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Increased Prevalence of Obstructive Sleep Apnea Syndrome in Obese Women with Polycystic Ovary Syndrome*

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ABSTRACT

Obstructive Sleep Apnea (OSA) is considerably more common in men than women. Preliminary data suggest that androgens may play a role in the male predominance of apnea. Polycystic Ovary Syndrome (PCOS) is characterized by menstrual disturbances, androgen excess, and frequently obesity. These features suggest that women with PCOS may be at increased risk for OSA. To determine whether obese women with PCOS have an increased prevalence of sleep apnea compared with age and weight-matched reproductively normal women, we performed overnight polysomnography for determination of the apnea-hypopnea index (AHI) in 18 obese women with PCOS and age and weight-matched control women. Additional measurements included waist, hip, and neck circumferences, serum total testosterone, unbound testosterone, and DHEAS. Women with PCOS had a higher AHI than controls (22.5 ± 6.0, *vs.* 6.7 ± 1.0, $P = 0.008$). Women with PCOS were also more likely to suffer from symptomatic OSA syndrome (44.4% *vs.* 5.5%, $P = 0.008$). AHI correlated with waist-hip ratio ($r = 0.51$, $P < 0.03$), serum testosterone ($r = 0.52$, $P < 0.03$) and unbound testosterone ($r = 0.50$, $P < 0.05$) in women with PCOS. We conclude that obese women with PCOS are at increased risk of OSA when compared with matched reproductively normal women. Women with PCOS should be carefully questioned regarding symptoms of sleep apnea. (*J Clin Endocrinol Metab* **86:** 1175–1180, 2001)

OBSTRUCTIVE sleep apnea (OSA) is a common disorder with important clinical consequences for affected individuals (1). This disorder is characterized by repetitive collapse of the pharyngeal airway during sleep yielding hypoxia and hypercapnia, with arousal being required to reestablish airway patency (2). The associated consequences include daytime sleepiness (3), decreased cognitive performance, decreased quality of life (4), and an increased risk of automobile accidents (5). There is also increasing evidence that OSA may lead to adverse cardiovascular consequences such as hypertension (6, 7), myocardial infarction (8), and stroke (9). OSA occurs in approximately 4% of middle-aged men and 2% of middle-aged women, respectively (1). The most important epidemiological risk factors for sleep apnea are obesity (10, 11) and male gender (12). Indeed, in studies of sleep clinic populations, the ratio of men to women is as high as 10:1 (13), whereas in community-based samples this ratio is closer to 3:1 (12). In addition, women typically have to become considerably more obese than men to develop substantial sleep apnea (14). The increased risk of sleep apnea in men compared with women is poorly understood with prior studies focusing on differences in airway anatomy (15), pharyngeal dilator muscle function (16), and ventilatory control mechanisms (17).

Several preliminary studies have suggested that androgen levels can directly influence the prevalence and severity of sleep-disordered breathing in both men and women. First, there are several reports demonstrating that administration of exogenous androgens to either men or women can precipitate apnea in a previously unaffected individual, without change in weight (18–20). Second, there is preliminary evidence that women with OSA have higher circulating androgens than age and weight-matched control women (21, 22). Finally, we have previously demonstrated that in a group of hypogonadal men that short-term testosterone replacement led to a statistically significant increment in the Apnea-Hypopnea Index (AHI, events per hour of sleep) (23). Taken together, these data clearly suggest that androgens can importantly influence the development of OSA.

Polycystic ovary syndrome (PCOS) is a common disorder affecting as many as 5–10% of women of reproductive age (24). This disorder is characterized clinically by oligomenorrhea and clinical signs of androgen excess. Biochemical features of PCOS include chronic annovulation and elevated circulating androgen levels. Obesity is seen in many of these women and is frequently central in nature (increased waist to hip ratio). Insulin resistance is also a common finding. Women with PCOS have an increased prevalence of type 2

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diabetes (25) and lipid abnormalities (26). There is also emerging evidence to suggest a link between PCOS and cardiovascular disease (27, 28).

The clinical (obesity) and biochemical (increased serum androgens) features of PCOS suggest that these women may be at increased risk for the development of OSA syndrome. To test this hypothesis, we compared the prevalence of sleep apnea in a group of overweight women with untreated PCOS to that in a group of age and weight matched control women.

Materials and Methods

Study population

We studied 18 overweight women with PCOS and compared them with 18 age- and weight-matched controls. Women with untreated PCOS were recruited from the Division of Women's Health at the Brigham and Women's Hospital and the Reproductive Endocrine Unit of the Massachusetts General Hospital. All women were overweight (Body Mass Index ≥ 28 kg/m^2), healthy and between the ages of 18 and 45 yr. They were not currently taking any medications. PCOS was defined by chronic oligomenorrhea (six or fewer menses per year) along with elevated serum androgen levels (total or biologically available testosterone levels) (29). Nonclassical 21-hydroxylase deficiency was excluded by a 1-h ACTH stimulation test. No woman had an elevated plasma PRL level. Control women were recruited by means of advertisement within the community and had normal menstrual cycles (28–35 days), no clinical signs of androgen excess, and normal serum levels of androgens. Both groups were recruited consecutively, and, to avoid any potential recruitment bias no questions regarding symptoms of any sleep disorder were asked. Women in both groups were without evidence of other diseases including diabetes and hypertension. All women gave written informed consent before participation in this study, which had the approval of the Human Subjects Committee of the Brigham and Women's Hospital.

Subject evaluation

Each woman underwent a brief examination by one of the authors (RBF) including measurement of height, weight, minimal waist circumference, and maximal hip circumference. Each filled out a brief sleep questionnaire, which included a subjective evaluation of daytime sleepiness. The Epworth Sleepiness Scale (ESS) (30), asks subjects to rate the probability of falling asleep in eight different situations on a scale of 0 (not likely at all) to 3 (extremely likely). Thus scores can range from 0–24 with higher scores indicating greater sleepiness. This questionnaire has been validated both in normal subjects and in patients with disorders of excessive daytime sleepiness (30, 31).

Measurement of serum hormones

A single fasting blood sample for hormone analysis was obtained between 0800 and 1000 h. Assays for serum Testosterone (T) and dehydroepiandrosterone sulfate (DHEAS) were performed by using Diagnostic Products (Los Angeles, CA) Coat-A-Count kits. Non-SHBG-bound (unbound) testosterone was measured by a modification of the procedure of Tremblay and Dube, as previously described (32).

Polysomnography

Polysomnography was performed according to standard laboratory protocol. Data recorded included four channels of EEG (two central and two occipital), two channels of EOG, submental EMG, arterial oxygen saturation (Healthdyne, Model 930, Marietta, GA.), nasal-oral airflow (thermistor), nasal pressure (Validyne Engineering Corp., Northridge CA), EKG, chest and abdominal wall motion (piezo electrodes, Pro-Tech Services, Woodinville, WA) bilateral anterior tibialis EMG, snoring (tracheal microphone) and body position (mercury gauge). All signals were simultaneously recorded and stored using the ALICE 3 digital polysomnography system (Respironics, Inc., Murraysville, PA). Bedtime was set between 2200 and 2300 h, and waketime occurred between 0600 and 0700 h. Thus, we attempted to record sleep for ≥ 7 h in each subject/patient.

All of the polysomnographic records were scored by one of the authors (SDP) who was blinded to all subjects' diagnosis. Sleep was staged according to standard criteria (33). Arousals were defined according to American Academy of Sleep Medicine (AASM) guidelines (34). Respiratory events were scored according to the recently published AASM guidelines for measurement in clinical research (35). Specifically, apnea was defined as a complete cessation in airflow of ≥10 sec. They were classified as central if there was no associated effort, and obstructive if respiratory effort was present. Hypopneas were scored as a clear reduction in amplitude in the nasal pressure signal for ≥10 sec that was associated with either an oxygen desaturation of >3%, EEG arousal or both. The apnea-hypopnea index (AHI) was calculated as the number of apneas plus hypopneas divided by the number of hours of sleep.

Data analysis

We quantitatively compared demographic, hormone, and sleep variables, between patients with PCOS and controls using unpaired *t* tests for data that was normally distributed and nonparametric methods (Mann-Whitney Rank Sum Test) for data that were not normally distributed (SigmaStat, SPSS, Inc. Chicago, IL). In addition, the proportion of PCOS women and controls with sleep apnea syndrome was compared using the Fisher Exact Test. Correlation analyses were performed using standard least squares linear regression techniques for single variables, and forward stepwise regression for multiple variables. Data are presented as the mean ± SEM. For all analyses, two-tailed significance was set as $\alpha < 0.05$.

Results

Demographic characteristics of women with PCOS and controls are shown in Table 1. PCOS and control women were well matched for age and BMI. However, as can be seen, women with PCOS had a significantly higher waist-hip ratio (WHR) than control women (0.88 ± 0.02 *vs.* 0.82 ± 0.01, $P = 0.01$). Women with PCOS also had significantly higher circulating testosterone (94.44 ± 8.5 ng/dl *vs.* 22.77 ± 2.5 ng/dl, $P < 0.001$) and unbound testosterone levels (34.06 ± 2.3 ng/dl *vs.* 5.05 ± 0.8 ng/dl $P < 0.001$) than controls.

Polysomnographic data as well as the subjective sleepiness score are shown in Table 2. Women with PCOS had a sig-

TABLE 1. Subject characteristics

	PCOS		Controls	
	Mean	Range	Mean	Range
AGE (yr)	31.1 ± 1.3	22–38	32.3 ± 1.3	26–39
BMI (kg/m^2)	36.9 ± 1.3	28.2–47.1	36.9 ± 1.4	30.4–47.0
Waist-Hip ratio	0.88 ± 0.02[a]	0.71–1.0	0.82 ± 0.01	0.76–0.88
Testosterone (ng/dL)	94.4 ± 8.5[a]	52–184	22.8 ± 2.5	7.0–40.2
Non-SHBG bound testosterone (ng/dL)	34.1 ± 2.3[a]	18–51	5.05 ± 0.8	0.6–12.3

Data are presented as Mean ± SEM.
[a] $P < 0.01$ PCOS *vs.* controls.

TABLE 2. Sleepiness and polysomnographic data

	PCOS		Controls	
	Mean	Range	Mean	Range
Epworth sleepiness score	9.5 ± 0.9[a]	4–18	5.8 ± 0.8	2–14
Sleep onset latency (min)	9.9 ± 2.8	1.5–51.0	8.6 ± 2.2	1.5–58.0
Sleep efficiency (%)	80.9 ± 3.7	65–97.1	88.2 ± 2.2	74–97
Stages 3 & 4 (%)	22.5 ± 2.4	0.2–37.6	20.9 ± 1.6	10–34.4
REM sleep (%)	11.8 ± 1.3	0.2–22.6	15.1 ± 1.7	5.0–27.5
AHI (all sleep stages)	22.5 ± 6.0[a]	1–102	6.7 ± 1.4	0.3–20.2
AHI (REM sleep)	41.3 ± 7.5[a]	4.3–103	13.5 ± 3.3	0.4–47.3

Data are presented as mean ± SEM.
[a] $P < 0.01$ PCOS *vs.* controls.

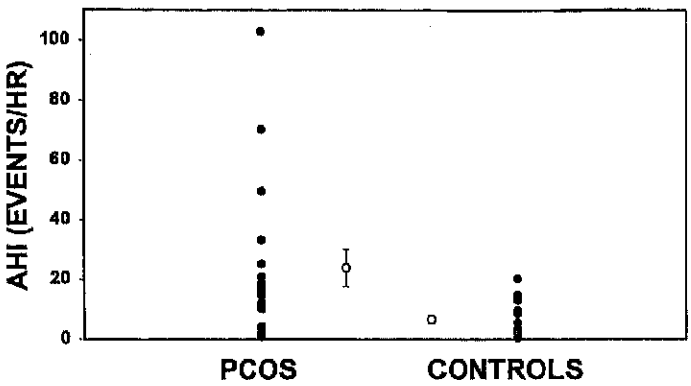

FIG. 1. AHI in women with PCOS and matched controls. Mean (± SEM) AHI of women with PCOS was greater than control women (22.5 ± 6.0 *vs.* 6.7 ± 1.4 $P < 0.01$). There was, however, substantial overlap between groups.

nificantly higher mean AHI than matched control women (22.5 ± 6.0 *vs.* 6.7 ± 1.7, $P < 0.01$) (Fig. 1), a difference that was even more pronounced during REM sleep (41.3 ± 7.5 *vs.* 13.5 ±3.3, $P < 0.01$), (Table 2). There was no difference in other polysomnographic variables including sleep onset latency, Stages 1 and 2 sleep, slow-wave sleep or REM sleep. Overall, sleep efficiency appeared lower in the women with PCOS (80.1 ± 3.7% *vs.* 88.2 ±2.2%); however, this difference did not reach statistical significance. Finally, women with PCOS were subjectively sleepier than control women (mean ESS 9.5 ± 0.9 *vs.* 5.8 ± 0.8, $P < 0.01$).

The prevalence of OSA was compared in women with PCOS and matched control women using various prespecified criteria to define OSA (Table 3). Using an AHI cutoff of 5, 10, or 15 as abnormal, the prevalence of sleep apnea was always more common in women with PCOS. However, this difference only reached statistical significance at AHI cutoffs of 10 and 15. When OSA syndrome was defined according to the recently published AASM Task Force Guidelines (35), women with PCOS were significantly more likely than control women to suffer from symptomatic OSA (44.4% *vs.* 5.5%, $P < 0.01$).

Linear regression techniques revealed that for women with PCOS, AHI was significantly correlated with WHR ($r = 0.51$, $P < 0.03$) (Fig. 2), total serum testosterone ($r = 0.52$, $P < 0.001$) (Fig. 3), and unbound testosterone ($r = 0.50$ $P < 0.05$). There was no significant correlation between age, weight, waist circumference, or BMI with AHI. In the control women, AHI correlated significantly with WHR ($r = 0.56$, $P < 0.01$).

TABLE 3. Prevalence of OSA

	PCOS	Controls
AHI > 5 (% with OSA)	72[a]	39
AHI > 10 (% with OSA)	66.67[b]	16.67
AHI > 15 (% with OSA)	44.44[b]	5.5
AHI > 5 & EDS[c] (% with OSA)	44.44[b]	5.5

[a] $P = 0.10$.
[b] $P < 0.05$.
[c] EDS (Excessive Daytime Sleepiness) was defined as an Epworth Sleepiness Score ≥ 10.

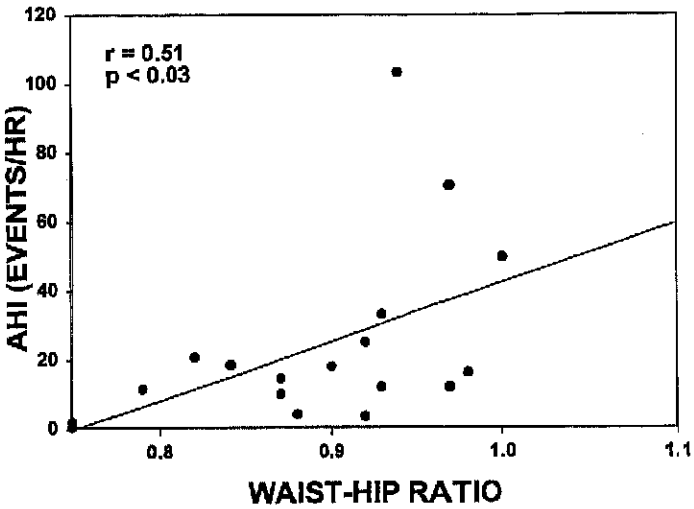

FIG. 2. Correlation between waist-hip ratio and sleep disordered breathing in women with PCOS. There was a statistically significant correlation between the degree of central obesity (WHR) and the severity of sleep disordered breathing (AHI), ($r = 0.51$, $P < 0.03$).

There was no correlation between serum androgens and AHI in the control group. Using stepwise regression analyses to determine the relative importance of WHR, total testosterone and free testosterone in predicting apnea severity in women with PCOS, combining WHR and total testosterone improved the predictive value ($r = 0.64$, $P < 0.001$). Free testosterone did not add significantly to the model.

Discussion

In this study, we have demonstrated that sleep-disordered breathing is considerably more common and severe in overweight women with PCOS than in a group of reproductively normal control women who were matched for age and weight. In addition, several specific features of PCOS,

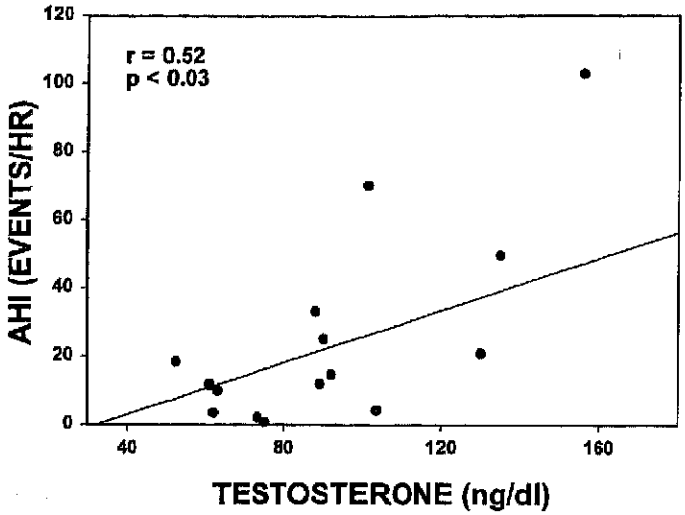

FIG. 3. Correlation between serum total testosterone and sleep disordered breathing in women with PCOS. The degree of androgen excess (serum testosterone) correlated with the severity of sleep disordered breathing (AHI), ($r = 0.52$, $P < 0.03$).

namely elevated serum androgens and central obesity, were significantly associated with the severity of sleep-disordered breathing.

The reasons for this markedly increased prevalence of sleep-disordered breathing in women with PCOS cannot be determined directly from this study, but several possibilities exist. It could be that the androgen excess associated with PCOS contributes to this finding. Several previous studies have suggested that elevated serum androgens may represent an independent risk factor for the development of OSA. Matsumoto *et al.* (18) showed that testosterone replacement in 5 hypogonadal men led to the development or substantial worsening of sleep apnea in two. In another such study, Cistulli *et al.* (20) demonstrated that testosterone administration to a young male with Marfan's Syndrome was associated with an exacerbation of OSA, along with increased upper airway collapsibility during sleep. A recent case report revealed that an androgen secreting ovarian tumor precipitated clinically significant sleep apnea in a previously unaffected woman, and that apnea disappeared following surgical resection of the tumor (19). Our laboratory has also demonstrated that in a group of hypogonadal men, short-term testosterone replacement led to a statistically significant rise in total nocturnal apneas + hypopneas, with several subjects developing clinical sleep apnea. In addition, there is preliminary evidence that women with OSA have higher circulating androgen levels than age and weight matched normal controls. Mohamed *et al.* (21) found higher androgen levels in four women with sleep apnea when compared with controls. Schwartz *et al.* (22) examined hormone levels in six obese women with OSA and compared them to obese and nonobese controls. Women with sleep apnea had higher free testosterone and dihydroepiandrostenedione (DHEAS) than both sets of controls.

It should be noted, however, that not all the available data are consistent in this regard. In fact several studies have found that testosterone levels (free and total) are lower in men with severe sleep apnea and improved with nasal CPAP therapy (36). This same group was also unable to demonstrate a statistically significant improvement in apnea severity using short-term (one month) androgen blockade with flutamide (37). Thus, the exact role of testosterone in sleep apnea pathogenesis is not clear.

In the current study, AHI correlated significantly with both total and free testosterone, although the relationship with free testosterone was no longer significant once waist-hip ratio and total testosterone was included. However, it is well known that sex hormones can affect body fat composition, with androgens leading to central obesity. Evans *et al.* (38) showed that women with PCOS had an increased WHR compared with weight-matched controls, and that WHR correlated with serum androgen levels. Thus, it is possible that the elevated serum androgens found in women with PCOS leads to increased central obesity, which numerous previous studies (39) have shown to be a better predictor of OSA than BMI. In addition to androgen excess, PCOS is often associated with both insulin resistance and elevated serum glucose levels. Both of these factors may contribute to central obesity and an increased risk of OSA. Thus, central obesity itself, rather than androgen excess, could be the factor that predisposes to OSA.

Elevated androgen levels could predispose to OSA by several potential mechanisms. First, it is well known that testosterone can affect body composition. It is possible that elevated androgen levels leads to increase soft tissue deposition in the pharynx (40). This could change either the size or compliance characteristics of the pharyngeal airway, making it more likely to collapse. Androgen receptors have also been localized in the hypoglossal motor nucleus (41), and it is possible that elevated androgen levels could affect the function of the pharyngeal dilator muscles. We have previously demonstrated differences in the pharyngeal dilator muscles in men when compared with women, a difference that may in part be due to testosterone (16). Finally, it is possible that testosterone could lead to alterations in ventilatory control mechanisms during sleep, rendering the airway more vulnerable to collapse.

These findings have important clinical implications. First, clinical recognition of sleep apnea in women is far from optimal. Both OSA and PCOS are relatively common disorders in the general population and often go undiagnosed. Both are associated with significant morbidity for the affected individual and are readily amenable to therapy. Although OSA is less common in women compared with men, there also appears to be a problem identifying women with sleep apnea. Clinic-based studies have typically reported a much greater difference in sleep apnea rates for men and women than have been seen in epidemiological studies (12). This has raised concerns that there is a selection bias for referral for evaluation that favors men. Based on data from the Wisconsin cohort, Young estimated that > 90% of women with moderate to severe OSA are undiagnosed (42).

Second, OSA may contribute to cardiovascular morbidity in women, an effect that could be greater in women with PCOS. Recent data from the Nurses Health Study has shown that snoring was associated with an increased risk for the development of cardiovascular disease, an association that

remained significant after controlling for potential confounding variables (43). Preliminary data from the Wisconsin Sleep Cohort Study has suggested a significantly greater 5-yr mortality rate for women with sleep-disordered breathing than for women without the disorder. This increased mortality was substantially higher in women than in men with OSA (44). In a case-control study, Mooe *et al.* (45) found sleep apnea (AHI > 5) to be an independent predictor of coronary artery disease (odds ratio = 4.1) that was more powerful than either hypertension or smoking. Although these data are only preliminary, they suggest a gender difference in susceptibility to adverse cardiovascular outcomes from sleep apnea.

Finally, we wonder whether OSA may contribute in small part to the metabolic abnormalities seen in women with PCOS. In some, but not all studies, OSA has been associated with an increased prevalence of insulin resistance and type 2 diabetes, characteristic features of PCOS. Although Stoohs *et al.* (46) found this relationship to be due entirely to obesity, others have found an increased prevalence of insulin resistance in OSA patients, even after controlling for confounding variables (47, 48). Brooks and colleagues also demonstrated an improvement in insulin responsiveness in patients with type 2 diabetes and OSA following nasal CPAP therapy (49). Clearly, the majority of the metabolic abnormalities in PCOS are due to obesity and androgen excess.

Our study had several limitations, which should be recognized. First, the sample size is relatively small. However, the group differences were sufficiently robust that a larger sample size was not required to demonstrate substantial and significant differences. Second, there might be concern that the prevalence of OSA in the control women was quite low, given their degree of obesity. However, this finding is consistent with several prior studies. Sloan and Shapiro found a prevalence of OSA (AHI >10) in 10% of obese (mean BMI = 39 kg/m^2) women referred to an eating disorders clinic. Richman *et al.* (50) found a higher prevalence of OSA (AHI > 5) in a hospital-based obesity clinic (37.9%), but the women with OSA were substantially more obese (BMI = 46.1 ± 2.3) than those without OSA (37.5 ± 1.3), and the latter group more closely resembles our control women. Third, there may have been a participation bias in that women who agreed to be in this study may have done so because they suspected that they had a sleep problem. However, we doubt this was the case as the vast majority of the women we approached agreed to participate. Approximately 75% of women asked to participate agreed to do so. In addition, any potential bias should have existed for the control group as well. Finally, no questions regarding symptoms of sleep disorders were asked of any subject. Specifically no woman (control or PCOS) was asked about symptoms of snoring, daytime sleepiness or witnessed apneas. All those who completed the sleep study were included in the study, regardless of the results. The final limitation is that as we only studied obese women with PCOS, the results of this study may not be applicable to all women with this disorder.

In summary, we found that overweight women with PCOS were substantially more likely to suffer from the OSA syndrome than a carefully age- and weight-matched group of reproductively normal control women. As a result, women with PCOS, particularly those that are obese, should be carefully questioned regarding symptoms suggestive of sleep apnea. Specifically, these women should be questioned regarding snoring and daytime sleepiness, as these are the most common symptoms found in OSA. The mechanistic relationship between PCOS and OSA is likely complicated, but we suspect that this increased risk is related to chronic androgen excess in these women.

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