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The Impact of Polycystic Ovarian Syndrome, a Potential Risk Factor to Endometrial Cancer, on the Quality of Sleep

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Abstract Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in women during their reproductive age. Recent studies showed that PCOS may be a risk factor to the development of endometrial cancer. This risk factor may be associated with sleep disorders including sleep-disordered breathing and excessive daytime sleepiness. The mechanisms leading to this high prevalence of sleep disorders in PCOS have not yet been identified. However, possible causes include alterations in body fat composition due to excess androgen levels and/or the effects of the metabolic syndrome. These effects on sleep disorders may have an impact on daily physical activities.

Keywords: *PCOS, endometrial cancer, physical activity, sleep*

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1. Introduction

In the recent years, researchers have shown that patients with polycystic ovarian syndrome (PCOS) have a significantly higher prevalence of sleep disorders such as insomnia and obstructive sleep apnea (OSA) compared to populations without the disorder. So, screening for these disorders has been recommended for patients with PCOS [13,23].

The pathophysiological mechanisms leading to the high prevalence of sleep disorders in women with PCOS are not well understood. However, the main features of PCOS including obesity, insulin resistance and hyperandrogenemia are believed to contribute to this effect. These factors have a profound effect on body fat composition, thereby increasing the resistive load on the upper airway during sleep. In addition, sleep disorders including OSA have been shown to independently induce and exaggerate insulin resistance, which can further increase the severity of OSA in these patients. Although PCOS manifests in adolescence, studies evaluating for sleep disorders in this age group are very limited [5,17].

2. Role of Sex Steroids and Adiposity

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. Sleep disruption has been associated with a rise in plasma cortisol levels which affects the hypothalamic-pituitary-adrenal axis [19].

OSA has been associated with glucose intolerance and insulin resistance even after adjustments for obesity and age. Treatment of OSA with continuous positive airway pressure can improve insulin sensitivity and is associated with a reduction in postprandial glucose and glycohemoglobin levels in individuals with type 2 diabetes. Differences in concentrations of circulating sex steroids including estrogens, progestins, and androgens which occur in PCOS appear to play an important role in the pathophysiology of sleep disorders [1,12].

3. Role of Estrogen and Progesterone

Estrogens and progestins have been generally characterized as protective against the development of sleep disorders including 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 age and phases of the menstrual cycle, menopausal status or in response to hormone replacement therapy. Lower estradiol levels have been reported in association with poor sleep quality among women with a higher frequency of sleep apnea. Among post-menopausal women, there was a statistically significant decrease in the occurrence and frequency of sleep apnea in those who receive estrogen replacement therapy [20,22].

Progesterone is the key hormone thought to underlie the differences in sleep pattern that exist across the normal menstrual cycle. Progesterone levels are low during the follicular phase and rise during the luteal phase. When sleep patterns are compared between follicular and luteal phases, it is apparent that upper airway resistance is lower during the luteal phase**.** 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 before pregnancy. Progesterone is thought to promote its effects through direct stimulation of respiratory centre via an increased ventilatory response to both hypercapnia and hypoxia. Progesterone may also act to enhance upper airway dilator muscle activity and reduce airway resistance. Because women with PCOS are oligo- or anovulatory, they have low circulating progesterone concentrations which may contribute to the high prevalence of sleep disorders in PCOS [6,19].

4. Role of Androgens

Androgens are thought to play a significant role in the sexual dismorphism in sleep architecture and in the pathogenesis of sleep disorders. Women with obstructive sleep apnea appear to have a higher proportion of respiratory events in rapid eye movement (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 and upper airway mechanics. It was reported that testosterone increases apneic threshold in premenopausal women, thus leading to breathing instability during sleep [3].

5. Role of Body Fat and Its Distribution

The risk of sleep disorders 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 be highly correlated with OSA risk. 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 contribute to the pathogenesis of sleep disorders in women with PCOS [7,16].

6. The Relationship between Steroids and Sleep Disorders

The indications for steroid therapy are numerous and because rest and sleep are very important to the patients and their caregivers, many studies had monitored steroid associated sleep disturbance closely [24]. Sleep disturbance is not one of the best known side effects of steroids, but insomnia has medical and social sequelae that require recognition and action. Appropriate prescribing may allow the patient to benefit from steroids and have a good night's sleep [25]. Most patients receiving high dose steroids described changes to their sleep habits, insomnia and vivid dreams. These changes seem to resolve as the steroid dosage is decreased. Further relief of insomnia may be achieved by prescription of night sedation for patients taking steroids and the night time administration of other drugs which have sedative side effects, such as antihistaminics [14].

A bidirectional interaction exists between the electrophysiological and neuroendocrine components of sleep. Certain hormones (neuropeptides and steroids) play a specific role in sleep regulation. Changes in their activity contribute to the pathophysiology of sleep disorders. A reciprocal interaction of the peptides growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH) plays a key role in sleep regulation [21] GHRH promotes growth hormone secretion and, non-rapid eye movement sleep (NREMS), whereas CRH impairs NREMS, promotes rapid eye movement sleep (REMS) and stimulates secretion of adrenocorticotropic hormone and cortisol. Changes in the CRH: GHRH ratio in favor of CRH contribute to impaired sleep. A decline of orexin activity causes narcolepsy. In addition to CRH overactivity, hypercortisolism appears to be involved in the pathophysiology of sleep- electroencephalogram (EEG) changes in depression [25]. Various neuroactive steroids exert specific effects on sleep. Moreover, sleep-EEG changes in dwarfism, acromegaly, Addison's disease, Cushing's disease, brain injury, sleep apnea syndrome, primary insomnia, prolactinoma and dementia appear to be related to changes in the activity of peptides and steroids [21].

7. The Molecular Mechanisms by which PCOS Affects Sleep

Women with PCOS were shown to develop obstructive sleep apnea (OSA) at rates that may even exceed those in men. The high prevalence of OSA has been thought to be a function of both elevated levels of testosterone as well as the obesity that commonly accompanies PCOS [4]. 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 one study, even after controlling body mass index (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 other factors. It also appeared that women with PCOS taking oral contraceptives were less likely to have sleep disordered breathing [9]. Women with PCOS had a significantly higher mean apnea-hypopnea index compared to weight-matched controls with the difference being most pronounced in REM sleep [19].

Results of studies suggest that theca cells from PCOS ovaries are more efficient at converting androgenic precursors to testosterone than the normal theca cells [26]. Insulin plays an important role in the pathogenesis of hyperandrogenemia in PCOS. Insulin acts synergistically with LH to enhance theca cell androgen production. Insulin increases the proportion of free circulating

testosterone. However, some studies do not support a major role for hyperandrogenemia in the pathogenesis of OSA in PCOS. In one study, it was found that both total and free testosterone levels were identical in PCOS women with and without OSA [11].

In the presence of chronic oligo- or anovulation, as in PCOS, the normal post-ovulatory rise in progesterone does not occur [18]. So, circulating progesterone levels in PCOS women are lower than those in normally cycling women [11]. 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 precursors [2]. These disturbances in oestrogen and progesterone levels may have a major role in the development of sleep disorders. 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 [19].

8. Impact of Sleep Disorders on the Quality of Life and Daily Physical Activities

Many patients with sleep disorders seek medical attention because of daytime symptoms which may impair their daily physical activities [15]. This suggests that the night-time symptoms may be less bothersome than the daytime consequences of sleep problems [10]. Recent studies suggest that sleep disorders may have a negative impact on the physical, psychological and social aspects of wellbeing. There is increasing evidence that sleep disorders are associated with impaired daytime wellbeing and functioning [8].

9. Conclusion

There is a strong relationship between PCOS and sleep disorders which may affect the daily physical activities. It is attributed to body fat and its distribution, adrenal steroids and androgens. Further studies are needed to explore the molecular mechanisms responsible for the increased incidence of sleep disorders in PCOS and methods of management of these disorders.

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