

# Pathogenesis and Consequences of Disordered Sleep in PCOS

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**ABSTRACT:** Polycystic ovary syndrome (PCOS) is a common hormonal disorder that is characterized by hyperandrogenism and menstrual irregularity. Affected women have a high prevalence of insulin resistance and related metabolic complications. The frequency of sleep disturbances appears to be increased in women with PCOS, although most studies so far have included more severely affected obese women with PCOS who are referred to tertiary care clinics and may not represent the general population of women with PCOS. This article provides an overview of sleep disturbances in PCOS with the focus on obstructive sleep apnea (OSA), the most commonly reported sleep disturbance among these women. The pathogenesis and risk factors for OSA in PCOS and its association with metabolic disorders is discussed in detail.

**KEYWORDS:** Obstructive sleep apnea, Insulin resistance, Visceral adiposity

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## Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that is characterized by hyperandrogenism and menstrual irregularity.<sup>1,2</sup> Affected women have a high prevalence of insulin resistance and related metabolic complications.<sup>1</sup> The frequency of sleep disturbances appears to be increased in women with PCOS, although most studies so far have included more severely affected obese women with PCOS who are referred to tertiary-care clinics and may not represent the general population of women with PCOS.<sup>3</sup> This article provides an overview of sleep disturbances in PCOS with the focus on obstructive sleep apnea (OSA), the most commonly reported sleep disturbance among these women. The pathogenesis and risk factors for OSA in PCOS and its association with metabolic disorders is discussed in detail.

## Abnormalities in Sleep Architecture

Adult and adolescent women with PCOS are known to have abnormalities in sleep architecture. A study that used polysomnography in obese adolescent girls with PCOS, demonstrated a significant reduction in the percentage (%) of rapid eye movement (REM) sleep and percent sleep efficiency, as well as a significant increase in sleep-onset latency compared to both normal weight and obese adolescent girls without PCOS.<sup>4</sup> In a study of obese adult women with PCOS, sleep efficiency, amount of time spent in REM sleep as well as non-REM sleep, was significantly reduced compared to healthy age-matched nonobese control women as assessed by the Pittsburgh Sleep Quality Index.<sup>5</sup> In the same study, sleep latency was increased in obese women with PCOS compared to nonobese control women by the use of questionnaires.<sup>5</sup> In another study that employed polysomnography, sleep latency was increased in PCOS compared to control women ( $P = .05$ ).<sup>6</sup> However, no

other significant differences in sleep architecture between women with PCOS and controls was found in this study.<sup>6</sup>

Difficulty falling asleep and maintaining sleep has been reported among women with PCOS. In a community-based study of 87 women with PCOS and 673 women without PCOS, women with PCOS had twice the odds of increased difficulty falling asleep (odds ratio [OR] = 1.94, 95% confidence interval [CI]: 1.28–2.95) that was attenuated slightly after adjustment for body mass index (BMI; OR = 1.85, 95% CI: 1.21–2.83) and further attenuated after adjustment for depressive symptoms (OR = 1.57, 95% CI: 1.03–2.38) but still remained significant after both factors were added to the model (OR = 1.54, 95% CI: 1.01–2.36).<sup>7</sup> In the same study, women with PCOS had a significantly increased odds of awakening without cause and an inability to resume sleep >15 minutes (OR = 1.92, 95% CI: 1.12–3.31) compared to control women, although this was no longer statistically significant after adjustment for both BMI and depressive symptoms (OR = 1.73, 95% CI: 0.98–3.03).<sup>7</sup> Increased daytime sleepiness has also been reported in association with PCOS in multiple studies.<sup>5</sup> More recently, in a large community-based cohort study from Australia, women with PCOS reported more difficulty initiating sleep, more restless sleep, and more severe tiredness despite similar duration of sleep than women without PCOS even after adjustment for BMI, depressive symptoms, and other comorbid conditions.<sup>8</sup> Taken together, these data suggest that women with PCOS are at an increased risk for sleep disturbances, and obesity and depression are associated with the increased risk.

## Obstructive Sleep Apnea

Clinical diagnosis of OSA is based on the presence of symptoms such as daytime sleepiness, loud snoring, witnessed



breathing interruptions and the presence of 5 apnea or hypopnea events (Apnea-Hypopnea Index [AHI]  $\geq 5$ ) per hour of sleep as detected by polysomnography.<sup>9</sup> The diagnosis of OSA can also be established based on AHI  $\geq 15$  in the absence of symptoms.<sup>9</sup> The risk for OSA among reproductive age women in the general population is reported at 3% which is lower than the risk among men at any age or that in older women.<sup>10</sup> Numerous studies have demonstrated an increased risk for OSA in PCOS.<sup>9</sup> Most of these studies are clinic based and may be limited by small sample sizes and inclusion of mostly obese and even morbidly obese women with PCOS.

In one of the original studies that described this association, women with PCOS had an increase in risk for OSA than control women (OR=28.7, 95% CI: 4.9-294.4) although women with PCOS were significantly heavier than control women ( $38.7 \pm 0.9$  vs  $26.4 \pm 0.3$ ,  $P < .01$ ).<sup>6</sup> Furthermore, in this study, women with PCOS who had OSA had significantly higher insulin levels and a lower glucose-to-insulin ratio than women without PCOS, suggestive of a higher degree of insulin resistance that remained significant after adjustment for BMI.<sup>6</sup> In another cross-sectional study that included only obese women with PCOS and obese control women of similar age and BMI, the prevalence of mild and moderate OSA (AHI  $> 10$  and  $> 15$ , respectively) was significantly increased in women with PCOS (44.44% in PCOS vs 5.5% in control women,  $P < .05$ ).<sup>11</sup>

In one of the first studies from our group that included obese women with PCOS, there was a high prevalence of OSA and oxygen desaturations that occurred predominantly during REM sleep.<sup>5</sup> In this study, the measures of glucose tolerance were strongly associated with severity of sleep-disordered breathing.<sup>5</sup> In a follow-up study from our group, the prevalence of OSA was significantly increased in women with PCOS at 56% compared to control women at 19%.<sup>12</sup> Most women in both groups were overweight or obese, and the risk for OSA was significantly higher among women with PCOS even after adjustment for BMI (OR=7.7, 95% CI: 1.7-45.7;  $P = .01$ ).<sup>12</sup> In this study, only women with PCOS who had OSA had worsened metabolic profile compared to control women although women with PCOS with OSA were statistically more obese and also statistically older than women with PCOS without OSA.<sup>12</sup>

Evidence for an increase in risk for OSA among women with PCOS has been confirmed in more recent studies. In a prospective cross-sectional study of 50 women with PCOS, the prevalence of OSA was high at 66%.<sup>13</sup> In this study, women with PCOS who had OSA were more obese and had significantly higher glucose and triglyceride levels and a higher prevalence of metabolic syndrome than women with PCOS without OSA.<sup>13</sup> Consistent with these findings, in a recent meta-analysis of clinic-based studies, adult women with PCOS had a significantly higher risk for development of OSA (OR=9.74, 95% CI: 2.76-34.41).<sup>3</sup>

A few population-based studies have also demonstrated elevated risk for OSA in women with PCOS.<sup>14,15</sup> One study

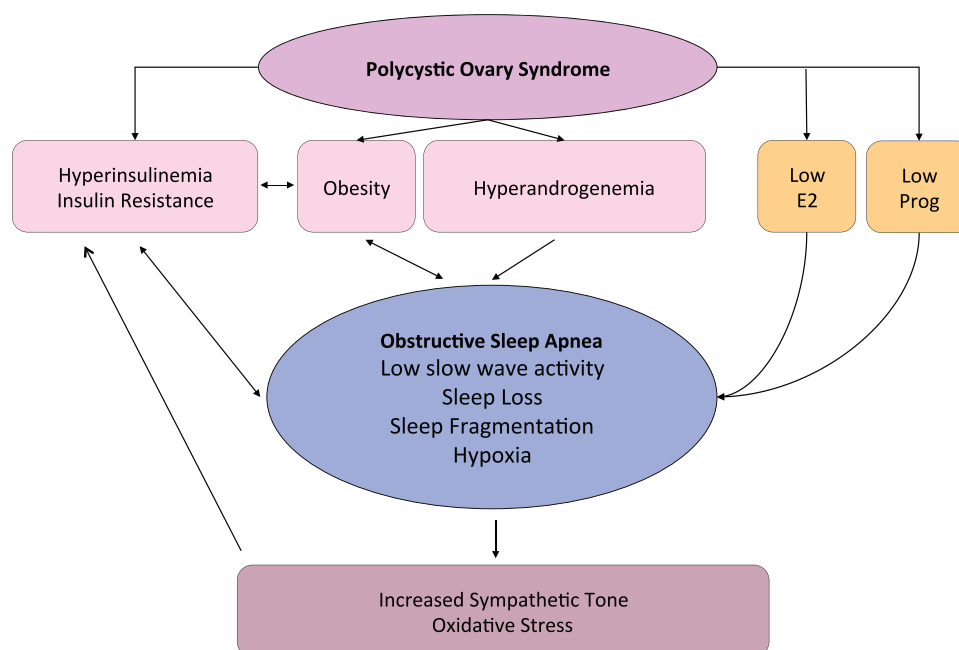
used the Taiwan National Health Insurance Database and enrolled 4595 women with PCOS and 4595 age-matched control women between 1998 and 2009 and identified new cases of OSA during this period. Cases were identified using diagnostic coding in the medical records, bringing some limitation to the study.<sup>14</sup> Despite this caveat, the prevalence of OSA was greatly increased in women with PCOS (1.71 vs 0.63 1000 person-years,  $P < .001$ ). The risk persisted after adjustment for demographic data and comorbid disorders (hazard ratio [HR]: 2.63, 95% CI: 1.57-4.04). In a separate population-based cohort study from the Taiwan National Health Insurance Database,<sup>15</sup> the risk for OSA was significantly increased among 5431 women with diagnosis of PCOS compared to 21 724 matched-control women without PCOS. Most recently, a population-based study from the United Kingdom reported a significantly higher incidence rate for OSA in PCOS versus control women independent of BMI (8.1 and 3.3 per 10 000 million, HR=2.26, 95% CI: 1.89-2.69,  $P < .001$ ).<sup>16</sup>

Overall, both the clinic- and population-based studies demonstrate increased risk for OSA among women with PCOS. Affected women with PCOS are at the highest risk for metabolic disorders. While obesity plays a role in this association, the increased risk persists even among nonobese women with PCOS and after adjustment for BMI in a number of studies.

### Risk Factors for OSA in PCOS

Consistent with data in the general population,<sup>17,18</sup> risk of OSA in women with PCOS increases with age. In a meta-analysis of 12 studies related to PCOS and OSA, the risk of OSA was increased in adult patients with PCOS (OR=9.74, 95% CI: 2.76-34.41) but not in adolescents with PCOS (OR=5.54, 95% CI: 0.56-36.43).<sup>3</sup> Findings from one of the few population-based studies of OSA and PCOS also indicate that the risk of OSA increases in later life in PCOS compared to control women.<sup>14</sup>

Obesity, especially central adiposity, is a well-known risk for the development of OSA in the general population<sup>17,18</sup> and is strongly associated with OSA risk in PCOS. Obesity is a common feature of PCOS,<sup>19,20</sup> and increased accumulation of fat in central depots has been demonstrated even among nonobese women with PCOS.<sup>20,21</sup> Overall, obesity is strongly linked to OSA in women with PCOS.<sup>11,22,23</sup> In the largest population-based study of PCOS and OSA, obesity was the only factor that was significantly associated with increased risk of OSA (HR=6.17, 95% CI: 2.43-15.69).<sup>14</sup> Accumulation of fat in structures surrounding the upper airway increases the likelihood for airway collapse.<sup>18</sup> Upper-body adiposity may reduce lung volume and adversely impact respiratory control.<sup>18</sup> Moreover, obesity increases risk for other sleep disorders beyond OSA, and obese individuals report increased daytime sleepiness independent of OSA.<sup>24</sup> However, the increase in risk for OSA in PCOS may not be entirely mediated by obesity.<sup>16</sup> The increased OSA risk in PCOS has persisted after adjustment for BMI in a number of studies.<sup>5,6</sup> Women with PCOS



**Figure 1.** PCOS is characterized by hyperandrogenism and anovulation. The disorder is also associated with adiposity and insulin resistance. These abnormalities predispose to development of sleep disorders especially obstructive sleep apnea. Obstructive sleep apnea leads to increased sympathetic tone and oxidative stress which in turn worsens insulin resistance associated with PCOS promoting a vicious cycle.

have been shown to have higher AHI regardless of OSA diagnosis and BMI. In a study that included only nonobese control and PCOS women, AHI was increased in PCOS compared to BMI-matched controls, although it was not elevated enough to be diagnostic of OSA.<sup>25</sup> Most recently a large population-based retrospective cohort study in the United Kingdom demonstrates that women with PCOS are at increased risk of developing OSA compared to control women with similar increased HR (HR=2.26, 95% CI: 1.89-2.69) among normal weight, overweight, and obese women.<sup>16</sup> These data suggest that PCOS is associated with OSA even among nonobese women but obesity likely increases this association.

Hyperandrogenemia is a hallmark of PCOS<sup>2</sup> and has been correlated with the risk for OSA in women with PCOS in some<sup>11,13,25</sup> but not all studies.<sup>5,6</sup> The prevalence for OSA is significantly higher in men than women, especially women of reproductive age, and suggests that higher testosterone levels may predispose to OSA.<sup>18</sup> Central adiposity is more common in men than women, and hyperandrogenism among reproductive age women is associated with central adiposity. Alterations in pharyngeal anatomy that may predispose to OSA have been reported in association with higher testosterone levels. Furthermore, hyperandrogenism has been linked to alteration in sleep architecture in PCOS.<sup>26</sup> Testosterone is not the only hormone that has been implicated in the pathophysiology of OSA. Progesterone is a dilator of upper airway muscle activity,<sup>27</sup> and lower progesterone levels in PCOS due to anovulation may increase risk for OSA.

Insulin resistance is a common finding in PCOS especially among obese women with this condition<sup>2</sup> and is strongly associated with OSA in these women (Figure 1).<sup>5,12,28</sup> This

association maybe mediated by abdominal adiposity.<sup>29</sup> It is well known that visceral adiposity predisposes to insulin resistance through the activation of inflammatory pathways and reduction in insulin-sensitizing adipokines such as adiponectin as well as direct communication between visceral depots and liver via the portal circulation.<sup>30</sup> In some studies, metabolic disorders such as insulin resistance are only present in women with PCOS who have OSA although almost all women in these studies are also obese.<sup>5,12</sup>

### Additional Mechanisms Linking Sleep Disturbance to PCOS

A number of small studies have demonstrated increased levels of melatonin metabolites in women with PCOS.<sup>31</sup> Melatonin is a well-known regulator of circadian rhythm but has been shown to have a role in regulation of reproductive processes and insulin secretion. In one small study, melatonin levels were increased at nights in women with PCOS who also had significantly reduced sleep quality than control women.<sup>32</sup> A more recent study has demonstrated later melatonin offset after wake time, later melatonin offset relative to sleep timing and longer duration of melatonin secretion in obese adolescent girls with PCOS compared to obese control adolescent girls. In this study, these abnormalities were associated with hyperandrogenism and insulin resistance.<sup>33</sup> Furthermore, in a genome-wide association study of approximately 500 Chinese Han women with PCOS and similar number of healthy control women of the same ethnicity, certain single-nucleotide polymorphisms (SNPs) in the melatonin receptor gene have been associated with a predisposition to PCOS and its metabolic complications such as insulin resistance.<sup>34</sup> Oral contraceptives

reduced melatonin levels in PCOS in one study.<sup>35</sup> In a more recent study, melatonin supplementation for 12 weeks improved sleep quality and measures of depression and was associated with lowering of insulin levels and upregulation of gene expression of peroxisome proliferator-activated receptor gamma and low-density lipoprotein receptor.<sup>36</sup> At this time, the significance of role of melatonin in the pathogenesis of PCOS and sleep disorders requires further investigation.

Mood disorders such as depression and anxiety are associated with adverse changes in sleep architecture and the associations appear bidirectional.<sup>37</sup> Women with PCOS have higher rates of depression, anxiety, and sleep disorders.<sup>15</sup> The reasons for the higher incidence of mood disorders in PCOS are not well established, but the presence of comorbid psychiatric disorders contributes as an additional risk factor that predisposes to OSA in this population.

### Interactions between PCOS and OSA

As discussed above, hyperandrogenemia may predispose to OSA in PCOS by promoting abdominal adiposity or by altering upper airway physiology. Furthermore, OSA either directly or by its association with insulin resistance may lower levels of sex-hormone-binding globulin and contribute to hyperandrogenemia in PCOS.<sup>38</sup> Sleep disturbances such as short sleep or interruptions in sleep have been shown to affect levels of gonadotropins and gonadotropin-releasing hormones (GnRHs) and may impact reproductive function in PCOS.<sup>38,39</sup> The metabolic abnormalities in PCOS such as insulin resistance are worsened by the presence of OSA as discussed in the following section. Polycystic ovary syndrome is associated with increased sympathetic tone<sup>40</sup> and oxidative stress<sup>41</sup> that predispose to insulin resistance. Both of these abnormalities are exacerbated by recurrent hypoxia related to OSA,<sup>29</sup> contributing to worsening of insulin resistance in PCOS (Figure 1).<sup>29</sup>

### Association of OSA with Metabolic Comorbidities in PCOS

The presence of OSA in women with PCOS is associated with higher levels of fasting glucose, glucose intolerance, and insulin resistance.<sup>6,12,13</sup> Although these findings may be confounded by obesity; in these studies, women with PCOS who have OSA are significantly more obese than those without OSA.<sup>6,12,13</sup> It has been suggested that women with PCOS who have OSA represent a higher metabolic risk population than those without OSA.<sup>42</sup> The increased risk for metabolic disorders with OSA has persisted after adjustment for BMI in these studies.<sup>6,12,13</sup> In support of heightened metabolic risk associated with OSA in PCOS, our group has demonstrated improvements in insulin sensitivity and reduction in sympathetic output (24-h profiles of norepinephrine) and blood pressure in women with PCOS after successful treatment with continuous positive airway pressure (CPAP).<sup>43</sup> These findings must be interpreted with caution, as the sample size was small and the

findings were limited to those subjects who were compliant with the use of CPAP.<sup>43</sup>

Similarly, women with PCOS who have OSA have been shown to have significantly higher systolic and diastolic blood pressure and triglyceride levels than those without OSA.<sup>13</sup> Again, these associations are confounded by adiposity and after adjustment for BMI, not all remain significant.<sup>12</sup> In a study of obese adolescents with PCOS, those with OSA had higher BMI, Homeostatic Model Assessment of Insulin Resistance (HOMA IR), and higher prevalence of metabolic syndrome than those without OSA.<sup>44</sup> Again, the adolescents with OSA had higher BMI than those not affected by OSA. In another study from the same group, the prevalence of OSA was higher among obese PCOS than obese control adolescent girls and similar to obese adolescent boys.<sup>45</sup> Among adolescents with PCOS, those with OSA had a higher prevalence of insulin resistance, hypertension (HTN), dyslipidemia, and triglycerides than those without OSA.<sup>45</sup> Obstructive sleep apnea has been linked to increased risk for nonalcoholic fatty liver in women with PCOS<sup>46</sup> although the association may be mediated by increased adiposity as well as hyperandrogenism.<sup>47</sup>

In summary, OSA and metabolic abnormalities occur at increased frequency among obese women with PCOS. The presence of OSA among these women is associated with worsening of metabolic parameters. Obesity, in general, and abdominal adiposity in particular are likely strong mediators in this relationship.

### Conclusions

Sleep disturbances are common in PCOS, although most studies so far are limited by small sample size and have been conducted in clinic-based cohorts with referral bias and overrepresentation of women with more severe symptoms. Nonetheless, in a recent meta-analysis, adult women with PCOS had a 9.74 times higher risk for OSA compared to reproductive age women of similar age.<sup>3</sup> The risk for sleep disturbances in PCOS increases with age and adiposity although hormonal dysregulation associated with PCOS likely contributes to the elevated risk. The presence of OSA in PCOS is associated with worsening of metabolic parameters.<sup>48</sup> In addition to OSA, other forms of sleep disturbance are also common in PCOS and may have an association with increased risk for anxiety and depression. Current guidelines advocate screening for sleep disturbances among obese women with PCOS and if the screen is positive appropriate diagnosis and treatment for these comorbid conditions.<sup>49</sup>

### Author Contributions

SS, DAE conceived and designed the manuscript. SS wrote the first draft of the manuscript. DAE contributed to the writing of the manuscript. SS, DAE made critical revisions and approved final version. All authors reviewed and approved of the final manuscript.

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