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Gender Differences in Obstructive Sleep Apnea and Treatment Implications

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Abstract

Obstructive sleep apnea is a common cause of daytime sleepiness for millions of Americans. It is also a disease associated with an increased likelihood of hypertension, cardiovascular disease, stroke, daytime sleepiness, motor vehicle accidents, and diminished quality of life. A number of population based studies have shown that obstructive sleep apnea is more common in men than in women and this discrepancy is often evident in the clinical setting. There are a number of pathophysiological differences to suggest why men are more prone to the disease than women. Although the exact mechanisms are unknown, differences in obesity, upper airway anatomy, breathing control, hormones, and aging are all thought to play a role. The purpose of this review was to examine the literature on gender differences in obstructive sleep apnea and to analyze whether or not these differences in pathogenic mechanisms affect diagnosis or treatment.

Keywords

Obstructive sleep apnea; sleep disordered breathing; gender

Introduction

Disordered breathing during sleep is a common abnormality resulting in excessive daytime somnolence and numerous physiologic illness for millions of Americans. Sleep apnea is defined as a repetitive, intermittent cessation of air flow at the nose and mouth while sleeping, and the clinical syndrome is marked by recurrent episodes of apneas (complete cessation of breathing) and hypopneas (partial decrease in breathing) during sleep. These episodes can be

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due to two causes which include occlusion of the upper respiratory tract (URT) airway (obstructive) or absence of breathing effort (central).(1) Obstructive sleep apnea (OSA) is an independent risk factor for hypertension and other cardiovascular disease such as stroke and myocardial infarction.(2,3,4,5,6) It has also been reported to play a role in the pathogenesis of insulin resistance and Type II diabetes.(7) In addition to these effects, the excessive daytime sleepiness associated with OSA has been implicated in motor vehicle accidents and a general decrease in quality of life.(8,9) OSA represents a major public health issue.

One intriguing aspect of OSA is the difference in the prevalence of the disease between genders. Research study has repeatedly and consistently confirmed that OSA is more common in men than women.(10,11) Although this complex topic is still poorly understood, it is believed that inherent differences in fat distribution, length and collapsibility of the upper airway, neurochemical control mechanisms, arousal response, and sex hormones all contribute to the disparity in prevalence between the genders.(12)

Clinical Presentation

Sleep-disordered breathing occurs in 24% of young-middle aged men and 9% of women(13) and in 70% of older men and 56% of older women.(14) The male-to-female ratio is estimated between 3:1 to 5:1 in the general population and at 8:1 to 10:1 in some clinical populations. (10,11) It has been postulated that the higher clinical ratio may be a result of the fact that women do not show the “classic” symptomotology and thus may be under diagnosed. Women presenting with daytime sleepiness may be misdiagnosed with depression or other illness. This may also be a result of the fact that women are more reluctant than men to complain of snoring, a symptom some think masculine and most think “unlady like.” A third hypothesis is that men have more severe OSA and thus are more likely to be diagnosed by their primary care physician and then referred to a sleep medicine center. (Summary Table 1)

In contrast to this hypothesis, Young et al. noted that regardless of severity, women did not report symptoms that differed significantly from those of men and snoring was still the most sensitive and strongest predictor of OSA.(15) Despite this, men tend to be referred to sleep medicine centers more often than women(16), suggesting a discrepancy regardless of “similar” symptoms; frequency of snoring and daytime somnolence was similar in both genders, witnessed apneas were more frequent in males.(11,17) Vagiakis et al. reported in a large Greek study that men had a significantly greater mean duration of apneas and hypopneas than women. (18) Other studies reported that men tend to have relatives who were more concerned about witnessed apneic events. (19) In addition, women came to clinical interviews alone, accompanied by their partner less frequently than men(11), suggesting that snoring (perhaps an embarrassing symptom) and apneic events may be under-reported or under-observed.

Baldwin et al. observed that although women reported feeling sleepy at similar rates to men, they were less likely to have an Epworth Sleepiness Scale score of >10, suggesting that this questionnaire often used to screen for OSA daytime sleepiness may be more sensitive for men. (20) It is also possible that the threshold at which women feel ‘sleepy’ or complain about it is different from that of men. Several studies have pointed out that women were more likely to have no sleep related complaints or symptoms at all. Perhaps women just use different words to describe their sleep deprived feelings. Young et al. observed that 40% of women versus 20% of men with an apnea/hypopnea index (AHI) of greater than 15 did not report any of the “classic” OSA symptoms.(15) Ambrogetti et al. noted a “subgroup” of women diagnosed with OSA who had no complaints of apnea, arousals, or restless sleep.(19)

An additional factor may be that although women may feel similar symptoms to men, they oftentimes present with vague, non specific symptomotology. In general, women of all adult age groups report more sleep problems than men, including inadequate sleep time and

insomnia.(21) In fact, difficulty initiating sleep, fatigue, morning headaches, insomnia, depression, and use of sedatives were all more frequent in women than in men.(10,11,19,22) A Swedish study found that women tended to have more generalized daytime symptoms than men, but it was unclear if this was affected by their daily occupation or other social habits. (16) Since women tend to present with a myriad of symptoms in comparison to men, it widens the differential diagnosis and can either delay the true diagnosis or lead to misdiagnosis. This in turn could adversely affect the numbers presenting at sleep medicine centers.

In a recent publication by Valipour et al from Austria, the authors find whereas men complain of snoring and apneic episodes, women complain of insomnia, restless legs, depression, nightmares, palpitations and hallucinations. 23 It is possible that snoring is quieter, not noticed by the sleeping male and in any case embarrassing so that women are reluctant to complain of snoring. The bottom line is that women have OSA, they do go to doctors and complain, but their physicians do not suspect OSA and often miss the correct diagnosis.

As mentioned above, it is possible that men tend to have more “severe” cases of OSA, thus contributing to their greater numbers in sleep clinics. O’Connor et al. noted that the male-to-female ratio was 3.2:1 for all OSA patients (similar to other studies) but ranged from 2.2:1 for patients with mild OSA (AHI 5-25 events/hr) to 7.9:1 for patients with severe OSA (AHI>50 events/hr).(24) Cross-sectional results of the Sleep Heart Health Study indicated a decreasing percentage of women within increasing AHI quartiles, ranging from 70% in the lowest quartile to 35% in the highest quartile.(5,25) The Cleveland Family Study also indicated that gender independently influenced the incidence of sleep-disordered breathing (SDB) in general, with more men than women developing the disorder over the five-year study.(26)

Several factors could explain why the prevalence of OSA in the clinical population does not always correlate with the prevalence in the community. Regardless it is clear that there is a gender discrepancy and that more men are affected and diagnosed with the disease than women. Clinicians need to remember OSA in their differential diagnosis when evaluating women patients.

Pathophysiology

Sleep architecture and arousal

Men and women with OSA have notable differences in sleep architecture.(27) A study by Valencia-Flores et al. noted that in OSA patients, women had longer sleep latencies, greater amounts of slow wave sleep, and fewer awakenings during the night than men despite no significant differences in age, respiratory disturbance index, or oxygen saturation.(28) O’Connor et al. showed that women tended to have milder OSA which occurred predominately during rapid eye movement (REM) sleep, in contrast to men who had more severe OSA that was position, but not sleep stage, dependent.(24) Recently, a large-scale study of Greek subjects with OSA indicated that in non-rapid eye movement (NREM) sleep, men had a higher AHI than women but there was no significant difference during REM sleep. Women also tended to have clustering of respiratory events during REM sleep in contrast to the men who had mainly NREM sleep apnea.(18) The reason behind the observation that REM sleep apnea is more common in women is unknown and may be a reflection of differences in upper airway function during sleep. At present it is unclear if baseline differences in sleep architecture contribute to the gender differences or if the disease affects the sleep architecture of men and women differently.

Aside from the different sleep architecture between men and women, the general onset of sleep is associated with many physiological changes that could contribute to breathing disturbances and to the pathogenesis of OSA. These alterations include changes in respiratory control

stability as well as changes in upper airway musculature and pharyngeal resistance. This changing milieu of the upper airway results in the obstructive events that occur during sleep. At arousal, many of these changes are reversed and airway patency is re-established. The increase in breathing after arousal from sleep is thought to arise from increased chemoresponsiveness, a relatively high partial pressure of arterial carbon dioxide ($PaCO_2$), and a sudden reduction in upper airway resistance. A type of 'waking reflex' has also been thought to be involved in returning the airway to a pre-sleep state.(29) Jordan et al. showed the ventilatory response to arousal from non-REM sleep was higher in men than in women but that men developed a greater subsequent hypoventilation upon return to sleep. Men also had an increased peripheral vasoconstrictor response, suggesting that neural inhibition of respiration after the greater hyperpneic phase in men could contribute to the differences in the post-arousal ventilatory response.(30) This propensity to "undershoot" ventilation after arousal may help explain why men have relatively more severe disease.

Several of these results were confirmed in a follow-up study where the investigators found that the b response to spontaneous arousal from non-REM sleep was greater in men than in women with OSA and was greater when airway resistance was elevated. They subsequently noted that arousal from non-REM sleep was occasionally associated with central and obstructive respiratory events on return to sleep, suggesting that elevated upper airway resistance prior to arousal may predispose to upper airway instability on return to sleep.(31) Therefore, a combination of hypoventilation, as well as upper airway collapsibility, may be the result of arousal 'destabilizing' an individual's respiration with effects more prominent in men versus women. (Summary Table 2)

Obesity

Increased weight and obesity are both highly and increasingly prevalent in the United States and have continued to pose a public health problem.(32) The 1999-2002 National Health and Nutrition Examination Survey (NHANES) indicated that over 60% of the adult population in the United States is overweight or obese.(33) Obesity has long been known to be associated with OSA, and in both genders body mass index (BMI) correlates positively with the severity of the disease.(34) Data indicates that in terms of percentage, more women (33.4%) than men (27.5%) have a BMI $\geq$ 30.(33) Thus, one would expect accordingly that more women would be identified with the disease; however, this has not been the case. Instead, it is possible that differences in fat distribution have different implications for men and women. While fat accumulates in the tongue with weight gain, (35) women in general have lower Mallampati scores suggesting that fat does not play as large a role in the female tongue as it does in the male tongue. (36) As is discussed later, one explanation for the difference in men and women is that women have a shorter oropharynx and therefore a smaller section of upper airway at risk for night time collapse. Assuming this is true, then the fat of obesity, has a shorter section of airway to adversely affect.

Clinical studies have indicated that women with OSA tend to be more obese that men with the same level of OSA.(17,37) It has also been noted in clinical studies that when men and women are matched for BMI, men tend to demonstrate more severe disease.(18,37,38,39,40) Jordan et al. felt that female gender alone was "protective" in the sense that it was "equivalent" to 11.7 kg/m^2 reduction in BMI.(37) Thus, women seemed better able to 'tolerate' a higher BMI without clinically evident disease. Tishler et al. noted in the Cleveland Family Study that age, gender, BMI and waist-hip ratio remained significant predictors of AHI but that waist/hip ratio reduced the odds ratio for sex by about 35%, suggesting that some of the association between gender and sleep disordered breathing is mediated by body fat distribution.(26) Patel and Davidson show waist and neck circumference are better markers for OSA than is BMI (36) A similar finding was also suggested by earlier analysis of the Wisconsin Sleep Cohort Study

population where including the waist/hip ratio and neck girth in the model and not BMI resulted in the risk of developing OSA to be similar between the genders.(41) The Sleep Heart Health Study showed modest changes in weight were related to an increase or decrease in SDB and this association was stronger in men than in women. (42)

It is an established notion that men classically have a more android (upper body) versus gynoid (lower body) fat distribution.(40) Early studies suggested that large deposits of fat were present posterolateral to the oropharyngeal airspace at the level of the soft palate and in the soft palate itself in patients with OSA in comparison to BMI-matched controls,(43) which in turn suggested that fat distribution, and not simply the amount of fat, was important. In comparison to controls, non-obese patients with OSA were noted to have significantly more neck fat in the anteriolateral segments.(44) This finding of extra distribution of body fat in the trunk, head, and neck has led to a hypothesis that men are more prone to OSA simply due to increased deposition of fat around the airway. In analyzing neck soft tissue and fat distribution, Whittle et al. noted that in age and BMI-matched patients, men tended to have a higher mean body weight, fat free mass, and neck circumferences than women.(45) Magnetic Resonance Imaging (MRI) has confirmed that there is a decreased proportion of pharyngeal fat and soft tissue volume in the neck of obese women in comparison to obese men.(46) This has been contested however; Malhotra et al. noted that there were no important sex-related differences in pharyngeal fat distribution.(47) Schwab et al. acknowledged regional differences in fat distribution but showed that the lateral airway narrowing in patients with OSA was explained by larger pharyngeal walls (muscular, not adipose tissue) and that the fat pad size at the level of the minimum airway was not greater in OSA patients.(48) It has been proposed that although the amount of fat may not be significantly different, it may affect pathogenesis through alterations in airway tone and laxity.(38) It has also been noted that men have more bulky tongues and soft palates as well as a larger absolute volume of fat in the anterior segments inside the mandible and subcutaneously in the neck while women have greater fat deposition in the retroglossal region.(45) A most recent autopsy study showed the posterior tongue to contain up to 30% fat. Tongue weight was greater for men than women and increased with weight gain as did the percent fat.(37 above) Lingual fat maybe a function of central obesity, not peripheral obesity, another important concept for obesity and OSA. All of these areas may affect airway stability through volume loading in various positions. Thus, the above data suggest that fat deposition in the upper airway, particularly the posterior tongue is likely to affect disease pathogenesis and is gender-related.

Differences in the “regional” distribution of adipose tissue can also be examined in terms of visceral (abdominal) obesity. Obese men with OSA have a significantly greater amount of visceral fat than BMI-matched controls and the indices of sleep-disordered breathing were positively correlated with visceral fat but not with BMI or total subcutaneous fat. The quantity of visceral fat has also been shown to be a significant individual predictor of mortality in men and is a strong, independent predictor of dyslipidemia and insulin resistance (metabolic syndrome).(49) It has been suggested that obesity may indirectly affect respiratory control mechanisms, including the ventilatory response to hypoxic hypercapnia.(50) Studies have also linked visceral fat to an ‘inflammatory’ state, involving the production of cytokines (IL-6 and TNF-alpha) which are felt to be involved in physiological sleep regulation.(49) Vgontzas et al., in a comprehensive review on the topic, concluded that OSA is “systemic illness” that is in fact a manifestation of the metabolic syndrome.(51) Other neuroendocrine changes related to visceral obesity include changes in sex hormones (see [Hormones] section for further analysis). Each of these factors potentially play a role in the pathogenesis of the disease, and thus, the higher incidence of visceral obesity in males would naturally predispose them to the development of OSA. If one views central obesity as fat deposited along the GI tract, the tongue is part of the GI tract, further supporting the concept of lingual fat as a function of central obesity.

Finally, upper body and visceral adiposity have been associated with detrimental changes in lung function which may indirectly affect the prevalence of OSA. Collins et al. noted that in comparing patients with a waist/hip ratio <0.95 (lower body) and a waist/hip ratio >0.95 (upper body) that forced vital capacity, forced expiratory volume, and total lung capacity were significantly lower in those with an upper body fat distribution.(52) This finding was later repeated when studying aging men.(53) Interestingly, Harik-Khan and colleagues found that body fat distribution appeared to have independent effects on lung function that were more prominent in men versus women.(54) Obesity may not only affect the lung mechanics, but the physiological responses as well. A recent study by Buysse et al. showed that adaptation, or 'upgrading' of both hypoxic and hypercapnic chemosensitivity was found in obese women with OSA but was absent in obese men with the disease. It was thought that the goal of this adaptation might be to maintain adequate minute ventilation in the presence of an increased chest wall load.(55) Unfavorable lung mechanics coupled with a decreased level of chemoresponsivness illustrates more reasons as to why men appear to be more vulnerable to the disease than women.

Upper Airway Anatomy & Physiology

With the exception of brachycephalic dogs and pigs, man is the only mammal that experiences obstructive sleep apnea. It has been hypothesized that the same evolutionary anatomic differences that facilitated humans' ability to speak also predisposed them to the development of OSA (the "Great Leap Forward" hypothesis). This theory suggests that the same structures necessary for speech also placed the airway in jeopardy during sleep.(56) The key anatomic features in this evolution include laryngeal descent, a tongue that resides partially in the pharynx, shortening of the oral cavity and shortening of the soft palate permitting oral speech all of which facilitated the formation of vowels but also positioned the soft tissues so that they could obstruct respiration during sleep. This hypothesis was supported by the finding that these evolutionary anatomic changes were correlated with OSA severity in men.(57) Interestingly, the cephalometric abnormalities were also associated with severity in women, but the significant anatomic factors varied between genders such that factors that correlated klinorynchy, laryngeal descent, and craniobase angulation were different in men than women (Davidson, unpublished data). The investigators felt that the evolutionary pressures were greater for men than women and therefore the changes were greater in men. Ergo, OSA is worse in men, simply because they have a longer, floppy oropharynx, the pharyngeal segment involved in OSA and a larger, fatter, posterior tongue. (Summary Table 3)

Although it was a long-held belief that a descended larynx was a uniquely human attribute, Fitch and Reby documented this anatomical finding in deer.(58) They hypothesized laryngeal descent helped to elongate the vocal tract, which allowed animals to exaggerate their body size by decreasing vocal-tract frequencies, thus proposing that the original selective advantage was to 'falsify size'.(59) An adult man's voice is considerably deeper than that of an adult woman's; increasing levels of circulating testosterone lengthen and thicken the vocal cords and also facilitate secondary descent of the larynx.(60) A deep voice may have been a positively selected trait for attracting females as it may have served as an indication of body size and virility. (61) Laryngeal descent, which occurs during infancy (both genders) and puberty (men), reshapes the airway such that the epiglottis no longer interdigitates with the soft palate; thereby elongating the oropharynx. However, this leaves the anterior wall of the respiratory tract, namely the tongue, vulnerable to nighttime collapse.(62) It is suggested that the descent of the larynx in men, which deepens the voice increases the vulnerability of the airway, further predisposes the male airway to the development of OSA in comparison to women. (Summary Table 4)

The size of the upper airway has also been extensively studied due to its possible role in disease pathogenesis. The primary offense of OSA is obstruction of air flow; one would logically assume that a larger airway would be less susceptible to collapse or interference from other structures. In healthy patients, it has been shown that men have a significantly larger cross-sectional area at multiple levels of the airway than women.(47,63) It has also been observed that women have narrower upper airways than men in both the sitting and the supine positions.(34,63) Brooks et al. observed that men have a larger change in pharyngeal area with changing lung volumes than measured in women.(63) These trends have also been observed in patients with OSA. Women actually have a significantly smaller upper airway at the level of the oropharynx than men, even after adjusting for height.(38) Based on airway size alone, all of these factors suggest that it should be women, not men, who are more prone to OSA, although this is clearly not the case. Therefore, there must be other factors aside from the cross-sectional diameter of the upper airway that influence the development of the disease.

Ciscar et al. determined that the maximum and minimum cross sectional area of the velopharynx in healthy subjects were similar, but that in patients with OSA, the minimum cross-sectional area was significantly lower than the maximum, especially at set points in the respiratory cycle and notably during sleep.(64) Although the exact mechanism is not clear, patients with OSA appear to have a more ‘collapsible’ airway than normal subjects. Also, it appears that although men may have the advantage of a larger cross-sectional airway, the airway is actually more stable in women.(37) Mohesenin et al. found that in men, retrusive range of movement of the mandible results in significant decreases in the pharyngeal and oropharyngeal junction cross-sectional area in men but not in women.(46) In general, men tend to have more severe and predominately position-dependent OSA than women where it is less severe and less position dependent.(24,46) Only in men was there a significant inverse correlation between pharyngeal cross-sectional area and the severity of the patient’s OSA.(38) This suggests there are inherent functional and structural differences in the airway during sleep between the genders and that women appear to have more favorable airway mechanics.

Aside from diameter, length of the airway may also be important in disease pathogenesis. Malhotra and colleagues studied normal patients and found that pharyngeal airway length was greater in men than in women, even when normalized for body size (including height). The authors also noted that there were no important physiologic differences in upper airway mechanics or in muscle activation and responsiveness between men and women. Data were then used to construct a two dimensional “finite model” of the airway during sleep where it was observed that at pressures where the male airway collapsed, the female airway remained patent.(47) Due to the fact that levels of muscle responsiveness were similar between the genders, the group hypothesized that in men, the airway was more prone to collapse primarily as a result of an increased length of vulnerable airway. However, this model was based on healthy subject airways.

Upper airway dilator muscle activity is thought to contribute to airway patency. Pharyngeal airway patency is viewed as a dynamic interaction between both a patient’s intrinsic upper airway anatomy and muscle activity. The activity of pharyngeal dilator muscles is influenced by numerous variables including blood gases, the sleep-wake state, gender-specific hormones, blood pressure, temperature, lung inflation, pharyngeal airflow, and intrapharyngeal negative pressure.(65) As one of the largest pharyngeal dilator muscles, the genioglossus has been heavily studied in relation to OSA. Studies have shown that the fall in the activity of the genioglossus following the transition from wakefulness to non-REM sleep is greater in patients with OSA than in normal patients,(66,67) suggesting that these patients do not sustain the necessary muscle activity to maintain a patent airway. An early study by Popovic and associates found that in women, the inspiratory peak phasic and expiratory tonic genioglossus activity were both significantly greater than in men, suggesting that the female airway is more stable

and less collapsible.(68) Studies also showed that both peak phasic and tonic waking genioglossal activity were increased in OSA patients, possibly a result of a compensatory mechanism secondary to jeopardized upper airway anatomy.(65,69) However, Jordan et al. showed that there was no gender difference in the resting level activity of the genioglossus and that there was no gender difference in minute ventilation or genioglossal electromyography (EMG) activity during or after a hypoxic stimulus.(70) A lack of difference between genders in terms of muscle activation was also noted in several other studies.(47,71,72) Jordan and colleagues also disputed an earlier finding and found that there was no statistically significant changes in phasic or tonic activity of the genioglossus from wakefulness to non-REM sleep. (30) This conflict in the literature has yet to be resolved.

Measurement of the pharyngeal resistance and the pharyngeal critical closing pressure take into account many of the individual variables of airway collapsibility discussed above. At the onset of non-REM sleep, there is a fall in ventilation and an increase in upper airway (pharyngeal) resistance. It is at this moment that obstructive events are thought to occur. Thurnheer et al. showed that there were no major differences between the genders or with age in the changes in airway resistance from wakefulness to stable sleep in healthy subjects. However, at high flow rates, total respiratory resistance and resistance in the oropharynx increased during both non-REM and REM sleep, again supporting concepts of upper airway collapsibility.(34) This can be contrasted to a study performed by Trinder et al, who noted that state-related changes in ventilation and upper airway resistance did not differ between men and women, but that once NREM sleep was established, there was a more marked and progressive increase in upper airway resistance in men in comparison to women. This result in turn would indicate a greater susceptibility to collapse in men versus women.(73) Rowley et al. found that gender did not affect upper airway resistance and instead felt that the gender differences in OSA prevalence was not explained by upper airway structure or collapsibility. (74) Based on present results, it is still unclear whether or not there is truly a difference in upper airway resistance or if the disparities noted are merely the result of methodological differences.

Studies have also investigated upper airway collapsibility through measurement of the pharyngeal critical closing pressure (P_{CRIT}). This variable is the nasal pressure below which the upper airway collapses and it encompasses factors including upper airway size, length, muscle activity, and intrinsic properties of the airway structures. Rowley et al. noted in that in healthy patients there was no difference in P_{CRIT} between men and women,(74) however, Sforza et al. compared P_{CRIT} in men and women with equally severe OSA and found that even though the women were more obese than the men, the P^{CRIT} was more negative in women, indicating a more stable upper airway.(75) Findings by Pillar and colleagues support these results as they observed that men responded to inspiratory resistive loading with increasingly greater decreases in tidal volume in comparison to women. They also noted that the central response to loading was similar between the sexes and there was no gender difference in muscle activation. Thus, the authors hypothesized that differing anatomic supports or tissue characteristics (i.e. differences in collapsibility) were responsible for the gender differences observed.(72) Jordan et al. confirmed this by showing that in BMI matched OSA patients P^{CRIT} was lower in women while respiratory control stability remained similar between the genders, indicating that women are less susceptible to the disease due to an anatomically more stable airway.(37)

Respiratory Control Stability

Respiratory stability is determined by the efficiency of gas exchange, circulatory delays to central and peripheral chemoreceptors, chemoresponsiveness, and potentially by ‘respiratory neural memory.’ (76) Although disruption of central mechanisms of respiration has been implicated mainly in the central form of sleep apnea, it has also been suggested to contribute

to the pathogenesis of obstructive sleep apnea.(51,77) Younes et al. discovered that the chemical control center was more unstable in patients with severe OSA in comparison to those with milder OSA.(77) This work was supplemented by that of Hudgel et al. which suggested a similar finding when comparing patients with OSA to healthy controls.(51)

After a fall in the arterial pressure of oxygen, the initial response of the body to this hypoxia is hyperventilation. This succeeds in increasing the pressure of oxygen in the blood but also leads to a decrease in carbon dioxide. Chemoreceptors within the medulla respond to the decrease in hydrogen ion concentration with ventilatory inhibition. This response, otherwise known as the hypoxic ventilatory response (HVR), is an important indication of the stability of the respiratory center. It has been noted to be both lower in awake women(78,79) and higher in awake women.(80) Although studies by White et al. showed that men and women had similar responses to hypoxia during sleep, the response to low oxygen also represented a considerable decline from the baseline awake response in men whereas there was little change from the awake state in women.(80) Early studies have indicated that HVR is affected by menstrual status(55) while studies in healthy pregnant women indicated an increased resting ventilation as well as increased HVR in these patients,(81) suggesting that it is influenced by female sex hormones. However, pregnancy is a hypermetabolic state, which could contribute to alterations in the HVR. The effect of basal metabolism on ventilatory function was studied by Aitken and colleagues who showed in healthy subjects that the HVR was affected by metabolic rate, which differed significantly between men and women.(81)

The ventilatory response to carbon dioxide levels during sleep is also an important factor contributing to respiratory control stability. Many of the same mechanisms that ensure optimal blood gases during the awake state also apply during sleep, although in sleep the set point of CO_2 is higher and some ventilatory mechanisms may decline.(82) The hypercapnic ventilatory response has been shown to be greater in men than women(78,81), however, van Klaveren et al. noted that both the hypercapnic and hypoxic ventilatory responses were independent of gender and that men and women have similar respiratory drives.(83) Interestingly, in a study by Sin and colleagues, the investigators noted in men, the hypercapnic ventilatory response was correlated to daytime $PaCO_2$ levels while in women it was correlated to BMI.(84) At the opposite end of the CO_2 spectrum, Zhou et al. pointed out that the change in the end-tidal PCO_2 necessary to cause a central apnea was significantly different between men and women, and that women were less susceptible to hypocapnic dysfunction in NREM sleep than men. (85) These results suggest that ventilatory stability in men may be more susceptible to the influence of chemical factors than women. Therefore, even though respiratory stability is not the primary culprit in the pathogenesis of OSA, gender differences are present.

Loop gain is a measure of an individual's susceptibility to periodic breathing and incorporates many of the variables involved in determining the stability of the respiratory control system previously mentioned. In a recent study, Jordan et al. noted that in both AHI-matched men and women as well as BMI-matched men and women with OSA, loop gain did not differ significantly between the two genders, indicating that respiratory control stability was less important than upper airway collapsibility in the pathogenesis of the disease.(37) Indeed, in a prior study, the investigators felt that loop gain had a substantial impact on the severity of OSA only in certain subgroups of patients with the disease, notably those with specific pharyngeal pressures.(86) Thus, it is still uncertain whether or not respiratory center instability plays a large role in disease pathogenesis.

Last, but not least, the changes in ventilation that occur after an initial stimulus (hypoxia or hypercapnia) are vital in disease pathogenesis. A time-dependent decay in ventilation after termination of a brief respiratory stimulus has been thought to protect against cyclic breathing disorders such as OSA.(87) Zhou et al. noted that in healthy patients, men had a higher

chemoresponsiveness than women, suggesting that men were more susceptible to ventilatory inhibition upon withdrawal of a chemical stimuli.(85)

However, Jordan et al. showed the rate of post-stimulus ventilatory decline was not different between the genders and not different between the follicular and luteal menstrual phases in women.(88) This second study was completed in awake patients and it is unclear if these results can be fully translated to the sleep state. However, if men are more prone to ventilatory inhibition after initial arousal and hyperventilation, it would provide another mechanism to the gender difference inherent within the disease.

Hormones

Differing hormone levels have always been a probable “culprit” in the explanation of the OSA differences between genders. Some literature has suggested that these differences begin as early as puberty. Normally, risk factors for obstructive sleep apnea in the younger population include craniofacial abnormalities, conditions that predispose to larger upper airway structures (allergic rhinitis or enlarged tonsils), and obesity.(89) Nonetheless, normal postpubertal adolescents showed sex differences in clinical and polysomnographic parameters related to sleep-disordered breathing that were not observed in pre- or peri-adolescents after controlling for age and BMI.(90) It has also been reported that pubertal development in girls is associated with an increase in general sleep problems.(21) Although the exact interactions are unclear at this time, it can be inferred that beginning as early as adolescence, the genders start to diverge in terms of sleep parameters. (Summary Table 5)

In women, the onset of menopause has been heavily studied as a “turning point” in prevalence of OSA. Depending on which study population is used, disordered breathing during sleep is more common among postmenopausal women than among their premenopausal counterparts with estimates ranging from 4-22% in the sixth or seventh decade.(91) Early clinical observations by Wilhoit et al. noted that OSA was quite rare in premenopausal women in comparison to postmenopausal women, attributing the disease to craniofacial abnormalities and severe obesity.(92) Bixler and coworkers studied the relationship between menopause and OSA and after adjusting for several potential cofactors, determined that in comparison to premenopausal women, postmenopausal women with HRT were not at increased risk of OSA (odds ratio 0.9; 95% CI 0.1 to 5.8) but postmenopausal women without HRT had an almost four-fold risk (odds ratio 4.3, 95% CI 1.1 to 17.3).(93) Young et al. found that the prevalence of SDB increased across menopausal categories (premenopausal, perimenopausal, and postmenopausal) and found no indication that the higher odds of sleep disordered breathing was primarily due to differences in age or BMI distribution. Compared with premenopausal women, the postmenopausal group was 3.5 times more likely to have SDB defined by an AHI of 15 or more, indicating that menopause was an independent risk factor for the development of SDB.(94)

Several different mechanisms have been proposed to explain how male (or female) specific hormones would affect the propensity of one gender towards OSA. One hypothesis is that the different hormones affect the distribution of body fat. As mentioned above, body fat and its distribution is quite important in the pathogenesis of the disease. In normal subjects, men tend to have greater lean tissue mass and lower fat mass then age-matched women. However, it has also been noted that postmenopausal women have a greater fat mass than premenopausal women and that the distribution of that fat tended to be android (upper body and trunk) versus gynoid (lower body).(95,96) The proportion of android fat also increases with both age and years of onset after menopause. Interestingly, years since menopause was a significant predictor of body fat mass and trunk fat whereas age itself was not a predictor of fat distribution variables.(96) A preferential increase in visceral (abdominal) fat that was independent of age and total fat body mass has been noted in women as well.(97,98) This suggests that acquiring

a “male/android” body fat distribution, notably after menopause, is a risk factor for the development of OSA.

Hormone levels have also been hypothesized to affect central and neural respiratory control mechanisms. Early studies of women suggested that OSA was a disease of postmenopausal women and premenopausal women were spared because of the respiratory stimulant effect of progesterone,(99) although treatment with 30 mg/day of medroxyprogesterone failed to significantly improve sleep disordered breathing in postmenopausal women.(100) However, in a cohort of patients with surgically-induced menopause, combined estrogen/progesterone treatment led to a decrease in the number of apneas and hypopneas during sleep.(101) A small pilot study of six postmenopausal women with moderate sleep-disordered breathing, estrogen monotherapy reduced the AHI from a mean of 22.7 events/hr to 12.2 events/hr.(102) Although the prevalence of sleep apnea was significantly lower in premenopausal women than postmenopausal women, menopausal status accounted for <30% of the variability in the OSA prevalence between these groups,(103) indicating that factors other than hormonal effects on ventilation are involved.

Rarer endocrinopathies have also offered another glimpse into illuminating the role in hormones, specifically testosterone. In a study of women with polycystic ovarian syndrome (PCOS), Fogel et al. discovered that compared to age-matched controls, women with PCOS had a higher apnea/hypopnea index and disturbed sleep.(104) Dexter et al. described a case of the resolution of documented OSA after removal of a benign testosterone-producing tumor.(105) The elevated testosterone levels present in both of these conditions suggests a possible role in OSA pathogenesis similar to the female hormones discussed above. The hormone may be involved not only through affecting weight and weight distribution, but also by altering respiratory control or airway structure and function.

In summary, current literature suggests that either the higher levels of progesterone/estrogen or lower levels of testosterone may be protective against the development of OSA in women. It is possible that differing levels of hormone starting from puberty, further modified by later hormonal changes (menopause), affect OSA development. It is still unclear as to the exact mechanisms by which these hormones work and whether or not addition of hormone treatment affects the disease process.

Pregnancy

Many changes occur in the respiratory system during pregnancy. Elevation of the diaphragm, secondary to an enlarging uterus, leads to alterations in pulmonary mechanics including a reduced functional residual capacity.(106) Upper airway dimensions are also altered; a British study of 242 pregnant women showed that by 38 weeks gestation, the number of Grade 4 Mallampati scores (Mallampati is a grading system for tongue size developed by an anesthesiologist to predict the difficult airway, but now used in sleep medicine to also predict OSA presence and severity) had increased by 34%,(107) thought to be secondary to fluid retention and edema. Pregnant women also have larger neck circumferences than non-pregnant women(108,109) and nasal patency is reduced as well (rhinitis of pregnancy).(110) Circulating estrogen and progesterone levels increase markedly, and although these hormones are primarily responsible for the maintenance of the pregnancy, as noted above there are a number of physiological side effects as well. Weight gain also comes into play, for during pregnancy women typically gain 25-35 pounds.(111) All of these factors suggest pregnancy may precipitate or exacerbate OSA.

An early study by Loube and colleagues demonstrated that self-reported snoring was more prevalent in pregnant women (14%) versus non-pregnant controls (4%).(112) A recent French study showed that 45% of the patients had habitual snoring during pregnancy and that 85%

were non-snorers prior to pregnancy.(113) Izci et al. confirmed that snoring and daytime sleepiness were significantly more common in pregnant women, but felt as if sleepiness in pregnancy was mainly due to factors other than upper airway obstruction.(108) However, a recent prospective study by Pien et al. showed that loud snoring, snorting/gasping, and witnessed apneas all increased significantly over the course of pregnancy.(109) Although the authors felt that the increase in symptoms was relatively modest among the group as a whole, they suspected that approximately 10% of the subjects may have developed incident obstructive sleep apnea. Therefore, obstructive sleep apnea is an important diagnosis to consider with daytime sleepiness in pregnancy, especially in lieu of possible adverse side effects including pregnancy-induced hypertension and intrauterine growth retardation.(109,110,114)

Aging

A last factor to take into account in the pathogenesis of sleep apnea is normal aging. Aging in itself is associated with numerous physiological changes. Ancoli-Israel and coworkers conducted in-home modified sleep studies on 427 men and women between 65 and 95 years of age and found that OSA (defined as AHI $\geq$ 10) occurred in 70% of the men and 56% of the women.(14) Later studies by Bixler et al. showed that in both men and women, those between 65 and 100 years had an OSA prevalence approximately twice that of middle-aged men and women,(93,115) with a similar observation made in the Sleep Heart Health Study.(41) Hader et al. showed that the male dominance in regard to the prevalence and severity of OSA did not disappear over the age of 65 years and the risk for sleep-disordered breathing increased two to three times with age, although at any given age women were less susceptible than men.(39) However, an interesting observation in another study was that the risk of OSA increases only moderately with age in men but rises steadily and markedly in women.(26)

A recent cross-sectional study by Malhotra and coworkers pointed out some enlightening considerations to take into account when considering the gender differences of OSA in the elderly. In terms of upper airway anatomy and physiology, they noted that there was an age-related decrease in the response of the genioglossus to negative pressure which was significant in men but not women.(116) A decline in this reflex mechanism would leave the male airway more prone to collapse. They also noted that the bony shape surrounding the pharynx changed markedly with age and that soft palate length increased with age in women significantly more than men. In both genders, the pharyngeal fat pads significantly increased in size with increasing age, independent of BMI.(116) Early work by Fogel et al. also supported the hypothesis that the primary difference between older and younger men was an anatomical one, although in contrast to the prior study found that there was a higher level of genioglossal activity during wakefulness.(67) Martin and colleagues measured the upper airway using the acoustic reflection method showed that upper airway caliber decreased in both men and women with increasing age, but that men showed greater collapsibility of the upper airway.(117) Cross-sectional analysis of Sleep Heart Health Study participants indicated that men, but not women, showed evidence of poorer sleep with aging.(27) Thus, anatomical changes related to normal aging as well as loss or decline of the ‘waking reflex’ may also contribute to the difference prevalence between the genders.

Notably, the prevalence of sleep apnea does not increase linearly throughout all age groups. In one study, the prevalence of OSA in men increased monotonically from 20-59 years but decreased thereafter.(115) A similar trend was observed in women,(26) and it was estimated by age 50 years, the incidence rates among men and women were similar. In addition, the effect of BMI decreases with age, as evidenced by the fact that although BMI increases, the severity of OSA decreases.(26,115) Therefore it is evident that the normal anatomical and physiological changes that occur with aging (including menopause) influences disease development.

However, it is not yet clear how important these changes are, when they start to take effect, or exactly what role they play in modulating the gender differences in OSA.

Treatment Implications

It is clear that numerous mechanisms are at play when it comes to the disease pathogenesis of obstructive sleep apnea. Despite the widely disparate variables that contribute to disease pathogenesis, treatment options for the disease are surprisingly limited. Currently, the cornerstone of treatment of OSA is continuous positive airway pressure (CPAP). Essentially, application of CPAP acts as a 'pneumatic splint' of the upper airway and also works to dilate upper airway musculature.(118) Oral appliances, devices which are designed to lift the soft palate and depress the base of the tongue, are another mainstay of OSA treatment. There have been nine studies comparing the effectiveness of oral appliances with CPAP; results show that oral appliances were less effective than CPAP in reducing the AHI. A third option available to OSA patients is surgical intervention. This treatment is usually reserved for those with the most severe disease or those who are unable to tolerate other medical management strategies. However, the results of surgical interventions are often suboptimal with some patients requiring more than one surgery and others remaining with persistent disease. Surgery is most effective in patients with 4+ tonsils, nasal polyps or other obstructive anatomic lesions. It is also most effective for patients with mild OSA, snoring included.

One of the most intriguing (and possibly the most controversial) aspects of future therapy lies in hormone replacement (HRT). As mentioned above, the prevalence of OSA for premenopausal women was 0.6% in comparison with 1.9% of postmenopausal women. However, postmenopausal women on HRT had a prevalence rate similar to those that were premenopausal.(93) It has been estimated that the prevalence of sleep disordered breathing is approximately half of the prevalence among non-HRT users, even when the results are adjusted for BMI and neck size.(92) However, other studies have indicated that although HRT users did have lower odds of OSA, it was not statistically significant.(94) To date, there has been one small clinical study which demonstrated that estrogen administration appeared to have a substantial benefit on the measures of sleep-disordered breathing.(102) However, HRT has been shown to be associated with notable risks including an increased chance of cardiovascular disease, stroke, and cancer.(119)

As discussed above, there is conflicting evidence as to the true role of hormones on the development of OSA. However, as Young stated in a recent editorial, there is widespread belief that menopause is an established risk factor for SDB despite the fact that strong supportive evidence is lacking. The question, "Are we ready for the heat?" pointedly addresses whether or not obstructive sleep apnea and its associated clinical sequelae should be tossed into to the debate surrounding hormone replacement therapy.(120) As evidenced by the results of Women's Health Initiative,(119) the answer is far more complicated than a simple weighing of the risks and benefits, and it is clear that longitudinal data will be necessary to elaborate on the temporal role that menopause has on the development of the disease.

Based on the evidence presented above, OSA is a multifactorial disease. However, each of these factors play different roles in the pathogenesis of OSA, suggesting that different therapeutic approaches should also apply. It should be noted that even mild OSA, UARS included, should be treated, especially in women. Faulx et al. showed that even moderate levels of sleep disordered breathing are associated with impaired conduit and reduced endothelial function in women, suggesting that women may be more vulnerable to early sleep-disordered breathing cardiovascular disease than men.(121) The common theme that runs throughout all forms of current treatment is that gender is essentially ignored when determining interventions and it is unknown whether or not a particular gender responds more favorably to a specific

treatment. Compliance with therapy, as well as efficacy, should also be considered. For example, Sin and colleagues noted that women were more adherent to long-term CPAP therapy than men.(122) It is unclear whether or not there are other gender-specific differences in current treatment modalities, as this has not been formally studied. Nonetheless, it is clear that even mild disease should be treated and that perhaps gender should be taken into consideration when designing treatment strategies.

Summary

Obstructive sleep apnea is more common in men than women. Presenting symptoms, are often different, women complaining of insomnia and depression. Thus, it is possible that women are underdiagnosed, which in itself poses a large public health problem and places many women at risk for cardiovascular and neurocognitive sequelae as well as decreased quality of life. Differences in upper airway anatomy, neurochemical mechanisms, the response to arousal, fat distribution, and sex hormones all contribute to the pathogenesis of the disease. It has been demonstrated that gender plays a substantial role in modulating these variables, although it unclear whether one factor predominates over another.

OSA is clearly a multifaceted disorder and despite the fact that the pathogenesis of the disease is likely to differ between the genders, both researchers and clinicians alike continue to group them together in scientific investigations and clinical trials. It may be beneficial to see how the genders respond to different treatments or if alternative future treatments can be pursued. This review focused on the gender differences in presentation and underlying pathophysiology of OSA as well as current diagnosis and treatment to ensure that clinicians do not overlook this diagnosis in women. It is hoped that the findings will stimulate ongoing research on mechanisms behind this disparity between the genders, as well as shape new trends in designing clinical trials that might better elucidate these pathways as well as improve treatments and outcomes.

Practice Points

1. Men and women report different symptoms for OSA
2. OSA is seriously under reported and under diagnosed in adult women
3. Health care professionals need to ask women of all ages about their sleep to try to identify occult sleep problems

Research Agenda

In the future, the investigation of gender differences associated with obstructive sleep apnea should:

1. recognize the substantial differences in OSA between men and women and should report data by gender, not as combined data
2. study sleep apnea in pregnancy to improve gestation, decrease preeclampsia with improved understanding of hormonal effects in OSA
3. study ethnic and age differences in OSA

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Nomenclature

OSA
ostructive sleep apnea

AHI
apnea/hypopnea index

SDB
sleep-disordered breathing

REM
rapid eye movement

NREM
non-rapid eye movement

$PaCO_2$
partial pressure of arterial carbon dioxide

NHANES
National Health and Nutrition Examination Survey

BMI
body mass index

MRI
Magnetic Resonance Imaging

EMG
electromyography

P_{CRIT}
pharyngeal critical closing pressure

HVR
hypoxic ventilatory response

PCOS
polycystic ovarian syndrome

CPAP
continuous positive airway pressure

HRT
hormone replacement therapy

Summary Table I

Clinical Presentation

Prevalence		
	Female	**Male**
AHI 5	9%	24%
AHI 15	2%	4%
Presenting Symptoms		
Female-	insomnia, restless legs, depression, nightmares, palpitations, hallucinations	
Male-	snoring, daytime sleepiness	

Summary Table II

Pathophysiology

Sleep Architecture: longer	
Sleep latencies: increased slow wave sleep and fewer arousals	
Obesity	
Female-	34%
Male-	28%
Clinical correlates	
Female-	waist circumference, neck circumference, BMI
Male-	waist circumference, neck circumference, BMI, Mallampati

Summary Table III

Evolutionary anatomic changes associated with OSA

Short maxilla and mandible
Short ethmoid and palate
Smaller teeth
Anterior foramen magnum
Acute cranial base angulation
Oropharyngeal tongue
Descended larynx
Shortened soft palate

Loss of epiglottic – soft palate lock up

Narrow, distensible supralaryngeal vocal tract (SVT)

1:1 ratio of SVT_H: SVT_V

Summary Table IV

Evolutionary anatomic changes associated with OSA

	Female	Male
Maxilla/Mandible	Shorter	Longer
Laryngeal descent	Less	More
Speech frequency	Higher	Lower
SVT_H: SVT_v	1:1	1:1
Oropharyngeal length	Shorter	Longer

Summary Table V

Hormones

Menopause – increased prevalence of OSA
HRT decreases prevalence of OSA
High estrogen/progesterone or low testosterone protects against OSA