



When do gender differences begin in obstructive sleep apnea patients?

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Higher prevalence of obstructive sleep apnea (OSA) in men compared to women has been consistently reported by previous clinic-based and community-based studies. In addition, OSA is more severe in men compared with women matched for body mass index, although this sex difference decreases with increasing age. Even in terms of symptomatic presentation differences have been reported between genders: women are more likely to report non-specific symptoms such as headache, fatigue, depression, anxiety and sleep onset insomnia whereas men frequently report snoring, gasping, snorting and apnea, which are primary hallmarks of OSA (1). Pharyngeal cross-sectional area is similar in men and women, but men show greater upper airway collapsibility than women, when measured by the critical collapsing pressure. Longer airway length and larger volume of soft tissues on the lateral pharyngeal walls are deemed to be associated with greater susceptibility to collapse in men (2). Alternatively, the difference in collapsibility has been also explained by the different amount of fluid displacement from the legs to the neck during recumbency in men versus women (3), as it has been shown that this fluid shift contributes to upper airway narrowing (4).

Hormonal differences between the sexes have been thought to account for the increased prevalence of OSA in men. Since the study reporting that the apnea-hypopnea index (AHI) increased in hypogonadal men after testosterone administration (5), numerous studies

have been conducted to elucidate the influence of testosterone on ventilatory control and its potential role in OSA pathogenesis. It has been shown that the acute administration of testosterone increases the ventilatory response to hypoxia and hypercarbia (6) that may in its turn enhance ventilatory instability and the so-called loop gain of the ventilatory system (7), increasing the predisposition to sleep apnea. Several studies showed also an increased ventilatory response to carbon dioxide or hypoxia in men *vs.* women during wakefulness (1), although this difference seemed attenuated or absent during sleep. It is important to note that low levels of testosterone are associated with obesity, and weight loss lead to increased testosterone levels (8). Given that obesity is a definite aggravating factor for OSA (7), this link may help to interpret some conflicting results showing that men with OSA have lower testosterone levels compared to age-matched subjects without OSA (1).

The impact of female sex hormones, *i.e.*, estrogen and progesterone, has also been investigated in several studies with inconsistent results. It was previously reported that the genioglossus muscle activity was positively correlated with progesterone levels, and was significantly increased by combined estrogen and progesterone replacement in postmenopausal women (9) suggesting a hormonal role in maintaining the upper airway stiffness by dilator muscles recruitment. In another pilot study to investigate the impact of hormone replacement therapy (HRT) on OSA severity, HRT had a significant AHI-lowering

effect (10). However, minor improvement in OSA severity was observed on subsequent placebo-controlled, randomized, cross-over trials (11,12). To further complicate the picture, some studies showed that sleep apnea severity increases during pregnancy, a condition characterized by increased levels of estrogen/progesterone, therefore questioning the protective effect of female hormones in regard to OSA (13). Overall, the effect of sex hormone on OSA still remain uncertain but a future personalized approach to patients with sleep-disordered breathing that takes into account different pathogenic traits (14) and hormones levels in males and females, may help to explain different effects of sex hormones on the severity of the disorder.

Like in adults, also during childhood OSA is more common among boys than girls after puberty whereas its incidence is similar between two different sexes in prepubertal children (15). The peak prevalence of OSA in children ranges 2–8 years of age, which coincides with the peak age of adenotonsillar hypertrophy (16). Given that adenotonsillar hypertrophy is a main cause of OSA in prepubertal children, similar distribution of OSA between sexes appears to be natural. Above this age group, however, the pathogenetic mechanisms of OSA may differ. According to a recent analysis of 267 pre-school and school-age children, the relationship between the degree of adenotonsillar obstruction and OSA severity was present only in pre-school children, while there was no relationship in the school-age children group, suggesting that other inter-individual differences such as anatomical or neurological factors can determine OSA at this age (17).

Only a few studies investigated thus far the pathophysiology of OSA in adolescents (18). In this regard, the current study by Inoshita and colleagues is a welcome addition to understand more about the characteristics of OSA in this subgroup of children (19). In the current study, adolescent boys (range, 9–15 years old) demonstrated more severe OSA than adolescent girls while the degree of tonsillar hypertrophy did not differ between them. By contrast, in the pre-adolescent group (3–8 years old), boys and girls showed similar OSA severity and similar degree of tonsillar hypertrophy, suggesting that the pathophysiology of OSA among pre-adolescent and adolescent children may be different.

Some limitations of this study leave open questions regarding the interpretation of these findings. First, these findings are partly in contrast with previous reports that showed that tonsillar hypertrophy is an independent factor for the increased severity of OSA in both children and

adolescents (20,21). In the current study, there was no statistical difference in the tonsillar size between boys and girls, however, this could be due to the small sample size. Among adolescents, only one boy had small tonsils (grade 1), whereas 50% of girls did, which is likely to influence the higher AHI measured in boys compared to girls.

Second, when it comes to the difference in the upper airway area and the adenoid size, adolescent boys had statistically significant smaller upper airway areas and greater adenoid size than adolescent girls, based on the lateral radiography in the present study. It was concluded that girls may have spontaneous remission of adenoid tissues while boys may not. However, we are not aware of any study showing the gender differences in the prevalence of adenoid hypertrophy in adolescents. Moreover, lateral radiography is 2-dimensional and provides only longitudinal cross-sectional area in the sagittal plane, thus offering limited information for estimating the airway areas, particularly in the case of big palatine tonsils. Indeed, in this situation, the airway is often shadowed by the contour of the palatine tonsils, and the remaining patent airway between bilateral palatine tonsils is visually identifiable through the examination of the mouth but not when measured by lateral radiographic images. Therefore, the difference in the upper airway area between adolescent boys and girls might have been affected by the degree of palatine tonsillar hypertrophy.

Lastly, the authors' hypothesis was that presumed protective effect of estrogen and/or progesterone against OSA may play a role in adolescents at puberty. As mentioned above, however, the effect of estrogen and/or progesterone against OSA remains unclear and the author did not provide the measurement of hormone levels from serum or saliva. Given the inter-individual variabilities in the initiation of the puberty, the difference between two age groups separated by age of 9 cannot to be a strong evidence for the hormonal hypothesis.

Despite several abovementioned concerns, the current study by Inoshita and colleagues provided a new hypothesis regarding the onset of male predominance of OSA in adolescents. We look forward to seeing future research including follow-up of pre-adolescent subjects and the measurement of sex hormone levels.

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Footnote

Conflicts of Interest: L Taranto-Montemurro has a financial interest in Apnimed, Inc., a company developing pharmacologic therapies for sleep apnea. His interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. SW Kim has no conflicts of interest to declare.

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