Obstructive Sleep Apnea in Women: Specific Issues and Interventions

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Abstract

Obstructive sleep apnea (OSA) has traditionally been seen as a male disease. However, the importance of OSA in women is increasingly being recognized, along with a number of significant gender-related differences in the symptoms, diagnosis, consequences and treatment of OSA. Women tend to have less severe OSA than males, with a lower apnea-hypopnea index (AHI) and shorter apneas or hypopneas. Episodes of upper airway resistance and flow limitation that do not meet the criteria for apneas are more common in women. Differences in symptoms between men and women, particularly at low AHI values, along with the reluctance of women to acknowledge OSA symptoms and seek medical help, and failure of medical professionals to respond to OSA symptoms in women contribute to the lower diagnosis of this sleep-disordered breathing in women. While prevalence rates may be lower in women, proportionally fewer are receiving a correct diagnosis. Research has also documented sex differences in the upper airway, fat distribution and respiratory stability in OSA. Hormones are implicated in some gender-related variations, with differences between men and women in the prevalence of OSA decreasing as age increases. In addition, changes in the airway and lung function during pregnancy can contribute to snoring and OSA that might have an adverse effect on the fetus. The limited data available suggest that although the prevalence and severity of OSA may be lower in women than in men, the consequences of the disease are at least the same, if not worse. Women with OSA have greater endothelial dysfunction compared with men, are more likely to develop comorbid conditions such as anxiety and depression, and have increased mortality risk. Few studies have investigated gender differences in the effects of OSA treatment. However, given the differences in physiology and presentation, it is possible that a CPAP therapy that takes these differences into account may offer a more effective therapeutic option for women with OSA. One such novel therapy is the AutoSet for Her algorithm which aims to target these differences in women with OSA. A study comparing standard AutoSet with AutoSet for Her in women with OSA showed that AutoSet for Her was equivalent in efficacy, as shown by the AHI and ODI, however significantly decreased flow limitation whilst utilising lower CPAP pressures throughout the night.

Introduction

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing (SDB), and is typified by repetitive complete or partial collapses of the upper airway during sleep. The prevalence of OSA has been increasing steadily, in part due to the rise in obesity, with recent estimates suggesting that it affects from 3% to 20% of the general population [1-3].

SDB, encompassing OSA and other abnormal breathing during sleep including snoring, upper airway resistance and central sleep apnea, has been estimated to have a male to female ratio of between 3:1 and 5:1 in the general population and a much higher ratio of between 8:1 and 10:1 in some clinical groups [4-6].

Perhaps not surprisingly then, OSA has historically been regarded as a male disease [7]. Prevalence data do show that more men than women are affected by OSA, with approximate rates of 24% and 9%, respectively [4]. However, up to 50% of women aged 20-70 years had OSA (apnea-hypopnea index [AHI] ≥5/h) in a recent study [7]. Of those aged 55-70 years, 14% had severe OSA (AHI ≥30/h) and the rate of severe OSA in obese patients aged 50-70 years was 31% [7]. Such results suggest that OSA is just as important for women as it is for men.

Diagnosis

It has been suggested that discrepancies between males and females in the prevalence of OSA could be a result of women frequently being misdiagnosed or underdiagnosed [6]. Despite reporting similar rates of daytime sleepiness as men, women are less likely to have an Epworth Sleepiness Scale (ESS) score of >10, meaning that this popular screening tool may be less sensitive in women [8]. It is also possible that women have a different threshold for feeling sleepy and/or complain differently about sleepiness compared with men [6].

Making a differential diagnosis of OSA in women might be more difficult given that they tend to present with more generalized daytime symptoms than men [6]. Women with OSA complain of symptoms such as insomnia, restless legs, depression, nightmares, palpitations and hallucinations whereas men are more likely to report snoring and apneic episodes [9]. Women may consider their own snoring "unladylike" and therefore be less likely to mention it [6]. In addition, women are more likely to attend clinical appointments on their own, whereas men often attend with their partner [5]. Therefore, information from a partner on snoring and witnessed apneas may not be as readily available for women versus men. Less frequent reporting of 'typical' OSA symptoms by women, plus a higher prevalence of atypical symptoms such as headache, anxiety and depression, could contribute to the under-evaluation of OSA in women, lower referral rates to sleep clinics, and under-representation in clinical studies [10, 11]. Data from the Wisconsin University Sleep Laboratory showed that lower rates of recognition of OSA in women versus men only occurred in the subset of patients with an AHI of 5-20/h [12]. Their findings led the study authors to hypothesize that there may be greater gender-related differences in OSA symptom expression at lower AHI values, particularly with respect to characteristic symptoms such as snoring, witnessed apneas and excessive daytime sleepiness. The extent and location of white matter injury in the brain differs between sexes, which might relate to the differences in reported symptoms, particularly with respect to psychological symptoms such as depression and anxiety [13].

In a community-based sample, women with OSA reported the same symptoms as men across a range of severities, and snoring was the most significant predictor of OSA for both sexes [11]. There were no OSA symptoms that were unique to women, suggesting that factors other than symptoms also contribute to gender disparity in OSA populations [11]. These include failure of women to acknowledge OSA symptoms and seek medical help, or failure of medical professionals to respond to OSA symptoms in women [11]. Thus, although women probably do seek medical help and complain of symptoms that could be indicative of OSA, this diagnosis is not 'top of mind' for healthcare professionals when treating women compared with men, meaning that a correct diagnosis is often missed [6].

Manifestations

There are a number of gender differences in the manifestations of OSA. Both the severity of OSA and its distribution across the sleep cycle differ in males and females.

In a study of patients already diagnosed with OSA, women had a significantly lower overall AHI compared with men (20.2/h vs 31.8/h; $p<0.001$); AHI during non-REM sleep was also significantly lower in women vs men (14.6/h vs 29.6/h; $p<0.001$) but there was no difference between females and males with respect to AHI during REM sleep (42.7/h vs 39.9/h, respectively), suggesting a greater clustering of apneic events during REM sleep in women [14]. This study also showed that OSA in the supine position occurred almost exclusively in men, indicating that positional OSA is not really an issue for women [14]. Polysomnographic data from patients referred for suspected sleep disorders also showed that a difference between males and females in AHI was evident during stage 2 sleep, but not during REM sleep [15]. In addition, women had shorter apnea events and less severe oxygen desaturations than men (both $p=0.001$) [15].

An interesting finding is that women are symptomatic at lower AHI cut-off values compared with men [11]. Females with an AHI of 2-5/h had a similar level of symptoms to those with an AHI of ≥15/h. In contrast, males with an AHI of 2-5/h were indistinguishable from those with an AHI of 0-2/h with respect to symptoms. One possibility is that the long-term effects of REM sleep disruption contribute to greater symptomatology at lower AHI values in women compared with men [16].

Another theory is that women may be more symptomatic because they have more episodes of upper airway resistance during sleep. Obstructive events can be thought of as a continuum of partial to complete upper airway obstruction. Upper airway resistance occurs early in this spectrum, and describes events where resistance to airflow in the upper airway increases during sleep, presenting as flow limitation during polysomnography [17]. This increase in upper airway resistance could increase work of breathing, cause arousals and disrupted sleep, and impact on daytime cognitive function [17]. Upper airway resistance alone, without complete obstructive apnea or respiratory disturbance, has been shown to produce clinical symptoms such as daytime fatigue and depression [18], both of which are symptoms reported by women with OSA.

Sleep architecture is another aspect that has been shown to differ between males and females. A study of 307 patients by Valencia-Flores and colleagues found that women took longer to fall asleep than men, and once asleep had fewer awakenings from sleep and had more slow wave (deep) sleep, despite no differences between the sexes in age, respiratory disturbance index or oxygen saturation [19].

The occurrence of multiple episodes of upper airway resistance without frank apneas mean that an AHI value may not provide a physician with a true indication of the degree of airway obstruction being experienced by patients. As a result, episodes during sleep where flow is reduced, respiratory effort increases, and the episode is terminated by an arousal have been termed Respiratory Effort Related Arousals (RERAs) [17] (Figure 1). The importance of measuring and reporting on RERAs has been emphasized by a task force of the American Academy of Sleep Medicine (AASM) [20]. Women with partial upper airway obstruction have been shown to have similar symptoms, including sleepiness, to women with OSA, resulting in a call for partial upper airway obstruction to be clinically recognized in the same way as OSA in women [21]. It has also been suggested that recognizing and understanding the different features of SDB in women is central to effectively detecting and treating the condition [22]. Updating of current guidelines to reflect the growing body of evidence pointing to marked differences in the presentation of SDB in men and women would go some way to facilitating this.

Gender differences in the upper airway, fat distribution and respiratory stability in OSA

Definitive explanations for differences between men and women in the symptoms, characteristics and severity of OSA are not yet available, but various factors may contribute.

The focus of a number of studies has been on the upper airway. MRI imaging has shown that airway length, the tongue, the soft palate, and the total amount of soft tissue in the throat are all smaller in women than in men [21]. Although, intuitively, a smaller airway might be expected to occlude more easily than a larger one, this doesn't seem to be the case. It appears that men have a longer, softer oropharynx, and a larger, fatter, more posterior tongue, increasing the susceptibility of the large airway to collapse [6]. Upper airway collapsibility, determined by the pharyngeal critical closing pressure, has been shown less in women versus men when the severity of OSA is the same [23]. Sex differences in airway collapsibility were most evident during non-REM sleep, suggesting that men may be more susceptible to pharyngeal collapse than women during established sleep, but not during sleep transition [24].

Obesity is a well-recognized risk factor for OSA, and higher body mass index (BMI) indicates a greater severity of OSA for both sexes [25]. However, for the same AHI, women tend to be more obese than men [23, 26]. One potential explanation for this is differences in fat distribution between the sexes [27]. For the same BMI, men tend to have higher mean body weight, free fat mass and neck circumference

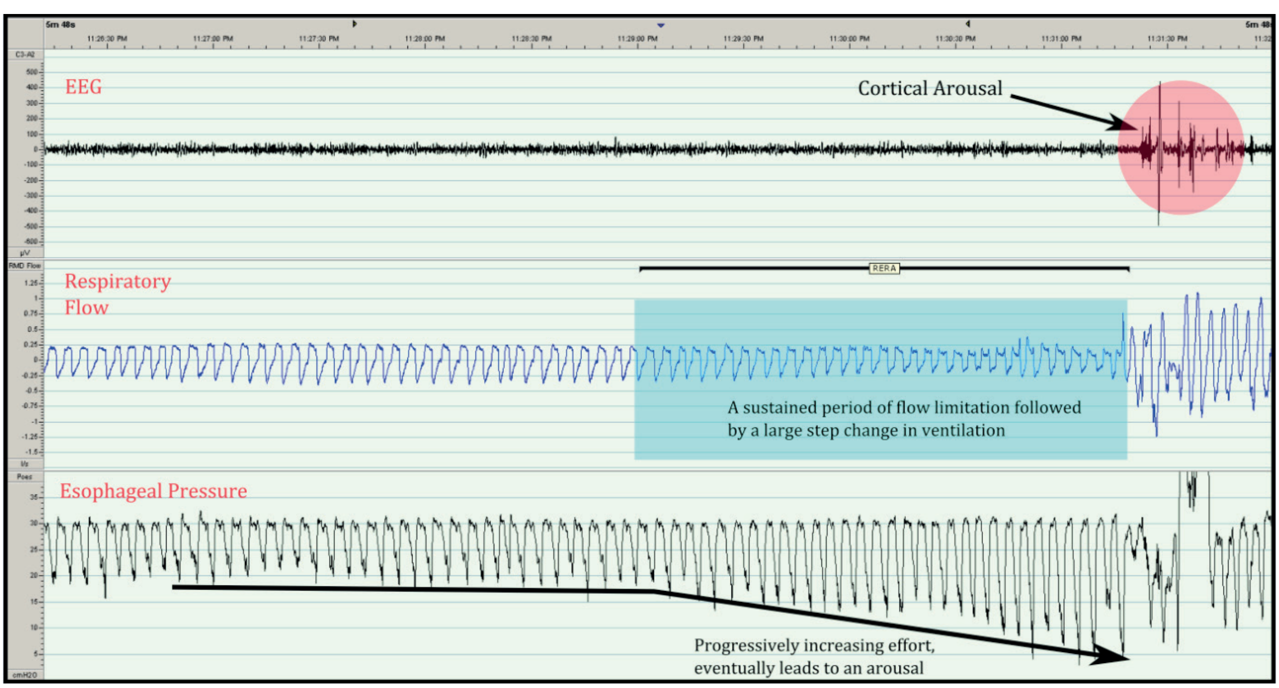

Figure 1. Respiratory effort related arousal (RERA)
EEG = electroencephalography. Trace shows a sustained period of flow limitation leading to increasing respiratory effort and arousal typical of RERAs.

compared with women [28]. MRI studies have confirmed less pharyngeal fat and lower soft tissue volume in the neck for obese women versus obese men [29]. Upper airway fat distribution, particularly in the posterior tongue, appears to be important in the pathogenesis of OSA and is related to gender [6].

Upper body and visceral adiposity have been associated with reductions in lung function, including total lung capacity, forced vital capacity and forced expiratory volume [30]. In addition, the independent effects of body fat distribution on lung function were more pronounced in men than in women [31].

Fat distribution might have physiological as well as mechanical effects in patients with OSA. Obese women, and especially those with OSA, have been shown to have significantly increased hypercapnic and hypoxic responses, whereas this was not the case in obese men [32]. This adaptation might maintain adequate minute ventilation when the chest wall load is increased. Reduced lung function and decreased chemoresponsiveness are additional reasons why men are more susceptible to OSA than women.

Gender differences have been documented in the susceptibility to hypocapnic inhibition, which has been suggested as another factor influencing the development of OSA in males versus females [33]. Men and women required different levels of carbon dioxide in the blood to cause respiratory instability, and men were more susceptible to hypocapnic dysfunction during non-REM sleep than women. It is possible that women preserve ventilation output during hypocapnia more efficiently than men [33]. Indeed, the ventilatory response to hypercapnia has been shown to be greater in men than in women [34].

There may also be gender differences in the arousal response to apneas. Jordan and colleagues found that during non-REM sleep men had a higher ventilatory response to apneas than women, but then they developed greater hypoventilation when they went back to sleep, especially in the supine position. This prolonged hypoventilation often leads to ventilatory instability upon returning to sleep. The study authors hypothesized that this may play a role in explaining why sleep apnea syndromes are more severe in men [35].

Menopause and pregnancy

Differences between men and women in the prevalence of OSA decrease as age increases, largely as a result of a marked increase in the prevalence and severity of SDB in women after menopause [36-38]. Therefore, it has been suggested that female sex hormones have a protective effect on upper airway patency and/or ventilatory drive [16]. The hormone progesterone is a known respiratory stimulant which increases chemoreceptor responses to hypercapnia and hypoxia, and has been shown to increase upper airway muscle tone [39]. Progesterone levels decrease after menopause.

Hormones may also play a role in the distribution of body fat. Postmenopausal women have a higher fat mass than prior to menopause, and fat distribution is more likely to be in the upper body and trunk area compared with the lower body [40, 41]. In female volunteers, activity of the genioglossus muscle during wakefulness was lower in postmenopausal compared with premenopausal women, and significantly increased after 2 weeks of hormone replacement therapy [42].

Women may be at increased risk of OSA during pregnancy due to a number of factors. The growing uterus elevates the diaphragm, changing pulmonary mechanics [43]. In addition, during pregnancy, neck circumference increases [44, 45], nasal patency is reduced [46] and pharyngeal edema occurs [47]. Substantial increases in snoring, snorting/gasping and witnessed apneas have been documented in pregnant women [45]. Snoring during pregnancy appears to be a risk factor for both pregnancy-induced hypertension and intrauterine growth retardation [48].

Health consequences

The long-term health consequences of OSA have been well-documented in patient populations with a predominance of males. More recently, however, studies are starting to specifically look at the consequences of OSA in female patients. Sympathetically-mediated responses to autonomic challenges in patients with OSA are blunted to a significantly greater extent in women versus men with OSA; this deficit is likely to reduce the effectiveness of BP regulation, and brain perfusion [49]. It is possible that women with moderate sleep apnea are more susceptible to the adverse cardiovascular consequences of OSA than men, having been shown to have more marked endothelial dysfunction [50]. Certainly, untreated severe OSA has been independently and significantly associated with cardiovascular death in women [51]. Conversely, the contribution of OSA to hypertension has been shown to be lower in women versus men [52].

Women with OSA are more likely than their male counterparts to develop a number of comorbid conditions, including mood disturbances such as anxiety and depression, hypothyroidism, arthropathy, cognitive impairment and dementia [53, 54]. These comorbidities probably explain the increased mortality risk that has been documented in women compared with men [55]. Women with OSA experience worse health status, use more psychoactive drugs, and have higher healthcare costs (by 1.3-fold) compared with men [53, 54].

Thus, the limited data available suggest that although the prevalence and severity of OSA may be lower in women than in men, the consequences of the disease are at least the same, if not worse [56].

Treatment

Sex differences in the response to different OSA treatment strategies have not been extensively studied to date. Treatment with CPAP in women with OSA was associated with cardiovascular mortality rates similar to those in controls without OSA, whereas patients with untreated OSA had a significantly increased rate of cardiovascular death [51]. Furthermore, clinical trial data suggest that men require higher pressures during CPAP therapy than females, after adjusting for baseline OSA severity or BMI [57, 58]. However, there do not appear to be differences between men and women in the types of interfaces used for CPAP or overall satisfaction with mask treatment [59]. Given that there are marked differences between men and women in the physiology and presentation of OSA (as described above), it is possible that treatment options specifically targeting female presentations of OSA may result in better treatment outcomes for these patients.

AutoSet for Her Algorithm

The AutoSet for Her algorithm, as applied in the AirSense 10 AutoSet for Her device, has been specifically designed to treat OSA in female patients. The algorithm aims to address female-associated OSA characteristics, such as shorter respiratory events [15], predominantly REM-based OSA [14], and increased flow limitation [60] (Table 1). Compared to standard AutoSet algorithms, the AutoSet for Her algorithm has increased sensitivity to flow limitation and optimised response gain. It is driven predominantly by flow limitation and snoring rather than apneas and has an adaptive minimum pressure.

Due to women exhibiting predominantly REM-based events [14], the algorithm's adaptive minimum pressure aims to prevent a string of apneas at the onset of REM sleep. It does this by preventing decay of the therapy pressure below a level where apneas are still occurring. If two apneas are detected within a minute, the adaptive minimum pressure will prevent pressure decaying below this level for the remainder of the session. To avoid reaching excessively high minimum pressures, the adaptive minimum pressure will not exceed 10 cm H_2O

A one night randomised, double-blind, cross-over clinical trial of 20 female OSA patients, investigated the efficacy of the AutoSet for Her algorithm compared to the standard AutoSet algorithm using full in-lab polysomnography. The AutoSet for Her algorithm was found to treat OSA as effectively as standard AutoSet, however the algorithm

Table 1. Summary of AutoSet for Her therapy features and their relevance to female-associated OSA characteristics.

Female-associated OSA characteristics	AutoSet for Her Therapy
Women experience shorter obstructive events [15]	Device includes RERA reporting to indicate the occurrence of respiratory events not strictly meeting the definition of an apnea or hypopnea.
Women are prone to more upper airway resistance and flow limitation [60]	A single breath index is used to calculate and respond to the patient's flow limitation (3 breath average used in standard AutoSet).
Women have predominantly REM-based events [14]	If 2 apneas are detected within a minute, an 'adaptive minimum pressure' prevents therapy pressure decaying below this level for the remainder of the session. Minimum pressure will not exceed 10cmH2O.
Women require lower CPAP pressures than males [57, 58]	The maximum pressure due to a closed airway apnea is 12 cm H_2O. The therapy pressure still increases above 12 cm H_2O if it is driven by either continued snoring or flow limitation. This reduces the likelihood of reaching high pressures over short periods.
Women may experience more arousals from sleep [61]	The algorithm contains several modifications to the internal gains of the algorithm which effectively result in a slower (and lower) pressure rise and decay when compared to standard AutoSet.

RERA, respiratory effort-related arousal; REM, rapid eye movement; CPAP, continuous positive airway pressure was also able to significantly reduce the proportion of flow-limited breaths (Table 2). As females with OSA tend to exhibit greater amounts of upper airway resistance [60] and less frank apneas [15], the AutoSet for Her algorithm is able to treat OSA as effectively as the standard AutoSet algorithm whilst also targeting residual flow limitation.

In addition, whilst no significant differences were found in sleep parameters between AutoSet for Her and standard AutoSet, improvements were seen in the number of RERAs and the percentage of REM sleep when patients were treated with the AutoSet for Her algorithm (Table 2). This trend may be attributed to the algorithm's adaptive minimum pressure which aims to not decay below the critical airway pressure during REM sleep. As female OSA patients are more prone to REM-based apneic events [14], the AutoSet for Her algorithm is able to counter these events, reduce arousals, and consolidate REM sleep.

Furthermore, 95th percentile CPAP pressure required to effectively treat OSA in this female population was significantly lower with the AutoSet for Her algorithm compared to the standard AutoSet algorithm (Table 2 & Figure 2). Mean and median CPAP pressures delivered by the AutoSet for Her algorithm also showed a trend toward lower pressure further suggesting that while both algorithms effectively treat OSA in female patients, AutoSet for Her does so by utilising lower CPAP pressures. As female OSA patients frequently require less pressure than males, the AutoSet for Her algorithm may provide increased therapy comfort by delivering lower yet more targeted, effective therapy pressures for females.

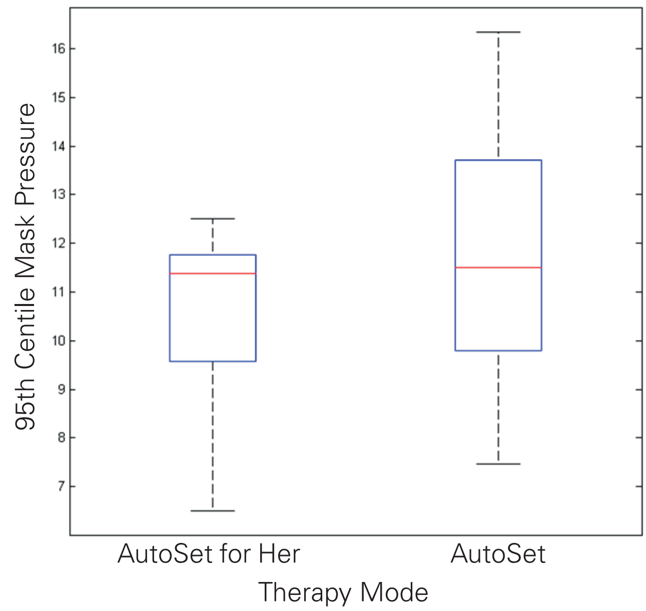

Figure 2. 95th percentile mask pressure ranges during 1 night each of standard AutoSet and AutoSet for Her algorithm treatment in female OSA patients.
Boxplots depicting the median, interquartile range, and range for 95th percentile mask pressure (mm Hg) during 1 night of AutoSet for Her (left) and standard AutoSet (right) treatment.

Conclusions

A growing body of evidence suggests that there are substantial differences between females and males in the symptoms, diagnosis and consequences of OSA. The majority of existing data relate to populations with a predominance of males, particularly with respect to treatment. Better knowledge of gender differences in OSA will help to improve the awareness and diagnosis of OSA in women, and the development and availability of therapeutic options that take into account differences in the physiology

Table 2. Mean ± SD sleep parameters and therapy mask pressures following 1 night each of standard AutoSet and AutoSet for Her algorithm treatment in female OSA patients.

Measurement	Standard AutoSet	AutoSet for Her	P value
Sleep Parameters			
AHI (events/hr)	1.0±1.4	0.9±0.9	0.87
4% ODI (events/hr)	1.92±1.82	2.19±2.15	0.48
RERAs (#)	2.6±3.32	1.3±1.84	0.1
Flow-limited breaths (%)	0.2±0.13	0.14±0.09	0.003
Time in REM Sleep (%)	17.93±11.05	19.77±7.54	0.47
Pressure			
Median Mask Pressure (mm Hg)	8.31±2.71	7.94±1.97	0.22
Mean Mask Pressure (mm Hg)	8.34± 2.23	7.89±1.67	0.13
95th Percentile Mask Pressure (mm Hg)	11.63±2.62	10.56±1.72	0.048

AHI, apnea-hypopnea index; ODI, oxygen desaturation index; RERA, respiratory effort-related arousal and presentation of OSA in women, such as AutoSet for Her, could have the potential to improve outcomes for these patients.

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