

# Polycystic Ovary Syndrome Is Associated with Obstructive Sleep Apnea and Daytime Sleepiness: Role of Insulin Resistance\*

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## ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of premenopausal women, characterized by chronic hyperandrogenism, oligoanovulation, and insulin resistance. Obstructive sleep apnea (OSA) and excessive daytime sleepiness (EDS) are strongly associated with insulin resistance and hypercytokinemia, independently of obesity. We hypothesized that women with PCOS are at risk for OSA and EDS. Fifty-three women with PCOS (age range, 16–45 yr) and 452 control premenopausal women (age range, 20–42), from a general randomized sample for the assessment of prevalence of OSA, were evaluated in the sleep laboratory for 1 night. In addition, women with PCOS were tested for plasma free and weakly bound testosterone, total testosterone, and fasting blood glucose and insulin concentrations. In this study, PCOS patients were 30 times more likely to suffer from sleep disordered breathing (SDB) than the controls [odds ratio = 30.6, 95% confidence interval (7.2–139.4)]. Nine of the PCOS patients (17.0%) were recommended treat-

ment for SDB, in contrast with only 3 (0.6%) of the control group ( $P < 0.001$ ). In addition, PCOS patients reported more frequent daytime sleepiness than the controls (80.4% vs. 27.0%, respectively;  $P < 0.001$ ). PCOS patients who were recommended treatment for SDB, compared with those who were not, had significantly higher fasting plasma insulin levels ( $306.48 \pm 52.39$  vs.  $176.71 \pm 18.13$  pmol/L,  $P < 0.01$ ) and a lower glucose-to-insulin ratio ( $0.02 \pm 0.00$  vs.  $0.04 \pm 0.00$ ,  $P < 0.05$ ). Plasma free and total testosterone and fasting blood glucose concentrations were not different between the two groups of PCOS women. Our data indicate that SDB and EDS are markedly and significantly more frequent in PCOS women than in premenopausal controls. Also, insulin resistance is a stronger risk factor than is body mass index or testosterone for SDB in PCOS women. These data support our proposal that, independently of gender, sleep apnea might be a manifestation of an endocrine/metabolic abnormality in which insulin resistance plays a principal role. (*J Clin Endocrinol Metab* 86: 517–520, 2001)

**P**OLYCYSTIC OVARY SYNDROME (PCOS), the most common endocrine disorder of premenopausal women, is characterized by chronic, hyperandrogenic oligoanovulation and oligoamenorrhea (1). PCOS women have insulin resistance, which is frequently exacerbated by obesity, especially of the central type (2, 3). The elevated plasma insulin concentration and the suppression of IGF-1 binding protein-1 that takes place in insulin resistance have been proposed to result in enhancement of pituitary LH response to LH-releasing hormone and potentiation of its action in the ovarian theca and stroma, with inhibition of androgen aromatization to estrogen in the granulosa. These changes and the development of polycystic ovaries lead to ovarian hyperandrogenism, suppression of the midcycle LH surge, oli-

goanovulation, stromal growth, and accumulation of dysfunctional, cystic follicles in the ovaries (1–6).

Obstructive sleep apnea (OSA) is most common in middle-aged, obese men (7), whereas it is quite infrequent in premenopausal women (men-to-women ratio, 6.5:1); interestingly, the prevalence of OSA increases significantly, after the menopause, in women receiving no gonadal hormone replacement therapy (men-to-women ratio, 1.4:1) (8). The etiology of the gender differences in the prevalence of OSA is not well understood. The gonadal steroids have been implicated, with androgens presumed to be conducive to, and estrogens protective of, OSA.

Recently, we demonstrated that OSA and excessive daytime sleepiness (EDS) in men are associated with visceral obesity and insulin resistance, independently of obesity (9). The purpose of this study was to test the hypothesis that the insulin resistance of PCOS women may be associated with OSA and EDS. In this study, we assessed the prevalence of OSA and EDS in premenopausal women with PCOS, compared with controls.

## Materials and Methods

### Subjects

Fifty-three premenopausal women with PCOS [age range, 16–45 yr; body mass index (BMI) range, 24.3–67.7] were prospectively studied in

Received July 12, 2000. Revision received October 11, 2000. Accepted October 19, 2000.

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\* Supported by USPHS Grant HS K08-HD-0118 (to R.S.L.), The National Cooperative Program for Infertility Research at University of Pennsylvania–Brigham and Women's Hospital–University of California at San Francisco–Pennsylvania State University Grant U54-HD-34449 (to R.S.L.), General Clinical Research Center Grant M01-RR-10732 (to Pennsylvania State University), and NHLBI Grant R01-HL-51931 (to E.O.B.).

the sleep laboratory. The diagnosis of PCOS was made by the presence of chronic anovulation (six or fewer menstrual periods per year) in association with elevated circulating androgen levels (total testosterone more than 201.1 nmol/L and/or free and weakly bound testosterone more than 55.5 nmol/L) (10). Fourteen women were taking sex steroid medication (oral contraceptives), whereas no one was taking medication affecting carbohydrate metabolism at the time of the sleep study. Non-classic adrenal 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors were excluded by appropriate tests before the diagnosis of PCOS was made. All of the PCOS women had oligoamenorrhea and polycystic ovaries, by ultrasound examination. Seventy-five percent were hirsute and nulliparous.

Control women were 452 premenopausal women (age range, 20–42 yr; BMI range, 16.1–59.9) selected from a general randomized sample (8). We have previously established the prevalence of sleep apnea in premenopausal women to be 0.6% (0.2–1.8%) (8). A case control study is designed to contrast the characteristics in 2 populations, not to establish prevalence. This becomes especially critical when the expected prevalence is this low. Thus, to establish a stable estimate of the prevalence of sleep apnea in premenopausal women, we have included all of the women who were premenopausal and 42 yr of age or younger. These control women were a subset of a larger epidemiological study designed to assess the prevalence of sleep apnea in the general public. The sample for this epidemiological study was obtained using a 2-stage strategy. In the first stage of this study, a sample of women (age  $\geq$  20 yr) was randomly selected from telephone households, and 12,219 completed a telephone interview. In the second phase of this study, a random sample from those previously interviewed by telephone was selected for study in our sleep laboratory, to assess for sleep apnea. This selection was based on risk factors reported in the telephone interview (snoring, daytime sleepiness, obesity, hypertension, and menopause), and those with a higher risk for sleep apnea were oversampled. The sleep laboratory sample consisted of 1,000 women. For analysis purposes, compensatory weights were developed to obtain estimates of prevalence of the original target population of women. The studies were approved by the Institutional Review Board of Hershey Medical Center, Penn State University, and all subjects gave written informed consent.

### Procedures

Each subject provided a comprehensive medical history, including completing a detailed standardized questionnaire, and each subject underwent a physical examination and routine blood tests. Control subjects were not specifically screened for the presence of PCOS.

All subjects were evaluated for 1 night in the sleep laboratory in sound-attenuated, light- and temperature-controlled rooms. During this evaluation, they were continuously monitored for 8 h using 16-channel polygraphs (model 78d, Grass Instrument, Quincy, MA). The three-channel electroencephalogram, three-channel electrooculogram, and an electromyogram were recorded. The sleep records were subsequently scored independently, according to standardized criteria (11).

Respiration was monitored throughout the night by use of thermocouples at the nose and mouth (model TCT 1R, Grass Instrument) and thoracic strain gauges. All-night recordings of hemoglobin oxygen saturation (SaO<sub>2</sub>) were obtained with an oximeter (Model 8800, Nonin Medical, Plymouth, MN) attached to the finger. An apnea was considered present if a breath cessation exceeded 10 sec. Each apnea was categorized in terms of obstructive (chest wall movement present) or central (chest wall movement absent). In addition, hypopneas were considered present when a reduction in airflow of approximately 50% was indicated at the nose or mouth and was associated with a reduction of 4% SaO<sub>2</sub>.

OSA was diagnosed using Sleep Disorders Clinic criteria, which employed sleep laboratory plus clinical findings. This diagnosis was made by a Sleep Disorders Medicine specialist (A. N. Vgontzas) based on whether immediate treatment was considered appropriate. This diagnosis required an apnea/hypopnea index  $\geq$  10 per hour of sleep plus the presence of clinical symptomatology, e.g. daytime sleepiness, hypertension, or other cardiovascular complication (7, 8). Upper airway resistance syndrome was diagnosed based on the presence of loud snoring as recorded in the sleep laboratory, snoring-induced sleep fragmentation, and daytime sleepiness (12). The symptoms associated with either OSA or upper airway resistance syndrome were severe enough to warrant recommendation for treatment with continuous positive airway pressure.

Degree of obesity was estimated by calculating a BMI (kg/m<sup>2</sup>). The established threshold of obesity (BMI  $\geq$  32.3) used by the National Health and Nutrition Examination Survey was used to categorically define obesity (13).

Daytime sleepiness was assessed subjectively using a sleep questionnaire on a 4-point scale (none, mild, moderate, or severe). In addition, in women with PCOS, blood was drawn after an overnight fast to assess glucose, insulin, testosterone, and nonsex hormone-binding-globulin-bound testosterone.

### Assays

Assays for testosterone were performed using Diagnostic Products (Los Angeles, CA) Coat-A-Count kits; the interassay coefficients of variation (CVs) were 8% and 5%, respectively (14). Unbound testosterone was measured by a modification of the procedure of Tremblay and Dube (15); the interassay CV was 7%. Insulin was determined with a double-antibody method using reagents obtained from Linco Research, Inc. (St. Charles, MO). The sensitivity of this assay is 2  $\mu$ U/mL, with 0.2% cross-reactivity with proinsulin. The inter- and intraassay CVs are less than 10%. Plasma glucose levels were determined by the glucose oxidase technique (14).

### Data analysis

For comparisons between two groups, a Student's *t* test was used. Odds ratios (ORs) were calculated to evaluate differences between prevalences. Differences, in terms of BMI between the two groups, were controlled for by use of analysis of covariance. To assess which variables were significant predictors of the presence of sleep disordered breathing (SDB) in PCOS women, we used logistic regression analysis, with age, BMI, testosterone, insulin, and glucose-to-insulin ratio as independent variables. The values are expressed as the mean  $\pm$  SE. All five independent variables were included as continuous variables in this analysis. The statistical confidence level selected for all analyses was  $P < 0.05$ .

## Results

Controls (n = 452) and PCOS (n = 53) patients were similar in terms of age [ $32.1 \pm 0.3$  vs.  $30.4 \pm 0.9$  yr, respectively, not significant (NS)], whereas PCOS women were heavier than the controls, as indicated by mean BMI values ( $38.7 \pm 1.1$  vs.  $26.4 \pm 0.3$ ,  $P < 0.01$ ).

### Prevalence of sleep apnea and sleepiness

In this study, PCOS women were 30 times more likely to suffer from SDB than controls [OR = 30.6, 95% confidence interval (CI) (7.2–139.4),  $P < 0.0001$ ]. Specifically, 9 of the PCOS women (17.0%) were recommended treatment for OSA (6) or upper airway resistance syndrome (3), in contrast with only 3 (0.6%) controls (2 for OSA and 1 for upper airway resistance syndrome) (see Table 1). Even when we controlled for BMI, the difference between the 2 groups remained significant. In the nonobese category (BMI  $<$  32.3), 1 out of 12 (8.3%) of PCOS patients required treatment for SDB, in contrast with 0 out of 386 (0.0%) controls (OR undefined). In the obese category (BMI  $\geq$  32.3), 8 out of 41 (19.5%) of PCOS patients and 3 out of 66 (4.5%) of controls required treatment for SDB [OR = 5.1, 95% CI (1.1–31.3),  $P = 0.03$ ]. Finally, 7% of PCOS women with SDB were using oral contraceptives, in contrast with about 20% of PCOS women without SDB (NS).

Fifty-one PCOS patients completed the sleepiness questionnaire. PCOS patients frequently reported more daytime sleepiness than did controls (80.4% vs. 27.0%) [OR = 9.0, 95% CI (4.0–22.1),  $P < 0.001$ ]. This relation remained significant, even when we controlled for BMI. In the nonobese category,

**TABLE 1.** Prevalence of sleep disordered breathing and daytime sleepiness in PCOS women and controls

	Controls	PCOS	OR (95% CI)	P
Sleep apnea	2 (0.4%)	6 (11.3%)	28.7 (4.9–294.4)	<0.0001
Upper airway resistance syndrome	1 (0.2%)	3 (5.7%)	27.6 (2.1–1423.0)	0.008
SDB	3 (0.6%)	9 (17.0%)	30.6 (7.2–179.4)	<0.0001
SDB by BMI				
<32.3	0/386 (0.0%)	1/12 (8.3%)	Undefined	
≥32.3	3/66 (4.5%)	8/41 (19.5%)	5.1 (1.1–31.3)	0.03
EDS by BMI				
<32.3	87/386 (22.5%)	9/12 (75.0%)	10.3 (2.5–60.0)	0.0005
≥32.3	36/66 (54.5%)	32/39 (82.1%)	3.8 (1.4–11.6)	0.007

OR, Odds ratio (95% confidence interval).

9 out of 12 (75.0%) of PCOS patients reported daytime sleepiness, in contrast with only 87 out of 386 (22.5%) of the control women [OR = 10.3, 95% CI (2.5–60.0),  $P = 0.0005$ ]. In the obese category, 32 out of 39 (82.1%) of PCOS patients reported daytime sleepiness, in contrast with 36 out of 66 (54.5%) of controls [OR = 3.8 (1.4–11.6),  $P = 0.007$ ].

The nighttime sleep patterns of PCOS and control women, when adjusted for BMI, were similar, with the exception of sleep latency, which was significantly longer in women with PCOS ( $44.2 \pm 7.1$  vs.  $29.6 \pm 2.2$  min,  $P < 0.05$ ) (see Table 2).

#### Predictors of sleep apnea in PCOS

PCOS patients with ( $n = 9$ ) and without ( $n = 44$ ) SDB were similar, in terms of age ( $34.0 \pm 2.8$  vs.  $29.6 \pm 0.8$  yr, NS), whereas PCOS women with SDB were heavier (BMI of  $45.7 \pm 2.6$  vs.  $37.2 \pm 1.1$ ,  $P < 0.003$ ). PCOS patients who were recommended treatment for SDB showed significantly higher fasting insulin levels ( $306.5 \pm 52.4$  vs.  $176.1 \pm 18.5$ ,  $P < 0.01$ ) and a lower glucose-to-insulin ratio ( $0.02 \pm 0.006$  vs.  $0.04 \pm 0.003$ ,  $P < 0.05$ ) than those who were not (Table 3). The difference between the insulin levels remained significant when adjusted for BMI ( $P < 0.05$ ). Plasma free or total testosterone and fasting blood glucose concentrations were not different between the two subgroups of PCOS patients.

To understand further the relation between the presence of SDB in PCOS patients and potential predictive factors, we used logistic regression analysis to predict PCOS patients requiring treatment for SDB vs. those not requiring treatment for SDB. In this model, we included age, BMI, free and total testosterone, fasting insulin levels, and glucose-to-insulin ratio as potential predictors of the presence of SDB in PCOS women. All predictor variables were initially entered into this analysis as continuous variables. The backward conditional analysis eliminated all variables except insulin and glucose-to-insulin ratio, suggesting that insulin resistance was a stronger predictor than age, BMI, or testosterone.

#### Discussion

OSA was much more prevalent in premenopausal women with PCOS than in normal controls (ratio, 30:1). This difference remained significant, even when we corrected for BMI differences between the two groups. We previously demonstrated that, in a general randomized sample, the prevalence of sleep apnea in women was 1.2 vs. 3.9% in men (8). Furthermore, the prevalence of sleep apnea was quite low in premenopausal women (0.6%) and exclusively associated

**TABLE 2.** Nighttime sleep patterns of PCOS women and controls

	PCOS	Controls	P <sup>a</sup>
SL (min)	$44.2 \pm 7.1$	$29.6 \pm 2.2$	0.05
WTASO (min)	$48.2 \pm 9.0$	$56.2 \pm 2.8$	NS
TWT	$92.4 \pm 11.5$	$85.9 \pm 3.5$	NS
% ST	$79.8 \pm 2.4$	$82.0 \pm 0.8$	NS
% 1	$5.3 \pm 0.8$	$4.3 \pm 0.2$	NS
% 2	$66.3 \pm 1.3$	$70.6 \pm 0.4$	NS
% SW	$9.7 \pm 1.6$	$7.0 \pm 0.5$	NS
% REM	$18.7 \pm 1.5$	$18.1 \pm 0.4$	NS

SL, Sleep latency; WTASO, wake time after sleep onset; TWT, total wake time; ST, sleep time; SW, slow wave; REM, rapid eye movement.  
<sup>a</sup> Mean values were adjusted for BMI.

with obesity (BMI  $\geq 32.3$ ) (8). Our study shows that in premenopausal patients with PCOS, OSA is quite prevalent and present, even in nonobese women (BMI  $\leq 32.3$ ).

Eighty percent of PCOS patients reported daytime sleepiness, in contrast with 25% of normal controls. Daytime sleepiness was equally distributed among obese and nonobese women with PCOS, suggesting that in PCOS women, daytime sleepiness exists independently of obesity or sleep apnea. The nighttime sleep patterns of the PCOS and control groups were similar, with the exception of increased difficulty in falling asleep for the group of PCOS patients. It is possible that PCOS, with its neurohormonal abnormalities, may be compounded by, or elicit increased activity of, the stress system, which, in turn, may lead to increased difficulty in falling asleep (16). It has been suggested that women with PCOS have increased psychopathology, which may lead to difficulty initiating sleep (17).

In our study, the strongest risk factor for sleep apnea was fasting plasma insulin levels and glucose-to-insulin ratio. We have previously shown that a fasting glucose-to-insulin ratio correlates well with more intensive measures of insulin action (18). Plasma free and total testosterone concentrations were not different between PCOS patients with and without SDB. We recently demonstrated that in obese men, there is a strong association among sleep apnea, insulin resistance, and visceral obesity (9). The latter may be the principal culprits, progressively leading to worsening metabolic syndrome manifestations and sleep apnea. The finding of increased prevalence of sleep apnea in PCOS women, a condition strongly associated with insulin resistance, provides further support to this hypothesis. It seems that progressive deterioration of PCOS leads to sleep apnea, which, in turn, accelerates the metabolic abnormalities associated

**TABLE 3.** Biochemical profiles of PCOS women with and without SDB

	SDB group	Non-SDB group	P
Free testosterone (nmol/L)	124.81 ± 44.52	118.11 ± 16.54	NS
Total testosterone (nmol/L)	276.20 ± 73.1	284.77 ± 26.41	NS
Glucose (nmol/L)	5.65 ± 0.31	5.48 ± 0.25	NS
Insulin (pmol/L)	306.48 ± 52.39	176.71 ± 18.53	0.01
Glucose/insulin ratio	0.02 ± 0.006	.04 ± 0.003	0.05

with PCOS, possibly through progressive elevation of hormones such as insulin.

That sleep apnea is more prevalent in men than women, and that testosterone is associated with upper airway collapsibility in patients with sleep apnea (19) or may even induce apnea in women (20) have led to the belief that testosterone abnormalities may be a principal factor in the pathogenesis of sleep apnea. Our data do not support this hypothesis in the PCOS patients studied, who, in the worst case, have testosterone levels that are only a fraction of normal male levels. On the other hand, we have shown that treatment of postmenopausal women with hormone replacement therapy is associated with a significant reduction of SDB, suggesting that estrogen is indeed protective (8). Also, in this study, the use of oral contraceptives seems to protect PCOS women from developing SDB. Estrogen suppresses IL-6 secretion, which is elevated in sleep apnea (9, 21), potentiates the transcription of the CRH gene, and stimulates the noradrenergic system in the brain by inhibiting norepinephrine clearance (22, 23). This could explain its antisleep apnea effect in postmenopausal women receiving estrogen replacement.

Because the prevalence of sleep apnea in premenopausal women in the general population is quite low (0.6%) (8), a large, carefully obtained sample is required to make a reasonably stable estimate of this parameter. Thus, we chose to employ, as control, all premenopausal women who were 42 yr or younger, from our random sample of the general population (8). Both the control group and the PCOS women in our study were recorded in the same sleep laboratory under the same experimental conditions and at approximately the same time. PCOS women were recruited randomly from a larger PCOS population, and it is possible that a selection bias exists, in that those patients with sleep problems were more likely to volunteer to participate in the study. Further, it is possible that because we did not systematically assess for PCOS in the controls, the prevalence in the control group may, in fact, be slightly inflated, leading to a conservative comparison. Interestingly, none of our PCOS patients who were recommended treatment for SDB were previously diagnosed or referred to a sleep center for sleep apnea. This suggests that every PCOS woman should be screened for symptoms and signs associated with SDB.

The pathophysiology of sleep apnea remains obscure, and most currently available treatments for this disorder are mechanical and associated with either variable responses and/or poor compliance. Furthermore, the application of these treatment modalities in milder but quite prevalent forms of SDB, such as snoring, which may lead to cardiovascular complications such as hypertension (24) and coronary heart disease, is impractical. Cumulative evidence, including this study, sug-

gests that sleep apnea should be viewed as a metabolic disorder. Further understanding of the mechanisms underlying this metabolic disorder may lead to new and more effective methods for its prevention and treatment.

### Acknowledgments

We thank Karen Sanchez and Deborah Kantner for their technical assistance with this study and Barbara Green for her overall preparation of the manuscript.

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