REVISTA DE INVESTIGACIÓN CLÍNICA

Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

PERMANYER

Rev Inves Clin. 2016;68:281-5 BRIEF REVIEW

Obstructive Sleep Apnea and Perinatal Risk

Margarita Reyes-Zúñiga and Luis Torre-Bouscoulet*

Sleep Clinic, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico

ABSTRACT

Obstructive sleep apnea is characterized by total or partial interruptions of airflow during sleep, despite ongoing efforts to breathe. These pauses result from repeated upper airway obstructions that generate a systemic inflammatory condition with consequences for the endothelial function that increase the risk of cardiometabolic events. The prevalence of obstructive sleep apnea during pregnancy is greater than that observed in the general population and increases in the third trimester. Although limited, the information currently available supports the notion that obstructive sleep apnea is an independent, and potentially modifiable, risk factor for maternal and perinatal morbidity and mortality. Experimental and prospective studies in humans have demonstrated an association between obstructive sleep apnea and low birth weight. Endothelial dysfunction may be the link that underlies the association of obstructive sleep apnea with high perinatal risk. The information reviewed herein suggests that treating obstructive sleep apnea with positive-pressure devices could be an effective strategy for decreasing perinatal morbidity and mortality. (REV INVES CLIN. 2016;68:281-5)

Key words: Maternal risk. Pregnancy. Sleep apnea. Sleep-disordered breathing.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by intermittent interruptions of breathing during sleep that may be total (apneas) or partial (hypopneas), and are caused by repeated collapses of the upper airway during sleep[1]. Apneas and hypopneas reduce oxygenation, which triggers the most widely studied damage mechanism in OSA patients, namely, hypoxemia-reoxygenation[2]. Other mechanisms that cause biological damage in OSA include an increase in sympathetic traffic caused by recurrent micro-arousals, variations in intrathoracic pressure, and episodes of hypercapnia-hypocapnia[2]. When OSA is accompanied by certain symptoms, especially excessive daytime somnolence, it is called obstructive sleep apnea syndrome (OSAS).

According to the 1993 Wisconsin Sleep Cohort Study[3], the population-based prevalence of OSAS is 2% in women and 4% in men. Similar figures have been reported for Latin America[4]. However, due to the epidemic of obesity in recent years, studies now demonstrate that the incidence of OSAS is greater, reaching levels as high as 5% in women and 14% in men[5].

Corresponding author:
*Luis Torre-Bouscoulet
Subdirector de Investigación Clínica
Instituto Nacional de Enfermedades Respiratorias
Ismael Cosío Villegas
Calzada de Tlalpan, 4502
Sección XVI, Del. Tlalpan
C.P. 14080, Ciudad de México, México
E-mail: luistorreb@gmail.com

Received for publication: 03-06-2016
Accepted for publication: 24-10-2016

OBSTRUCTIVE SLEEP APNEA AND PREGNANCY

It has been amply demonstrated that OSAS causes cardiovascular diseases[6], motor vehicle- and work-related accidents[7,8], and poor quality of life[9]. Other associations proven recently include mortality due to cancer[10] and morbidity during pregnancy[11].

In 2014, an important research study analyzed a representative sample of maternal discharges from hospitals in the USA for the period 1998-2009[11]. The study including almost 56,000,000 events showed that patients with OSAS were at a higher risk for pregnancy related morbidities (Table 1), and that the risk was even greater when OSAS was associated with obesity. It is well known that obesity is associated with morbidity during pregnancy; in fact, the in-hospital mortality risk among pregnant women with OSAS was five times higher (95% CI: 2.4-11.5) than for women without this condition[11]. In addition, a systematic review and meta-analysis published by Pamidi, et al. confirmed that maternal OSAS was significantly associated with preeclampsia (OR: 2.34) and gestational diabetes (OR: 1.86)[12]. Another recent systematic review also supports the notion that moderate-to-severe sleep-disordered breathing is associated with most adverse perinatal outcomes, including low birth weight (OR: 1.75; 95% CI: 1.33-2.32), admissions to neonatal intensive care units (OR: 2.43; 95% CI: 1.61-3.68), intrauterine growth restriction (OR: 1.44; 95% CI: 1.22-1.71), and Apgar scores < 7 at one minute (OR: 1.78; 95% CI: 1.10-2.91)[13].

The prevalence of OSAS among women of reproductive age ranges from 0.7 to 7.0%, but increases to 11-20% in pregnant patients[11]. The highest prevalence of OSAS occurs in pregnant women who are also obese[14]. Other studies have demonstrated that the frequency of OSAS is three per 10,000 pregnancies (95% CI: 2.8-3.2), but this figure rose from 0.7 in 1998 to 7.3 in 2009, representing an annual increase of 24%[11]. The annual increase in obesity in the same period was 20%. This virtually parallel behavior of the incidence of OSAS during pregnancy and the prevalence of obesity suggests a possible causal association since it is well-known that obesity is the principal risk factor for developing OSAS[1]. Furthermore, a study by Pien, et al. found that by the third trimester of pregnancy, 26.7% of women had OSAS, and identified that both higher baseline body mass index and maternal age were risk factors for the onset of third-trimester OSAS among women without baseline sleep-disordered breathing[15].

Table 1. Associations between diagnosis of obstructive sleep apnea syndrome and maternal morbidity and mortality

Maternal morbidity/ mortality	Odds ratio	95% Confidence interval
Cardiomyopathy	9.01	7.47-10.87
Heart failure	8.94	7.45-10.73
Pulmonary edema	7.50	4.63-12.15
Eclampsia	5.42	3.29-8.92
In-hospital mortality	5.28	2.42-11.53
Pulmonary embolism	4.47	2.25-8.88
Hospital stay > 5 days	3.06	2.76-3.40
Cerebrovascular disease	2.93	1.07-8.04
Acute renal failure	2.73	1.69-4.41
Preeclampsia	2.50	2.19-2.85
Gestational diabetes	1.89	1.67-2.14
Gestational hypertension	1.28	1.08-1.52
Premature birth	1.20	1.06-1.37
Cesarean section	1.12	1.01-1.23

Unfortunately, there are no highly predictive strategies that are capable of properly identifying OSAS during pregnancy. The Berlin Questionnaire, a popular screening tool used in adults, was shown to have poor diagnostic performance in 43 pregnant women[16]. Other studies have similarly failed to demonstrate a causative association between the Berlin Questionnaire and OSAS[17], perhaps because the clinical manifestations of OSAS in pregnancy diverge from those seen under "typical" conditions. For instance, women report more fatigue and less snoring than men[18].

Table 2 shows data from Mexico's 2012 National Health and Nutrition Survey related to the frequency of overweight and obesity in Mexican women of reproductive age[19]. We believe that recognition of the coexistence of obesity with OSAS could be substantially contributing to the modest advances that have been made in reducing maternal mortality[20].

Regarding the potential effects of OSAS on newborns, we found that information is scarce. Studies using animal models have proven that intermittent hypoxemia

Table 2. Prevalence of overweight and obesity in Mexican women of reproductive age

Age (years)	Overweight BMI 25.0-29.9 kg/m^2		Obesity BMI ≥ 30.0 kg/m^2	
	Prevalence (%)	95% CI	Prevalence (%)	95% CI
12-19	23.7	22.1-25.5	12.1	10.9-13.4
20-29	30.6	28.5-32.8	24.0	22.0-26.1
30-39	38.1	36.2-40.1	37.3	35.3-39.4
40-49	37.6	35.3-40.0	46.1	43.8-48.4

Data from Mexico's 2012 National Health and Nutrition Survey (Encuesta Nacional de Salud y Nutrición).
BMI: body mass index; 95% CI: 95% confidence interval.

causes low birth weight due, apparently, to a reduction of placental perfusion. Concerning humans, a recent cohort study of 234 patients showed that after adjusting for maternal parity, pre-pregnancy body mass index, ethnicity, gestational age, and newborn gender, the presence of OSA (documented objectively by polysomnography) was indeed found to be associated with low birth weight in relation to gestational age[21]. The main indicator of the severity of OSAS, the apnea-hypopnea index (> 10 events/hour), was also significantly associated with low weight for gestational age (OR: 2.65; 95% CI: 1.15-6.10). Also, the desaturation index (4%) was seen to be related to low weight for gestational age (OR: 1.17 for each event; 95% CI: 1.03-1.34). It is important to note that low birth weight has been shown to be clearly associated with a high risk for cardiac, metabolic, and neurological complications in adulthood[22]. An interesting recent study by Tapia, et al. demonstrated that ex-preterm schoolchildren have a tendency to suffer more OSAS later in life compared to the general population of similar age[23]. The findings reported previously by Rosen, et al. are similar[24].

MECHANISMS OF BIOLOGICAL DAMAGE LINKED TO OBSTRUCTIVE SLEEP APNEA SYNDROME

The physiopathological marker of OSAS is the collapse of the upper airway during sleep, caused by an imbalance between factors that promote it and others that oppose it[25]. The main factor that promotes this collapse is an increase in the extraluminal pressure secondary to an exaggerated deposition of fatty tissue in the parapharyngeal space. Negative intraluminal pressure is another factor that promotes collapse. In terms of the mechanisms that oppose such a collapse, the main factors are the downward traction force exerted by pulmonary volume combined with the contraction of the dilator muscles of the pharynx[1,25].

The possible mechanisms that may link OSAS to maternal morbidity and mortality are similar to those described in relation to cardiovascular damage[2]. It is well known that OSAS is associated with an increase in the sensitivity of chemoreceptors and a reduction in baroreflex sensitivity[2,26]. These mechanisms are at the very center of the biological damage caused by OSAS[2]. The exaggerated sensitivity of the chemoreceptors induces a state of generalized vasoconstriction that occurs not only while the person is asleep, but also persists during wakefulness[27]. This chemoreceptor dysfunction is mediated by oxygen-reactive substances that are generated in unusually high quantities during episodes of hypoxemia and reoxygenation[2]. The oxidative state of OSAS is associated with systemic inflammation and the activation of the endothelium[28], so it is possible that intermittent hypoxemia and increased sympathetic traffic generate an endothelial dysfunction that increases the risk of complications during pregnancy, such as preeclampsia and eclampsia. The effect of the oxidative state of OSAS on placental perfusion and the endothelial function could be the factor that underlies the association with hypertensive states during pregnancy[11]. Poor regulation of blood pressure secondary to reduced baroreflex sensitivity may well be another factor related to the vascular complications observed in pregnant women with OSAS[27]. However, additional mechanisms, such as insulin resistance, dyslipidemia, reduced availability of

nitric oxide, and over-activation of the sympathetic nervous system, among others, could also cause vascular damage in patients with OSAS[2,28-32].

TREATMENT

Continuous positive airway pressure (CPAP) is the preferred treatment option for patients with moderate-to-severe OSAS[33]. Positive pressure prevents collapse of the upper airway by forming a kind of "pneumatic splint" that normalizes the respiratory pattern. Until now, the benefits of CPAP for patients with *OSAS* have been shown to be clear and consistent[6,34,35], since numerous studies have demonstrated that CPAP reduces the incidence of both fatal and non-fatal cardiovascular events compared to observations in the general population[6]. The effectiveness of nasal CPAP during pregnancy, however, has been little studied and most information comes from small case series. A study of 12 pregnant women diagnosed with sleep-disordered breathing carried out by Guilleminault, et al. demonstrated that nasal CPAP is a safe and effective treatment during pregnancy[36]. Furthermore, in a small randomized study conducted by Poyares, et al. evaluating the effectiveness of nasal CPAP in pregnant women with hypertension and chronic snoring, the authors found that eight weeks of CPAP use was associated with better blood pressure control when compared to standard prenatal care[37].

PERSPECTIVES AND CONCLUSIONS

The growing problem of obesity in women of reproductive age in Mexico leads us to predict that the frequency of OSAS during pregnancy will increase significantly in coming years. Today, a strong body of evidence supports OSAS as an independent risk factor of maternal and perinatal morbidity and mortality. Although the nasal CPAP strategy has potentially favorable implications for reducing negative outcomes during pregnancy, implementing it as a public health approach is not feasible at this time, simply because the sleep medicine infrastructure in Mexico's health system is insufficient. As a result, any public health policies designed to decrease OSAS-related morbidity or mortality during pregnancy through the use of sleep laboratories attended by qualified physicians are inappropriate. Thus, it is important to implement simple and effective means. For example, implementing better weight-control programs before and during pregnancy may be a particularly useful and cost-effective strategy for reducing maternal morbidity associated with OSAS.

REFERENCES

1. Carrillo-Alduenda JL, Arredondo-del-Bosque F, Reyes-Zúñiga M, Castorena-Maldonado A, Vázquez-García JC, Torre-Bouscoulet L. [Obstructive sleep apnea syndrome in adult population.] Neumol Cir Torax. 2010;69:103-15.
2. Torre-Bouscoulet L, Castorena-Maldonado A, Sada-Ovalle I, Meza-Vargas MS. [Mechanisms of cardiovascular damage in obstructive sleep apnea]. Rev Invest Clin. 2008;60:502-16.
3. Young T, Palta M, Dempsey J, et al. The occurrence of sleep disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230-5.
4. Bouscoulet LT, Vázquez-García JC, Muiño A, et al. Prevalence of sleep-related symptoms in 4 Latin American cities. J Clin Sleep Med. 2008;4:579-85.
5. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177:1006-14.
6. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046-53.
7. Garbarino S, Guglielmi O, Sanna A, Mancardi GL, Magnavita N. Risk of occupational accidents in workers with obstructive sleep apnea: Systematic review and meta-analysis. Sleep. 2016;39:1211-8.
8. Karimi M, Hedner J, Häbel H, Nerman O, Grote L. Sleep apnea-related risk of motor vehicle accidents is reduced by continuous positive airway pressure: Swedish Traffic Accident Registry data. Sleep. 2015;38:341-9.
9. Garvey JF, Pengo MF, Drakatos P, Kent BD. Epidemiological aspects of obstructive sleep apnea. J Thorac Dis. 2015;7:920-9.
10. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med. 2012; 186:190-4.
11. Louis JM, Mogos MF, Salemi JL, Redline S, Salihu HM. Obstructive sleep apnea and severe maternal-infant morbidity/mortality in the United States, 1998-2009. Sleep. 2014;37:843-9.
12. Pamidi S, Pinto LM, Marc I, Benedetti A, Schwartzman K, Kimoff RJ. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and meta analysis. Am J Obstet Gynecol. 2014;210:52.e1-14.
13. Ding XX, Wu YL, Xu SJ, et al. A systematic review and quantitative assessment of sleep-disordered breathing during pregnancy and perinatal outcomes. Sleep Breath. 2014;18:703-13.
14. Louis J, Auckley D, Miladinovic B, et al. Perinatal outcomes associated with obstructive sleep apnea in obese pregnant women. Obstet Gynecol. 2012;120:1085-92.
15. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. Thorax. 2014;69:371-7.
16. Wilson DL, Walker SP, Fung AM, O'Donoghue F, Barnes M, Howard M. Can we predict sleep-disordered breathing in pregnancy? The clinical utility of symptoms. J Sleep Res. 2013;22:670-8.
17. Antony KM, Agrawal A, Arndt ME, et al. Association of adverse perinatal outcomes with screening measures of obstructive sleep apnea. J Perinatol. 2014;34:441-8.
18. Bourjeily G, Barbara N, Larson L, He M. Clinical manifestations of obstructive sleep apnoea in pregnancy: more than snoring and witnessed apnoeas. J Obstet Gynaecol. 2012;32:434-8.
19. Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, et al. Encuesta Nacional de Salud y Nutrición 2012. Resultados nacionales. 2a. ed. Cuernavaca, México: Instituto Nacional de Salud Pública (MX), 2013.
20. World Health Organisation. Millennium objectives. Available at: http://www.who.int/topics/millennium_development_goals/about/es/

21. Pamidi S, Marc I, Simoneau G, Lavigne L, Olha A, Benedetti A, et al. Maternal sleep-disordered breathing and the risk of delivering small for gestational age infants: a prospective cohort study. Thorax. 2016;71:719-25.
22. McIntire DD1, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med. 1999;340:1234-8.
23. Tapia IE, Shults J, Doyle LW, et al. Perinatal risk factors associated with the obstructive sleep apnea syndrome in school-aged children born preterm. Sleep. 2016;39:737-42.
24. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr. 2003;142: 383-9.
25. White DP. Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med. 2005;172:1363-70.
26. Cooper VL, Pearson SB, Bowker CM, Elliott MW, Hainsworth R. Interaction of chemoreceptor and baroreceptor reflexes by hypoxia and hypercapnia - a mechanism for promoting hypertension in obstructive sleep apnoea. J Physiol. 2005;568:677-87.
27. Schöbel C, Fietze I, Glos M, et al. Nocturnal snoring decreases daytime baroreceptor sensitivity. Respir Med. 2014;108:1049-55.
28. Muñoz-Hernandez R, Vallejo-Vaz AJ, Sanchez Armengol A, et al. Obstructive sleep apnoea syndrome, endothelial function and markers of endothelialization. Changes after CPAP. PLoS One. 2015;10:e0122091.
29. Varadharaj S, Porter K, Pleister A, et al. Endothelial nitric oxide synthase uncoupling: a novel pathway in OSA induced vascular endothelial dysfunction. Respir Physiol Neurobiol. 2015;207: 40-7.
30. Korcarz CE, Stein JH, Peppard PE, Young TB, Barnet JH, Nieto FJ. Combined effects of sleep disordered breathing and metabolic syndrome on endothelial function: the Wisconsin Sleep Cohort study. Sleep. 2014;37:1707-13.
31. Kaczmarek E, Bakker JP, Clarke DN, et al. Molecular biomarkers of vascular dysfunction in obstructive sleep apnea. PLoS One. 2013;8:e70559.
32. Fleming WE, Ferouz-Colborn A, Samoszuk MK, Azad A, Lu J, Riley JS, et al. Blood biomarkers of endocrine, immune, inflammatory, and metabolic systems in obstructive sleep apnea. Clin Biochem. 2016;49:854-61.
33. Kushida CA, Littner MR, Hirshkowitz M, et al.; American Academy of Sleep Medicine. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep. 2006; 29:375-80.
34. Batool-Anwar S, Goodwin JL, Kushida CA, et al. Impact of continuous positive airway pressure (CPAP) on quality of life in patients with obstructive sleep apnea (OSA). J Sleep Res. 2016. [Epub ahead of print].
35. Martínez-Cerón E, Barquiel B, Bezos AM, et al. Effect of CPAP on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. Am J Respir Crit Care Med. 2016;194:476-85.
36. Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med. 2004;5:43-51.
37. Poyares D, Guilleminault C, Hachul H, et al. Pre-eclampsia and nasal CPAP: part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention. Sleep Med. 2007;9:15-21.