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Obstructive sleep apnoea and its association with gestational hypertension

K. Champagne*, K. Schwartzman*, L. Opatrny#, P. Barriga¶, L. Morin+, A. Mallozzi+, A. Benjamin+ and R.J. Kimoff§

ABSTRACT: Hypertension develops in 10% of pregnancies. Snoring, a marker of obstructive sleep apnoea, is a newly identified risk factor for gestational hypertension. Moreover, obstructive sleep apnoea is an independent risk factor for incident hypertension in the non-pregnant population. The aim of the present study was to test the hypothesis that obstructive sleep apnoea is associated with new onset of hypertension among pregnant females.

A case–control study was performed involving 17 pregnant females with gestational hypertension and 33 pregnant females without hypertension. Subjects were frequency-matched for gestational age and recruited in a tertiary obstetrical centre. Obstructive sleep apnoea was ascertained by polysomnography and defined by an apnoea/hypopnoea index (AHI) of $\geqslant$15 events·h^{-1}, without requirement for desaturation.

The mean$\pm$SD AHI for normotensive pregnant females was 18.2$\pm$12.2 events·h^{-1} compared with 38.6$\pm$36.7 events·h^{-1} for females with hypertensive pregnancies. The crude odds ratio for the presence of obstructive sleep apnoea given the presence of gestational hypertension was 5.6. The odds ratio was 7.5 (95% confidence interval 3.5–16.2), based on a logistic regression model with adjustment for maternal age, gestational age, pre-pregnancy body mass index, prior pregnancies, and previous live births.

In conclusion, gestational hypertension appears to be strongly associated with the presence of obstructive sleep apnoea.

KEYWORDS: Hypertension, obstructive sleep apnoea, pre-eclampsia, pregnancy, sleep-disordered breathing

Hypertension develops in ~10% of pregnancies and is a leading cause of maternofoetal morbidity and mortality. Females who develop gestational hypertension with proteinuria (pre-eclampsia) or without proteinuria are at increased risk for subsequent hypertension, stroke [1], metabolic syndrome [2] and premature cardiovascular death decades later [3]. Known risk factors for pre-eclampsia include diabetes, pre-existing hypertension and obesity [4]. Obstructive sleep apnoea is associated with obesity and is an independent risk factor for hypertension [5], insulin resistance/glucose intolerance [6] and cardiovascular morbidity [7]. The relationship between obstructive sleep apnoea and cardiovascular events raises the intriguing possibility that obstructive sleep apnoea may be associated with gestational hypertension.

Snoring, a marker for obstructive sleep apnoea, was recently demonstrated to be associated with gestational hypertension, with an odds ratio (OR) of 2.03 (95% confidence interval (CI) 1.01–4.01) after adjustment for maternal weight, age and smoking habits [8]. The present authors hypothesised that obstructive sleep apnoea was associated with new onset of hypertension in pregnancy. To address this hypothesis, polysomnography was performed on females with and without gestational hypertension.

METHODS

Study setting

Subjects were recruited at a tertiary obstetrical centre with services for fertility and high-risk obstetrics, serving a multiethnic population. Healthcare at the centre is covered by public insurance. Females with significant gestational hypertension, or suspected pre-eclampsia, are ordinarily admitted for observation and treatment.

Participants

From May 1, 2004, through to April 30, 2006, once per weekday, a research nurse screened charts to identify potential cases on the antenatal ward. All females diagnosed with gestational hypertension by an obstetrician were approached for

AFFILIATIONS
*Dept of Medicine, Respiratory Epidemiology and Clinical Research Unit, McGill University,
#Dept of Medicine, FetoMaternal Unit, McGill University,
Depts of +Obstetrics and §Medicine, McGill University, and ¶Dept of Microbiology, Santa Cabrini Hospital, Montreal, QC, Canada.

CORRESPONDENCE
K. Champagne
Montreal Chest Institute, Respiratory Epidemiology and Clinical Research Unit, 3650 St-Urbain, Montreal, QC, Canada, H2X 2P4.
Fax: 1 5148431695
E-mail: kateri.champagne@muhc.mcgill.ca

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STATEMENT OF INTEREST
None declared.

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participation. During the same period, approximately once weekly, the research nurse recruited control subjects from antenatal clinics, obstetrical ultrasound clinics and the antenatal ward. Before clinics, the research nurse reviewed charts to identify all pregnant normotensive females. All females who agreed to be approached were then contacted for participation. To avoid preferential booking of females with sleep complaints, the research nurse did not provide advance notice of her attendance. All females were recruited while pregnant.

Case definition

Gestational hypertension was defined as the new onset of diastolic blood pressure >90 mmHg, measured twice during pregnancy, ⩾4 h apart in a previously normotensive female [9]. At the time of polysomnography, case patients were either pregnant with a singleton pregnancy (⩾20 weeks of gestation) or had delivered within the past month.

Controls

Controls were pregnant females, at >20 weeks of gestation, with a singleton foetus. Controls were frequency-matched to cases, in a 2:1 ratio, stratified according to gestational age: 20–27, 27–34, >34 weeks.

Exclusion criteria

Females with known pre-gravid hypertension, treated obstructive sleep apnoea, neuromuscular disease or previous stroke were excluded, as were those who lived >30 km from the study centre or who were unable to communicate in English or French. The study protocol was approved by the Research Ethics Board of the Royal Victoria Hospital (Montreal, QC, Canada). Participants provided written informed consent.

Measurements

Participants completed a nurse-administered questionnaire. Their hospital charts were reviewed for obstetrical and foetal outcomes. Participants had one overnight unattended polysomnographic study, performed at home or in hospital (at the bedside on the obstetrics ward), using a portable device (Suzanne™; Tyco, Ottawa, ON, Canada) to record electroencephalogram, electrooculogram, electromyogram and airflow by both nasal pressure transducer and thermistor, thoracoabdominal motion using piezoelectric bands, oxygen pulsed arterial saturation, electrocardiogram, and snoring by microphone. All signals were digitised and written to disk for subsequent analysis (Sandman®; Tyco).

A certified technologist scored the polysomnogram according to standard sleep–wake [10], arousal [11] and respiratory [12] criteria. Apnoeas were ⩾10-s events with ⩾90% decrease in airflow. Hypopnoeas were ⩾10-s events with either: 1) a 50–90% decrease from baseline airflow amplitude; or 2) a <50% decrease in airflow associated with ⩾4% desaturation or arousal. Obstructive sleep apnoea was defined as an apnoea/hypopnoea index (AHI) of ⩾15. All studies were reviewed by a sleep physician; both the physician and technician were blinded to the clinical status of subjects.

The criteria used to define respiratory events can substantially alter AHI [13], and there is some variability in the literature with respect to the AHI threshold used to define obstructive sleep apnoea. Therefore, sensitivity analysis was conducted in which alternate event definitions and thresholds were considered, in order to assess the robustness of any association between gestational hypertension and obstructive sleep apnoea. Specifically, the analysis was re-performed using: 1) a stricter definition for hypopnoeas, discounting events with <50% reduction in airflow; and 2) a threshold of 10 apnoea/hypopnoea events·h^{-1} sleep. The AHI calculated using all respiratory events was referred to as AHI1, while the more conservative index excluding hypopnoeas with <50% reduction in airflow was termed AHI2.

Statistical analysis

Standard summary descriptive statistics, odds ratio (OR) estimates were generated using logistic regression for the association between gestational hypertension and obstructive sleep apnoea, and for the relationship between gestational hypertension and potential predictors and confounders that were determined *a priori*.

RESULTS

Between May 2004 and April 2006, 135 hypertensive pregnant females and 150 normotensive pregnant females were screened for inclusion. Inclusion and exclusion data for the cases and for the controls are shown in figures 1 and 2, respectively. The mean±SD ages of participating and non-participating females were similar at 33.9±5.5 and 32.8±5.8 yrs, respectively.

Among the 17 cases, seven had >300 mg proteinuria on a 24-h urine collection, nine had proteinuria on spot urinalysis without completion of a 24-h urine collection and one had no proteinuria on spot urinalysis and did not complete a urine collection. Six cases had their polysomnographic studies postpartum only, at a median of 4 days.

Cases and controls frequently had other obstetrical, medical or psychiatric conditions, most frequently, gestational diabetes, asthma or allergic rhinitis (table 1). Hypertensive females were slightly older with marginally higher reported pre-gravid body mass index (BMI) than normotensive controls (table 2).

At the time of polysomnography, two hypertensive females were taking magnesium sulphate, five were taking alpha-methyl dopa (three in combination with labetalol, one in combination with hydralazine), and four were taking labetalol alone. One normotensive female was taking nifedipine for preterm labour, and one was taking paroxetine at the time of the polysomnography.

Prevalence of obstructive sleep apnoea among hypertensive and normotensive pregnant females

Sleep-related breathing indices are described in table 3. The mean and nadir of nocturnal oxygen saturation were similar in the two groups but respiratory event indices were significantly worse in the hypertensive group. The prevalence of obstructive sleep apnoea was 14 out of 17 (82%; 95% CI 57–96%) among the hypertensive females, compared with 15 out of 33 (45%; 95% CI 26–64%) among the normotensive pregnant females, based on a definition of ⩾15 apnoea/hypopnoea events·h^{-1} sleep, as described in the Methods section.

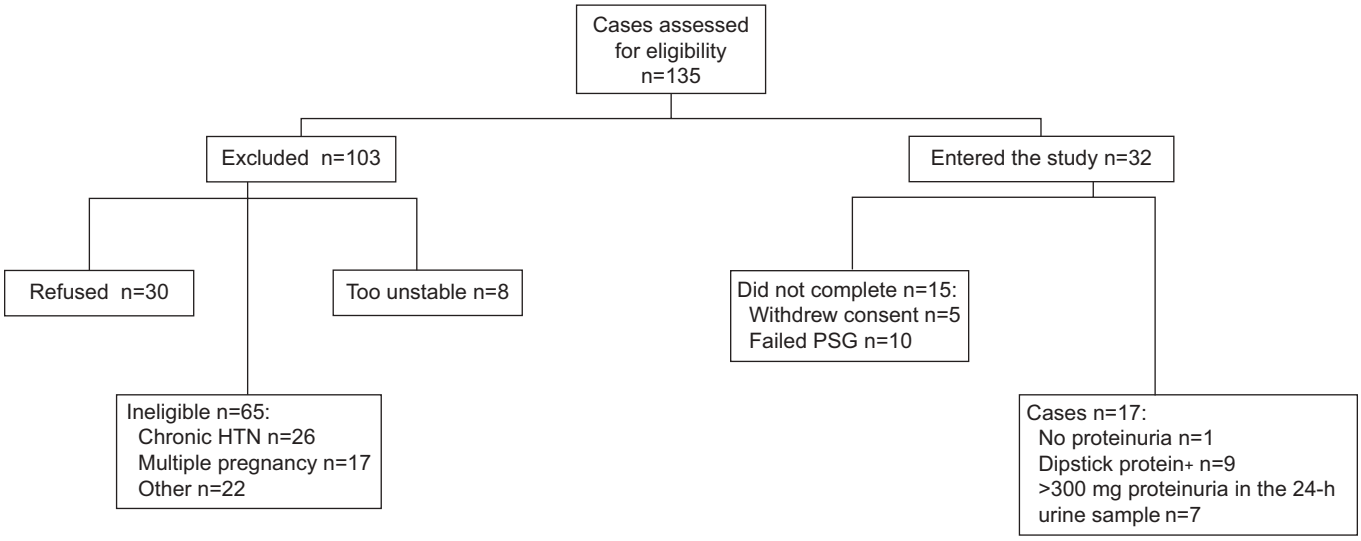

FIGURE 1. Inclusion and exclusion of potential participants with gestational hypertension (HTN). Among the females excluded, eight were judged by the treating team to be too unstable (*e.g.* intensive care unit admission, foetal loss) to be approached for participation. The two main exclusion criteria were chronic HTN and multiple pregnancies. Rare exclusions were: treated obstructive sleep apnoea, language barrier, age <18 yrs, and distant residence (>30 km from the research site). Among females who had consented, five withdrew prior to the polysomnography (PSG); failed PSGs were due to intolerance of the equipment [7] and failure to sleep [3].

Association of obstructive sleep apnoea with gestational hypertension

Obstructive sleep apnoea was associated with gestational hypertension, with a crude OR of 5.6 (95% CI 1.4–23.2; p=0.018). After adjustment for maternal age, gestational age, pre-gravid BMI, previous pregnancies and previous live births, the OR was 7.5 (95% CI 3.5–16.2; p<0.0001). Each of these variables was found to be a significant confounder and was thus kept in the final model. In this multivariable model, obstructive sleep apnoea, past pregnancy without live births, and BMI were the strongest predictors of gestational hypertension, as shown in table 4. Compared to females with previous live births, those with previous abortions only (spontaneous or induced) were at increased risk of gestational hypertension. The size of the present dataset prevented adjustment for smoking, pre-existing diabetes and ethnic origin.

Sensitivity analysis examined alternative definitions for respiratory events as well as alternative thresholds for the number of respiratory events needed to diagnose obstructive sleep apnoea. The results consistently supported the association of gestational hypertension with obstructive sleep apnoea (table 5).

Four normotensive and three hypertensive females completed both antepartum and postpartum polysomnographies, at a median of 8 days postpartum. All showed a reduction in AHI postpartum, by an average of 32%.

The six hypertensive females who were only able to complete polysomnography postpartum (at a median of 4 days postpartum) had more severe sleep apnoea and more severe obstetrical conditions than the hypertensive females who completed antepartum studies. Four subjects had gestational hypertension with adverse events (eclampsia and HELLP (haemolytic anaemia, elevated liver enzymes and low platelet count; n=1); HELLP with blurred vision (n=1); placental abruption (n=1); diastolic blood pressure >110 mmHg (n=1)). Among the six females who were only able to complete polysomnography postpartum, the mean AHI was 53; five of the six met the present study's definition of obstructive sleep apnoea. In comparison, among the 11 hypertensive females who were able to complete an antenatal study, the mean AHI was 31; nine had obstructive sleep apnoea and three had similar obstetrical adverse events (HELLP (n=1); diastolic blood pressure >110 mmHg (n=2)).

DISCUSSION

The results of this study suggest a strong association between gestational hypertension and obstructive sleep apnoea. The association was even stronger after adjustment for confounders including maternal age, gestational age, BMI, previous pregnancies and previous live births. The results were also robust to different obstructive sleep apnoea definitions.

Only a small number of participants successfully completed the study (figs 1 and 2). The present authors believe this reflects the poor sleep of pregnant females in their third trimester, potentially compounded by hospitalisation for unstable blood pressure, attendant interventions and related psychological distress. Some withdrew consent after foetal death or their infant's admission to the intensive care unit. Similar difficulties in completing full polysomnography among hypertensive pregnant females were reported by other researchers, who adopted a tonometry approach [14].

The requirements for intensive nursing and medical surveillance of both the mothers and the foetuses precluded the use of in-lab polysomnography. While the use of portable complete polysomnography provided a more feasible alternative, the present study's inclusion criteria had to be modified to permit postpartum polysomnography because the instability of the hypertensive females precluded a delay of 1 night for polysomnography before delivery. The present study therefore

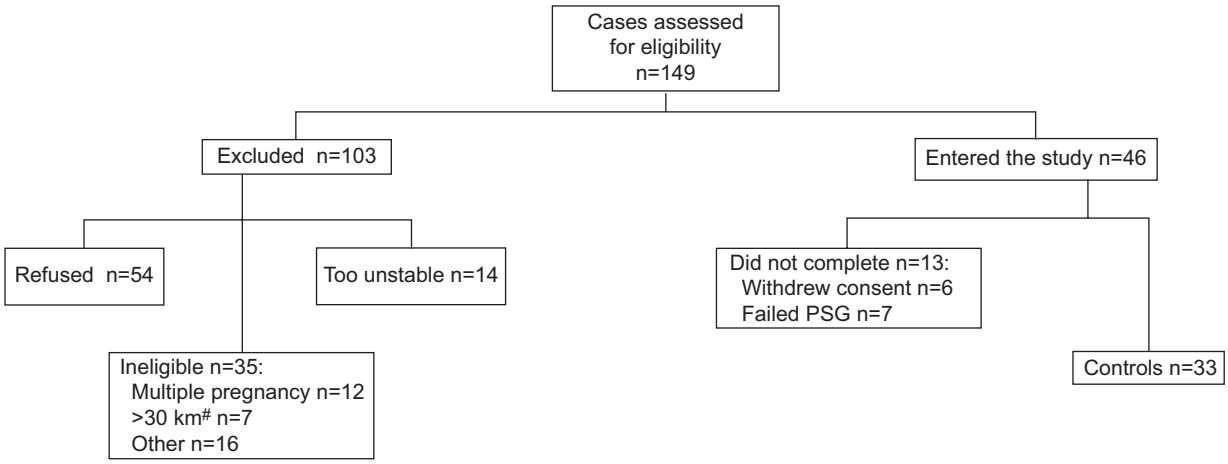

FIGURE 2. Inclusion and exclusion of potential participants without gestational hypertension. Of the potential participants, 14 were excluded because the treating team judged them too unstable for recruitment (*e.g.* intensive care unit, foetal loss). Polysomnography (PSG) recording failed because of lack of sleep or difficulty tolerating the equipment in seven subjects. Six withdrew consent prior to the PSG. #: from the research site.

included six subjects with gestational hypertension who were studied postpartum. If the urgency to deliver was related to difficult blood pressure control in those with obstructive sleep apnoea, as is observed in the non-pregnant population [15], the exclusion of these subjects would have led to an underestimation of the association. Based on previous case series, obstructive sleep apnoea tends to worsen during pregnancy [16] and improve postpartum [17]. Similarly, in the present small subset with both ante- and postpartum data, the AHI decreased by a third after delivery. Thus, postpartum polysomnography is likely to have underestimated the severity of obstructive sleep apnoea during pregnancy among these six females, thereby attenuating the potential association between gestational hypertension and obstructive sleep apnoea.

There are several potential mechanisms that may link obstructive sleep apnoea to pregnancy. These include changes in body habitus mimicking truncal obesity, reduced upper airway calibre [18] secondary to lung volume effects [19], fluid retention, pregnancy-related rhinitis [20], increased soft tissue mass (related to placental growth hormone secretion), and increased airway collapsibility because of muscle relaxation (due to relaxin and other hormones). Obstructive sleep apnoea is thought to predispose to hypertension in the non-pregnant population through endothelial dysfunction, oxidative stress, sympathetic activation enhanced by hypoxia, flow limitation, sleep fragmentation and arousals [21, 22]. The pathophysiology of gestational hypertension includes endothelial dysfunction, oxidative stress, and sympathetic activation enhanced by

TABLE 1 Comorbidities of females with and without gestational hypertension

	Gestational hypertension	Normotensive pregnancy
Subjects	17	33
No comorbidities	1	12
Gestational diabetes	7	1
Preterm labour	0	4
Premature rupture of membrane	0	1
Pre-existing diabetes mellitus type I or II	1	1
Asthma	5	9
Allergic rhinitis	7	14
Past depression	1	5
Coagulopathy	1	3
⩾2 previous spontaneous abortions	4	4
Other	1#	7¶

Data are presented as n. Among the 17 cases, 16 had comorbidities, mainly gestational diabetes, allergic rhinitis and asthma. Among the 33 controls, 21 had comorbidities, most commonly allergic rhinitis, asthma and past depression. #: hyperthyroidism. ¶: infrequent comorbidities among controls included hypothyroidism [2], past fertility treatment (two subjects, including one whose pregnancy at the time of study was medically assisted) and micro-prolactinoma [1]. Controls were newly diagnosed during the pregnancy with pancreatitis due to hyperlipoproteinemia type III (one subject), hepatolenticular degeneration (one subject), and cardiomyopathy secondary to adriamycin administered remotely for lymphoma (one subject).

TABLE 2 Baseline demographics

	Gestational hypertension#	Normotensive pregnancies
Subjects n	17	33
Age yrs	35.4±4.3	32.7±5.5
Pre-gravid BMI kg·m^{-2}	26.7±4.6	23.8±3.9
Gestational age at PSG weeks	33.4±4.7	32.4±4.6
First pregnancy	5 (29)	7 (21)
No previous live birth	11 (65)	16 (48)

Data are presented as mean±SD and n (%), unless otherwise stated. BMI: body mass index; PSG: polysomnography; #: six cases were 2, 3, 3, 5, 14 and 29 days postpartum at the time of the PSG.

TABLE 3 Sleep-related breathing indices

	Gestational hypertension	Normotensive pregnancies	p-values
Subjects n	17	33	
Respiratory events			
AHI1 events·h^{-1} sleep	38.6±36.7	18.2±12.2	0.0053
AHI2 events·h^{-1} sleep	21.6±35.2	5.6±5.6	0.013
ODI events·h^{-1} sleep	4.0±9.7	0.2±0.7	0.028
Central and indeterminate event index events·h^{-1}	1.9±2.4	1.3±2.0	0.37
Oximetry data			
Mean oxygen saturation %	96.7±1.2	97.0±1.1	0.33
Nadir oxygen saturation %	90.2±4.8	92.4±3.0	0.061

Data are presented as mean±SD, unless otherwise stated. AHI1: apnoea/hypopnoea index including all apnoeas and hypopnoeas; AHI2: apnoeas plus hypopnoeas restricted to 50–90% reduction in airflow; ODI: ⩾4% oxygen desaturating apnoeas and hypopnoeas.

hypoxia [23]. It is the present authors' belief that similar mechanisms promote hypertension among pregnant females with obstructive sleep apnoea.

It has been proposed that pregnancy is a physiological stress test, identifying females most likely to develop metabolic and cardiovascular complications later in life, as documented by several cohort studies [2, 3]. In parallel fashion, the present authors hypothesise that pregnancy is a physiological stress test that identifies women with either unrecognised obstructive sleep apnoea or those who are at risk for obstructive sleep apnoea should predisposing conditions, including truncal obesity, reappear later in life.

The high prevalence of obstructive sleep apnoea in the present control group may relate to the inclusion of normotensive controls with obstetrical and medical complications. This was a representative sample of the population serviced in the tertiary obstetrical centre of the Royal Victoria Hospital (McGill University Health Centre, Montreal, QC, Canada); normal pregnant females (no comorbidities, low-risk pregnancies) are managed in non-tertiary institutions. If any of the medical or obstetrical complications described were also associated with obstructive sleep apnoea, the inclusion of such females as controls would bias the association of gestational hypertension with sleep apnoea towards the null. In addition, polysomnography was performed in the mid-to-late third trimester, which previous studies have identified as the time of peak snoring and obstructive sleep apnoea-related symptoms among pregnant females [8, 24]. The present authors believe that the high proportion of controls with obstructive sleep apnoea in pregnancy is related to the high-risk population and the timing of polysomnography, and reduces the observed association between gestational hypertension and obstructive sleep apnoea.

As expected from the obstetrical literature, females with hypertensive pregnancies were slightly older and had a marginally higher pre-pregnancy BMI than those who maintained normal blood pressure levels in pregnancy. As planned *a priori*, age and pre-pregnancy BMI were accounted for in the multivariable analysis. The magnitude of the association between obstructive sleep apnoea and hypertension in the present study

TABLE 4 Adjusted odds ratio (OR) for each variable and its association with gestational hypertension

Variables	Adjusted OR (95% CI)	p-values
Sleep apnoea# *versus* no sleep apnoea	7.5 (3.5–16.2)	<0.0001
BMI per 1 kg·m^{-2} increase	1.2 (1.1–1.4)	0.001
Maternal age per 1-yr increase	1.2 (0.95–1.4)	0.14
Pregnancy status		
Previous pregnancy but no live birth	12.8 (3.5–46.0)	<0.0001
First pregnancy	3.4 (0.25–45.5)	0.35
Previous live birth¶	1	
Gestational age		
20–27 weeks	1.1 (0.4–3.2)	0.80
27–34 weeks	0.8 (0.5–1.2)	0.32
>34 weeks¶	1	

CI: confidence interval; BMI: body mass index. #: sleep apnoea was defined by an apnoea/hypopnoea index ⩾15·h^{-1}; ¶: this category served as the reference group.

TABLE 5 Sensitivity analysis: adjusted odds (OR) ratio for the association of obstructive sleep apnoea and gestational hypertension

	Threshold# n	Adjusted OR (95% CI)	p-values
AHI1	10	4.3 (2.8–6.7)	<0.0001
AHI1	15	7.5 (3.5–16.2)	<0.0001
AHI2	10	5.4 (1.3–23.0)	0.04
AHI2	15	8.4 (1.1–66.2)	0.02

CI: confidence interval; AHI1: apnoea/hypopnoea index including all apnoeas and hypopnoeas; AHI2: apnoeas plus hypopnoeas restricted to 50–90% reduction in airflow. #: the number of respiratory events·h^{-1} needed to diagnose obstructive sleep apnoea.

was much larger than previously described in the non-pregnant population, where reported OR ranged 1.4–2.9 [5, 25, 26].

This may reflect two potential mechanisms: the rapid evolution of both obstructive sleep apnoea and hypertension among pregnant females, as well as the relatively young population studied.

The evolution of obstructive sleep apnoea over the 9 months of pregnancy is likely to be very rapid, compared to its natural progression over years among other individuals [27]. The collateral physiological responses may thus be more dramatic and, conversely, compensatory mechanisms may have less time to develop fully. There are also data suggesting that increased progesterone levels may augment blood pressure responses to respiratory events [28].

Furthermore, in community-based studies, and particularly among older individuals, hypertension is the end product of various aetiologies, only one of which is obstructive sleep apnoea. If obstructive sleep apnoea contributes only modestly to the burden of hypertension in older adults, observed associations between obstructive sleep apnoea and hypertension will likewise be modest in community-based studies of older adults. To the extent that other aetiologies are less relevant in young adults, a more important role for obstructive sleep apnoea might be anticipated.

The present authors' observation that obstructive sleep apnoea among females with gestational hypertension is characterised predominantly by obstructive hypopnoeas without $\geqslant$4% oxygen desaturation (table 3) is in keeping with previous studies. CONNOLLY *et al.* [29] reported increased periods of inspiratory flow limitation among 15 pre-eclamptic females compared with normotensive pregnant females, although the AHI based on the $\geqslant$50% reduction in airflow did not differ between study groups. EDWARDS *et al.* [30] reported similar findings, although the flow limitation episodes were not quantified. In a more recent study, YINON *et al.* [14] used oximetry with arterial tonometry; they reported an increased respiratory disturbance index among females with pre-eclampsia compared to females with normotensive pregnancies, but nearly 50% of events were not associated with $\geqslant$4% oxygen desaturation. Unlike these earlier studies, the present authors: ascertained obstructive sleep apnoea using polysomnography, including electroencephalography; defined obstructive sleep apnoea as a binary variable; included hypopnoeas with arousal in the AHI; and corrected for several confounders.

The present authors chose not to distinguish between gestational hypertension and pre-eclampsia for several reasons. First, the present authors' own systematic review of the literature on pre-eclampsia and sleep apnoea demonstrated that some cases previously labelled as pre-eclampsia actually involved gestational hypertension according to current diagnostic criteria [31]. Secondly, the Canadian guidelines for hypertensive disorders of pregnancy acknowledge a continuum of disease between gestational hypertension, gestational hypertension with proteinuria (pre-eclampsia in other countries) and complicated gestational hypertension with proteinuria [9]. There were major logistical obstacles to 24-h urine collection prior to polysomnography in an unstable group of patients, as those who had reached 37 weeks of gestation were rapidly delivered. All the hypertensive pregnant females did reach a systolic blood pressure of >140 mmHg prior to delivery, fulfilling most international criteria for gestational hypertension. Classification of females according to blood pressure was performed by the obstetrician, reflecting current Canadian clinical management. Finally, the mistaken inclusion of normotensive females as hypertensive cases in the present study would tend to obscure any true underlying association between gestational hypertension and obstructive sleep apnoea.

The cross-sectional design of this study prevents inference about causality. However, a possible causal role for obstructive sleep apnoea in the development of gestational hypertension is congruent with other observations. In a case series, treatment (continuous positive airway pressure) administered to 11 pre-eclamptic females with inspiratory airflow limitation reduced nocturnal blood pressure by a mean of 18 mmHg, without any change in antihypertensive medication [32]. In a randomised controlled study of 16 females with chronic hypertension and newly documented obstructive sleep apnoea in early pregnancy, continuous positive airway pressure treatment was associated with a reduced requirement for anti-hypertensive drugs and better control of blood pressure in the third trimester [33]. In the non-pregnant population, it has clearly been established that obstructive sleep apnoea is an independent risk factor for incident hypertension [25]. However, prospective cohort studies of females with and without obstructive sleep apnoea who become pregnant are needed to establish a causal role for obstructive sleep apnoea in the development of gestational hypertension.

In summary, the present study suggests a strong association between obstructive sleep apnoea and gestational hypertension in females with singleton pregnancies attending a tertiary care obstetrical referral centre. The association was even stronger after adjustment for multiple known confounders and was consistent across several definitions of obstructive sleep apnoea. Further studies should address the natural history and the best management of obstructive sleep apnoea and gestational hypertension among pregnant females.

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