



Sleep disordered breathing: is it different for females?

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Predominance of low AHI and partial upper airway obstruction may lead to undertreatment of female SDB <http://ow.ly/TKN7d>

Obstructive sleep apnoea (OSA) is no longer considered to be a disease of males only. The latest prevalence estimates of moderate-to-severe OSA in women range from 6% to 20% [1, 2], resulting in male/female ratio from 3/1 to 2/1 [1]. These figures may still underestimate the prevalence of sleep disordered breathing (SDB) in women, in whom the upper airway obstruction often manifests as noncountable, nonapnoeic respiratory events (snoring, flow limitation or partial upper airway obstruction) [3–6]. Failure to recognise the distinct clinical presentation and partial obstruction in sleep studies may lead to under-recognition of SDB in females [7, 8]. For instance, prior to diagnosing OSA, women are twice as likely as men to be treated for depression [7].

Atypical OSA is typical for females

In terms of symptoms, women are less likely to report snoring or witnessed apnoea but are more likely to complain of daytime fatigue, lack of energy, insomnia, morning headaches, mood disturbance and nightmares compared to men [7, 8].

In sleep studies, compared to men, women have a lower apnoea–hypopnoea index (AHI), and their apnoeic episodes are shorter and less often associated with complete upper airway collapse [7]. Women have less supine OSA but clustering of apnoea during rapid eye movement (REM) sleep is common [7]. Lower AHI in women is contrasted with higher occurrence of prolonged episodes of partial upper airway obstruction [3–6], which typically appear in slow-wave sleep and are associated with increased carbon dioxide levels [9, 10]. Increased carbon dioxide during sleep could be one possible reason [9, 10] why women are symptomatic at relatively low AHI [11] and have a different symptom profile [7]. This is supported by the finding that in women, excessive daytime sleepiness and daytime fatigue are associated with habitual snoring, independent of AHI, age, obesity, smoking or sleep parameters [12]. Partial obstruction is related to increased respiratory resistance [13], which is characterised by an increase in end-tidal [14] and transcutaneous carbon dioxide [9]. Correcting prolonged flow limitation with continuous positive airway pressure (CPAP) treatment is associated with a higher attentiveness and a higher efficiency in normalising daytime vigilance than when eliminating only apnoea, hypopnea and snoring [15]. Furthermore, hypercapnia is associated with electroencephalography (EEG) slowing and daytime sleepiness in SDB [16], and CPAP treatment corrects the EEG slowing together with decreased daytime sleepiness [17].

Role of hormones in female SDB

Hormonal changes in women may either protect against or predispose to SDB. Progesterone is a powerful respiratory stimulant [18]. Both progesterone [19] and oestrogen [20] enhance genioglossus contractility,

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counteracting the upper airway collapsibility during sleep. Progesterone prevents sleep disturbances [21] and may therefore stabilise nocturnal breathing. The increased respiratory drive caused by female hormones, particularly progesterone, may protect upper airway patency by enhancing upper airway dilator muscle activity [19]. Conversely, the increased ventilatory drive associated with increased levels of progesterone [18, 22] might cause a vacuum effect and increase the risk of upper airway collapsibility. By increasing respiratory drive and decreasing arterial carbon dioxide tension, higher progesterone levels might predispose to periodic breathing [23]. The phase of the menstrual cycle also influences control of breathing. Carbon dioxide sensitivity is higher and upper airway resistance lower during the luteal phase (high progesterone levels) compared to the follicular phase [24, 25]. Administration of testosterone increases the apnoeic threshold in women. Since the hypocapnic apnoeic threshold is higher in men than women, this suggests that the increased breathing instability during sleep in men is related to the presence of testosterone [26].

Pregnancy, polycystic ovary syndrome and menopause are female-specific and sex hormone-dependent conditions that may predispose to SDB. Progesterone and oestrogen levels increase during pregnancy and decline during menopausal transition, whereas polycystic ovary syndrome is associated with androgen excess.

Prevalence of snoring in pregnant women ranges from 10% to 45% and up to 75% in pre-eclampsia [27]. The prevalence of OSA during pregnancy is unknown. Lean women are well protected from OSA even in cases of multiple pregnancy [28], whereas in obese women, the prevalence is estimated to increase up to 10% by the first and 27% by the third trimester [29]. Increased minute ventilation, preference for the lateral sleeping position in late gestation and decrease in REM sleep may protect against OSA, whereas gestational weight gain, oedematous nasal mucosa, decreased lung functional residual capacity (FRC) and increased arousals increase the OSA risk [31]. The enlarged uterus causes diaphragmatic elevation leading to increased end-expiratory abdominal pressure, and reduced expiratory reserve volume and FRC [22], which may result in less caudal traction of the trachea and pharynx, predisposing to increased airway collapsibility [23]. Furthermore, the increased ventilatory drive associated with increased levels of progesterone [22] may cause a vacuum effect and increase the risk of upper airway collapsibility.

An obvious concern is that intermittent hypoxia could predispose to placental ischaemia and fetal growth retardation [30, 31]. In an animal model, gestational chronic intermittent hypoxia resulted in intrauterine growth restriction and increased the risk of the offspring for metabolic diseases in adulthood [32]. Especially in obese women, OSA may be associated with increased risk of gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, intrauterine growth retardation, preterm delivery, caesarean section and neonatal intensive care [30, 31]. Conversely, pre-eclampsia might predispose to OSA through fluid retention, rostral fluid shift and upper airway oedema. Potential shared pathophysiological mechanisms include oxidative stress, increased sympathetic activity, inflammation, adipokine effects and insulin resistance [30, 31].

SDB in women with pre-eclampsia typically manifests as flow limitation with increases in nocturnal carbon dioxide levels but with low AHI despite increased frequency of oxygen desaturations, particularly during REM sleep. Blood pressure responses to episodes of obstructive apnoea are augmented in normal pregnancy and further in pre-eclampsia [30]. The increased sympathetic activity during the third trimester contributes to the increased prevalence of OSA, which in turn probably further augments sympathetic tone predisposing to pre-eclampsia [30]. CPAP treatment reduces sleep-induced blood pressure increments and upper airway collapsibility [30] and improves fetal movement activity [33] in pre-eclampsia.

The prevalence of SDB in females doubles after menopause [34–36] independently of age and BMI [35], the peak being at the age of 65, 10 years later than in men [34]. Less hyperpnoea after episodic hypoxia and more stable respiratory effort in non-REM sleep in response to hypercapnia and arousals might protect premenopausal females from OSA [37]. During menopausal transition, respiratory drive decreases [38]. Increased arousals predispose to respiratory instability and increased soft tissue collapsibility aggravates upper airway obstruction. Weight gain further increases the risk of OSA. However, obesity may have a sex-specific impact on prevalence and type of OSA. In a study of more than 20 000 patients, OSA severity increased linearly with age in normal-weight and obese women and in normal-weight men, whereas in obese men, AHI increased from age 20 to 40 years and remained stable thereafter [39]. In 233 age- and BMI-matched male–female pairs, OSA increased with increasing BMI only in men, whereas partial obstruction increased with moderate to morbid obesity in both sexes after the age of 65 years [40].

Does lower AHI in women mean less severe OSA?

The impact of OSA on cardiovascular risk in women has not been established. Most studies have included only men and the few studies in females have had inconsistent results. Some studies have suggested higher [8, 41], some similar [42] and some even lower cardiovascular risk [43, 44] in women with SDB compared to men. Lower risk of hypertension has been suggested in postmenopausal women with mild SDB (snoring or AHI <15 per h) and using hormone therapy [45] or in those presenting with predominantly

partial upper airway obstruction [46]. Severe SDB has more consistently been associated with increased cardiovascular risk. Females with untreated OSA, followed for 6.8 years, had a greater incidence of stroke and chronic heart disease than women without OSA [47]. Severe OSA was also associated with cardiovascular death in women [48]. Adequate CPAP therapy reduced these risks [47, 48]. The Sleep Heart Health Study found no association between OSA and mortality in women [49].

Women seem to have a greater impairment in quality of life and higher healthcare expenditure than men with similar AHI severity [50]. Women with OSA had a two-fold increased risk of lost work days due to work disability compared to controls [51]. Furthermore, the excess risk in women was already pronounced 5 years prior to the year of OSA diagnosis, whereas in men, the highest risk was noticed 1 year before the year of diagnosis [51].

Female-specific criteria for diagnosing SDB?

Conventionally, the diagnosis of SDB is based on AHI, with an AHI >5 per h being considered significant for diagnosis. A higher AHI is sometimes required for initiation of nasal CPAP therapy and an AHI >30 per h is considered severe SDB, associated with marked comorbidity and decreased quality of life.

In women, “mild OSA” may translate into as severe health consequences as OSA with higher AHI in men [46, 52]. Considering increased fatigue in women with OSA despite low/normal AHI, it has been suggested that symptomatic women with snoring or partial upper airway obstruction should be considered for treatment even if AHI <5 per h [5, 12]. This approach is supported by good CPAP adherence in women with predominantly partial obstruction [4].

Should women be treated differently?

Irrespective of sex, weight loss is the corner stone of treatment of SDB in obese patients. In women, weight loss may, however, be less efficient in decreasing OSA severity [53]. Oral appliances may work better in women than in men [54].

Nasal CPAP is the treatment of choice. For women in particular, it is important to titrate the pressure to control not only OSA but also episodes of partial upper airway obstruction [15, 16]. Recent female-specific autotitrating algorithms for CPAP devices may reduce flow limitation more efficiently but whether this results in better treatment outcome remains to be shown [55].

There are no common specific guidelines for treating SDB during pregnancy or *post partum*. However, it is reasonable to apply similar, if not less stringent, criteria for treatment. Autoadjusting CPAP devices are a feasible option responding to required pressure adjustments during pregnancy and *post partum*. Oral appliances may be impractical during pregnancy, since they may need multiple fitting sessions. Weight reduction or surgical procedures should be avoided until their safety in pregnant women is well-enough established. Positional treatment or reduction of mucosal oedema with nasal corticosteroids may be beneficial [18].

Menopause is associated with depletion of female sex hormones with concomitantly increased OSA risk [34, 35]. Epidemiological studies suggest that hormone therapy could alleviate OSA [34, 56]. Hormone therapy might increase genioglossal activity [19] and apnoea threshold resulting in decreased propensity to periodic breathing and OSA [49]. However, small interventional studies using different formulas of hormone therapy have provided conflicting results in alleviating SDB severity [18, 57, 58]. The inconsistent evidence and risks of hormone therapy do not justify its use to prevent or treat OSA.

Conclusions

Pre-menopausal women are relatively well protected from SDB. Larger epidemiological studies of OSA prevalence and fetal outcome during normal pregnancy and pre-eclampsia are needed. SDB in women may be more severe and symptomatic than AHI would predict. This is due to the high prevalence of partial upper airway obstruction, resulting in clinically significant carbon dioxide increases during sleep. In symptomatic women with low AHI but marked partial upper airway obstruction, a CPAP trial is often justified. Better understanding of the mechanisms through which different hormonal environments during a woman's life span predispose to or promote progression of OSA will ultimately lead to novel therapeutic options to prevent and treat SDB in women across all ages.

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