Obstructive sleep apnea in multiple pregnancies

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Abstract

Obstructive sleep apnea (OSA) during pregnancy has been associated with gestational diabetes mellitus, hypertension and low birth weight. Multiple pregnancy is associated with similar adverse perinatal outcomes. Multiple pregnancy rates have risen with increased access to assisted conception; simultaneously advancing maternal age and weight are also driving a rise in the incidence of OSA in pregnancy. The intersection of OSA and multiple pregnancy would be presumed to have significant maternal and fetal morbidity, however specific data is sparse. We review the current state of knowledge on OSA in multiple

pregnancy.

Introduction

Obstructive sleep apnea (OSA) involves occlusion of the upper airway causing cessation of breathing numerous times during sleep, this results in oxygen desaturation, transient hypertension and tachycardia, arousal from sleep and sleep fragmentation [1]. OSA causes daytime sleepiness, fatigue, and reduction in quality of life [1]. OSA is associated with cardiovascular events, insulin resistance and mortality in non-pregnant patients [2–4].

In pregnancy, OSA is associated with gestational diabetes mellitus (GDM), hypertensive disorders, preterm birth and reduced birth weight [5]. In pregnancy pre-existing OSA can worsen, but OSA can also present de novo [5]. Multiple pregnancy is associated with many of the same adverse perinatal outcomes as OSA, including preterm birth, intrauterine growth restriction, GDM and hypertensive disorders [6,7]. When OSA occurs in a multiple pregnancy these risks may be compounded.

Rates of both OSA and multiple pregnancy have recently increased in parallel with advancing maternal age and greater prevalence of obesity [8,9]; the intersection of these conditions warrants urgent examination. In this review we describe proposed physiological mechanisms, and present the available data on prevalence, investigation and management of OSA in multiple pregnancy.

Physiology of obstructive sleep apnea in multiple pregnancy

Awake respiratory function is remarkably stable during healthy pregnancy. Any compression of the thoracic cavity by the enlarging uterus appears to be compensated by a reduction in residual lung volume and increased minute ventilation. McAuliffe et al [10], did not show any significant differences in lung function throughout the trimesters between twin or singleton pregnancies in healthy women, suggesting that respiratory compromise from the larger abdominal burden of a multiple pregnancy is unlikely to directly contribute to OSA.

Progesterone has a significant role in sleep physiology, and progesterone levels increase throughout pregnancy. It is likely progesterone levels are higher in multiple pregnancy compared with singleton pregnancy [11]. Progesterone increases blood flow to pharyngeal tissues predisposing to sleep apnoea. However, progesterone also acts as a respiratory stimulant, increasing minute ventilation and has been associated with increased awakenings from sleep in pregnancy [12] thereby reducing the frequency and severity of pauses in ventilation during sleep. The balance of these effects has not been determined and any subsequent augmentation in multiple pregnancy is undefined.

Prevalence of obstructive sleep apnea in multiple pregnancy

The prevalence of OSA in multiple pregnancy is unknown. In singleton pregnancies in nulliparous women the prevalence is 3.6% in early pregnancy, rising to 8.3% in mid pregnancy [13]. The prevalence is higher in obese pregnant women at 15.4% [14]. Furthermore, rates of OSA in pregnancy have been increasing over time. This trend was demonstrated in a retrospective cross sectional analysis [8], which showed an overall increase in OSA diagnosis from 0.7 to 7.3 per 10,000 from 1998 to 2009, with an average annual increase of 24%

coinciding with a similar rise in rates of obesity (20%).

The increased proportion of multiple pregnancies has been attributed to increased access to assisted conception, as well as increasing maternal age and BMI. In 2016 there were over 4500 multiple births in Australia; over 200 more than in 2015 [9]. In addition as spontaneous dizygotic twinning is more likely with an increased BMI, multiple pregnancy rates are likely to continue increasing as obesity rates rise [15,16].

Only one study has specifically examined sleep related apneas in multiple pregnancies [17]. Nikkola et al (1996) investigated 10 multiple pregnancies; 8 twin, 1 triplet and 1 quadruplet between 30 and 36 weeks' gestation. All subjects had a normal pre-pregnancy BMI, except the mother with quadruplets (BMI 28.4kg/m2). OSA was not identified in any of the patients, although significantly increased respiratory resistance was noted in the patient with quadruplets. This study used a charge-sensitive bed to record nocturnal breathing patterns, oxygenation and leg movements. This methodology underestimates the severity of sleep disordered breathing [18] and has not been validated in pregnancy, furthermore fetal movements may substantially compromise the scoring of events. At the time of writing this remains the largest study investigating sleep apnea in multiple pregnancy.

In 2014, multiple pregnancy was included within a study of OSA in high risk pregnant women [21]. Patients with a BMI >30kg/m2, chronic hypertension, pre-gestational diabetes, prior preeclampsia and/or twin pregnancy were included. Of 188 participants 11 were twin gestations, all subjects had an in-home sleep study between 6-20 weeks. A repeated sleep study was performed in 128 in the final trimester; the actual number of multiple pregnancies

in this subsequent group was not reported. In the entire cohort OSA was common in early pregnancy with new-onset OSA in 20% of these high-risk women. In the analysis describing incident OSA in the third trimester, only twin gestation was significantly associated, however the small sample size prevented accurate calculation of risk. This study used a portable wrist worn device (Watch-PAT) which measured multiple variables including oxygen saturation, and estimated sleep time using actigraphy (movement detection). O'Brien at al [19] have demonstrated that results from the Watch-PAT device correlated well with laboratory based polysomnography (PSG) in the third trimester.

Other data on OSA in multiple pregnancies has been published in case reports [20–22] (see table I). Further studies are required to evaluate the prevalence of OSA in multiple pregnancies. Given the dynamic physiology of pregnancy screening at a single time point may under estimate the prevalence of this disorder, particularly as OSA is known to be more prevalent in the third trimester of singleton pregnancy [23].

Investigation of obstructive sleep apnea in multiple pregnancy

At present there is no standardised screening tool for assessing risk of OSA in pregnancy although several have been proposed and validated [24]. Two studies [25,26] have evaluated OSA assessment tools in high risk cohorts which share many comorbidities with multiple pregnancy. Neither the Epworth Sleep Scale nor the Berlin Questionnaire in these studies could accurately predict OSA risk in women with chronic hypertension, pre-gestational diabetes, obesity and or prior history of preeclampsia [25]. Tantrakul et al [26] also concluded both tools had limited use in the first trimester but improved as the pregnancy progressed.

Any tool developed to screen for OSA in pregnancy needs to assess proven risk factors for

OSA in singleton pregnancies including snoring, elevated BMI and increased neck circumference; features that were also observed in three case reports [20–22] of OSA in twin pregnancies. Advanced maternal age has also been shown to increase the risk of OSA in singleton pregnancies recently [27], and should therefore also be considered in future screening for OSA.

The optimal diagnostic test for women with suspected OSA has not been defined and pregnancy-specific recommendations are absent from guidelines such as the American Academy of Sleep Medicine [28]. Laboratory PSG is the gold standard measurement of sleep physiology as it obtains continuous electroencephalogram (EEG) data thereby precisely documenting sleep stage, as well as respiratory events and consequences such as oxygen desaturation. The successful use of PSG to diagnose OSA in multiple pregnancies has been documented [20–22].

More limited data can be obtained in the home setting; involving either reduced channel EEG or actigraphy (movement detection) as a proxy measure of sleep state. Home based sleep studies may be more convenient, particularly as multiple pregnancies already require supplementary antenatal visits, therefore additional sleep study visits may be burdensome. Conversely, pregnant mothers with young children report a more restful night in a sleep laboratory compared with sleeping at home [29].

Management of obstructive sleep apnea in multiple pregnancy

In the non-pregnant population positional therapy, oral devices and continuous positive airway pressure (CPAP) therapy can be used to improve outcomes in OSA [30]. In singleton

pregnancies CPAP has been shown to improve symptoms [31] and reduce hypertension [32]. In two case reports involving CPAP in multiple pregnancies; CPAP controlled or reduced the effects of sleep apnea [21,22], whereas in a third case report supplemental oxygen and more complex non-invasive ventilation were required [20]. In each case clinicians felt nocturnal ventilatory support improved pregnancy outcome, however this limited observational data highlights the need for further research.

Conclusion

Multiple pregnancy and OSA are both separately associated with an increased risk of GDM and hypertensive disorders of pregnancy, including preeclampsia [13,33,34]. In addition, fetal morbidites such as low birth weight, preterm delivery and neonatal intensive care admission are all more likely with maternal OSA in studies of singleton pregnancies [5]. However, there is little information describing these adverse outcomes in multiple pregnancies complicated by OSA. Investigation or management of OSA is not mentioned in any international obstetric guidelines [35,36], and evidence to support intervention is absent. Consequently OSA is rarely considered in routine antenatal practice [37,38].

We have described the limited data available regarding OSA in multiple pregnancies. This is a substantial knowledge gap given the rising prevalence of both OSA and multiple pregnancy. The significant maternal and fetal morbidity that can result from OSA in pregnancy should drive further research to provide an evidence-base and improve patient centred care.

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Table I. Published studies of obstructive sleep apnea in multiple pregnancy

Study	Study design	Participants	Clinical features pre-study	BMI (kg/m2)	Type of Sleep Study	Treatment	Maternal outcomes	Fetal outcomes
Nikkola et al, 1996 [17]	Prospective observational	8 twins 1 triplet 1 quadruplet	-	Mean 22.3 in 8 twin and 1 triplet (range 19.4-24.4) Quadruplets 28.4	Laboratory study using static charge sensitive bed with finger oximeter Sleep staging estimated by actigraphy	-	-	8 small for gestational age 6 growth restricted
Langer et al, 2007 [20]	Case report	1 twin	Snoring	-	Laboratory PSG Sleep staging by EEG	BiPAP-ST with oxygen	Progressive preeclampsia	Premature delivery 31/40
Faco et al, 2014 [23]	Prospective cohort	Total 188 high risk cases **Only 11 twins**	-	32.8	Home sleep evaluation with Watch-PAT100 Sleep staging estimated by actigraphy	-	Preeclampsia in 17.6% (for entire high risk cohort)	Premature birth 9% (for entire high risk cohort)
Gruca-Stryjak et al, 2014 [21]	Case report	1 twin	Severe daytime sleepiness Snoring	28	Laboratory PSG Sleep staging by EEG	CPAP	Urgent caesarean section at 35/40 due to abnormal CTG of one fetus	Healthy baby

			Pauses in breathing during sleep					
Carnelio et al, 2017 [22]	Case reports	Total 3 **Only 1 twin**	Neck circumference 58cm Bilateral papillodema Crowded oropharynx	48.5	Laboratory PSG Sleep staging by EEG	CPAP	Caesarean section after failed induction of labour at 37/40 due to intrahepatic cholestasis	Healthy baby