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Premature Birth: An Important but Frequently Overlooked Risk Factor for OSA

Commentary on Raynes-Greenow et al. Sleep apnea in early childhood associated with preterm birth but not small for gestational age: a population-based record linkage study. SLEEP 2012;35:1475-1480.

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Obstructive sleep apnea (OSA) in childhood is not a distinct disease, but rather a syndrome of upper airway dysfunction in a sleeping individual, usually resulting from a combination of disease entities.[1] Upper airway patency is maintained by complex interactions between resistance to airflow, pharyngeal collapsibility, and tone of pharyngeal dilator muscles along with negative intrapharyngeal pressure generated by the inspiratory muscles.[2] Abnormalities of one or more components of the upper airway may impair this fine balance of mechanical forces leading to intermittent partial and/or complete pharyngeal lumen obstruction during sleep (obstructive sleep disordered breathing [SDB]).

Pediatric OSA is under-diagnosed because parents underreport its nocturnal symptoms, and upper airway dysfunction is not always apparent to clinicians.[3] Hence, the primary care physician has to suspect the diagnosis when risk factors related to OSA are present. Adenotonsillar hypertrophy, obesity, neuromuscular disorders, and craniofacial abnormalities are well-recognized risk factors, whereas history of premature birth, recurrent wheezing, and family history of OSA are lesser known conditions associated with SDB in childhood.[1,4-6]

In this issue of *SLEEP*, Raynes-Greenow and colleagues[7] report finding that preterm birth and low birthweight for gestational age were risk factors for sleep apnea diagnosis in early childhood, prospectively. To achieve this goal, the investigators analyzed medical records from almost 400,000 children born over a 5-year period in New South Wales in Australia.

Premature birth, but not low birthweight for gestational age, is a risk factor for sleep apnea in early childhood. Investigators in three longitudinal epidemiologic studies, each with far fewer participants than Raynes-Greenow et al., attempted to answer a similar research question to that of the report by Raynes-Greenow et al. Data from the Cleveland Children's Sleep and Health Study and the Penn State Child Cohort indicated that SDB was 3-5 times more frequent in former preterm compared to term children.[4,8] In the Helsinski Study of Very Low Birth Weight Adults, it was found that this epidemiologic association persists into young adulthood.[9] Until now, no significant differences regarding prevalence of sleep apnea have been demonstrated in prematurely born subjects with birthweight appropriate as compared to small for gestational age.[9,10]

Analyzing medical records from a large population sample, Raynes-Greenow et al.[7] not only reproduced the findings of these earlier studies on premature birth as a predictor of SDB, but they also found that the risk of sleep apnea in early childhood increased progressively with decreasing gestational age. Of note, the increased risk level for OSA was not influenced by low birthweight for gestational age. Therefore, strong evidence is provided for a clinically important relationship since preterm children are more vulnerable to neurocognitive sequelae in the presence of OSA.[11] More specifically, preterm children with obstructive SDB have deficits in academic abilities, language comprehension, and planning and organizational skills.[11]

As a result of the selection by Raynes-Greenow et al.[7] of a population-based record linkage analysis, and the large number of study participants, the definition of sleep apnea was probably heterogeneous (i.e., sleep apnea, central or obstructive) and likely based on consistent symptoms and varying cutoff values for polysomnography parameters (e.g., apnea-hypopnea index). Another limitation of the report by Raynes-Greenow et al. is the absence of information about conditions possibly modifying the risk for OSA such as adenotonsillar hypertrophy or obesity.

Prenatal factors and neonatal morbidity increase the risk for sleep apnea in early childhood. The findings of Raynes-Greenow et al. confirm that prenatal factors related to maternal health contribute to the association of prematurity with OSA. For example, history of hypertension during pregnancy increases the risk of OSA in the offspring.[8,10] Surprisingly, children with maternal history of smoking during pregnancy were less likely to be diagnosed with sleep apnea, whereas the opposite relationship was demonstrated in the Penn State Child Cohort and the Helsinski Study of Very Low Birthweight Adults.[8,9]

Delivery by cesarean section frequently reflects the presence of maternal and fetal morbidity, and this fact explains the epidemiologic association of delivery type with sleep apnea. Indeed, sick neonates requiring support in a neonatal intensive care unit (NICU) are at risk of sleep apnea in later life.[8] Nevertheless, it is unclear why cardiopulmonary resuscitation at birth was a protective factor against OSA in the Australian cohort,[7] especially when taking under consideration that peripartum resuscitation and need for oxygen at birth have been found to be associated with increased risk of SDB in earlier work.[8,10]

Recognition of prenatal and neonatal risk factors for OSA suggests more research is needed to understand its pathogenesis. In a recent analysis of a nationwide dataset from Taiwan, it has been concluded convincingly that pregnant

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women with OSA have almost 2.5-fold higher rate of preterm birth relative to mothers without OSA.[12] It is thus possible that OSA in preterm born children is due—at least in part—to familial predisposition for upper airway obstruction during sleep.

Although xanthine use is associated with augmented risk for SDB, a clear relationship between apnea of prematurity and OSA in later life has not been demonstrated.[10,13] However, special craniofacial characteristics of prematurely born children, such as facial asymmetry and dolichocephaly, may predispose them to OSA.[14] The correlation of NICU stay with increased risk for sleep apnea could include the effect of prolonged endotracheal intubation on the shape of palate and airway growth.[14]

Increased prevalence of adenotonsillar hypertrophy as indicated by the increased frequency of prior adenotonsillectomy in preterm compared to born-at-term children can be another pathogenetic mechanism connecting prematurity and OSA.[4,15] Insulin resistance, an essential component of the metabolic syndrome, is a potential pathogenetic link of premature birth with sleep apnea, since metabolic syndrome frequently coexists with OSA and formerly preterm children have increased prevalence of insulin resistance.[16,17]

In conclusion, the prospective study by Raynes-Greenow et al.[7] underscores the susceptibility of formerly premature children to sleep apnea and the need to entertain the diagnosis of upper airway dysfunction in this population vulnerable to multiple morbidities. Moreover, OSA in the context of prematurity represents a unique research model for the study of interactions between prenatal risk factors and postnatal exposures resulting (eventually) in upper airway dysfunction during sleep.

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