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Review Article

Obstructive Sleep Apnea: Women's Perspective

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Abstract

The main characteristics of sleep-disordered breathing (SDB) are airflow limitation, chronic intermittent hypoxia, or apnea; which may lead to tissue hypo-perfusion and recurrent arousal from sleep. These episodes of hypoxia or apnea can lead to tissue inflammation, and are causal factors of disturbed sleep in both men and women. Several lines of evidence suggest that sleep patterns differ along the lifespan in both male and female subjects, and this may result from the influence of female gonadotropic hormones on sleep. Compared to men, women have more sleep complaints, as women's sleep is not only influenced by gonadotropins, but also by conditions related to these hormones, such as pregnancy. It is therefore not surprising that sleep disturbances are seen during menopause, too. Factors that may play a role in this type of SDB in women include vasomotor symptoms, changing reproductive hormone levels, circadian rhythm abnormalities, mood disorders, coexistent medical conditions, and lifestyle factors.

INTRODUCTION

Women are continuously under the influence of hormonal changes from menarche to menopause, and pregnancy also causes hormonal fluctuations. These hormonal changes place women at an increased risk of sleep disturbance. Before menopause the risk of obstructive sleep apnea (OSA) is less than men, but women still experience more sleep problems than men. OSA is one of the major causative factors of disturbed sleep in the general population [1]. Women with OSA are considered a separate group from men with OSA; and women with OSA have polysomnographic differences from men.

OSA is also one of the major risk factors for cardiovascular disease (CVDs) in both men and women [2, 3]. Women with OSA have a higher risk of adverse pregnancy outcomes than women without OSA. Women with OSA also experience more depressive symptoms than men [4] (Figure 1).

Although exercise, weight loss, and continuous positive airway pressure (CPAP) therapy have beneficial effects on sleep apnea, CPAP therapy also decreases cardiovascular morbidity and mortality [2,5].

Obstructive Sleep Apnea's Severity and Prevalence

One of the more common sleep disorders is OSA, a sleep-related breathing disorder (SDB) characterized either by intermittent episodes of breathing cessations (hypopnea) or complete collapse of the airway (apnea) [6] (Table 1). There are three categories of sleep apnea:

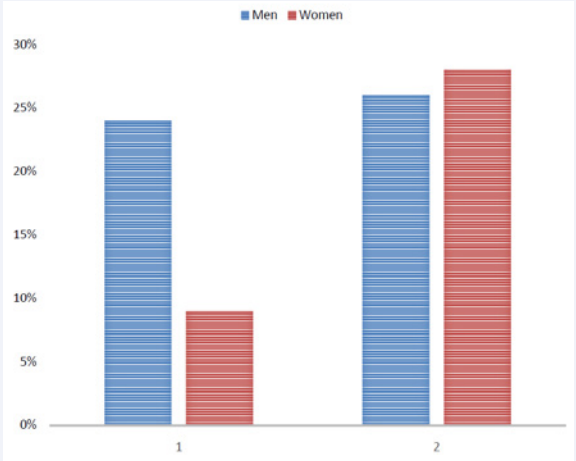

Figure 1 9% to 28% of women and 24% to 26% of males having apneic events in general population.

OSA can lead to oxidative stress, inflammatory processes, endothelial damage, sympathetic activation and metabolic dysregulation that predispose to atherosclerosis, and so OSA is a common cause of systemic hypertension [5] (Table 2).

In the USA, twenty-five percent of women are at high risk for OSA [2]. In these women, the common symptoms of OSA were habitual snoring (61%), sleep onset insomnia (32%) or maintenance insomnia symptoms (19%),daytime sleepiness (24%), observed apnea (7%), body movement (60%) or restless legs syndrome (RLS) symptoms (33%). Women with obstructive sleep apnea also frequently reported chronic medical disorders [2]. Snoring was the most frequent symptom, where as observed pauses in breath accounted for a minority of the results in this study. Clinically, it indicates that in absence of observed pauses, screening for OSA should not be withheld. Some other symptoms e.g., nocturnal enuresis, are frequent among women with OSA, and clinicians should ask about them during the clinical examination of postmenopausal women [7] (Table 3).

Studies show a higher risk for OSA when age and BMI both increase together. Women who were older and had a higher BMI showed a higher risk for OSA [2] (Table 4).

During OSA, episodes of hypoxemia can drop the oxyhemoglobin saturation from 95% to 80%, depending on the length of the period of apnea [8]. OSA is an independent risk factor for cardiovascular and cerebrovascular diseases. Due to hypoxia, the oxidative stress leads to overproduction of reactive oxygen species which can cause endothelial dysfunction, resulting in atherosclerosis [9]. The inflammatory marker C-reactive protein (CRP), tumor necrosis factor α (TNFα), and interleukin-6 (IL-6) were increased in patients with obstructive sleep apnea, and they were significantly higher in cases of severe obstructive sleep apnea, where the AHI was 15 or greater [10].

Sleep Disordered Breathing in Women and Cardiovascular Risks

As respiratory events during OSA can trigger an inflammatory process and endothelial damage, this metabolic dysregulation ultimately leads to atherosclerosis in the blood vessels, and is one of the major etiological factors in hypertension and ischemic heart diseases. OSA could be an independent risk factor for left ventricular hypertrophy in women, and is associated with incident heart failure and death among females, but not males. High levels of troponin T (TNT) were also noted in women during the study [11]. Patients with obstructive sleep apnea have worse diastolic dysfunction compared to those without OSA [12]. Obstructive sleep apnea is related to an increased risk of heart failure in women, after adjustment for previous myocardial infarction, menopausal status, age, waist circumference, alcohol or tobacco use, and hormone replacement therapy [3]. One major risk factor

Table 1: Categories of sleep apnea [6].

Apnea/hypopnea index (AHI) /hour		
Mild sleep apnea	**Moderate sleep apnea**	**Severe sleep apnea**
≥5-15episodes/hour	≥15-30 episodes/hour	≥30 episodes/hour

Table 2: OSA and increased comorbidities worldwide.

OSA	Associated Comorbidities	Study Designed	N	Study Title	Future Intervention	Ref
Positive	Depression	Stepwise linear regression analysis.	1,327	Prevalence and Predisposing Factors for Depressive Status in Chinese Patients with Obstructive Sleep Apnea: A Large-Sample Survey.	CPAP	(Dai et al, 2016)
Positive	COPD	Cross-sectional	404	Predictive Factors Warrant Screening for Obstructive Sleep Apnea in COPD: a Taiwan National Survey	CPAP	(Hang et al, 2016)
Positive	Type 2 D.M HTN Ischemic Hrt Diseases Stroke Arrhythmias Depression	Cross-sectional	1,704,905	The Effect of Sex and Age on the Comorbidity Burden of OSA: An Observational Analysis from a Large Nationwide US Health Claims Database.	CPAP	(Mokhlesi et al, 2016)
Positive	HTN (39%) Obesity (34%) Depression (19%) GERD (18%) DM (15%) Hyperchol-esterolemia (10%) Asthma (4%)	Retrospective	100	Comorbidities Associated with Obstructive Sleep Apnea: A Retrospective Study	CPAP	(Pinto et al, 2016)
Positive	Nocturnal Heart block	Cross-sectional	72	Screening and Managing Obstructive Sleep Apnea in Nocturnal Heart Block Patients: An Observational Study	CPAP	WU et al, 2016)

Table 3: Prevalence of high risk for OSA by (1) BMI or (2) Age [2].

(1) BMI in women	OSA prevalence %	(2) Age of women	OSA Prevalence %
<25	9	18-29	19
25-30	21	30-49	25
31-35	57	50-64	32
36-40	64		
>40	74		

Table 4: Prevalence of high risk for OSA by Age and BMI [2].

BMI	Age 18-29 yrs, OSA prevalence	Age 30-49 yrs, OSA prevalence	Age 50-64 yrs, OSA prevalence
<25	0-5 %	0-8 %	0-12 %
25-30	0-15 %	0-19 %	0-28 %
>30	0-55 %	0-65 %	0-60 %

for cardiovascular diseases is visceral fat accumulation, and it is closely related to OSA. As increased fat deposition is more noted in men than women, it's more of a major risk factor for men than women [13].

OSA is also associated with atrial fibrillation and heart failure, independent of obesity [14]. Even in participants with mild to moderate sleep disorders, the odds of hypertension were significantly increased. OSA is a major risk factor in hypertension and cardiovascular morbidity in the general population [15,16], but among OSA patients, treatment of the disease through CPAP can cause a significant reduction in blood pressure [5] (Figure 2).

Sleep apnea is an independent risk factor for coronary artery disease, regardless of obesity. Coronary artery calcium (CAC), a marker of subclinical coronary artery disease, plays a major role in the formation of coronary artery atherosclerotic plaque. Buildup of CAC increases with the severity of sleep apnea [17]. The early finding of coronary artery atherosclerosis is intima media thickening, which is associated with OSA [18]. Patients with sleep apnea have a high risk of strokes, and women with OSA aged 35 or younger have a greater risk of strokes [19].

Placental Hypoxia

OSA in pregnant women may cause hypoxia in fetoplactenal circulation, as it is shown as normoblastemia and elevated placental carbonic anhydrase IX immunoreactivity, but the causative mechanism should be further investigated [20]. OSA does not have any adverse effects on neonatal and infant neuromotor development; but it may interfere with social development at age one [21].

OSA is also associated with increased pregnancy-related morbidity, preeclampsia and eclampsia, pulmonary embolism, and cardiomyopathy [22]. Further, pregnant women with OSA have a higher risk of gestational hypertension and are more likely to undergo a cesarean section than women without OSA [23]. During pregnancy, women with hypertension and diabetes are at a higher risk of sleep apnea and should regularly be screened for OSA [24]. An inflammatory marker IL-18 is found to be increased in pre-eclampsia patients with OSA, which might increase the risk of pre-eclampsia in OSA [25].

The adverse effects of obstructive sleep apnea are exacerbated by obesity, and there is a fivefold increase in hospital mortality as well. Treating OSA may improve the outcomes of pregnancy [26]. Another study shows that OSA is a risk factor for CVDs and cardiovascular mortality, and increased perinatal morbidity among pregnancies, such as gestational diabetes, gestational hypertension, and pre-eclampsia and eclampsia [27]. Patients with pre-eclampsia had more severe symptoms of OSA [28]. OSA increases during pregnancy, and 10% of women with OSA can develop sleep apnea [29]. There is an increased risk of low birth weight, preterm labor, small infants, caesarean section and pre-eclampsia, compared to pregnant women without OSA [4, 30-36] (Figure 3).

Sleep Disordered Breathing and Menopause

Almost 50% women experience insomnia in mid-life, whether in initiating or maintaining sleep (or both). 20% of women develop OSA during menopause [37]. OSA in menopause is more significant compared to pre- and perimenopausal women, because in this age group the female physiological system is changed, and due to hormonal fluctuations during this age group (estrogen and progesterone decline is a major contributing factor in disturbed sleep), the decline of hormones pushes women more toward OSA. The incidence of OSA increases in the perimenopausal period and the menopausal transition [1]. Sleep disturbances during menopause have a significant negative impact on women's social life, physical and psychological health, and workplace productivity [38].

The prevalence of OSA in females rises markedly after menopause. 47% to 67% of post-menopausal women have been found to have OSA. Women tend to gain weight after menopause, and this result in a higher BMI, larger neck circumference, and higher waist-hip ratio, but whether menopause also increases the chances of central obesity is still controversial. In this manner, the upper airway becomes anatomically different after menopause and results in compromised breathing during sleep. Thus, post-menopausal women have a higher prevalence of OSA as compared to pre-menopausal women. However, body weight does not appear to be the only factor responsible for this condition. Despite a comparable body mass index, post-menopausal women had more severe OSA, and spent a larger amount of sleep time with OSA when compared to pre-menopausal females [1] (Figure 4).

Effect of OSA on Mood and Cognition

Lal et al (2016) reported that women who were at high risk of OSA had more frequent depressive symptoms and had worse cognition compared to women without OSA [39]. However, the prevalence of depressive symptoms was comparable between men and women with OSA [40].

Effect of OSA on Social Life and Work Disability

OSA symptoms can cause a worker to be absent from work for a long period. Daytime sleepiness, apnea/hypopnea episodes, and snoring can make a person unable to work. OSA can also be

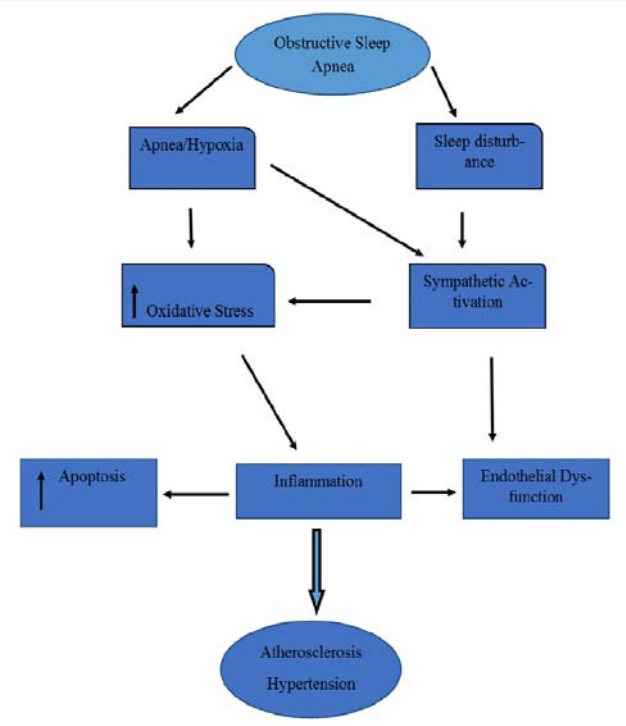

Figure 2 Consequences of sleep apnea/hypoxia in endothelial damage.

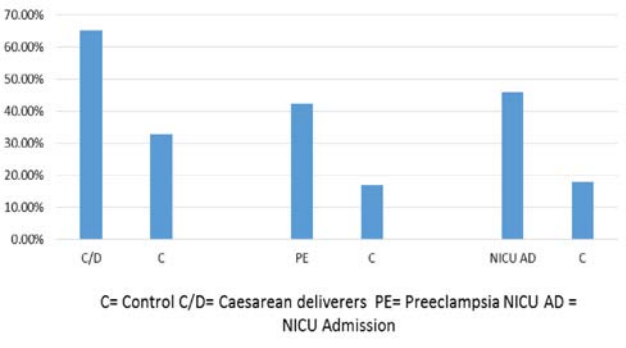

Figure 3 Sleep disordered breathing and adverse pregnancy outcomes.

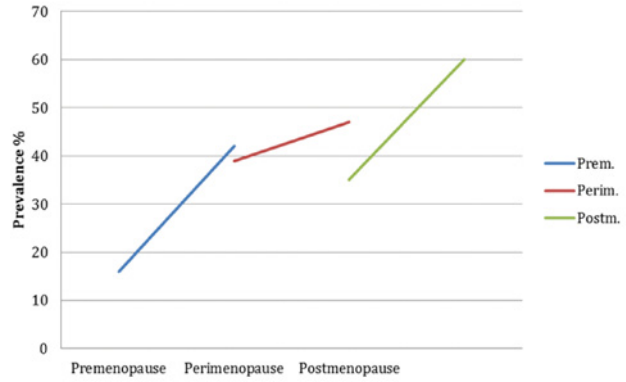

Figure 4 Sleep in Premenopause, Perimenopause, and Postmenopause.

a cause of permanent disability. OSA is a sleep disorder, and is an independent risk factor in sleep disturbances, disabilities, social life dysfunctions, and driving problems [41, 42].

Night work, Daytime sleepiness, Economic Crises and Overall Health of a Worker

Night shift working can disturb the circadian rhythm and could also be a cause of daytime sleepiness and driving accidents. Poor health is related to poor sleep in night shift workers [43]. Working night shifts affect the psychosocial life, and can also cause increased sleepiness during the daytime. Night shift work impairs attention and performance [44]. In night shift workers, the disruption of the natural circadian rhythm leads to impaired cognitive functioning and excessive daytime sleepiness [45].

Economic crises in any nation put a negative impact on the psychosocial health of workers. Studies showed that economic crises in Italy not only increase the unemployment rate but also compromised the general health of a worker. The economic crises in the year 2007 and 2008, especially in the USA, globally impacted the overall health of workers and became a significant source of stress in the workplace. This global recession had negative effects on workers' mental and physical health, and the suicide rate increased in this period. This recession involved many countries, and still continues in many of them. People are still feeling the effects of these crises in many parts of the world [46-48].

Treatment of Sleep Disordered breathing in women

Weight Loss and Exercise: Obesity and low levels of physical activity are associated with moderate to severe OSA. Exercise helps in decreasing weight, blood pressure, depression or anxiety, and fatigue [49].

Hormone Replacement Therapy: Hormone replacement therapy can help with other sleep disorders, such as vasomotor symptoms, but are not a helpful strategy in patients with obstructive sleep apnea [50]. Perimenopausal and postmenopausal women are treated with different pharmacological and non-pharmacological measures. The non-pharmacological approach that is widely used is cognitive behavioral therapy for insomnia. Therapeutic techniques may be beneficial for other menopausal symptoms, such as vasomotor symptoms and anxiety or depression [51-53]. Treatment of sleep disorders other than OSA during menopause will improve women's mental and physical health and increase lifespan [54].

Studies shows that OSA is associated with sexual dysfunction in pre and post-menopausal women, but progesterone can play an important role in reducing sleep disordered breathing and can improve sexual function in pre and post-menopausal women [55].

CPAP

The conventional treatment for OSA is a continuous positive airway pressure (CPAP). This therapy uses a machine to deliver a constant airflow to a patient's airway via a nasal, facial, or oral interface to maintain airway patency during sleep [56]. CPAP treatment significantly relieved OSA symptoms and improved functional status in both male and females, although women's

pathophysiological conditions and clinical presentations of OSA are different from men, and should be addressed further [54].

Early signs of atherosclerosis are improved if OSA is treated when it is an independent risk factor for atherosclerosis [57]. Untreated OSA in women causes serious cardiovascular outcomes and risk of stroke, but CPAP treatment reduces this [58].Severe OSA is a risk factor for CVD-associated death in women, and adequate treatment may reduce this risk [59]. In the US, among the older adult population, OSA is highly prevalent. Prevention and treatment of OSA can improve the quality of life and reduce disability-related healthcare expenses in this age group [60]. Further, CPAP treatment has been found to bring down the cortisol level among women with OSA [61].

OSA is one major risk factor for cardiovascular diseases. Hypoxia, which is the result of the upper airway obstruction, leads to inflammation in the blood vessels. Continuous CPAP therapy decreases inflammation in the blood vessels. Study shows that continuous CPAP therapy for more than three months improved the endothelial function compared to untreated patients [62].

DISCUSSION

In this article, we discuss the impact of OSA on women's health and sleep. Good sleep hygiene, regular exercise, weight loss, and a balanced diet can help alleviate OSA in women. In addition, an adherence to CPAP therapy can provide a definite treatment to this breathing disorder, and can help maintain better sleep in women of childbearing age and menopausal women. OSA should be diagnosed early to get a definite diagnosis, to avoid confusing it with other medical disorders such as depression or anxiety due to similarities in the presentation of the symptoms. Early diagnosis and treatment of this condition can relieve sleep problems and the associated anxiety or depression disorders as well.

During pregnancy, OSA increases the risk of pre-eclampsia, eclampsia, caesarian deliveries, and neonatal death; as well as exaggerating hypertension and CVDs in the mother. In menopausal women, sleep apnea disturbs women's sleep almost in the same ratio as men's due to hormonal fluctuations (estrogen and progesterone decline in a menopausal woman). Post-menopausal women are at increased risk for vasomotor symptoms and other medical conditions, and have a greater likelihood to develop sleep disturbances. These sleep problems could be the causative factors of anxiety and depression, which need a proper diagnosis and treatment. Good sleep hygiene and appropriate treatment can provide a better night of sleep. CPAP therapy can improve the health in sleep apnea patients if it is used properly and regularly. Counseling regarding weight loss, diet, and exercise should be given at every office visit. There is a need to do more research for sleep disordered breathing in women so that women's health could be improved without compromising quality of life.

CONCLUSION

There is a great amount of research being conducted on OSA in men and women in order to provide better treatment for patients, especially in primary care settings, not only in developed countries but in underdeveloped regions as well. OSA could be a major risk factor for significant morbidity and mortality, and is a known risk factor for hypertension. OSA prevalence is the same in Pakistan as in western countries (9%= women= 24% men) [63].

OSA not only disturbs sleep, but is also a major risk factor of CVDs. There is more anxiety and depression in women than men, depending on the severity of sleep apnea [64]. Exercise and weight loss is helpful in reducing the risk of sleep apnea. A lack of exercise and obesity can place patients at greater risk [65, 66].

Good sleep is essential for living a healthy life, and is an important determinant of life expectancy for women in their reproductive years, and during menopause and post-menopause. But, in menopause, women's sleep is disturbed due to a lack of estrogen and progesterone [67]. Also, in menopause, sleep disorders are also associated with vasomotor symptoms, which could also be a causative factor of disturbed sleep in postmenopausal women [68-73].

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DISCLOSURE STATEMENT

The authors have read the journal's policy and have the following potential conflicts: This study was not an industry-supported study. S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. This does not alter his adherence to all of the journal policies. He declares that he has no competing interests that might be perceived to influence the content of this article. All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

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