Gender and Obstructive Sleep Apnea Syndrome, Part 2: Mechanisms

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Summary: Epidemiologic studies have reported that obstructive sleep apnea syndrome (OSAS) is a common disorder affecting about four percent of adult males and two percent of adult females. This difference in OSAS prevalence suggests that the female gender may reduce the risk of sleep breathing disorders in adults. We review several interrelated factors that may explain the differences in risk related to gender. These include differences in obesity and the distribution of adipose tissue, upper-airway anatomy, upper-airway muscle function, control of ventilation, the effect of sex hormones and leptin. The gender related protective effect decreases in females who are postmenopausal and not on hormone replacement therapy.

Key words: Sleep apnea; gender; sex; hormones; control of breathing; obesity

INTRODUCTION

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) IS A DISORDER IN WHICH PEOPLE REPETITIVELY STOP BREATHING DURING SLEEP AND HAVE THE NIGHT TIME CONSEQUENCES OF HYPOXEMIA AND SLEEP FRAGMENTATION, and the daytime consequences of sleepiness and cardiovascular comorbidity.1 OSAS which was once thought to be very rare in females, is actually common in them. In an accompanying review,2 we discuss gender-related differences in clinical presentation and polysomnography. Epidemiologic studies have reported that OSAS affects about four percent of adult males and two percent of adult females.2,3 This difference in prevalence suggests that the female gender may reduce the risk of sleep breathing disorders in adults. In addition, most large series have shown that episodes of apnea in females are less frequent and may be clustered in rapid-eye movement (REM sleep).4 The upper-airway resistance syndrome (UARS), which results from cyclic increases in upper airway resistance leading to brief arousals and daytime sleepiness,3 may be a more common problem in females than males.6 Here we review the mechanisms that could explain gender differences in OSAS which can be divided into several separate but interacting categories: obesity pattern and fat distribution; upper-airway anatomy and function; the control of breathing; and hormone status.7,8

Fat and its Distribution Pattern

Weight. OSAS is characterized by recurrent upper-airway obstruction. If men have more frequent and severe apnea episodes, they should have different structure or function or different control of their upper airways. Obesity is the most important predisposing factor in OSAS.3,8,9 It is one of the major common links that drives the expression of sleep apnea in both men and women. It has been recognized that even subtle changes in BMI may significantly affect upper-airway collapsibility as well as the severity of apnea.8 There may be clinical improvement in OSAS after only modest weight loss.10

Women are more frequently obese than are men,11 and morbid obesity (BMI>35 kg/m2) occurs twice as often in women (4%) compared to men (2%).12 Since obesity may be the main risk factor for the development of sleep apnea, one would predict that women should have OSAS more frequently than men. But epidemiologic evidence supports the opposite. Thus obesity by itself cannot explain the higher male prevalence. What appears to be more important is the location of the adipose tissue.

Fat distribution. Upper-body (chest and abdomen) obesity which is the characteristic pattern of fat distribution of middle-aged men has been found to be statistically better related to cardiovascular morbidity than is the degree of fatness.13-15 Additionally, in postmenopausal women it has been shown that central body obesity is correlated with higher morbidity.13 In both men and women waist-to-hip ratio is the best indicator of risk for cardiovascular disease.13

Millman and colleagues16 compared body-fat measurements of 25 female OSAS patients (12 premenopausal and 13 postmenopausal) to 45 males with OSAS. The AHI was best correlated with the sum of subscapular and triceps skin fold as measures of the severity of obesity. The severity of sleep apnea in women seemed to be related to upper-body obesity. Despite similar BMI and waist circumference, men had a greater degree of upper-body obesity with smaller hip circumference, higher waist-to-hip ratio and a larger subscapular skin-fold thickness.

Fat in the upper airways. The upper-body fat distribution in men may partly explain why men have OSAS more frequently than women. There is a relationship between overall neck size and airway obstruction in men,17 but there is still controversy about the significance of the precise anatomic distribution of fat deposition in the neck.8,16 Obesity predisposes to OSAS because of mass loading of the upper airway by adipose tissue in the neck.
The lateral parapharyngeal fat pads are increased in OSAS patients. In addition, in nonobese OSAS patients, deposition of adipose tissue anterolateral to the upper airway has been shown to increase the risk for development of airway obstruction independently of the BMI or the neck circumference. Gender differences in fat deposition, especially in the neck, might play a role in the male predominance of OSAS.

There are few studies comparing neck-tissue composition between males and females. Whittle et al. using MRI techniques compared the necks of normal men and women and studied the distribution of fat. They did not find differences in the amount of fat in the neck between men and women, however they found the total neck soft-tissue volume was greater in men. The larger soft tissue volume in the necks of men was mainly due to soft tissue (muscle) other than fat. However, the necks of men contain a higher proportion of fat than do their bodies as a whole, while the reverse is true for women matched for BMI. They found two regions of the upper-airway in which the men had a larger absolute volume than women. These were the soft palate and the upper part of the tongue. Upper-airway obstruction can occur at the retroglossal region where women had both greater fat deposition and a narrower airway at the retroglossal airway below the level of uvula. The effect of gender on the site of airway collapse has not been studied, thus it isn’t known if this region is more prone to collapse in women than in men. Whittle et al. concluded that the larger soft-tissue bulk in combination with dynamic properties of the upper airway may play a role in gender related differences in sleep apnea.

In summary, obesity per se cannot explain the higher prevalence of OSAS in males. The upper-body pattern of obesity in males seems more closely linked to the development of OSAS. Gender differences in fat deposition, especially in the neck, might play a role in the male predominance of OSAS.

**Upper Airway Anatomy and Function**

**Craniofacial anatomy.** Differences in craniofacial anatomy could be important in gender differences in the severity of OSAS and are described in the companion review. Both males and females with OSAS may have cephalometric differences compared to normals (for example retrognathia). It has been suggested that women have less upper airway anatomic abnormalities or require greater body fat infiltration before they have reduction in pharyngeal airway space. Sforza et al. examined the pathophysiologic role of the anatomic factors in male OSAS patients and found that elongated soft palate and lower hyoid bone position increased the tendency of pharyngeal collapse. It is not known whether these could explain gender influence on the prevalence of OSAS.

Craniofacial abnormalities may predispose females to develop UARS. Guilleminault et al. found abnormal craniofacial features in 45% of 338 women with UARS. The same group later reported that about 32 percent of patients in a large series of UARS were of Asian origin.

**Upper-airway dimensions.** According to the findings of the above-described studies, one would predict that men with OSAS would have a smaller pharynx than women. The opposite appears to be true. Brooks et al. found that gender was the most important independent factor contributing to pharyngeal size in normals, and men had a significantly larger pharynx than women. Despite men’s larger airway, it has been shown that men have a larger change in pharyngeal area with lung-volume change than do women. So according to these studies, although one would expect that the smaller size of the pharynx in women would make them more prone in developing sleep apnea, it seems that the pharynx of men is more vulnerable due to the greater change in size. Thus normal men may have a greater tendency to collapse their airways and this mechanism is suggested as a possible explanation of gender differences in the development of OSAS. Women have stiffer upper airways. Rowley et al. have suggested that a narrow upper airway may be stiffer and hence less prone to collapse.

Mohsenin found that females with OSAS had a smaller pharynx than did males with OSAS; pharyngeal size was correlated with apnea severity in males but not females with OSAS. Millman et al. found that men had more severe apnea for the same degree of upper-body obesity, which suggests that fat distribution in the neck may play a greater role in men than in women. One possibility is that the addition of even small amounts of fat around the pharynx of men with OSAS might augment normal gender differences in the mechanical properties of the pharynx.

**Upper-airway function—awake.** In OSAS patients upper-airway dilator-muscle activity is higher than in normal subjects during wakefulness. This probably protects the airway from collapse during wakefulness. During sleep the loss of muscle activation results in airway collapse. At sleep onset there is a reduction in the activity of both tonic (tensor palatini) and phasic (genioglossus) upper-airway muscles. But in NREM sleep genioglossus activity is either maintained at waking levels or augmented. Thus at sleep onset there is an increase in upper-airway resistance (UAR) that may lead to obstruction. Most of the studies have examined male subjects.

If men have lower resting upper-airway dilator-muscle tone and higher UAR they should be more vulnerable to the development of OSAS. There are data that indicate that in wakefulness UAR is higher in men than in women, but Popovic et al. showed similar waking pharyngeal airway resistance in men and women. It has been shown that women have a more active genioglossus electromyogram than do men during wakefulness and it has been postulated that this might protect women from obstruction during sleep. On the other hand, Jordan et al. reported that in healthy men and women there were no gender-related differences in the genioglossus EMG at rest and in genioglossus and diaphragm response to brief hypoxia. The latter is a measure of respiratory afterdischarge, which is an index of the damping of the respiratory-control system. A short respiratory afterdischarge could result in respiratory-system instability. Theoretically, differences between genioglossus and diaphragm respiratory afterdischarge could also predispose an individual to instability. Jordan et al. concluded that gender-related differences in neural control could not explain the higher prevalence of OSAS in males.

**Sleep.** Few studies have examined the influence of gender on UAR during sleep, and almost all were done in healthy people, not patients with OSAS. Thurnheer et al. in a study of healthy people tested the hypothesis that middle-aged men narrow their upper airways more during sleep than women or younger men. They failed to show any gender differences in airway resistance from wakefulness to NREM or REM sleep in healthy persons.
They found that men had a greater increase in resistance during the transition period from wakefulness to NREM sleep.

Rowley et al found no gender-related differences in awake versus NREM-sleep UAR, and found no gender-related differences in UAR during stage 2 sleep in healthy males and females. This group also reported no differences in airway collapsibility during sleep between males and females, a finding that is in contrast with that of Pillar et al, (see below). Methodologic differences were present between the two studies. Rowley et al suggest that immediate load compensation is more impaired in men than women, and the resulting anatomic changes (reduction in lung volume) lead to increased pharyngeal collapsibility.

Trinder et al. studied UAR during sleep in healthy people in an attempt to explain the greater susceptibility of men to sleep apnea. They compared the changes in ventilation and UAR to see if the progressive increase in UAR—previously observed in men as NREM sleep deepens—is greater in men than in women. They did not find differences during the sleep-onset period, but in NREM sleep (stage 2) UAR increased more in men than in women and men had a greater tendency to develop flow limitation. This finding could be explained by greater attenuation of tonic upper-airway muscle activity in men than in women, or the decrease of tonic activity is similar but the activity of the phasic upper-airway dilator muscles is greater in women, which protects them from further increase of UAR as NREM sleep develops.

Pillar et al. demonstrated that the pharyngeal airway in healthy men when asleep is more collapsible than in women. They increased the load to airways by exposing the airways to greater intraluminal negative pressure. The men showed less ventilatory response to the extra load. This could be due either to increased pharyngeal-wall compliance or decreased pharyngeal-muscle activation, which might lead to increased collapsibility, or to decreased central ventilatory drive. The measured central ventilatory response to loading was similar in men and women so it was concluded that the men have more collapsible upper airways. The same group found that upper-airway size and airflow resistance was similar in men and women. Women had a shorter airway (measured from hard palate to epiglottis), and it was suggested that the longer airway in men may play a role in the increased collapsibility along with different pharyngeal-tissue properties. An airway could be either stiff or compliant depending on the given wall properties of the structure. The elastic properties of the airway wall, depending on the amount of connective tissue, may affect the upper airway compliance. So the observed differences in airway resistance between awake and various sleep stages might reflect age and gender-related differences in activity of the upper-airway muscles or the elasticity of the pharynx.

In summary, although some craniofacial differences are present between males and females, it is not likely that they are important in determining gender-related prevalence differences in OSAS. Craniofacial abnormalities may explain the relatively high prevalence of UARS in females. Although females (normals and OSAS patients) have a smaller pharynx than do corresponding males, they are either protected from developing OSAS or have a disorder that is generally less severe than in males. The central drive to upper-airway muscles seems similar in men and women and increased airway collapsibility in males may be one of the most important factors in explaining the higher prevalence of OSAS in males. It must be remembered, however, that most of the articles that examined upper-airway physiology in sleep studied relatively small numbers of normal people and not OSAS patients. What may be important are not the physiologic differences between healthy males and females, but what physiologic differences exist between males and females with and without OSAS.

Control of Ventilation

In normals. Gender-related differences in the control of ventilation may play a role explaining the male predominance of OSAS. It has been shown that a collapsible airway is dependent on the ventilatory motor output under conditions of flow limitation. Sufficient sensitivity to CO2 may be a critical factor for adequate tone in the upper airway muscles during wakefulness. Pillar et al. showed that the dilator pharyngeal muscles are unresponsive to rising PCO2 during NREM sleep.

Men have increased ventilatory sensitivity to hypoxia and hypercapnia during wakefulness when compared to women. If this difference is maintained during sleep, it could explain the sleep-related upper-airway instability of males. Hypercapnic ventilatory response is decreased during sleep in both men and women, which results in a slight increase of PCO2. An arousal may lead to ventilatory overshooting, hypocapnia, and a central apnea or hypopnea. Zhou et al studied the incidence of hypocapnia-related apnea or hypopnea during NREM sleep in both sexes. Healthy young women were less susceptible than men to develop apnea during sleep. Zhou et al suggested that the gender difference in apneic threshold indicates a difference in chemoresponsiveness. Men seem more vulnerable to airway collapse in the presence of hypocapnia. This may contribute to gender difference in prevalence and severity.

Jordan et al studied the ventilatory decline after relief of hypoxia or hypercapnia since prolonged hyperventilation may produce breathing instability and predispose a person to develop apnea. It has been suggested that the gradual decay in ventilation after removal of a respiratory stimulus may protect against breathing instability. Jordan et al did not find differences between the sexes and concluded that this is not a likely mechanism for the increased prevalence of OSAS in men.

In obesity. To maintain ventilation in the presence of obesity or upper-airway obstruction requires an augmentation in the neuromuscular drive to breathe. In OSAS patients, during wakefulness there is activation of pharyngeal-dilator muscles, which compensates for the collapsible airway of OSAS. The mechanism of this compensation is not well understood. Recent studies suggest that the hormone, leptin, which is increased with obesity, may play a role in preventing hyperventilation with obesity (see below).

Harman et al studied breathing during sleep in obese subjects and found more oxygen desaturations in men than in women. In contrast, Catterall et al reported that the irregular breathing patterns and hypoxemia that develop during sleep are similar in normal nonobese men and women. White et al. reported that normal men in the awake state had greater ventilatory response to hypoxia than women did in the awake state. Both men and women had similarly depressed responses during sleep. The magnitude of the decrease from the awake response is greater in males than in females. The authors speculated that if
the same relationship between sleep and waking was found in obese subjects, obese male patients might have further depressed ventilatory responses to hypoxia during sleep compared to female obese patients.

Kunitomo et al.\textsuperscript{56} examined the hypoxic and hypercapnic ventilatory drive in obese men and women and normal weight controls. The responses in male and female obese subjects were not different. In obese female subjects, the ventilatory responses were greater than in the normal weight females. On the other hand, there was no major difference in ventilatory drive between obese and healthy males. So the relatively depressed chemosensitivities in obese men could predispose them to developing apneas in sleep. Women with mass loading of their respiratory system enhanced their hypoxic and hypercapnic chemosensitivities, but men did not.

Sin et al.\textsuperscript{57} studied the relationship of hypercapnic ventilatory response and presence of OSAS in both men and women. This group found that OSAS is not associated with blunted hypercapnic ventilatory chemoresponsiveness. Similar results came from the study of Appelberg et al.\textsuperscript{48} who reported that ventilatory response to CO\textsubscript{2} in patients with OSAS is increased under conditions of hypoxia and hyperoxia.

The obesity-hypoventilation syndrome (OHS) is the most severe form of sleep-disordered breathing.\textsuperscript{59} Females seem to make up a very high proportion of patients with the OHS. In four reports they made up more than half of all cases.\textsuperscript{60-63} Many previous studies have shown depression of hypoxic and hypercapnic ventilatory responses in OHS.\textsuperscript{64,65} The presence of hypercapnia in obese patients is associated with more severe abnormal breathing during sleep than in eucapnic patients with the sleep apnea syndrome.\textsuperscript{56} Thus in obesity, abnormalities in chemosensitivity of ventilatory control during wakefulness may play a role in inducing sleep-disordered breathing. Recent studies suggest that in OHS there might be a failure of the mechanisms that compensate for the increased work of breathing in obesity and that failure may involve resistance to the central effects of leptin\textsuperscript{63} (see following section Hormonal status). The reason why females make up such a large proportion of OHS cases is not clear but may reflect the fact that morbid obesity is more common in women than in men.

In summary, the observed gender-related differences in chemical drive to breathe during wakefulness in normals may in part explain the propensity of males to develop OSAS. Females are less susceptible than males to develop apnea or hypopnea in response to hypocapnia during sleep. Obese women enhanced their hypoxic and hypercapnic chemosensitivities compared to normal weight controls but men did not. OSAS is not associated with blunted chemical drives to breathe in either male or female patients. OHS seems at least as common in females as in males and in both genders is associated with blunted chemical drives to breathe. The reason for the large number of female OSAS cases may relate to the fact that morbid obesity is more common in them, or perhaps they may develop more resistance to the central effects of leptin.

**Hormonal status**

**Female hormones.** It was shown many years ago that progesterone increases ventilatory chemoresponsiveness.\textsuperscript{67} Sutton et al. reported that medroxyprogesterone improved the clinical features of OHS,\textsuperscript{68} but that study only reported data obtained in wakefulness. Kryger et al. showed that the same agent improved oxygenation during sleep in patients with chronic mountain sickness.\textsuperscript{69}

The protective effect of progesterone on awake and sleep ventilation is not entirely understood. Progesterone has been reported to increase the ventilatory response to hypercapnia and hypoxia.\textsuperscript{70} In pregnancy the increased ventilation is attributed to higher levels of progesterone.\textsuperscript{71} Normal weight healthy women have a reduction in AHI from already low normal values during pregnancy in spite of increasing weight and worsening of lung mechanics.\textsuperscript{72} Even very obese pregnant women seem protected from developing OSAS.\textsuperscript{73} Ventilation is also higher in the luteal phase of the menstrual cycle.\textsuperscript{44,74}

The protective role of the female hormones may be due to an effect on the upper-airway dilator muscles. Popovic et al.\textsuperscript{75} studied the influence of sex hormones on upper-airway muscle activity in healthy women in three natural hormone states. They showed that the activity of dilator upper-airway muscles was greater during the luteal phase, when progesterone levels are high; less in postmenopausal women; and increased with hormonal replacement. All these studies were conducted during wakefulness. If present in sleep, these hormone influences may protect the female upper airway from obstruction during sleep.

Sleep apnea has been reported to be more frequent in postmenopausal women than premenopausal women.\textsuperscript{16,24,76-79} Dancey et al.\textsuperscript{1} in a recent very large study of 1967 women, confirmed that the prevalence and severity of sleep apnea increases in women after menopause.\textsuperscript{79} The prevalence in postmenopausal women was at least double that seen in the premenopausal women. This suggests that the gonadal hormones, particularly progesterone, may protect premenopausal women from developing OSAS.

Using hormone replacement therapy in the treatment of OSAS in postmenopausal females has yielded conflicting results. Administration of estrogen alone resulted in modest improvement in OSAS in a study involving 6 postmenopausal OSAS patients; AHI was reduced by about 25%.\textsuperscript{80} Addition of a progesterational agent resulted in a further significant improvement with AHI falling by 50% from no treatment. Bixler et al.\textsuperscript{76} in a large population based study reported that hormone replacement therapy in postmenopausal women, is associated with a reduction of prevalence of OSAS to the level of premenopausal women. Franklin et al. reported a postmenopausal patient in whom the combination of estradiol and cyclic medroxyprogesterone abolished the patient’s OSAS.\textsuperscript{81} Moore et al.\textsuperscript{82} reported that in healthy postmenopausal women the number of apnea events per night decreased from 15 to 3 when they were treated with an estrogen and progesterone combination. Cistulli et al.\textsuperscript{83} showed that estrogen alone or the combination of estrogen and progesterone did not result in an improvement in the clinical severity of OSAS, although the authors did find a small reduction in the number of apneas in REM sleep.

Because progesterone had been shown to be effective in some cases of OHS,\textsuperscript{68} this hormone was tried in male patients with OSAS who did not have awake hypoventilation; the treatment was not effective.\textsuperscript{84,85}

**Male hormones.** Testosterone does not appear to have an effect on hypercapnic drive to breathe when given to hypogo-
nadal males. Cistulli et al reported that testosterone increased upper airway collapsibility in a 13-year-old male resulting in exacerbation of sleep apnea. One study reported that hypoxic ventilatory response increased with testosterone replacement while another reported a decrease. Schneider et al reported that hypogonadal males treated with testosterone replacement had an increase in AHI from 6.4 to 15.4. Exogenous administration of testosterone was shown to induce sleep apnea in one woman. Fogel et al. reported that women with polycystic ovary syndrome (characterized by obesity and androgen excess) are at increased risk for OSAS. These women had higher AHI than controls (22.5 vs. 6.7). So the influence of testosterone may at least in part explain the male predominance in OSAS.

Leptin. It has been suggested that other nonreproductive hormone factors may link obesity with changes in ventilatory control. Leptin is a hormone produced by fat cells that has an action in the hypothalamus that decreases appetite and increases energy consumption. The circulating levels of leptin are higher in women perhaps because subcutaneous fat (lower) produces more leptin than visceral fat (upper) does/or because of the effect of reproductive hormones. Leptin may stimulate breathing and thus may compensate for the increased work of breathing in obesity. It is possible that leptin may thus play a role in control of breathing during sleep and high levels may stimulate ventilation in obese females. Animal studies using leptin-deficient female and male mice suggest that leptin deficiency in female obesity is even more detrimental to hypocapnic drive to breathe during wakefulness and NREM sleep than in obese, leptin-deficient males. It has been reported by Phipps et al that hypocapnic respiratory failure in obesity is associated with hyperleptinemia suggesting that there may be central resistance to the effect of the hormone. It has been reported that leptin levels are elevated in OSAS and the levels decrease when a patient is on CPAP. This field is evolving rapidly, but it appears that leptin metabolism may turn out to be an important factor in explaining gender difference in the expression of breathing disorders in sleep.

In summary, the prevalence of OSAS in postmenopausal women was at least double than that seen in premenopausal women, suggesting that the female hormones, particularly progesterone, may protect premenopausal women from developing OSAS. Testosterone, on the other hand, may increase the risk of developing OSAS. Some studies have shown that hormone replacement therapy may improve OSAS in postmenopausal women. Progestational agents have not been shown to improve OSAS in males. The hormone leptin may act centrally to increase ventilation. Leptin levels, which are linked to obesity, are higher in women and in patients with OSAS. It has been suggested that respiratory failure in OHS may be due to central resistance to the effect of the high circulating levels of leptin in these patients.

Table 1—Mechanisms explaining gender differences in OSAS

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<tr>
<th>Fat and its distribution pattern</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Body mass index&lt;sup&gt;24,96&lt;/sup&gt;</td>
<td>++</td>
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<td>Upper body fat distribution&lt;sup&gt;14-16&lt;/sup&gt;</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Neck circumference&lt;sup&gt;16&lt;/sup&gt;</td>
<td>++</td>
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<tr>
<td>Fat amount in neck&lt;sup&gt;21&lt;/sup&gt;</td>
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<td>+</td>
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<tr>
<td>Soft tissue amount in neck&lt;sup&gt;21&lt;/sup&gt;</td>
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<td>+</td>
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<tr>
<td>Soft palate volume&lt;sup&gt;21&lt;/sup&gt;</td>
<td>++</td>
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<th>Upper airway anatomy and function</th>
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<td>Upper airway collapsibility&lt;sup&gt;28,31,38&lt;/sup&gt;</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Upper airway resistance during wakefulness&lt;sup&gt;34&lt;/sup&gt;</td>
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<td>+</td>
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<td>Upper airway resistance during sleep&lt;sup&gt;31,37,39&lt;/sup&gt;</td>
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<td>+</td>
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<tr>
<td>Upper airway muscle activity in wakefulness&lt;sup&gt;35,36,75&lt;/sup&gt;</td>
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<th>Control of ventilation</th>
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<tr>
<td>Genioglossus and diaphragm afterdischarge&lt;sup&gt;36&lt;/sup&gt;</td>
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<tr>
<td>Hypocapnic ventilatory drive—wake&lt;sup&gt;44&lt;/sup&gt;</td>
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<td>Hypoxic ventilatory drive—wake</td>
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<td>Central drive to upper airway muscles&lt;sup&gt;38&lt;/sup&gt;</td>
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<td>+</td>
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<td>Apneic threshold during NREM sleep&lt;sup&gt;48&lt;/sup&gt;</td>
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<td>++</td>
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<tr>
<td>Mass loading enhancement of central drive&lt;sup&gt;56&lt;/sup&gt;</td>
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<th>d. Hormonal status</th>
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<td>Increased ventilation by progesterone&lt;sup&gt;70&lt;/sup&gt;</td>
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<td>Upper airway muscle activity by progesterone&lt;sup&gt;75&lt;/sup&gt;</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Pharynx collapsibility by testosterone&lt;sup&gt;88&lt;/sup&gt;</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Leptin level or resistance&lt;sup&gt;53,90,97&lt;/sup&gt;</td>
<td>++</td>
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Most of the studies were done in healthy people. The number of +s is a qualitative index comparing findings in males and females. For example, neck circumference is greater in males with OSAS than in females. For some of the mechanisms there may be studies which are not in agreement.
Conclusion

In spite of many pathophysiologic studies (Table 1), the reason for the gender-related differences in OSAS prevalence is not entirely understood. Many of the studies were done in healthy men and women and had relatively few subjects. Most men and women do not develop OSAS and so studies of physiology in normals may not supply the answer to the question of why females seem protected from OSAS. There are interactions among the factors mentioned above. For example, the female hormones may affect fat deposition, chemical drives to breathe, leptin levels, and perhaps the mechanical properties of the upper airways. Two factors seem to stand out as being important. First, the influence of hormones may be the most important determinant of the pathophysiologic differences between the two sexes. Second, differences in airway collapsibility between men and women seem to be the most likely physiologic mechanism that could explain the male predominance of OSAS. Certainly more studies are needed to address the possible mechanisms that protect females from sleep-related breathing disorders or that result in a different expression of sleep-related breathing disorders in females.

REFERENCES


