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OBSTRUCTIVE SLEEP APNEA AND METABOLIC DYSFUNCTION IN POLYCYSTIC OVARY SYNDROME

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Abstract

Obstructive sleep apnea (OSA) is an underrecognized, yet significant factor in the pathogenesis of metabolic derangements in polycystic ovary syndrome (PCOS). Recent findings suggest that there may be two "subtypes" of PCOS, i.e. PCOS with or without OSA, and these two subtypes may be associated with distinct metabolic and endocrine alterations. PCOS women with OSA may be at much higher risk for diabetes and cardiovascular disease than PCOS women without OSA and may benefit from therapeutic interventions targeted to decrease the severity of OSA. The present chapter will review what is currently known about the roles of sex steroids and adiposity in the pathogenesis of OSA, briefly review the metabolic consequences of OSA as well as the metabolic abnormalities associated with PCOS, review the prevalence of OSA in PCOS and finally present early findings regarding the impact of treatment of OSA on metabolic measures in PCOS.

Keywords

Cardiometabolic; Impaired glucose tolerance (IGT); Insulin resistance; Metabolic syndrome; Obstructive sleep apnea (OSA); Polycystic ovary syndrome (PCOS); Type 2 diabetes

BACKGROUND

Polycystic ovary syndrome (PCOS) affects approximately 5–8% of women in the United States and typically manifests at the time of puberty with menstrual irregularity, hirsutism, and obesity [1]. The ability to diagnose PCOS at an early age has important implications, since those affected have a substantial risk for subsequent development of a number of metabolic [2, 3] and cardiovascular [4–6] disorders. Specifically, women with PCOS have among the highest reported rates of early-onset impaired glucose tolerance and type 2 diabetes [7, 8] as well as a an increase in risk for hypertension [9], dyslipidemia [10, 11], coronary [10] and other vascular disorders [12–14]. An important addition to this list of health risks is obstructive sleep apnea (OSA), which now appears to be present in a disproportionate number of women with PCOS. Indeed, the risk for OSA is at least 5-fold higher, and perhaps as much as thirty-fold

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higher in PCOS [15], than in similarly obese women. Results of our recent studies suggest that there may in fact be two "subtypes" of women with PCOS -- those with OSA and those without OSA -- and that these two subtypes may be associated with distinct metabolic and endocrine alterations. Because nearly all published studies characterizing metabolic and cardiovascular abnormalities in PCOS have not controlled for the potential impact of OSA and chronic sleep loss, the precise role of OSA as a cause of these derangements is not yet known.

PCOS women with OSA may have a much greater predisposition for development of diabetes and cardiovascular disease than PCOS women without OSA. Further, data are beginning to emerge to indicate that metabolic alterations may improve from therapeutic interventions targeted to decrease the severity of OSA.

A. Chronic sleep loss and obstructive sleep apnea: role of sex steroids and adiposity

As reviewed elsewhere in this volume (CHAPTER ?), it is clear that the past several decades have witnessed a significant decline in the average duration of sleep for most Americans. During the 1960's, the mean sleep duration was between 7 and 8 hours per night; today, the percentage of both men and women who sleep less than 6 hours per night has increased dramatically [16]. Chronic sleep loss imposes a significant negative impact upon individual health as well as an enormous economic cost to society. A number of studies have reported that shortened sleep duration is associated with increased mortality [17, 18]. In the Nurses Health Study, it was found that sleeping less than 6 hours per night was associated with an increased risk of death, even after adjusting for age, smoking, alcohol, exercise, depression, snoring, obesity, and history of cancer and cardiovascular disease [18]. Reduced sleep time has also been reported as a risk factor for the development of obesity as for type 2 diabetes [19–23]. Results of the Sleep Heart Health Study showed that subjects sleeping 5 hours or less per night had an adjusted odds ratios for diabetes of 2.51 (95% CI, 1.57–4.02) when compared to those who slept 7 to 8 hours per night [20]. This trend in shorter sleep duration mirrors the progressive rise in overweight and obesity in the United States [24] and evidence continues to emerge to support a causal link between these two conditions. Should either or both trends continue along their current trajectory, the metabolic and cardiovascular health consequences as well as economic costs will be staggering.

Obstructive sleep apnea (OSA) is one of the major causes of chronic sleep disruption. It is characterized by episodic partial or complete upper airway obstruction during sleep leading to intermittent hypoxia, sleep fragmentation and a reduction in the quantity of deep non-rapid eye movement (NREM) sleep (stages 3 and 4, commonly referred to as slow wave sleep [SWS]). Sleep disruption resulting in reduced SWS has been associated with a rise in plasma cortisol levels and interpreted to indicate that SWS has a "restraining" effect on the hypothalamic-pituitary-adrenal axis [25]. Consistent with this is the finding that pharmacologic augmentation of SWS leads to a significant decline in salivary free cortisol levels [26].

Current estimates of OSA prevalence in the United States [27, 28] are likely to underestimate the true prevalence of the disorder since 82% of men, and an even greater (93%) proportion of women with moderate to severe OSA have not been clinically diagnosed [29]. It has been consistently noted that men have a higher prevalence of OSA compared to women [29]. In community based studies, the male:female ratio is usually between 2:1 and 3:1 [30] in contrast to a ratio of 8:1 in clinic-based studies [31].

OSA has been independently associated with glucose intolerance and insulin resistance even after adjustments for obesity and age [32–36]. Treatment of OSA with CPAP can improve

insulin sensitivity [37] and is associated with a reduction in postprandial glucose and glycohemoglobin levels in individuals with type 2 diabetes [38].

Differences in concentrations of circulating sex steroids – estrogens, progestins, and androgens – appear to play an important role in the differences between men and women, both in normal sleep as well as OSA. However, women tend to be underrepresented in most studies of OSA (Table 1).

Role of Estrogen and Progesterone—Estrogens and progestins have been generally characterized as protective against the development of OSA in women. However, much of the evidence to support this view is derived from studies in which sleep was evaluated in relation to pregnancy status [39, 40], age and phase of the menstrual cycle [41, 42], menopausal status [43], or in response to hormone replacement therapy [43]. Lower estradiol levels have been reported in association with poor sleep quality among women aged 45 – 49 yr [44] and with a higher frequency of apneic events in women across a broader age spectrum of 24 to 72 yr [42]. Among post-menopausal women, there was a modest, but statistically significant, decrease in the occurrence and frequency of sleep apnea in those randomly assigned to receive estrogen replacement rather than placebo [43]. Estrogen levels have not been systematically evaluated among women with PCOS and OSA.

Progesterone is the key hormone thought to underlie the differences in sleep measures that exist across the normal menstrual cycle. Progesterone levels are low during the follicular (pre-ovulatory) phase and rise by up to two log orders during the luteal (post ovulatory) phase when progesterone is synthesized by the corpus luteum. When sleep measures are obtained and compared between follicular and luteal phases, it is apparent that upper airway resistance is lower during the luteal phase [41].

The expected rise in progesterone with pregnancy is thought to attenuate the severity of preexisting OSA as well as to “protect” from its development in women without OSA preconception [40]. These effects have been ascribed to levels of progesterone that would normally counterbalance the increase in OSA risk imparted by pregnancy-associated weight gain. Progesterone is thought to promote its effects through direct stimulation of respiratory drive via an increased ventilatory response to both hypercapnea and hypoxia [45, 46]. Progesterone may also act to enhance upper airway dilator muscle activity [47] and reduce airway resistance. Because women with PCOS are, by definition, oligo- or anovulatory, they characteristically have low circulating progesterone concentrations which may contribute to the high prevalence of OSA in this disorder.

Role of Androgens—Androgens are thought to play a significant role in the sexual dimorphism in sleep architecture and in the pathogenesis of OSA [48, 49]. O’Connor, et al [50] analyzed records of 830 patients with OSA to determine whether there were differences in polysomnographic features between men and women, particularly with respect to the distribution of respiratory events during REM and non-REM sleep. Although the apnea-hypopnea index (AHI) during total sleep time was significantly higher in men compared to women (31.8 ± 1.0 vs 20.2 ± 1.5; $P<0.001$), the number of respiratory events occurring in REM sleep was greater in women as reflected by the so-called REM difference (i.e., the difference in the AHI in REM and AHI in non-REM sleep) in women and men. The REM difference was greater in women than men (28.1 ± 1.5 vs. 10.3 ± 1.1; $P<0.001$) at all levels of severity of sleep apnea. These findings were consistent and remained significant even after adjustment for the effects of covariates including weight, age, and duration of apnea. Thus, women with obstructive sleep apnea appear to have a higher proportion of respiratory events in REM compared to men, and to have a higher prevalence of apnea occurring mostly during REM.

Several studies have also shown that testosterone influences both neural control of breathing [51] and upper airway mechanics [52]. Zhou et al [53] examined the effect of testosterone on apneic threshold in women during sleep. Eight normal, healthy, pre-menopausal women were studied before and after treatment with transdermal testostosterone (5 mg/day) administered in the follicular phase of the menstrual cycle. The authors concluded that testosterone increases apneic threshold in premenopausal women, thus leading to breathing instability during sleep.

Role of Body Fat and its Distribution—The risk of OSA is increased as a function of both total body fat mass as well as body fat distribution. Visceral fat appears to be more metabolically active and the quantity of visceral fat has been shown to highly correlate with OSA risk [54–56]. The relative proportion of visceral fat to total body fat is higher in obese men compared to obese women. This difference is thought to contribute to the higher prevalence of OSA in men than women. Factors responsible for gender differences in body fat distribution include sex steroid concentrations, especially androgens. These factors are particularly relevant to the pathogenesis of OSA in women with PCOS.

B. Metabolic Consequences of OSA

As previously noted, OSA is characterized by the combination of episodic sleep disruption and hypoxemia, each of which can trigger at least three major hormonal responses: activation of the hypothalamic-pituitary-adrenal (HPA) axis with increased cortisol production/secretion, increased catecholamine output from sympathetic nervous system stimulation, and increased release of adipokines from adipose tissue. These responses appear to contribute to the metabolic abnormalities associated with OSA, particularly to the decline in insulin sensitivity and glucose tolerance.

Hypothalamic-pituitary-adrenal axis—The onset of sleep is normally characterized by a modest inhibition of cortisol secretion that is concurrent with slow wave sleep (SWS) and lasts between 60 and 120 min [57]. Nocturnal awakenings are consistently followed by a pulse in cortisol secretion [58] whereas the final morning awakening (the awakening response) is associated with a rapid rise in cortisol lasting approximately 60 min [57]. Work from Van Cauter, et al [59] has shown that partial or total sleep deprivation results in increases in plasma cortisol levels by 37% and 45%, respectively. Most notably, this elevation is evidenced on the day following sleep loss and during the time when the HPA axis is usually quiescent.

Profiles of cortisol secretion in patients with OSA have been variably reported as normal in some studies and abnormal in others [60]. In one report, 8 of 28 OSA patients demonstrated a disruption in the circadian rhythm with cortisol levels that were higher late in the day than in the early morning. This so-called “inverted” cortisol profile was associated in all cases with abnormal blood pressure regulation. When compared to obese subjects without OSA, obese subjects with OSA had an exaggerated ACTH response to the administration of CRH although cortisol responses did not differ between groups [61]. Whether alterations in cortisol metabolism are a cause, consequence, or both in OSA remains unresolved.

Role of the sympathetic nervous system

Sympathetic Activity: Recurrent apneic episodes are associated with increased stimulation of sympathetic nervous activity in OSA patients. Sympathetic activity is measurable directly by microneurography and indirectly via catecholamine output, as reflected in serum and urine concentrations [62]. Catecholamine alterations in OSA are frequently evaluated but often lack consistency across studies. Both plasma and urine levels of norepinephrine, which is indicative of systematic sympathetic activity, are generally elevated in OSA patients,

whereas epinephrine levels have not been consistently altered in current, well-matched studies [63, 64].

Hypertension is often a physical manifestation of increased sympathetic activity in OSA. Elevated nocturnal norepinephrine levels are strongly associated with the prevalence and development of hypertension in untreated OSA patients. Hypoxia and hypercapnia initiate sympathetic activity via chemoreflexes, resulting in vasoconstriction and increased cardiac output. Blood pressure becomes elevated during apneic episodes, with marked, sharp rises in BP at the end of each event. Patients with OSA are also more likely to experience daytime hypertension than their non-apneic counterparts [65]. Interestingly, diurnal norepinephrine levels remain elevated in OSA patients, suggesting that over-activity of the sympathetic nervous system continues into non-apneic, daytime conditions [64]. The latter may lead to decreased responsiveness of the peripheral vasculature in OSA patients [62]. While chronic sympathetic activation is largely associated with the development of hypertension in OSA, it may also have effects on lipolysis and adipokine expression as measures of metabolic dysfunction.

Adipokines: Oxidative stress, systemic inflammation and increased sympathetic activity are common pathophysiologic consequences of OSA that may adversely affect adipokine expression [64]. Secreted by active white adipose tissue (WAT), adipokines function in the regulation of immune response and metabolism. Leptin and adiponectin are commonly investigated adipose-derived hormones and their abnormal expression in OSA may contribute to the development of systematic inflammation, hypertension and atherosclerosis in this disorder [63, 66].

Leptin, a key adipose-derived hormone, exhibits a circadian rhythm and promotes satiety by acting on hypothalamic receptors to inhibit the effect of potent feeding stimulants and to promote the synthesis of appetite suppressants. Despite its anti-obesity effect, leptin levels correlate with percentage of body fat and fail to regulate adiposity due to central leptin resistance present in obese individuals. Circulating serum leptin levels have been shown to be higher in overweight and obese OSA patients than BMI-matched controls [63, 66] and to positively correlate with the severity of OSA [32, 66–68]. Data regarding the prevalence of OSA and increased leptin levels in lean OSA patients are conflicting [61, 66], yet it has been suggested that elevated leptin levels in patients with OSA may be more closely associated with obesity confounders than with apneic episodes alone [63]. While OSA may be prove to be a leptin-resistant condition, further investigation of the physiological effects of leptin in OSA will be necessary.

Adiponectin, which does not exhibit a circadian rhythm, regulates metabolism by suppressing hepatic glucose production and stimulating fatty acid oxidation. It has also been ascribed anti-atherogenic and anti-inflammatory properties [69]. Obese individuals are found to have reduced levels of adiponectin, which is associated with cardiovascular disease, insulin resistance and type 2 diabetes [61, 63, 66]. Data on adiponectin levels in OSA remain highly inconsistent, but several studies show that adiponectin levels in OSA patients are lower both in the morning and evening compared to BMI-matched controls [63]. As with leptin, adiponectin levels have correlated with the severity of OSA in some studies [63, 70] but not in others[64, 68, 71]. Significant interaction between adiponectin levels and abdominal adiposity in patients with OSA has been observed [71], yet more research is needed to clarify this relationship.

C. Metabolic Abnormalities Associated with PCOS

Both lipid and non-lipid criteria identify individuals at increased risk for coronary heart disease and type 2 diabetes [72–77]. Because women with PCOS have high rates of impaired

glucose tolerance and type 2 diabetes [7, 8] as well as a substantial number of risk factors for cardiovascular disease [78], it has been generally assumed that many are also likely to meet criteria for the "metabolic syndrome". We recently reported that fully one-third of non-diabetic women with PCOS have developed the metabolic syndrome well before the end of their fourth decade, and usually prior to the end of their third decade of life. This prevalence is four times higher than that observed in women between the ages of 20 and 30 years and twice that of women between ages 30 and 40 years [79]. Indeed, the metabolic syndrome prevalence was similar to that in women between the ages of 50 and 60 years [79]. We have also found that the prevalence of the metabolic syndrome is similar across ethnic/racial backgrounds.

Insulin resistance and hyperinsulinemia in PCOS—Even though the molecular basis for insulin resistance in PCOS remains incompletely understood, it is well documented that the compensatory hyperinsulinemia contributes both directly and indirectly [80–82] to the increase in plasma androgen concentrations that characterize PCOS. Insulin acts directly by binding to its cognate receptor on the ovarian thecal cell to stimulate testosterone synthesis [83]. Insulin can also act indirectly to raise the serum concentration of free testosterone, the level of which does not appear to be tightly regulated in the female, by lowering the serum concentration of sex hormone binding globulin (SHBG) [82].

Insulin resistance is a central factor in the pathogenesis of the metabolic syndrome in both men and women and there is ample evidence to support a causal link between hyperinsulinemia and the characteristic features of PCOS. A reduction of serum insulin levels in women with PCOS results in a decrease in ovarian androgen biosynthesis, an increased SHBG concentration, and a resultant decrease in free testosterone concentrations [84, 85]. Insulin also plays a key role in the impaired glucose tolerance/diabetes [84, 85] of PCOS and attenuation of hyperinsulinemia, whether through weight reduction or administration of either metformin [86, 87] or a thiazolidinedione [88–90], substantially attenuates the metabolic perturbations of PCOS.

Insulin resistance and impaired glucose tolerance/type 2 diabetes—While obesity is a major factor in the development of insulin resistance in PCOS, it is now established that a component of insulin resistance in PCOS is independent of body weight [85, 91]. Both lean and obese women with PCOS are more insulin resistant than their non-PCOS counterparts matched for total and fat-free body mass as documented using the hyperinsulinemic-euglycemic clamp [85, 91], frequently sampled IVGTT [3, 89, 92] and protocols using a graded glucose infusion [89, 92].

In long-term follow-up studies of women with PCOS there is an increased prevalence of type 2 diabetes when compared to appropriate controls [9]. Two large, prospective studies in PCOS place the prevalence of IGT between 30–40% and type 2 diabetes between 5–10% [7, 8]. These prevalences approach those in Pima Indians, a population with one of the highest rates of development of type 2 diabetes [93]. More recently, we [7] and others [94] have found that the conversion rates from normal glucose tolerance to IGT or type 2 diabetes in PCOS are substantially elevated.

β-Cell Dysfunction in PCOS—Because glucose intolerance results only when defects in insulin secretion and insulin action co-exist [95], we postulated that insulin secretory defects could play an important role in the propensity to develop diabetes in PCOS. Initial evidence for β-cell dysfunction in PCOS was derived from analyses of basal and postprandial insulin secretory responses in women with PCOS relative to weight-matched controls with normal androgen levels [96]. The incremental insulin secretory response to meals was markedly reduced in women with PCOS, resulting from a reduction in the relative amplitude of meal-

related secretory pulses rather than from a reduction in the number of pulses present. This pattern, which resembled that of type 2 diabetes more than that of simple obesity, was striking in that it was evident in nondiabetic women with PCOS.

Insulin secretion is most appropriately expressed in relation to the magnitude of ambient insulin resistance. The product of these measures can be quantified [97] (the so-called "disposition index") and related as a percentile to the hyperbolic relationship for these measures established in normal subjects [97, 98]. When first-phase insulin secretion is analyzed in relation to the degree of insulin resistance, women with PCOS exhibit a significant impairment in β-cell function [3, 88]. We have additionally quantified β-cell function in PCOS by examining the insulin secretory response to a graded increase in plasma glucose and by the ability of the β-cell to adjust and respond to induced oscillations in the plasma glucose level [3]. Results from both provocative stimuli were consistent: when expressed in relation to the degree of insulin resistance, insulin secretion was impaired in PCOS subjects.

Dyslipidemia in PCOS—Women with PCOS are frequently characterized as having elevated triglyceride (TG) levels, increased levels of VLDL and LDL, and a lower HDL cholesterol [99], a lipid pattern similar to that seen in patients with type 2 diabetes. The mechanisms responsible for the adverse effects of PCOS on plasma TG homeostasis are not known. Insulin resistance has been postulated to play a key role in causing hypertriglyceridemia in PCOS. However, we found that treatment with the insulin sensitizing agent troglitazone markedly improved insulin sensitivity in PCOS women but had little, if any, effect on plasma TG concentration [100]. In addition, lean women with PCOS are found to have normal plasma TG concentrations despite being hyperinsulinemic [10]. Increased plasma TG concentrations in obese women with PCOS are likely due, at least in part, to hyperandrogenemia and relative progesterone deficiency; further there is the potential that OSA has a modulating effect upon triglyceride metabolism.

Hypertension in PCOS: Insulin resistance and hyperinsulinemia, which have long been associated with the development of hypertension, is nearly ubiquitous in women with PCOS. The relationship between insulin sensitivity and blood pressure levels in PCOS, however, remains unclear [101]. Zimmermann et al found no significant variation in 24-hour blood pressure profiles or echocardiographic assessment of left ventricular mass of PCOS patients and well-matched controls, despite a substantial difference in insulin sensitivity between the groups [102]. Thus, the presence of hypertension is not specific to PCOS as both groups exhibited a similar frequency of blood pressure abnormalities. Several recent studies suggest that obesity is the main determinant of hypertension in PCOS by promoting sympathetic activation [103, 104]. Luque-Ramírez et al observed that clinical and subclinical hypertension, as well as a nondipper pattern in nocturnal blood pressure, is correlated with obesity in adolescent females with PCOS [104]. However, these findings are complicated by the insulin resistance component in PCOS that functions independently of body mass . More studies are necessary to evaluate the mechanism of hypertension in PCOS. As the rate of obesity in PCOS continues to increase, there is growing concern over the risk of cardiovascular disease and mortality in women with PCOS.

D. Obstructive Sleep Apnea in Women with PCOS

Women with PCOS have been documented to develop OSA at rates that equal and may even exceed those in men. The high prevalence of OSA has been thought to be a function of both elevated levels of testosterone (a defining feature of PCOS) as well as the obesity that commonly accompanies the disorder. However, it appears that the high prevalence of OSA in PCOS cannot be fully accounted for on the basis of these two factors alone. In two studies

[15, 105], the severity of sleep apnea did not correlate with BMI and in a third [106], even after controlling for BMI, PCOS women were as much as 30 times more likely to have sleep disordered breathing and 9 times more likely than controls to have daytime sleepiness. Insulin resistance was found to be a stronger predictor of sleep disordered breathing than was age, BMI, or circulating testosterone concentrations [15]. It also appeared that women with PCOS taking oral contraceptives were less likely to have sleep disordered breathing [15], consistent with recent results from the Sleep Heart Health Study Research Group in which hormone replacement therapy was associated with a lower likelihood of sleep disordered breathing among postmenopausal women [107]. Finally, women with PCOS had a significantly higher mean apnea-hypopnea index compared to weight-matched controls (22.5 ± 6.0 vs. 6.7 ± 1.7; $P<0.01$), with the difference being most pronounced in REM sleep (41.3 ± 7.5 vs. 13.5 ± 3.3; $P<0.01$) [106]. Because the risk imparted by obesity does not appear to be sufficient to fully account for the high prevalence of sleep disordered breathing in PCOS, additional factors have been invoked including the hyperandrogenemia [28, 48–50] that is characteristic of PCOS, as discussed below.

Androgen levels in PCOS—In response to stimulation by LH, the ovarian theca cell synthesizes androstenedione and testosterone. Androstenedione is converted by 17β-hydroxysteroid-dehydrogenase (17β-HSD) to form testosterone or aromatized by the aromatase enzyme (cytochrome P450arom) to form estrone. Results of studies both in vivo and in vitro (using cultured theca cells) are consistent and suggest that theca cells from PCOS ovaries are more efficient at converting androgenic precursors to testosterone than are normal theca cells [10]. Clinically, this has been documented using a single, diagnostic dose of a GnRH agonist such as nafarelin or leuprolide [108]. Our studies [108], as well as those of others [109], have shown that the ovarian steroidogenic response of women with PCOS is more robust than that of normally cycling women and qualitatively similar to the response seen in normal men. This response has been used as a diagnostic tool as well as a probe to define the pathogenesis of steroidogenic dysfunction in PCOS.

Insulin plays both direct and indirect roles in the pathogenesis of hyperandrogenemia in PCOS. Insulin acts synergistically with LH to enhance theca cell androgen production. Insulin also inhibits hepatic synthesis of SHBG the key circulating protein that binds to testosterone, and thus increases the proportion of testosterone that circulates in the unbound, biologically available or “free”, state.

Results of our preliminary studies do not support a major role for hyperandrogenemia in the pathogenesis of OSA in PCOS. In a recent study, we found that both total and free testosterone levels were virtually identical in PCOS women with and without OSA [[112]]. Consequently, it is important to examine alternate hypotheses. We have proposed that the relative reduction in circulating progesterone concentrations as well as estrogen concentrations, as discussed below, may contribute to the apparent excess of OSA in PCOS.

Progesterone and estrogen levels in PCOS—In normally cycling women, the luteal phase of the menstrual cycle is characterized by an increase in progesterone production from the corpus luteum and consequent slowing of GnRH, and thus LH, pulsatility. In the presence of chronic oligo- or anovulation, as in PCOS, the normal post-ovulatory rise in progesterone does not occur and the restraint on the GnRH pulse generator is thus absent [110]. Thus, on average, circulating progesterone levels in PCOS women are lower than those in normally cycling women [111, 112]. Underproduction of ovarian estrogen results from low intraovarian aromatase expression and a consequent reduction in the production of the estrogens, estrone and estradiol, from their respective precursor androgens, androstenedione and testosterone. While estrone is also synthesized from peripheral aromatization (especially in adipose tissue), levels of this steroid are normal or even slightly elevated in PCOS.

However, estrone is a weak estrogen with approximately 1/10th the potency of estradiol [113]. In sum, estrogen levels are subnormal in PCOS [114, 115].

Revisiting the two PCOS "subtypes"—While the pathogenesis of OSA in PCOS remains unclear, growing evidence suggests that OSA is a strong predictor of insulin resistance and glucose intolerance in PCOS. To further examine this relationship, we recently studied 52 women with and 21 without PCOS [112]. These overweight/obese, pre-menopausal women were divided into three groups following overnight polysomnography and a 75-gram oral glucose challenge (Table 2).

As expected, PCOS women as a whole were more insulin resistant than controls, as shown by a significantly higher homeostatic model assessment (HOMA) index (adjusted P = 0.0002), fasting concentration of glucose (adjusted P = 0.0021), fasting concentration of insulin (adjusted P = 0.0001) and 2-h glucose level post glucose bolus (adjusted P = 0.0081). In addition, the prevalence of OSA in PCOS was more than 7 times that in controls (P = 0.01), further confirming the risk of OSA in PCOS women. Comparison of insulin resistance and glucose tolerance among the three groups of subjects appears to validate the proposed PCOS subtypes: non-apneic and apneic. While PCOS women without OSA had higher glucose levels (both fasting and during the OGTT) and higher HOMA indices than control women, these differences were almost entirely due to the presence of women with IGT, which may be attributed to β-cell dysfunction [112]. Interestingly, no significant differences in metabolic variation between non-apneic PCOS women with normal glucose tolerance and controls were observed (HOMA, fasting and OGTT glucose and insulin values, and AUC for glucose were not significant between groups). In fact, the OGTT insulin values for the non-IGT, non-apneic PCOS women and controls were nearly identical, which may demonstrate a reduced risk of OSA in PCOS women who maintain normal glucose tolerance. Upon comparison of PCOS women with and without OSA, it is increasingly apparent that the presence and severity of OSA helps predict the extent of glucose intolerance and insulin resistance. Among PCOS women with OSA, the prevalence of IGT increased in direct proportion to the severity of OSA, and markers of insulin resistance were indeed higher in PCOS women with OSA than those without OSA. Thus, PCOS women with OSA are thought to be at a higher risk for developing type 2 diabetes than their non-apneic PCOS counterparts. A strong correlation between the degree of sleep fragmentation (quantified by the microarousal index) and severity of OSA (quantified by the AHI, r = 0.86, P = 0.0001) suggests that episodic sleep disruption predicts the degree of insulin resistance and glucose intolerance, which is also observed in our recent studies with young, healthy adults [116]. As OSA is highly prevalent in women with PCOS, it serves as a predictor of glucose tolerance and gives rise to the possibility of two PCOS subtypes, each with distinct metabolic characteristics and implications.

PRACTICE POINTS

1. There is a significant increase in risk for OSA in PCOS. When present, OSA largely remains under-diagnosed and untreated.
2. Overweight and (visceral) obesity are exceptionally common in women with PCOS and contribute to the increased risk of OSA in this population.
3. Neither the degree of androgen elevation nor BMI fully account for the presence or severity of OSA in PCOS.
4. Impaired glucose tolerance and type 2 diabetes are present at an early age and in a disproportionate number of women with PCOS.

5. Treatment of OSA with CPAP in PCOS results in significant reductions in 24 hr secretory cortisol and norepinephrine profiles as well as improved insulin sensitivity.
6. The presence and severity of OSA may directly impact the mechanism of IGT in women with PCOS.

RESEARCH AGENDA

1. To better elucidate the pathogenesis of OSA in PCOS, trials further investigating cardiometabolic, hormonal and sleep parameters should be explored and expanded within the two PCOS subgroups.
2. While treatment of OSA with CPAP ameliorates metabolic and hormonal dysfunction in PCOS women with OSA, it is worthwhile to investigate the impact of estradiol and/or progesterone therapy in this population.
3. Trials examining the prevalence of OSA among obese men and obese women (with and without PCOS) should also be considered.

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Table 1

Authors	Reference #	Sample Size	Women in Sample (%)
Punjabi, et. al.	33	150	0
Ip, et. al.	32	270	27
Meslier, et. al.	34	595	0
Punjabi, et. al.	35	2,656	54
Tassone, et. al.	36	30	30
Harsch, et. al. (CPAP treatment)	37	40	15
Babu, et. al. (CPAP treatment)	38	25	36

Table 2

Polysomnographic, hormonal, and metabolic variables of the three groups

	Study Groups			Group Comparisons, *P* values	
Variable	**Control women without OSA (n=17)**	**PCOS women without OSA (n=23)**	**PCOS women with OSA (n=29)**	**PCOS women without OSA vs. control women without OSA**	**PCOS women without OSA vs. PCOS women with OSA**
Total sleep time (min)	445.5 ± 5.2	427.3 ± 6.4	422.7 ± 6.8	0.09	0.74
AHI (per hour of sleep)	2.3 ± 0.3	2.0 ± 0.4	19.4 ± 2.0	0.97	<0.0001
Microarousal index (per hour of sleep)	14.9 ± 2.0	10.5 ± 0.9	22.3 ± 1.6	0.13	<0.0001
Minimum oxygen saturation (%)	90.9 ± 0.7	92.0 ± 0.5	85.1 ± 1.3	0.7	0.002
Total testosterone (pg/ml)	40.5 ± 3.3	76.3 ± 6.4	67.9 ± 4.3	<0.0001	0.19
Free testosterone (pg/ml)	9.2 ± 0.7	21.3 ± 1.5	20.6 ± 1.3	<0.0001	0.32
SHBG (nM)	26.8 ± 3.6	16.6 ± 1.9	12.3 ± 1.2	0.0003	0.53
Fasting glucose (mg/dl)	87.5 ± 1.9	92.5 ± 1.5	97.2 ± 1.8	0.02	0.11
2-h glucose (mg/dl)	111.3 ± 6.4	120.6 ± 5.7	143.3 ± 4.4	0.09	0.16
AUC glucose	13528 ± 553	15681 ± 589	17550 ± 449	0.006	0.07
Fasting insulin (μU/ml)	10.9 ± 1.5	14.9 ± 1.8	23.7 ± 1.5	0.06	0.01
AUC insulin	8326 ± 882	10572 ± 1409	16802 ± 1589	0.13	0.11
HOMA index (mg/dl·μU/ml)	2.2 ± 0.4	3.5 ± 0.4	5.7 ± 0.4	0.01	0.006

Data are mean±SEM. *P* values are adjusted for age, BMI, and ethnicity-based diabetes risk.