—In a prospective study, 44 women with PCOS and 34 control women completed the Berlin questionnaire for assessment of OSA risk. All women underwent fasting determination of androgens, glucose and insulin.

Results—Women with PCOS were more obese compared to control women ($p=0.02$). However, there were no differences in BMI once subjects were divided into non-obese (PCOS $n=17$ and control $n=26$) and obese (PCOS $n=26$ and control $n=8$) groups. Women with PCOS had higher prevalence of high risk OSA compared to control women on the Berlin questionnaire (47% vs. 15%, $P<0.01$). However, none of the non-obese PCOS and control women screened positive for high risk OSA. Among the obese group, the risk did not differ between groups (77% vs. 63%, $P=0.65$).

Conclusions—Our findings indicate that even though the risk for OSA in PCOS is high, it is related to the high prevalence of severe obesity. The risk for OSA among non-obese women with PCOS is very low. However, our findings are limited by lack of polysomnographic confirmation of OSA.

Key Terms

Berlin questionnaire; Obesity; Insulin resistance; Body mass index

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive age women and is associated with significant metabolic morbidities including increased risk for type 2 diabetes, metabolic syndrome and dyslipidemia (1). Additionally, recent data indicates that reproductive age women with PCOS are at very elevated risk for obstructive sleep apnea (OSA) compared to women without PCOS (2–5). In women with PCOS, OSA appears to be strongly associated with insulin resistance (6). Indeed in some studies, insulin resistance was only present in obese women with PCOS who had OSA (6). As obesity is a common finding in PCOS, these studies have included mostly obese women many of whom have been severely obese (2–6). This raises the question of whether the high rates of OSA in women with PCOS is related to obesity or whether additional risk factors associated with PCOS predispose to OSA.

In non-PCOS populations, obesity (7–10) and more specifically central obesity is one of the most significant risk factors associated with OSA (11–15). OSA is also associated with insulin resistance and this association is to some degree accounted for by obesity although OSA by itself and independent of obesity has also been associated with insulin resistance (16–19). PCOS is frequently associated with both obesity (20) and insulin resistance (21), both of which are risk factors for OSA. The mechanisms by which PCOS increases the risk of OSA remains unclear and the role of androgen elevation in the pathogenesis of OSA in women with PCOS remains controversial (2–4). Importantly, treatment of OSA has been associated with improvements in insulin sensitivity and metabolic measures in both PCOS (22) and non-PCOS populations (23–25).

In the current study, we prospectively examined the risk of OSA in a group of reproductive age women with PCOS and control women. The study included both non-obese and obese women. Our objective was to assess the risk of OSA in both non-obese and obese women with PCOS in order to quantify the impact of obesity on the development of OSA in this population.

Subjects and Methods

Seventy-eight reproductive age women between 18 to 40 years of age were screened at the clinical research center of the University of Illinois for participation in the study). Women with PCOS (n=44) were recruited from endocrinology or reproductive endocrinology clinics or from local advertisements and reported a history of menstrual irregularity and androgen excess such as hirsutism, acne or androgenic alopecia. The diagnosis of PCOS was confirmed based on the National Institutes of Health criteria and defined by presence of oligomenorrhea (<6 menses per year) and biochemical hyperandrogenism based on elevated total or bioavailable testosterone levels (greater than two standard deviations above the mean value for the assay) (26). Thyroid hormone abnormalities, hyperprolactinemia and non-classical congenital hyperplasia due to 21 hydroxylase deficiency were excluded by appropriate laboratory testing in all women with PCOS.

Thirty-four control women were recruited from local advertisements. The selection criteria for control women were: 1) regular 27–35 days menstrual cycles throughout their reproductive life, 2) no history of hypertension, or personal or family history of diabetes mellitus, 3) no clinical or biochemical evidence of hyperandrogenism. Women with mild hyperandrogenemia who did not meet criteria for PCOS were excluded from controls. All control women had to have normal total and bioavailable testosterone levels and no clinical evidence for androgen excess.

Women (both PCOS and control) were excluded from participation if they were pregnant or lactating, had any chronic disease including diabetes, hypertension, psychiatric disorder or any surgical procedure on their ovaries and uterus. None of the women had received any oral contraceptive, other forms of hormonal contraception or fertility treatments for at least 3 months prior to their participation nor had they received progesterone for at least one month prior to their participation in the study. None of the women had ever received any cholesterol lowering medications, antihypertensives, insulin sensitizing agents, metformin or any other diabetes medication. The study was approved by the institutional review board at University of Illinois and all subjects signed written informed consent prior to their participation in the study.

Data Collection

All women were studied at the clinical research center of the University of Illinois and underwent a history and physical examination by a physician investigator that included detailed menstrual and medical history as well as assessment for hirsutism and other signs of hyperandrogenism and insulin resistance. Height, weight and waist measurements were determined on all subjects. All women were asked to complete the Berlin questionnaire to assess their risk of OSA during this visit. This is a validated survey assessing the risk of OSA and includes questions about snoring behavior/witnessed apneas (category 1), chronic daytime sleepiness/fatigue (category 2), and the presence of hypertension and/or BMI exceeding 30 kg/m² (category 3). The Berlin questionnaire has been validated in both men and women (27). This validated questionnaire predicts high risk of OSA with a sensitivity of 0.86, specificity of 0.77, a positive predictive value of 0.89, a negative predictor value of 0.71 and a likelihood ratio of 3.2 compared to the gold standard measure of apnea-hypopnea index (AHI) > 5 obtained from polysomnography (27). Therefore, a positive Berlin questionnaire is highly predictive of OSA and a negative Berlin questionnaire is highly predictive in ruling out OSA. Each of the categories was assigned a score of either 0 for no symptoms, 1 for frequent symptoms (<3–4 times a week), or 2 for persistent symptoms (≥3–4 times a week). To be considered as high risk for OSA, a patient had to have a score of 2 or higher.

A morning blood sample was obtained after an overnight fast from all subjects that included measurements of total and bioavailable testosterone, sex hormone binding globulin, lipid profile and fasting glucose and insulin levels.

Laboratory Methods

All laboratory evaluations with the exception of insulin were performed at Quest Diagnostics. Total testosterone was measured by turbulent flow liquid chromatography mass spectrometry that has an assay sensitivity of 0.034 nmol/L and no cross reactivity with 30 testosterone related compounds. Bioavailable testosterone was calculated based on constants for the binding of testosterone to sex hormone binding globulin (SHBG) and albumin. SHBG was measured by extraction, chromatography and radioimmunoassay and albumin was measured by spectrophotometry. Plasma glucose was collected in a fluoride/oxalate tube and analyzed using spectrophotometry. The intra- and inter-assay coefficient of variation for this assay was 1.1 and 1.5%. Insulin was measured by a chemiluminescent sandwich immunoassay measuring to as low as 14 pmol/L. The inter- and intra-assay coefficient of variation for this assay was 4 and 5%.

Statistical Analyses

The homeostatic index of insulin resistance (HOMAIR) was calculated according to the following formula: [fasting glucose (mmol/L) X fasting insulin (μ U/mL)] $\div$ 22.5] (28). Mean and standard deviations were used to summarize continuous data except for bioavailable testosterone, fasting insulin and HOMAIR for which data were summarized by median and 25th and 75th interquartile range. Women with PCOS and controls were divided based on BMI into 4 groups: non-obese PCOS (n=17, BMI<30 kg/m²), obese PCOS (n=27, BMI $\geq$ 30 kg/m²), non-obese control (n=26, BMI<30 kg/m²) and obese control (n=8, BMI $\geq$ 30 kg/m²). Continuous variables were log transformed if not normally distributed prior to all analyses and were compared by ANOVA with Tukey posthoc analyses. Categorical variables were compared using chi-square statistics. Logistic regression was used to identify the predictors for elevated risk of OSA in the entire group of women as well as separately in obese women with PCOS. The predictors for this model included age, BMI, bioavailable testosterone levels and diagnosis of PCOS (for the analysis in the entire group). In additional models, HOMAIR was also included as an independent predictor. General linear model was used to identify the predictors of HOMAIR in women with PCOS. The predictors for this model included age, BMI, bioavailable testosterone and presence of risk for OSA based on the Berlin questionnaire. Baseline and metabolic characteristics were compared among obese women with PCOS with and without risk for OSA using independent *t*-test if data was normally distributed and Mann-Whitney U if data was not normally distributed. Analyses were performed using the 18.0 PC package of SPSS statistical software (SPSS, Inc., Chicago, IL). A *P* $\leq$ 0.05 was considered significant.

Results

Forty-four women with PCOS and 34 control women were included in the study. The mean age for women with PCOS was 27 ± 5 years that was similar to control women at 29 ± 6 years (*P*=0.18). Women with PCOS were more obese (BMI 35.1 ± 11.4 kg/m²) compared to control women (28.8 ± 11.5 kg/m², *P*=0.02). The study included a mix of ethnicities; 7 Asian Indian, 6 East Asian, 14 Hispanics, 4 mixed race, 29 non-Hispanic Black and 17 non-Hispanic White but the ethnic distribution did not vary between PCOS and control women (*P*=0.10, data not shown). The groups were divided into a non-obese (n=17 PCOS and n=25 control) and obese group (n=27 PCOS and n= 8 control) based on BMI. Baseline clinical and laboratory characteristics of women with PCOS and control women in non-obese and obese groups are summarized in Table 1. Obese control women were slightly older than non-obese control (*P*<0.05) and non-obese PCOS women (*P*<0.01). There were no differences in BMI, waist circumference or waist to hip ratio (WHR) between non-obese PCOS compared to non-obese control and obese PCOS compared to obese control women. Women with PCOS had significantly higher bioavailable testosterone levels compared to control women in both non-obese and obese groups (*P*<0.001). Obese women with PCOS had significantly lower SHBG levels compared to non-obese control women (*P*<0.001), non-obese PCOS (*P*<0.01) and borderline lower SHBG levels compared to obese control women (*P*=0.07). Fasting glucose levels did not differ between PCOS and control women in neither non-obese nor obese groups. However, fasting insulin levels were significantly higher in non-obese PCOS compared to non-obese controls (*P*<0.05) and obese PCOS compared to both non-obese PCOS and non-obese control women (*P*<0.001). HOMAIR was borderline higher in non-obese PCOS compared to non-obese control women (*P*=0.08) and significantly higher in obese PCOS compared to both non-obese PCOS and non-obese control women (*P*<0.001).

Women with PCOS had significantly higher risk of OSA on the Berlin questionnaire compared to control women (47% vs. 15%, *P*<0.01). However, the risk for OSA was not

increased in women with PCOS compared to control women, when the risk was assessed separately in the non-obese and obese groups. None of the 17 non-obese women with PCOS or non-obese control women screened positive for OSA by the Berlin questionnaire (Figure 1). In the obese group, the risk for OSA was similar between the two groups (77% PCOS vs. 63% control, $P=0.65$). Our study had 93% power to detect this difference in prevalence of high risk for OSA between PCOS and control women assuming an alpha of 5%.

In a logistic regression model, BMI was the only independent predictor of OSA risk based on the Berlin questionnaire ($P<0.001$). Age, bioavailable testosterone or diagnosis of PCOS did not predict risk for OSA as assessed by the Berlin questionnaire independent of BMI (Table 2). Addition of HOMAIR to the independent variables did not alter the findings; BMI was still the only predictor of OSA risk (data not shown). Similarly, BMI was the only independent predictor of OSA risk in women with PCOS based on the Berlin questionnaire ($P=0.01$, Table 3). Addition of HOMAIR to the independent variables did not alter the findings; BMI was still the only predictor of OSA risk (data not shown). In a linear regression model, we evaluated whether the risk of OSA is a predictor of HOMAIR in women with PCOS. BMI was the only predictor of HOMAIR in women with PCOS (β coefficient 0.03 ± 0.007 , $P<0.001$) after adjusting for age, bioavailable testosterone, and OSA risk. Risk of OSA by Berlin questionnaire did not predict HOMAIR in women with PCOS after adjusting for BMI. We also compared obese women with PCOS who had high risk of OSA ($n=20$) to those at low risk of OSA ($n=7$) in terms of baseline characteristics and fasting insulin and HOMAIR levels. There were no significant differences in baseline characteristics, fasting insulin levels or HOMAIR between the two groups.

Discussion

Our findings in this study indicate that women with PCOS are at high risk of OSA based on the Berlin questionnaire but the increased risk is only present amongst the obese women. Non-obese women with PCOS do not seem to be at increased risk of OSA. A negative Berlin questionnaire is highly predictive in ruling out OSA so the fact that the risk for sleep apnea in non-obese women in both PCOS and control was 0% strongly suggests that the prevalence of OSA in non-obese women is very low even if they have PCOS. Furthermore, the risk amongst obese women is similar for PCOS and control women though this finding is limited due to the small number of obese control women included in the study. As expected, women with PCOS had higher bioavailable testosterone levels independent of obesity. However, bioavailable testosterone was not an independent predictor of OSA risk. BMI was the only independent predictor of OSA risk for the entire group of women consisting of PCOS and control as well as amongst women with PCOS alone.

Very high rates of OSA have been reported in women with PCOS in a number of studies (2–5). These studies have included mostly obese middle-aged women (2, 3), and in some studies women with severe obesity (4, 6, 22). In a study from Taiwan that included only non-obese women (29), women with PCOS had a higher apnea-hypopnea index (AHI) compared to control women (0.79 ± 0.21 vs. $0.29 \pm .09$, $P=0.041$). However, the diagnosis of OSA requires an AHI above 5 and the mean AHI for women with PCOS in this study was much lower than 5 and therefore none of the women met the clinical criteria for OSA. In a recent study from Germany, De Sousa and colleagues studied 31 mildly obese adolescents with PCOS. None of the mildly obese adolescents had OSA and the mean AHI was 0.95 (30). In another study, among 12 women with PCOS who had a BMI <32.3 kg/m² only 1 (8.3%) had OSA which was much lower than among the obese PCOS women with BMI >32.3 kg/m² (19.5%) (3). Taken together, these findings suggest that as women with PCOS age and gain weight their risk of developing OSA increases.

Previous studies have also indicated that obese women with PCOS who have OSA are more insulin resistant compared to obese women with PCOS who do not have OSA (4, 6). Some have argued that the presence of OSA identifies those women at risk for metabolic abnormalities (6). In other studies, fasting plasma insulin was the strongest risk factor for OSA in women with PCOS (3). We did not find a difference in fasting insulin levels or HOMAIR between obese women with PCOS who screened positive for OSA and those who screened negative for OSA. Furthermore, presence of OSA risk in women with PCOS was not a predictor of HOMAIR. The only predictor of OSA among the entire cohort consisting of women with PCOS and control as well PCOS women alone was BMI. Our findings differ from a previous study that included only obese women with PCOS in which PCOS was an independent predictor of OSA even after adjusting for BMI (5). It may be that compared to the previous study (5), our sample included a wider range of BMI with both non-obese and obese women.

A main limitation of our study is the lack of polysomnographic data to confirm the actual presence of OSA. Polysomnography is the gold standard for diagnosis of OSA. However, Berlin questionnaire has a good positive and negative predictive value for detection of OSA in both men and women compared to the diagnosis based on AHI obtained from polysomnography (27). Clinic-based studies have suggested that women with OSA may have a different clinical presentation compared to men, particularly a lower proportion of women complaining of hypersomnolence and loud snoring (31–34). It remains unclear whether these differences represent reporting bias or a difference in disease expression. It is possible that mild cases of OSA were missed by the Berlin questionnaire leading to underestimation of the actual prevalence of OSA in non-obese women with PCOS. If this was true, then indeed the Berlin questionnaire would be a less sensitive tool for assessing the risk of OSA in women compared to men. However, this sex difference in disease presentation did not seem to affect the accuracy of risk groupings when the Berlin questionnaire was originally validated because questions about fatigue were incorporated in the Berlin questionnaire and fatigue is more commonly reported in women with OSA (27). It is important to note that clinic-based studies that have reported gender differences in OSA symptoms have inherent limitations due to selection bias. Several large community-based epidemiologic studies have shown that there is no gender difference in symptoms and presentation of OSA (35, 36). Furthermore, a recent systematic review of various screening tools for OSA reported that the Berlin questionnaire had the highest sensitivity and specificity for predicting the presence of OSA ($AHI > 5$) (37).

Another limitation of our study is the small sample size of obese control women though even in the small sample the risk for OSA was not significantly different compared to the obese women with PCOS. It is plausible that with a larger sample size the differences in the risk of OSA between obese PCOS and obese control women may have become significant. The risk of OSA among the obese control women in our study was higher than the actual rate of OSA reported in severely obese women. In a community-based study, Vgontzas and colleagues reported that out of 194 women with BMI's similar to our obese controls ($> 40 \text{ kg/m}^2$) only 11 had an elevated AHI consistent with OSA (38). Therefore, the Berlin questionnaire may have been oversensitive in our cohort in categorizing OSA risk and if polysomnograms were available the actual prevalence of OSA could have been lower in our severely obese control women. The prevalence of OSA amongst obese or severely obese women with PCOS has been reported to be significantly higher than in severely obese non-PCOS. It may be that PCOS and obesity synergistically increase the risk of OSA. For example, it is known that only obese women with PCOS have hepatic insulin resistance and hypertriglyceridemia and that obesity and PCOS act synergistically to lead to these abnormalities (39, 40). Furthermore, women with PCOS are centrally obese (39, 41–43) and central obesity confers a higher risk for OSA than generalized obesity (11–15).

Notwithstanding our limitations, we believe that a strength of our study is having a relatively large cohort of non-obese PCOS women compared to prior studies.

In summary, significant number of reproductive age women with PCOS screen positive for OSA based on the Berlin questionnaire, but the increase in risk appears to be related to the high prevalence of obesity in this population. Whether the risk also applies to non-obese women with this condition is questioned and requires further studies using polysomnography.

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Figure 1.
Prevalence of OSA risk amongst PCOS and control women based on BMI

Table 1

Baseline and metabolic characteristics of nonobese and obese PCOS and control women

Variable	PCOS Women		Control Women	
	nonobese (n=17)	obese (n=27)	nonobese (n=26)	obese (n=8)
Age (years)	25 ± 4	28 ± 5	27 ± 6	33 ± 6 ^a
BMI (kg/m ²)	25.2 ± 2.4	41.4 ± 10.4 ^b	23.8 ± 3.2	44.5 ± 14.3 ^b
Waist (cm)	77 ± 9	105 ± 15 ^b	73 ± 8	110 ± 21 ^b
WHR	0.76 ± 0.06	0.82 ± 0.07 ^b	0.72 ± 0.06	0.83 ± 0.07 ^c
Bioavailable T (ng/dL)	17(12, 22) ^c	9(12, 24) ^d	6(4, 8)	6 (4, 9)
SHBG (nmol/L)	32 ± 14	23 ± 13 ^e	44 ± 18	40 ± 26
Fasting glucose (mg/dL)	79 ± 6	84 ± 7	80 ± 7	83 ± 8
Fasting insulin (uU/ml)	7 (2, 10) ^f	16 (8, 23) ^b	3 (2, 5)	7 (6, -) data few
HOMAIR	1.2 (0.4, 2.1) ^g	3.3(1.7, 5.2) ^b	0.5 (0.4, 1.0)	1.4 (1.4, -) data few

BMI: Body mass index; WHR: Waist to hip ratio; T: Testosterone; SHBG: Sex hormone binding globulin; HOMAIR: Homeostatic index of insulin resistance. All comparisons were made by ANOVA with Tukey posthoc analyses.

^aP<0.05 vs. nonobese control & P<0.01 vs. nonobese PCOS

^bP≤0.001 vs. nonobese PCOS & nonobese control

^cP<0.001 vs. nonobese control

^dP<0.001 vs. obese control

^eP<0.001 vs. nonobese control & P<0.05 vs. non-obese PCOS & P=0.09 vs. obese control

^fP<0.05 vs. nonobese control

^gP=0.08 vs. nonobese control

Table 2

Predictors of risk of OSA based on Berlin questionnaire for all women (PCOS and controls combined)

Variable	Odds ratio	CI (25, 75)	P-value
PCOS Status	3.24	0.49, 21.37	0.22
Age	0.87	0.74, 1.02	0.09
BMI	1.23	1.11, 1.36	<0.001
Bioavailable Testosterone	0.99	0.91, 1.08	0.85

Logistic regression was used to identify predictors of OSA risk

Table 3

Predictors of risk for OSA based on Berlin questionnaire for only women with PCOS

Variable	Odds ratio	CI (25, 75)	P-value
Age	0.86	0.71, 1.05	0.14
BMI	1.22	1.07, 1.37	<0.01
Bioavailable Testosterone	0.99	0.90, 1.08	0.75

Logistic regression was used to identify predictors of OSA risk