The association of obstructive sleep apnea and gestational hypertension

A thesis submitted to McGill University in partial fulfilment of the requirements of the

Master in Sciences of Katéri A. Champagne, on June 19th, 2006

Department of Epidemiology, Biostatistics & Occupational Health

McGill University, Montreal, Quebec, Canada

Your file Votre référence
ISBN: 978-0-494-28473-5
Our file Notre référence
ISBN: 978-0-494-28473-5

Acknowledgments

In the spring of 2003, I proposed this research project to Drs. Kevin Schwartzman and John Kimoff who enthusiastically decided to support and help in its realization. Three years later, I would like to thank them sincerely for their dedicated help, judicious advices, and full support in making this research project successful.

Many participated and helped to realize this project : Dr. Lucie Morin, obstetrician who facilitated recruitment and provided directions concerning obstetrical issues, Ms. Charlene Barber and Ms. Kathy Riches, research nurses who patiently, recruited one patient at a time, interviewed and assisted in the follow-up process, Mr. Naftaly Naor, research sleep technician, and Mr. Robert Kozak who helped in the setting of the database. I would like to thank Drs Peter Powles and Patricia Smith for reviewing prior versions of the protocol as well as Drs. Angela Mallozzi and Alice Benjamin for their assistance. I would like to thank the courageous mothers, many of whom were going through difficult times but were still eager to help us understand gestational hypertension.

I would like to acknowledge le Fonds de Sante en Recherche au Quebec for salary support and research grant (pilot project competition, axe apnee du sommeil), the Royal College of Physicians and Surgeons of Canada, and McGill University Research Institute.

Foremost, I want to thank my family for their continuous support during these three years. I want to thank my husband, Peter, for his courage and his presence, for his encouragement, scientific and personal advices, and continued support in this project despite the challenges. I want to praise our daughter, Camille, for the joy she brings every day into our lifes with her dancing, singing, jumping, happiness, and enthusiasm.

Preface

Contribution of co-authors in the systematic review reported in appendix 2

In the co-authored systematic review presented in Appendix 2, I made a substantial contribution to the paper. I first read a reference book on systematic reviews and read the course material used in systematic review course at McMaster in 2001, chose the research question, learnt how to use the search engines, did the systematic search of the literature, learnt Reference Manager to merge the 3 different databases of the search and prepare the bibliography, found the articles in 4 different universities, developed and filled the extraction data sheets, summarized the data, wrote the different drafts of the paper until its approval by the co-authors.

Drs Kevin Schwartzman provided guidance in the writing of the manuscript, its organization and syntax both from a general and an epidemiology point of view. Dr John Kimoff did the same from a general and sleep perspective. Dr Lucie Morin reviewed the adequacy of the obstetrical information. Dr Peter Barriga helped in the formulation of the research question, addressed methodological issues of systematic reviews, helped in the data summary, and commented on the writing and organization of the paper.

Table of content

List of tables

Table of appendices

Abbreviations

AHI	Apnea-Hypopnea Index
AASM	American Academy of Sleep Medicine
BMI	Body Mass Index
GH	Gestational Hypertension
HTN	Hypertension
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
95% CI	95% confidence interval
NREM	Non REM sleep
ODI	4%-oxygen desaturation index
PLM	Periodic Limb Movement
PSG	Polysomnography
REM	Rapid Eye movement sleep
SaO_2	Oxyhemoglobin saturation
SD	Standard Deviation
SHHS	Sleep Heart Health Study
TST	Total Sleep Time
WASO	Wakefulness After Sleep Onset

Abstract

Title: The association of obstructive sleep apnea and gestational hypertension
Rationale: Hypertension occurs in 10% of pregnancies. Snoring is a marker for sleep apnea, and is a newly identified risk factor for gestational hypertension. Moreover, sleep apnea is an independent risk factor for hypertension in the non-pregnant population. I hypothesized that sleep apnea was associated with gestational hypertension.
Hypothesis: The prevalence of sleep apnea is higher among pregnant women with hypertensive pregnancies than among those without hypertension during pregnancy.
Design: Case-control study of 17 pregnant women with gestational hypertension and 33 pregnant women without hypertension, with matching by gestational age. Sleep apnea was ascertained by polysomnography.
Results : The crude odds ratio for the presence of obstructive sleep apnea, given the presence of gestational hypertension, was 5.6. The odds ratio was 7.5 (95% CI 3.5-16), based on a logistic regression model with adjustment for maternal age, gestational age, nulliparity, first pregnancy, and body mass index.
Conclusion : Gestational hypertension was strongly associated with the presence of obstructive sleep apnea.

Résumé

Titre: L'association de l'apnée obstructive du sommeil et l'hypertension gravidique
Justification: L'hypertension complique 10% des grossesses. Le ronflement est un facteur de risque nouvellement décrit de l'hypertension gravidique. De plus, l'apnée du sommeil est un facteur indépendant pour l'hypertension dans la population non enceinte. J'ai émis l'hypothèse que l'apnée du sommeil devait être associée à l'hypertension gravidique.
Hypothèse: La prévalence de l'apnée du sommeil est supérieure chez les femmes enceintes avec hypertension gravidique comparativement à celles avec grossesse normotensive.
Méthodes: Étude cas-témoin de 17 femmes avec hypertension gravidique et 33 femmes enceintes avec grossesse normotensive, appariée pour l'âge gestationnel. L'apnée du sommeil fut évaluée par polysomnographie.
Résultats : Le rapport de cote de l'apnée du sommeil en présence d'hypertension gravidique est de 5.6. Le rapport de cote est de 7.5 (95% IC 3.5-16) basé sur une régression logistique avec correction pour l'âge maternal, l'âge gestational, la nulliparité, le statut gravidique et l'indice de masse corporelle.
Conclusion : L'hypertension gravidique est fortement associé à la présence d'apnée obstructive du sommeil.

Section 1. Introduction

Hypertension occurs in about 10% of pregnancies and is a leading cause of maternal and fetal morbidity and mortality. Women who develop gestational hypertension (GH) are at increased risk for subsequent hypertension and stroke, metabolic syndrome (1), premature cardio-vascular death decades later (2). Risk factors for GH with proteinuria include diabetes, pre-existing hypertension, and obesity (3). Likewise, obstructive sleep apnea (OSA) is associated with obesity. It is characterized by repeated episodes of upper airway obstruction during sleep. It is an independent risk factor for hypertension (4), metabolic syndrome (5) and cardiovascular morbidity (6). The well-documented relationship between OSA and cardiovascular events raises the intriguing possibility that OSA may be associated with GH.

I hypothesized that women with pregnancies complicated by GH are more likely to have OSA than women with normotensive pregnancies.

To address this hypothesis, I conducted a case-control study comparing pregnant women with gestational hypertension to normotensive pregnant women, matched for gestational age. The presence of OSA was ascertained by polysomnography (overnight recording of sleep-wakefulness state with respiratory monitoring).

Section 2. Literature review

I will first review the definition, risk factors, current hypothesis on the pathophysiology, clinical implications, prevention and therapy of GH then similarly review OSA. The literature on sleep apnea during pregnancy will be reviewed and discussed. I will then present my hypothesis that sleep apnea could be associated with GH.

2.1. Gestational hypertension (GH)

GH complicates 5-10% of pregnancies (7). It is defined as the onset of a diastolic blood pressure $\geq$ 90 mmHg, measured twice, $\geq$ 4 hours apart (8), during pregnancy in a previously normotensive woman. When associated with proteinuria, it is termed gestational hypertension with proteinuria or alternatively pre-eclampsia.

Most of the literature reviewed has focused on pre-eclampsia and ignored gestational hypertension without proteinuria (as defined by Canadian criteria). In this text, the term "pre-eclampsia" is used when quoting such references.

Risk factors for pre-eclampsia (9) include extremes of age, nulliparity, diabetes, pre-existing hypertension, obesity, especially if central (10), renal disease, asthma (11), personal and familial history of GH, multifetal gestation, black race, insulin resistance, thrombophilia, living in high altitude zones (12;13), collagen vascular disease/autoimmune diseases (14), and hydatiform mole.

The basic pathophysiology underlying pre-eclampsia has yet to be elucidated, though current theories revolve around the placenta. It does not occur in non-pregnant women, is more common in conditions of increased placental tissue (multiple pregnancies, hydatiform mole) and resolves after or soon after placental removal. Two major pathophysiologic hypotheses exist. First, there is the **placental ischemia hypothesis or « placental pre-eclampsia »** (15) which postulates that the process affects the spiral arteries in the placenta leading to ischemia, oxidative stress, and then to widespread endothelial dysfunction. There is the **immune maladaptation hypothesis or « maternal pre-eclampsia »** which views normal pregnancy as a mild inflammatory state whereas pre-eclampsia represents overwhelming inflammation with systemic lesions mainly of the endothelium, called acute atherosis, similar to those seen in allografts (16;17). In this model, hypertension, proteinuria, and edema are probably late manifestations of an ongoing process in the endothelium of the blood vessels including those of the kidneys, which has probably been evolving for weeks or months before it is clinically detected. The initial insult to the placental vessels is thought to occur between 9 and 12 weeks of gestational age. The endothelium of organs other than the kidneys may also be involved as part of the same spectrum of disease as in HELLP syndrome (18) and in intra-uterine growth restriction. When present, damage to these other end organs worsens the prognosis (18). Similarly, some cite a 2-stage condition, initially with reduced placental perfusion, then maternal response/expression to this decreased perfusion (19).

Hypertensive disorders of pregnancy are associated with increased morbidity and mortality for the mother and her child in the peripartum period (20). They contribute to a third of maternal deaths in Canada (8). They are a risk factor for maternal cerebro-vascular accident, end-organ failure, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, disseminated intravascular coagulation, and rarely convulsions (eclampsia) in the acute setting. Infants born to hypertensive mothers are at risk for intrauterine growth restriction (IUGR); GH accounts for 25% of all neonates under 1500g (21).

GH contributes to neonatal complications including prematurity, intrauterine death (8), necrotizing enterocolitis (adjusted OR 5.21, 95% CI 1.64-16.58) (22), and encephalopathy (adjusted OR 13.5, 95%CI 3.2- 56.7) (23). In turn, IUGR is associated with increased costs for health care, education, and child care compared to normal weight children (24;25). Pre-eclampsia is responsible for 15% of pre-term births (19).

Long term studies have demonstrated that the morbidity and mortality for mothers whose pregnancies were complicated by hypertension extends well beyond pregnancy. These mothers are at increased risk for subsequent hypertension, cardiovascular death, and metabolic syndrome.

In a retrospective cohort study (2), women who had delivered a first live singleton baby between 1951 and 1970 were retraced in 1997. 1197 women with GH and 1199 women with pre-eclampsia or eclampsia were matched for maternal age and year of

delivery to 1197 women with normotensive pregnancies. The OR for development of chronic hypertension, adjusted for maternal age, body mass index, social class, and smoking was 2.47 (95% CI 1.74-3.51). The adjusted OR was 3.98 (95% CI 2.82-5.61) for those with pre-eclampsia or eclampsia. Therefore GH with and without proteinuria is a risk factor for chronic hypertension.

In a cohort study of 626 272 women who had delivered a first child between 1967 and 1992 and were then followed for a median of 13 years, 4350 deaths occurred. Cardio-vascular death was more frequent in those with pre-eclampsia compared to normotensive women with term delivery (> 37 weeks of gestation) with a hazard ratio (HR) of 1.65 (95% CI 1.01-2.70) for term birth with pre-eclampsia, HR 8.12 (95% CI 4.31-15.33) for preterm birth with pre-eclampsia (26), adjusted for maternal age and year of delivery. Therefore Pre-eclampsia is a risk factor for premature cardiovascular death.

In another cohort study (1), 168 women with previous hypertensive pregnancies were matched for maternal age and year of index delivery (between 1989 and 1997) and compared an average of 7.8 years later to 168 women with previous normotensive pregnancies. The OR for metabolic syndrome comparing women with previous hypertensive and normotensive pregnancies was 3.6 (95% CI 1.4-9), after adjustment for numerous potential confounders. Therefore GH is a risk factor for metabolic syndrome.

Similarly children surviving IUGR are more at risk for hypertension, obesity, diabetes, cardiovascular disease (27). Hence, burden of disease for the mother, the baby, and society, both in the acute and long-term settings is significant.

Aspirin may have a limited role in the prevention of GH(28;29). Therapeutic options include a) pregnancy termination that brings with it the consequences of delivering immature babies, b) antihypertensive drugs however this is associated with reduced birthweights (30-32), c) Magnesium sulfate which decreases the likelihood of eclampsia in moderate and severe pre-eclampsia (33) but does not reduce overall maternal-fetal morbidity and mortality (34).

2.2 Sleep apnea

Sleep apnea is a prevalent, yet often unrecognized condition that may have major adverse consequences for women in their childbearing years. By far the most common form of sleep apnea is *obstructive* sleep apnea (OSA), where repeated dynamic collapse of the upper airways during sleep leads to frequent, intermittent cessation of airflow-despite ongoing respiratory efforts. More rarely, disorders of ventilatory drive lead to *central* sleep apnea, characterized by repeated pauses in respiratory efforts. Oxygen desaturation may occur with both types of sleep apnea. These respiratory disturbances are often terminated by transient arousals from sleep, which are associated with re-opening of the airways or resumption of respiratory efforts.

OSA has been studied in several population-based cohorts whereas central sleep apnea has not, because of the much higher prevalence of the former. Both lead to the same physiologic responses manifested by arousals, sympathetic surges, and hypoxemia; hence clinical consequences are considered similar (35).

In a population-based cross-sectional sample of 30 to 60 year-old workers, 10.8% of pre-menopausal women were found to have OSA (36). However, only 7% of the women determined to have moderate to severe OSA reported a previous diagnosis of OSA (37).

While women are generally less likely than men to develop OSA, other risk factors include age, obesity, post-menopausal state, craniofacial features associated with a narrowed upper airway, allergic rhinitis, and polycystic ovary syndrome (38). OSA is a chronic and progressive condition which often remains undiagnosed for many years or is misdiagnosed as depression, for example.

Large population-based studies have shown that OSA is an independent risk factor for *prevalent* hypertension, even after adjustment for obesity, age, and sex (39). In addition, the presence of OSA increased the odds of *incident* hypertension over a 4-year follow-up period with a dose-response relationship; moderate and severe OSA were associated with an odds ratio of 2.9 (95% CI 1.5 to 5.6) for development of hypertension compared to persons without OSA (40).

OSA is an independent risk factor for prevalent coronary disease, prevalent and incident strokes (41)'(42)'(43), prevalent congestive heart failure,(40)'(39;44) prevalent glucose intolerance and insulin resistance-even after adjustment for confounders (45)'(5). Moreover, the oxygen desaturation index (number of episodes of reduction in oxygen saturation by $\geq$4%, per hour of sleep) is a better predictor of insulin resistance than BMI (46). Both the insulin resistance and the cardio-vascular complications including blood pressure surges are thought to be mediated by sympathetic discharge triggered by repetitive desaturations and micro-arousals (47).

Diagnosis of OSA is based on the results of a polysomnogram. A polysomnogram is a standardized study which involves continuous recording of the following : electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram, electromyogram (EMG) of the submentalis and tibialis anterior muscles, thoraco-abdominal efforts, airflow at the nose or mouth, and pulse oximetry. It is painless and usually performed overnight. It is now recognized that presence of OSA on polysomnography does not imply necessarily that the person will have clinical symptoms including sleepiness. To diagnose Obstructive Sleep Apnea **Syndrome** (OSAS), in addition to compatible polysomnography results, symptoms must be present (Appendix 1).

Because of the complexity of the standard polysomnographic equipment, cost, the need for a sleep lab setting supervised by a technician and because of limited availability, simplified monitoring equipment has been developed. In those with a high pre-test

probability of moderate to severe OSA without co-morbidities, simplified monitoring without EEG, EOG, EMG (« cardio-respiratory monitoring ») may be sufficient to confirm the condition. However, a negative study does not rule out disease, and can occur even in presence of severe OSA if associated with arousals but no desaturation. Oximetry is sometimes used alone in similar situations, with more limitations.

Results of sleep studies are assessed using standard criteria (Appendix 1) (48). An apnea-hypopnea is a ≥10-second event with a) a decrease in airflow by 50%-90% regardless of saturation or arousal, or b) a clear decrease in airflow by less than 50% but associated with >3% desaturation or micro-arousal (49). The standard summary statistic is the mean number of respiratory events (apneas + hypopneas) per hour of sleep and is called the Apnea-Hypopnea Index (AHI).

Conventionally, sleep apnea is defined as present or absent based on a cut-off. In research, an AHI cut-off of 5 is recommended (Appendix 1) though 10 or 15 is most often used. The cut-off of 5 is recommended based on population-based studies in non-pregnant adults showing cardiovascular and neurocognitive morbidity with an index ≥5. However, prevalence of an AHI >5 is so high (33%) that a more conservative cut off of 15 is usually preferred (prevalence for an AHI>15 is 13%) (50). Usually, a cut-off ≥10 or 15 associated with symptoms (mostly excessive daytime sleepiness) is used as an indication for treatment in clinical settings as benefit of CPAP therapy has been mostly demonstrated in this population (51).

Treatment of OSA includes conservative measures such as avoidance of narcotics, muscle relaxants, benzodiazepines, and alcohol, promotion of weight loss, and positioning measures to avoid supine sleep. Control of OSA is most effectively achieved by application of a Continuous Positive Airway Pressure device (CPAP) during sleep (52). Briefly, this is a tightly fitting nasal mask connected to an air compressor delivering positive pressure, worn when asleep. Proven benefits of CPAP include improvement in quality of life, improved alertness, better mood, and decreased anxiety (52).

2.3. Sleep apnea during pregnancy

I will present the literature addressing the relationship between OSA and GH. Then I will review the literature on sleep apnea during pregnancy as well as briefly discuss the literature on snoring and pregnancy. Hypotheses about possible mechanisms by which pregnancy could worsen or provoke OSA and how in turn, OSA could increase blood pressure during pregnancy will first be presented.

2.3.1. Hypotheses regarding the association of GH and OSA;

GH and OSA may be linked through several pathophysiological mechanisms. Possibilities may include:

1. Pregnancy may initiate, sustain or aggravate OSA.
2. OSA may initiate, sustain or aggravate GH.
3. OSA and GH may co-exist because of shared risk factors.

Normal pregnancy leads to important physiological changes in women that may provoke or unmask OSA. Changes in upper airways including nasal passages, changes in waist circumference, and hormonal changes could contribute to development or worsening of OSA.

22% of pregnant women are known to develop a pregnancy-related rhinitis (53) which increases nasal airway resistance. Pregnancy rhinitis is associated with raised levels of placental growth hormone and normal levels of estradiol and progesterone (54) compared with pregnancy without rhinitis. Pregnancy-induced edema, facilitated by high levels of progesterone (55) could also increase nasal airway resistance. Upper airways are smaller among pregnant compared to non pregnant women, and normalize with delivery (56). There is a relationship between upper airway size and lung volume- i.e. at low lung volumes the cross-sectional area of the upper airway is reduced (57). Pregnancy decreases functional residual capacity leading to low lung volumes, therefore it is likely to reduce upper airway size (58). This would increase the chance of developing high resistance and partial or complete obstruction of the upper airway. Respiratory alkalosis of pregnancy may lead to unstable ventilatory control facilitating further upper airway obstruction(59;60).

Growth hormone is also suspected to worsen OSA (61). Excessive growth hormone secretion is associated with hypertension in acromegaly (62). Excessive growth hormone secretion likewise is thought to be associated with a higher chance of

developing hypertension in pregnancy (63;64) but no study has systematically compared growth hormone levels among those with normotensive and hypertensive pregnancies.

Pregnancy is associated with weight gain not to mention the enlarging uterus thus leading to an accelerated form of truncal obesity, a known risk factor for OSA (65) and for pre-eclampsia (66).

OSA in pregnant women can initiate, sustain or aggravate increases in blood pressure. In the non-pregnant population, when breathing difficulties occurred during sleep, photoplethysmography showed transient increases in mean arterial blood pressure from a mean of 77.8 (SD 10) to a mean 99.0 (SD 12.7), p= 0.015 lasting a few seconds associated with peripheral vasoconstriction (67). The blood pressure surges are thought to be mediated by sympathetic discharge triggered by repetitive desaturations and micro-arousals (47;68). Blood pressure is described to fail to decrease at night in some persons with OSA (non-dippers) (69). It is hypothesized that this eventually leads to sustained elevation of morning and daytime blood pressure.

Finally, **OSA and GH are both relatively frequent conditions that could co-exist by chance alone or because of shared risk factors** (obesity, age, insulin resistance).

2.3.2. Gestational hypertension and obstructive sleep apnea

No study has addressed the relationship of OSA to GH *without* proteinuria while very few studies have investigated the presence of OSA in women with GH *with* proteinuria.

In a case-control study describing sleep architecture among 25 pregnant women with pre-eclampsia and 17 normotensive pregnant women, all those with preeclampsia had airflow limitation on polysomnography with EEG (70). This might be considered very subtle evidence of OSA. These breathing abnormalities did not meet current criteria for the diagnosis of OSA, the American Academy of Sleep Medicine AASM criteria, appendix 1. However, precise criteria used were not detailed beyond quoting those standard criteria –and those criteria are open to interpretation. An odds ratio was not provided. The small sample size limited the power to detect a significant difference in AHI between hypertensive and normotensive pregnant women; the investigators reported a AHI of 7.6 (SD 12.5) in the hypertensive group vs 4.5 (SD 4.1) in the normotensive group, for a mean difference of 3.1 (95% CI –3.3-9.5).

In another case-control study, the sleep problems of 15 pre-eclamptic women, 45 normotensive pregnant women, and 15 non-pregnant women were compared using cardio-respiratory monitoring. Apneas were defined as a >75% decrease in airflow and hypopneas as a 50%-75% decrease in airflow. Relative to the standard AASM criteria, the hypopnea definition was more restrictive. Subtle obstructive events termed inspiratory flow limitations were present more frequently in those with pre-eclampsia- 31

+/-8 % sleep period time compared to 15.5 +/- 2.3 in the 3rd trimester and <5% in the non-pregnant, 1st and 2nd trimester pregnant women(71).

In yet another case-control study, the Watch_PAT100 monitor (Itamar Medical Ltd, Israel) was used to evaluate the presence of OSA in pregnant women and preeclamptic women. Watch_PAT100 consists of actigraphy which detects patterns of motion to estimate sleep and wakefulness, peripheral arterial tone, and oximetry. It measures periodic peripheral vasoconstriction associated with tachycardia or desaturation. This technology was previously validated in the non-pregnant population against standard polysomnography for the diagnosis of OSA (72).

In this study, 17 women with pre-eclampsia had a mean AHI_{PAT} of 18.4 (SD 8.4) compared to 25 normotensive pregnant women who had a mean of 8.3 (SD 1.3), for a mean difference of 10.1, 95% CI 6.7-13.5. No odds ratio was provided. No information on the number of women meeting a categorical definition of OSA was provided. The previous validation study suggested the possibility of misclassification with respect to OSA at this end of the spectrum. Mean birth weights differed between the 2 groups but were not adjusted for gestational age, a major confounder. Finally, the absence of validation in pregnancy and preeclampsia specifically could be an issue, as preeclampsia is itself a condition of sympathetic discharge and increased peripheral arterial tone (73).

Finally, in an interventional, non-randomized trial, treatment with CPAP in pre-eclamptic women with inspiratory airflow limitation reduced nocturnal blood pressure by a mean of 18 mmHg during stable dosing of antihypertensive medication (74).

These small studies suggest that in women with pre-eclampsia, breathing during sleep may be characterized by a mild degree of obstruction that usually does not meet standard criteria for OSA. However, these studies have been hampered by limited power, by the use of non-standard technology, and by non-standard scoring criteria.

2.3.3 Sleep apnea during pregnancy and maternal blood pressure

I conducted a systematic review to search for evidence of a potential link between sleep apnea during pregnancy and GH. The full description is in Appendix 2. Only case reports and case-series were retrieved. 19 papers published between 1978 and 2006 in English and French fulfilled inclusion criteria.

Fourteen of the 42 reported pregnancies with OSA were preceded or complicated by increased blood pressure. Ten women developed a hypertensive disorder during pregnancy. Six were labelled as pre-eclampsia, although not all met unequivocal criteria for this diagnosis. Two additional women had borderline blood pressure : one at term (140/88) (75) and one from the onset of pregnancy (138-142/90-91) (76). Two had chronic hypertension (77;78).

There were no reported cases of HELLP syndrome or eclampsia. One woman had severe pulmonary hypertension with right heart failure during pregnancy (79).

Inference is limited by the relatively small number of reported cases, the absence of relevant controls, and the probability of substantial publication bias. Specifically, pregnancies with severe complications are most likely to be reported. In addition, the articles I reviewed did not use a consistent format for collection and reporting of obstetrical data, and used varying definitions of hypertension, pre-eclampsia, and sleep apnea. Also technology used, if any, to document sleep-related events varied over the 28-year span of this review. Because very few cases were available and because physiologic responses are similar, we included cases of central sleep apnea despite differences from OSA with respect to pathophysiology. However, their exclusion would be unlikely to change the conclusions of this review.

Despite the limited evidence, several studies on snoring in pregnancy have been conducted recently; all listed the case reports just cited, as justification.

2.3.4. Snoring, a marker for OSA, and pregnancy

Several studies have investigated snoring (a marker for OSA) in pregnancy and its association with fetal growth and maternal blood pressure.

In a cross-sectional questionnaire-based study (no polysomnography) that enrolled 502 women, snoring was prevalent in pregnancy (23% women at delivery compared to

4% pre-pregnancy). Snoring was associated with GH. The OR was 2.03 (95% CI 1.01-4.01) after adjustment for maternal weight, age, and smoking habits. Snoring was associated with an OR of 3.45 (95% CI 1.26-9.42) for fetal growth restriction, adjusted for the same confounders (80). Mean birthweights were not reported.

In a cross-sectional study of 350 women (81), habitual snoring prevalence was higher in pregnant (14%) than non pregnant women (4%). The study did not detect significant birthweight differences based on maternal snoring status : on average, infants born to snorers were 84g lighter than those born to non-snorers (95% CI of -107, 275g). Prevalence of IUGR was very low (2/350). Maternal hypertension was not assessed.

In a prospective study of 267 healthy young women (82), the prevalence of habitual snoring was again shown to increase from 4% pre-pregnancy to 12% at 6 months of gestation. Loud habitual snoring was associated with the largest increase in blood pressure from the 6th week to the 6th month, on 24-hour blood pressure monitoring. However, no subject fulfilled the World Health Organization criteria for pregnancy-induced hypertension (150/95). This is surprising, given an expected incidence of 5-10%. It is probably related to selection of the sample (very healthy, with no past medical, surgical or psychiatric history, well-insured, likely working women) and the use of stringent diagnostic criteria (a cut off of 150/95 rather than simply a diastolic blood pressure > 90 mmHg). No correlation was found between the infant's weight and maternal snoring status.

In summary, GH occurs more frequently in obese, hypertensive, diabetic women and occurrence is linked to long term maternal cardiovascular and metabolic morbidity. OSA is a frequent and often missed diagnosis, also associated with obesity, metabolic and cardiovascular complications. I hypothesized that OSA is more frequent in women with new onset of hypertension during pregnancy than in women who maintain normal blood pressure during pregnancy. This hypothesis is supported by very limited existing data, consisting of 1) the case reports and small cross-sectional studies from the pregnant population, and 2) larger studies on the impact of OSA on blood pressure in the non-pregnant population. I believe that the potentially important association between GH and OSA merits further investigation, to the extent that detection and treatment of OSA could ultimately contribute to the prevention of GH. The objective of the present study was therefore to contrast the prevalence of OSA among women with GH versus its prevalence among women with normotensive pregnancies.

Section 3. Methods

3.1 Design:

This was a case-control study comparing the prevalence of sleep apnea in pregnant women with and without gestational hypertension.

3.2 Hypothesis

Women who develop gestational hypertension (with and without proteinuria) after 20 weeks of gestation have a higher prevalence of sleep apnea than women with normotensive pregnancies.

3.3 Overview

Women with gestational hypertension as defined by the Canadian Hypertension Society (8) (an onset of diastolic blood pressure above 90 mmHg measured twice, at least 4 hours apart) were compared to women with normal blood pressure in pregnancy for presence of sleep apnea. Sleep apnea was ascertained by polysomnography. Cases and controls were frequency-matched according to 3 strata of gestational age: 20-27, 27-34, and >34 weeks of gestation in a 1 to 2 ratio.

3.4 Study population

3.4.1. Inclusion criteria-cases

In addition to diastolic blood pressure above 90 mmHg, twice, 4 hours apart (8), cases were either pregnant ($\geq$ 20 weeks of gestation) or had delivered recently (ideally no more than 14 days, maximum 6 weeks) with a singleton pregnancy.

The inclusion criteria reflected the following considerations. Hypertension occurring prior to 20 weeks of gestation is usually considered chronic hypertension as opposed to gestational hypertension. OSA is already known to be a risk factor for chronic hypertension in the non-pregnant population. True gestational hypertension with proteinuria that occurs at less than 20 weeks is almost always as a result of hydatiform mole. In this case, dilatation and curettage is indicated, so diagnosis and treatment of OSA is not relevant to pregnancy. Multiple pregnancy is a potential confounder as it is clearly associated with GH, and is potentially linked to OSA (additional gain in weight and abdominal girth).

Inclusion criteria were broadened because of slow recruitment. I had originally restricted the study to women with gestational hypertension *with* proteinuria. However, completing a 24-hour urine collection to document proteinuria prior to delivery proved to be impractical, hence delivery often occurred prior to any recording of sleep. Most reported cases of women with obstructive sleep apnea diagnosed with "pre-eclampsia" were in fact women with gestational hypertension *without* proteinuria based on current criteria. Furthermore, emerging literature suggests that long-term complications of gestational hypertension occur regardless of proteinuria. Therefore, women with gestational hypertension without proteinuria were considered for recruitment. Inclusion criteria were expanded to include those who had recently delivered, e.g. those with maternal or fetal instability ante partum, once stabilized.

3.4.2. Exclusion criteria-cases

Pregnant women with known pre-pregnancy hypertension, neuromuscular disease, or cerebrovascular accident were excluded as those three conditions are clearly associated with OSA, and affected women should be routinely assessed for OSA in a clinical setting, not a research context. Those already treated for sleep apnea with CPAP, BiPAP or mandibular advancement orthesis were excluded for ethical reasons. Also women who lived beyond a 30-minute drive (for logistical reasons), and those unable to communicate in English or French were excluded.

Initially, pregnancy associated with maternal or fetal instability was excluded. This included mothers with eclampsia, active labor, endotracheal intubation, assisted ventilation including CPAP and BiPAP, low room air oxygen saturation (<95% measured in the mother, awake, lying on her side), and those with impending delivery (<4 hours of sleep anticipated before delivery). Any fetal instability requiring delivery within 4 hours was excluded. Once postpartum women were accepted, those with unstable conditions were eligible, after stabilization and delivery.

3.4.3. Inclusion criteria-controls

Women with $\geq$ 20 weeks of gestation or who had delivered recently ($\leq$ 14 days) of a single fetus were eligible.

3.4.4. Exclusion criteria-controls

Women with chronic or gestational hypertension as defined by the Canadian Hypertension Society (8;83) or with an exclusion criterion as listed for cases were not eligible.

Gestational age was based on the date of the last menstrual period. In case of discrepancy between the age as estimated by last period and on an ultrasound performed before 24 weeks, the gestational age was based on the ultrasound. We had planned to recruit all consenting women regardless of gestational age initially, and then subsequently to recruit preferentially so as to achieve overall frequency-matching with respect to gestational age.

3.4.5. Recruitment

From May 1, 2004 through April 2006, the research nurse screened the charts of potential participants. ***All*** patients newly diagnosed by their obstetrician with gestational hypertension identified in the birthing centre or the antenatal ward were approached for potential participation. During the same period, the research nurse recruited control subjects from 10% of the low and high risk antenatal clinics as well as from obstetrical ultrasound clinics. Before each clinic, the research nurse reviewed charts to identify all women without hypertension, with singleton 25-35 week pregnancy, living within a one-hour drive from the hospital; for each such patient, she left a form with the obstetrician to determine whether the patient agreed to be contacted. Clinics were not given advance notice that would have allowed preferential booking of women with sleep complaints on those days. All potential controls who agreed to be approached were then contacted for

participation by the research nurse.

This tertiary obstetrical centre delivers about 4000 women a year including 10% with hypertensive disorders of pregnancy, and has a Fertility Clinic. The population is highly mixed with respect to ethnic origin.

3.5. Intervention and Data collection:

Participants filled out a questionnaire (Appendix 3) on sleep and risk factors for gestational hypertension and hypertension. The questionnaire and the scoring scales were available in French and in English. Women were asked to undergo one polysomnography (PSG) before delivery (unless recruited postpartum) and another PSG after delivery. Obstetrical and birth data were extracted from the mother's and baby's charts.

Overnight unattended ambulatory polysomnography included recording of

1) Standard electroencephalogram (EEG) leads C3/A2 or C4/A1,

2) Bilateral electro-oculogram (EOG),

3) Submentalis and anterior tibialis muscles electromyogram (EMG),

4) Airflow via both nasal pressure transducer and thermistance,

5) Thoracoabdominal motions using piezoelectric bands around the thorax at the supra-mammary level and around the abdomen at the umbilical level,

6) Continuous arterial oxyhemoglobin saturation using digital pulsed oximetry monitoring (Ohmeda Biox 3700, Ohmeda Corp, Boulder CO),

7) Continuous electrocardiogram,

8) Sound via a microphone attached to the participant's clothing,

using a validated portable device (Suzanne ^{TM}, Tyco, Ottawa). Additional leads were placed on the woman's abdomen for fetal heart monitoring. A trained sleep technologist installed the equipment for the test which was performed at home or at the hospital. Signal verification ascertained electrode impedance < 5000 ohms with visual inspection of each bioelectric signal using portable signal verification display box. All signals were acquired on a digital data management system (Sandman, Tyco, Ottawa, Ontario).

Scoring of the PSG recordings was performed by a trained sleep technologist according to standard criteria (84). Scoring criteria are detailed in appendix 4. Scored studies were reviewed by an expert sleep physician. Both were blinded to the clinical status of subjects. An apnea-hypopnea index > 15 events per hour defined the presence of sleep apnea, the primary exposure of concern.

3.6. Statistics

3.6.1. Sample size

Sample size estimates used pre-eclampsia as the outcome of interest. In a previous study of habitual snoring (≥ 3 nights a week) in pregnant women (80), 10% of snorers (11/113) and 4% of non-snorers (15/389) were found to develop pre-eclampsia. The overall prevalence of snoring was 22.5% (113/502). The prevalence of pre-eclampsia was 5% (26/502).

		snoring		margin
		+	-	
Pre-eclampsia	+	11	15	26
	-	102	374	476
margin		113	389	502

Assuming that 50% of snorers (n=113) and 2% of non-snorers (n=389) had sleep apnea, we estimated that a total of 64 women had OSA. The horizontal margin comes from the article, the vertical margin from estimation.

		OSA		margin
		+	-	
Pre-eclampsia	+			26
	-			476
margin		64	438	502

Resolving the arithmetic equations gave us the following solution, a predicted Relative Risk (RR) of 3.45 and an OR of 4.88 with 95% CI 2.11, 11.31 (Appendix 5).

		OSA		margin
		+	-	
Pre-eclampsia	+	10	16	26
	-	54	422	476
margin		64	438	502

I used Edwardes' software for sample estimation for matched case-control studies (85). Because of uncertainty of distribution of the outcome (pre-eclampsia) with and without exposure (OSA), I assessed 9 potential scenarios. I modeled 3 proportion distributions of pre-eclampsia in women *without sleep apnea* for the 3 strata of gestational age (20-27, 27-34, over 34 weeks); 0.1, 0.2, 0.7; 0.2, 0.2, 0.6; 0.3, 0.2, 0.5. For example, in the first pre-eclampsia distribution (0.1, 0.2, 0.7), among women *without* sleep apnea, 10% of these women would be in the 20-27 week strata, 20% in the 27-34 week strata and finally 70% in the >34 week strata for a total of 100% of pre-eclampsia without sleep apnea. I similarly modeled 3 hypothetical distributions of pre-eclampsia in

women *with sleep apnea* for the 3 strata of the confounder (gestational age); 0.1, 0.4, 0.5; 0.2, 0.6, 0.2; 0.3, 0.4, 0.4. This gave me 9 scenarios.

Sample size estimate summary

Detailed information	β	α	OR	Probability exposure population	Case:control ratio	Mean sample size	Minimum sample size	Maximum sample size
Appendix 6	0.1	0.05 2-tailed	4.88	7%	1	75 /arm	67	84
Appendix 6	0.2	0.05 2-tailed	4.88	7%	1	55 /arm	49	61
Appendix 7	0.1	0.05 1-tailed	4	8%	2	57 cases	53	65
Appendix 7	0.2	0.025 1-tailed	4	8%	2	52 cases	48	58

At first, I calculated with a 2-tailed significance level, a case-control ratio (F) of 1, a population exposure probability of 7%, an odds ratio of 4.88, no interaction, and obtained a mean sample size of 74.7 e.g., 75 women per arm, minimum 67, maximum of 84 for a β 0.10 and α 0.05. For a power of 0.80, α 0.05, the mean sample size is 54.1 e.g., 55 women per arm, minimum 49, maximum 61 (Appendix 6). Then, because the limiting factor was expected to be recruitment of cases, I redid the calculations with a control-case ratio of 2, an odds ratio of 4, a population exposure ρ=0.08. Based on the literature available, snoring is a risk factor for pre-eclampsia so I didn't anticipate that OSA would protect against pre-eclampsia, and I used a one-sided alpha. With a power of 90%, α=0.05 (1-tailed), the estimated sample is 57.3 cases (58 women) and twice as many controls whereas with a power of 80%, α=0.025 (1-tailed), I estimated a mean sample size of **52 cases and 104 controls** (Appendix 7). For feasibility issues, I chose the latter sample size to conduct the study.

Justification:

Cases and controls were targeted for recruitment in a 1:2 ratio because of a limited pool of cases. Stratification was used because gestational age is a clear confounder with a large effect size (80), with respect to a potential relationship between OSA and gestational hypertension. According to internists specialized in fetomaternal medicine, distributions of gestational age among cases and unmatched controls were expected not to overlap (cases occur late in pregnancy whereas controls might have been much earlier in their pregnancies), limiting the robustness of adjusted estimates. Frequency matching was preferred to individual matching, because of simplicity and greater probability of successful matching. Frequency-matching was integrated in the design, recruiting by strata- targeting mainly the >34-week stratum as most cases were of that gestational age. In keeping with the design, the analysis was performed with gestational age as a categorical variable.

3.6.2. Feasibility

The rate-limiting step was expected to be recruitment of cases. I had initially planned to recruit at two hospitals but recruitment at the second hospital was not possible. I had anticipated 25 new cases of pre-eclampsia a month. With a participation rate of 30% and a sample size of 52, it was estimated that this study would require 12 months to complete. However, there were typically only 5 cases that came to the attention of the research nurse each month, so the recruitment period was extended to 24 months.

3.6.3. Analysis

I estimated a Mantel-Haenszel odds ratio adjusted for gestational age, with 95% CI (86). I used logistic regression modeling with gestational hypertension as the binary dependent variable to further adjust the odds ratio estimate for other potential confounders e.g. age, body mass index, race, smoking, nulliparity, primigravidity as well residual confounding by gestational age. In secondary analyses, I evaluated the AHI as a continuous predictor variable for the presence of gestational hypertension. I analyzed the data using Stata version 8, College Station (Texas).

3.7. Ethical considerations

The Royal Victoria Hospital Research Ethics Board approved the research project on March 10, 2004 (Appendix 8). Amendments were submitted in September 2004 and approved in November 2004. Approvals were renewed in November 2004 and November 2005. In agreement with article 19.2 of the Act respecting Health Services and Social Services, authorization of the Director of Professional Services was obtained to pre-screen charts of potential subjects without the patient's consent.

This observational study involved minimal discomfort and risk for subjects, since measurements entailed questionnaires, chart reviews, and noninvasive monitoring. All data were labeled by a unique study number for each subject, rather than by name or hospital number, and held in a password-protected database. Polysomnography and fetal monitoring done for this study were scored without knowledge of clinical status. Results were forwarded to the treating physician when requested for clinical purposes. As the

optimal management of sleep apnea in pregnancy remains undefined, no specific intervention was instituted during pregnancy. However, a sleep specialist assessed all patients postpartum who had evidence of sleep apnea, with further investigation and treatment when clinically indicated.

4. Results

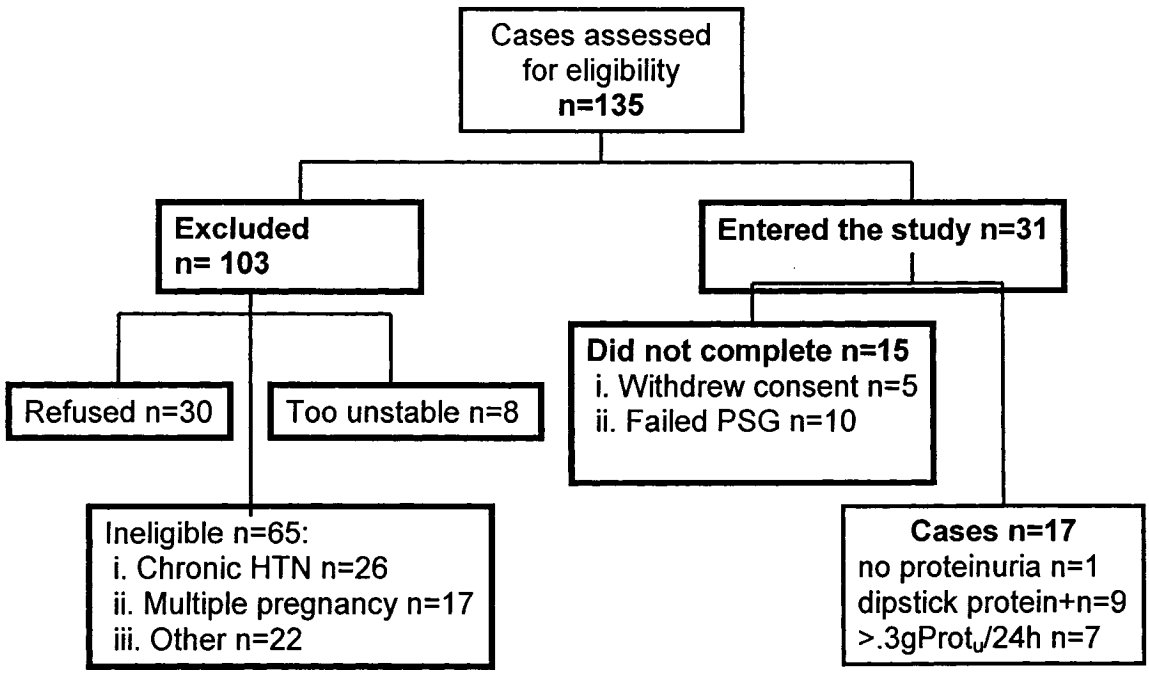
Between May 2004 and April 2006, 135 hypertensive pregnant women and 150 normotensive pregnant women were identified. The research nurse visited the antenatal ward and birthing center once per weekday, to identify all women with hypertension as well as potential controls. Controls were mainly recruited from a sample of the high and low risk antenatal clinics as well as from obstetrical ultrasound clinics. In all instances, the diagnosis of gestational hypertension was made by the treating physician, prior to any chart review or recruitment.

Inclusions and exclusions for the pregnant hypertensive women are shown in figure 1. Chronic hypertension, multiple pregnancies, and discharge prior to being approached were the main reasons for exclusion. Rare exclusions included treated OSA, language barrier, minor, distant residence, post-partum status (before the protocol was amended to allow post-partum enrolment). The treating team judged 8 potentially eligible women to be unstable (intensive care unit admission, fetal loss). Among the women who had consented, 5 withdrew prior to the polysomnography, 7 could not tolerate the sleep monitoring equipment, and 3 did not sleep during the monitored study. Finally among the 17 cases studied, most had proteinuria on spot urinalysis but did not complete a 24-hour urine collection, the standard to document proteinuria in suspected pre-eclampsia. Seven of the cases were studied only postpartum (median 5 days postpartum).

Among cases, 7 women had concomitant gestational diabetes and 4 had ≥ 2 spontaneous abortion. Only one case reported no past medical or psychiatric history. One

reported diabetes mellitus type II, 7 allergic rhinitis, 5 asthma, one coagulopathy, one hyperthyroidism, and one, a history of depression.

Figure 1



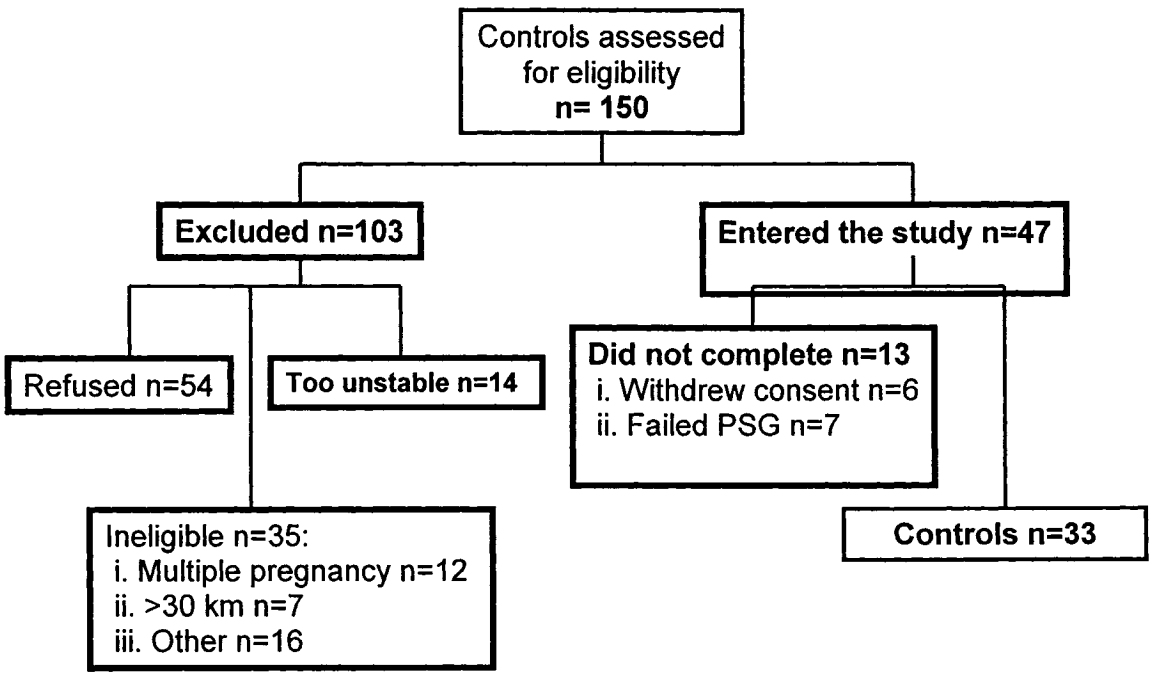
Inclusion and exclusions for controls are shown schematically in figure 2. The main reasons for exclusion were multiple pregnancy, distant residence, and incomplete contact information. The treating team judged 14 to be too unstable for recruitment. Among those consenting, polysomnographic recording failed because of lack of sleep or difficulty tolerating the equipment in 7 women.

At the time of recruitment, some controls had non hypertensive obstetrical conditions : 4 were hospitalized for preterm labor, one for premature rupture of membrane, one had gestational diabetes, one was diagnosed during the current pregnancy

with pancreatitis secondary to hyperlipoproteinemia III and one was diagnosed during the current pregnancy with Wilson's disease (hepatolenticular degeneration).

While 12 had no past medical or psychiatric history, 4 had ≥ 2 previous spontaneous abortions, one reported a diagnosis of polycystic ovarian syndrome, 3 had a coagulopathy, 2 past fertility treatments (current pregnancy was medically assisted in one), 9 asthma, 14 allergic rhinitis, 2 hypothyroidism, 5 past depression, one had type I diabetes, and one had cardiomyopathy secondary to adriamycine (post lymphoma), and one had a micro-prolactinoma..

Figure 2



The mean ages of participating and non participating women were similar, 33.9 years old, Standard Deviation (SD) 5.5 and 32.8, SD 5.8, respectively.

Baseline demographics

Hypertensive pregnant women were older and had higher reported pre-gravid body mass index than normotensive controls (table 1).

Table 1 Baseline demographics

	Pregnancy-induced hypertension (n=17)*	**Normotensive pregnancies** (n=33)
Age (years)	35.4 ± 4.3	32.7 ± 5.5
Pre-gravid BMI (kg/m^2)	26.7 ± 4.6	23.8 ± 3.9
Gestational age (weeks)	33.4 ±4.7	32.4 ± 4.6
Current smokers	1/17	1/33
Primigravida (1^{st} pregnancy)	5/17 (29%)	7/33 (21%)
Nulliparous (no previous viable fetus at birth)	11/17 (65%)	16/33 (48%)

Values are mean ± SD for age, BMI and gestational age
Abbreviations: BMI body mass index
* Seven cases were respectively 2, 3, 3, 5, 5, 14, and 29 days postpartum

Sleep characteristics

As a group, these women had poorer sleep quality than generally observed in the healthy non-pregnant population. Sleep efficiency (the ratio of total sleep time/total time in bed, normal > 85%) (87), arousal index (normal < 15/hour) were different than expected. Sleep was even poorer in the hypertensive group with worse sleep efficiency, high periodic limb movement index (normal <15/hour) (88) and more time spent in "Wakefulness After Sleep Onset" (WASO) which represents the time awake after initiation of sleep. All sleep stages were present, with an increase in non-REM sleep stage 1 (NREM 1) and a decrease in Rapid Eye Movement sleep (REM) among both groups of

pregnant women compared to normative data in the healthy non-pregnant population (87) (table 2).

Table 2 Sleep characteristics on polysomnography

	Pregnancy-induced hypertension (n=17)	**Normotensive pregnancies** (n=33)	***P*-values**
Total Recording Time (h)	7.2 ± 2.6	7.2 ± 2.1	0.98
Total Sleep Time (h)	4.4 ± 2.0	5.4 ± 1.7	0.069
Sleep Efficiency (%)	59 ± 15	76 ± 16	0.0009*
Wakefulness after sleep onset (h)	2.4 ± 1.3	1.3 ± 0.9	0.0011*
Stage1 shift index (#/TST)	8.4 ± 3.6	6.5 ± 2.8	0.056
Awakening index (#/TST)	6.5 ± 3.5	4.7 ± 1.8	0.024*
Arousal index (arousal /h)	58 ± 38	48 ± 18	0.23
NREM Stage1 (%TST) normal 2-5%§	11 ± 6	9 ± 4	0.085
NREM Stage2 (%TST) normal 45-55%§	55 ± 16	50 ± 9	0.21
NREM Stage3 (%TST) normal 3-8%§	11 ± 7	11 ± 6	0.82
NREM Stage4 (%TST) normal 10-15%§	8 ± 8	12 ± 10	0.19
REM (%TST) normal 20-25%§	15 ± 9	18 ± 6	0.15
PLM index (PLM/h)	7 ± 17	15 ± 24	0.24

Values are mean ± SD ** $p<0.05$*
Abbreviations:PLM: Periodic Limb Movement TST : Total Sleep Time
NREM : Non REM sleep REM : Rapide Eye Movement Sleep
§Normative values for NREM and REM sleep from Principles and Practice of Sleep Medicine, Kryger Roth and Dement 3rd edition, Chapter 2 Normal Human Sleep : An overview by MA Carskadon WC Dement page 20
Legend: Sleep was fragmented with low efficiency in the 2 groups of women but more so among the hypertensive women.

Sleep-related breathing characteristics

Compared to normotensive pregnant women, those with gestational hypertension had more obstructive and desaturating events. This applied whether we compared apneas, "big" hypopneas or "big and small" hypopneas or ODI (4%-desaturating event index) as continuous variables. There was no difference in central and indeterminate event index or mean saturation (table 3).

Table 3 Respiratory characteristics on polysomnography

	Pregnancy-induced hypertension (n=17)	**Normotensive pregnancies** (n=33)	***P*-values**
Respiratory events			
Obstructive+mixed apnea index (#/h)	6.7 ± 17.6	0.2 ± 0.6	0.037*
Obstructive hypopneas(big) index (#/h)	13.1 ± 18.3	4.1 ± 4.8	0.0098*
Obstructive hypopneas (big+small) index (#/h)	30.0 ± 21.7	16.7 ± 12.4	0.0078*
Central+indeterminate event index (#/h)	1.9 ± 2.4	1.3 ± 2.0	0.37
AHI (big hypopnea) (#/h)	21.6 ± 35.2	5.6 ± 5.6	0.013*
AHI (big+small hypopnea) (#/h)	38.6 ± 36.7	18.2 ± 12.2	0.0053*
Oximetry data			
Mean SaO_2 (%)	96.7 ± 1.2	97.0 ± 1.1	0.33
Nadir SaO_2 (%)	90.2 ± 4.8	92.4 ± 3.0	0.061
ODI (#/h)	4.0 ± 9.7	0.2 ± 0.7	0.028*

Values are mean ± SD ** $p<0.05$*

Abbreviations: AHI apnea-hypopnea index; ODI 4%-oxygen desaturation index

Big hypopnea: 50-90% reduction in flow or thermistor signal

Small hypopnea: 30-50% reduction in flow or thermistor signal with either an arousal or >3%-desaturation

Prevalence of OSA in normotensive and hypertensive pregnant women

With OSA defined as an AHI >15 and including apneas, big and small hypopneas, the prevalence of OSA was 82% (14/17) among the hypertensive pregnant women compared to 45% (15/33) among the normotensive pregnant women. The sample size prevented estimation of meaningful gestational age stratum-specific prevalence of OSA by blood pressure status (not reported).

Prediction of GH using univariable analysis

Crude odds ratios were estimated for each variable (table 4). Pre-gravid body mass index, OSA, and maternal age had the strongest associations with the outcome in univariable analysis. Multiparity was defined as a past pregnancy with a viable fetus at birth whereas primigravida was defined as a first pregnancy.

Table 4 Association of variables with GH: crude odds ratios with predictors

Variables	Odds Ratio	95% CI	*P*-values
OSA (AHI >15) vs no OSA (AHI <15)	5.60	1.35-23.2	0.018
Maternal age, per 1 year increase	1.19	0.98-1.27	0.087
Previous parity, reference	1		
Nulliparity (despite previous pregnancy)	1.89	0.47-7.59	0.37
Primigravida	1.53	0.46-8.89	0.35
Body Mass Index, per 1kg/m^2 increase	1.13	0.99-1.30	0.069
Gestational age, reference >34 weeks	1		
27-34 weeks	0.72	0.20-2.58	0.61
20-27 weeks	0.52	0.09-3.16	0.48

Prediction of GH using multivariable analysis

A full model was developed with maternal age, gestational age, body mass index, nulliparity, primigravid status, and OSA (table 5). In this model, OSA, nulliparity, and BMI were the strongest predictors of GH. Compared to women with previous live birth, women with previous pregnancies but no live birth (therapeutic or spontaneous abortion or late fetal loss) were much more at risk for GH. Also, a first pregnancy seemed to be a risk factor for GH compared to women with previous live birth but our sample was too small to be conclusive.

Table 5 Adjusted odds ratio for each variable and its association with GH

Variables	Adjusted OR	95% CI	*P*-values
OSA (AHI>15) vs no OSA (AHI <15)	**7.48**	3.5-16	0.000
BMI, per 1 kg/m^2 increase	**1.23**	1.1-1.4	0.001
Maternal age, per year increase	**1.16**	0.95-1.4	0.14
Previous parity, reference	**1**		
Nulliparity (despite previous pregnancy)	**12.8**	3.5-46	0.000
Primigravida	**3.41**	0.25-45.5	0.354
Gestational age, reference >34 weeks	**1**		
20-27 weeks	**1.14**	0.41-3.2	0.80
27-34 weeks	**0.79**	0.50-1.2	0.32

Smoking was not added to the model because only one woman in each group smoked. The same applied to pre-existing diabetes. Similarly, race was not added as our dataset had only 4 African-american women, the group at highest risk for pre-eclampsia.

Confounding

Maternal age, gestational age, nulliparity, BMI, primigravida status were all found to be confounders of the association between OSA and GH. Table 6 compares the magnitude of OR between the full model and the 4 different models where one independent variable is removed at a time. The presence of OSA is 7.5 times more likely in cases of gestational hypertension than in controls. In our sample, past failed pregnancy (nulliparity) was protective against OSA.

Table 6 Odds ratio for OSA in presence of GH with adjustments for confounders

OR for OSA	95% CI	Models
7.48	3.46-16.16	Full model OSA, mat. age, GA, nulliparity, BMI, nulligravida
7.39	3.89-14.06	Full model without gestational age
9.70	3.18-29.55	Full model without maternal age
3.56	1.20-10.55	Full model without parity and primigravid status
9.40	4.07-21.72	Full model without BMI

BMI: Pre-gravid body mass index GA: gestational age Mat. Age: maternal age

In summary, the crude odds ratio for OSA in presence of gestational hypertension is 5.6, 95% CI 1.76-17.81, p= 0.0096. The OR, adjusted for maternal age, gestational age, BMI, parity and gravid status, is 7.48, 95% CI 3.46-16.16, p< 0.0001.

Odds ratio using Mantel-Haenszel method

The stratified contingency table is presented in table 9. Because of the small dataset, Mantel-Haenszel estimates of crude ORs for individual gestational age stratum were highly imprecise, and could not be estimated in one stratum because of a cell with zero subjects (table 7). The pooled Mantel-Haenszel OR for the three strata is 5.24, 95% CI 1.3-22.

Table 7 Contingency table by gestational age strata

Stratum	Sleep apnea	GH +	GH-
>34 weeks (reference)	+	8	7
	-	1	7
27-34 weeks	+	4	6
	-	2	7
20-27 weeks	+	2	2
	-	0	4
Total participants		17	33

Sensitivity analysis

A sensitivity analysis was done to assess the impact of using different definitions of respiratory events and using different threshold. This was done because we used the recommended research criteria established by the American Academy of Sleep Medicine-AASM to score respiratory events but those criteria have not been extensively validated prospectively, and certainly not in the pregnant population. Most researchers have used a cut off of 10 or 15 events per hour to define OSA; these were often limited to desaturating events (as in the Sleep Heart Health Study) or to "big hypopneas." The results consistently highlighted the association of gestational hypertension with obstructive sleep apnea, despite varying AASM definitions used (table 8).

Table 8 Adjusted Odds Ratios for Association of OSA & GH

AHI	Cut-off value	OR adjusted	95% CI	*P*-values
Apnea + big + small hypopnea	10	**4.32**	2.78-6.71	< 0.001
Apnea + big + small hypopnea	15	**7.48**	3.46-16.16	< 0.001
Apnea + big hypopnea	10	**5.37**	1.25-23.00	0.043
Apnea + big hypopnea	15	**8.43**	1.07-66.20	< 0.023

Consistent with other studies in pregnancy, limiting the definition of OSA to desaturating events (as in the Sleep Heart Health Study) severely lacked sensitivity, as none of the controls and only 2/17 cases (respectively 18 and 38 /h) had an oxygen-desaturation index >5.

Prediction of GH using AHI as a continuous variable

I repeated the analysis using the AHI as a continuous variable (in this instance, defined as encompassing apneas, big, and small hypopneas). On univariable analysis, AHI remained a predictor of GH : for each increase in AHI by 5 events per hour, the odds of having GH increased by a factor of 1.35, 95% CI 1.08-1.71. When adjusted for maternal age, BMI, gestational age, parity and gravida status, each increase in AHI by 5 events/h was associated with an adjusted OR of 1.30, 95% 1.19-1.43, p <0.0001, for the presence of GH. In summary, the apnea-hypopnea index – whether considered as a continuous or as categorical predictor variable, and with the use of several alternative thresholds for diagnosis of OSA – was consistently and strongly associated with gestational hypertension.

5. Discussion

I demonstrated a strong association between obstructive sleep apnea and gestational hypertension. The association was even stronger after adjustment for multiple known confounders: maternal age, body mass index, nulliparity, first pregnancy, and gestational age. The results were robust to different definitions of OSA.

Previous research has demonstrated OSA to be an independent risk factor for prevalent and incident hypertension in the non-pregnant population. This study confirms that the association with incident hypertension holds true in a different population, women with singleton pregnancies.

Potential mechanisms linking OSA and hypertension in pregnancy include: 1) changes in body habitus mimicking truncal obesity, which is a strong predictor of OSA in the non-pregnant population; and 2) smaller upper airway calibre (57), In turn, smaller upper airway caliber likely reflects fluid retention (facilitated by hormonal changes), pregnancy-related rhinitis (53), increased soft tissue mass (related to placental growth hormone secretion), and increased airway collapsibility as a consequence of enhanced muscle relaxation (related to relaxin and other hormones).

Some have already proposed that pregnancy is a physiological "stress test," to the extent that pregnancy "unmasks" women most likely to develop metabolic and cardiovascular complications later in life, as documented by several cohort studies (1;26). I hypothesize that pregnancy is a physiological "stress test" that identifies those at risk for

OSA, should predisposing conditions (including truncal obesity) reappear later in life. Furthermore, OSA may in fact be on the causal pathway which leads pregnant and non-pregnant individuals to develop metabolic and cardiovascular morbidities.

The magnitude of the association between OSA and hypertension in this study was much larger than that previously described in the non-pregnant population (4;40;89), with adjusted odds ratios of 7.5 and 2 respectively. However, our results are consistent with my initial predictions as to the association between OSA and GH, derived from a cross-sectional study of snoring and GH (80). Using that study, I had estimated a crude OR of 4.88, linking OSA to pre-eclampsia (80), which is very close to the crude odds ratio of 5.6 that we estimated from our own study data.

I believe that the present study identified a much stronger association between OSA and hypertension than was previously found in non-pregnant individuals, for several reasons. These relate to the rapid evolution of both OSA and hypertension among pregnant women, the severity of the associated hypertension, and the relative homogeneity of our study population.

The evolution of OSA during pregnancy is likely to be very rapid, compared to its natural history among other individuals. In susceptible pregnant women, OSA may quickly develop or worsen, because of the rapidity of changes in body habitus and other related factors as discussed above-- whereas abdominal girth increases to an equivalent extent over several years in the non-pregnant population, eliciting different responses and

compensatory mechanisms. The cardiovascular response to respiratory disturbance events may also be augmented during pregnancy. Among pre-menopausal women with OSA, it has previously been demonstrated that blood pressure surges are higher in the luteal than the follicular phase, possibly due to progesterone (90). Pregnancy is the condition with the highest levels of progesterone, potentially promoting an enhanced blood pressure increase in response to respiratory disturbances. This could also contribute to the strong association we observed.

The rapid transformation of blood pressure from normal to elevated levels within 9 months is likely much more rapid and intense compared to what occurs in community-based cohorts of persons with OSA. In the non-pregnant population, OSA is linked to hypertension in a dose-response fashion. That is, the more severe the OSA, the more of an impact it is likely to have on blood pressure. Conversely, there is evidence in the non-pregnant population that, the worse the hypertension, the more pronounced any underlying OSA is likely to be, as it is the case in resistant hypertension (91). Compared to community-based cohorts of persons with variable OSA (and varying degrees of hypertension, if any), selection of pregnant women with a more severe form of hypertension (GH with proteinuria) might be predicted to highlight the presence of underlying OSA to a greater extent.

Our sample is very homogeneous compared to community-based cohorts of persons with OSA or hypertension—by definition, all our participants were young women, of childbearing age. Hypertension in community-based studies is the end-

product of various etiologies which may include OSA; in most cases, the cause is uncertain and individuals are labeled as having "essential hypertension". One study demonstrated that among adults < 60 years old, the association between OSA and hypertension was stronger than among those > 60 (89). If OSA is contributing only a small attributable fraction to hypertension in older adults because of competing causes for hypertension, it would dilute the strength of the association in studies of that group. I hypothesize that young adults are more likely to have OSA-induced hypertension than older groups, and this likely contributes to the stronger association between OSA and hypertension in the pregnant than non-pregnant populations.

This study's findings are consistent with other studies investigating the link between GH and self-reported snoring, a marker for OSA. In a cross-sectional study on snoring and GH (80), the OR of having GH in presence of snoring was 2.03, adjusted for smoking, maternal weight and age. Similarly, in another cross-sectional study, snoring-sleepiness complex was associated with GH with a crude OR of 2.7 (80). Not surprisingly, the present study, using *objective* measurements of OSA rather than *subjective* reports of snoring, showed a stronger association with GH--possibly because previous investigations were hampered by misclassification of snoring status, limitations of snoring as a clinical marker for OSA in women (92) or incomplete adjustment for confounding variables.

This study's findings are congruent with those of three earlier reports investigating the link between pre-eclampsia and OSA (70;71;93). Those studies

suggested more sleep-related breathing events among women with pre-eclampsia compared to those with normotensive pregnancies. Connolly and Edwards had reported more frequent inspiratory flow limitation but no frank OSA among those with pre-eclampsia. This may reflect the technology used to assess OSA, the definition of hypopneas, sample size, and the absence of correction for confounders. Yinon reported a higher apnea-hypopnea index as a continuous outcome but provided no data on presence of frank OSA as a binary outcome or odds ratio, and there was no correction for confounders.

In contrast, a prospective cohort study of 267 healthy pregnant women with no past medical, obstetrical or psychiatric history found no association between OSA and GH (82). In that study, some subjects had inspiratory airflow limitation but none had frank OSA, and none of the 267 women developed GH. However, if OSA is associated with any medical or psychiatric condition, restricting to healthy women would contribute to the absence of observed OSA. Likewise the cohort design likely limited the ability to investigate GH - a relatively rare outcome- particularly in a healthy, fairly affluent American study population (all had private health insurance coverage).

Measurement error is important in assessing variables including blood pressure, AHI, and BMI. The definition of GH relied on blood pressure measurements by the clinical team. Also, inter-night variation in the determination of AHI is known to occur and pre-gravid BMI was estimated based on recollection of pre-pregnancy weight by the participants. However, random measurement error should regress the association towards

the null value. On the other hand, systematic measurement error, e.g. interpretation of polysomnographic recordings coloured by knowledge of subjects' disease status (case vs. control) could create or exaggerate an association. In this study, the interpretation of polysomnographic recordings was blinded.

To properly assess the magnitude of the association, adjustment is necessary for known as well as potential confounders. Despite our small dataset, we were able to adjust the odds ratio associating OSA with GH for 4 confounders. This included a correction for pre-gravid BMI--however, there is a possibility that this could represent "over-adjustment." The association between OSA and obesity is well known and it is usually assumed that obesity causes OSA. However, there is speculation that in addition, OSA could contribute to obesity, and thus some epidemiological debate whether adjustment for BMI represents overadjustment (4;40).

In the present study, inclusion of BMI in the multivariable logistic regression model reduced the estimated OR from 9.4 to 7.5. I did not adjust for baseline blood pressure, as I believe it might lead to over-adjustment in that it is likely related to unrecognized OSA before pregnancy. Whether correction for diabetes is needed is also debatable, as OSA is an independent risk factor for insulin resistance and glucose intolerance. Our small sample did not allow correction for diabetes, race, coagulopathy, smoking, and medication use (e.g. the muscle relaxant magnesium sulfate and narcotics) because subgroups were too small. These are potential confounders, which should be addressed in larger studies.

Major challenges to recruitment, despite our best efforts, meant that only a small proportion of targeted women actually completed the study. For potential cases, their GH often precluded approaching them for participation, or obtaining polysomnography. Women who presented with hypertension after 34 weeks of gestation often proceeded directly to delivery. By attending the obstetrical ward once daily, we were more likely to recruit stable women who could be observed at least 24 hours, whereas the most unstable women likely delivered immediately and were not even seen by the research nurse as they were sent to the postnatal ward, in a different building. This potential length bias (incidence-prevalence bias) was offset by allowing recruitment after delivery. If the urgency to deliver was related to difficult-to-control blood pressure in those with OSA (as observed in the non-pregnant population) (91;94), then the odds ratio might have been underestimated. Similar difficulties in recruiting pregnant women using polysomnography with electroencephalography were reported by another author (93). I believe that the large number of patients not participating and not completing the study was indicative of the population studied.

Prevalence of OSA was high in cases but also in controls. This is higher than previously documented in other studies among pregnant women using different technology, different scoring criteria and could be related to the inclusion of normotensive controls with obstetrical complications. If any of these complications (preterm labor, premature rupture of membrane, coagulopathy, recurrent miscarriages) is also associated with OSA, the inclusion of those women as controls would bias the

association towards the null. The fact that participants in the control group had a higher frequency of non-hypertensive complications than pregnant women in the general population should not limit the generalizability of the key association I identified, between OSA and GH--unless these non-hypertensive complications are associated with a *diminished* risk of OSA, which seems highly implausible.

Although the advertisement and pamphlets available to potential candidates deliberately did not mention the primary hypothesis of the study, it is also possible that women with sleep apnea were more willing to participate than those without sleep disturbance, increasing the prevalence among controls. Once again, inclusion of those women as controls would have biased the association towards the null. However, consistent with other studies of gestational hypertension, with the stricter Sleep Heart Health Study scoring criteria (> 5 desaturating events/hour), the prevalence in cases was 12% (2/17) and 0% in controls, similar to the expected prevalence in the non-pregnant population.

This study includes seven cases studied after delivery. From one case-series of women with OSA documented prior to pregnancy, OSA tends to worsen during pregnancy (76). Similarly, in another case series, OSA documented in pregnancy decreased in severity post-partum (55). Therefore, those 7 women are likely to have had somewhat less severe OSA measured postpartum, compared to during pregnancy. Studying them after delivery could therefore have underestimated the true association of GH with OSA prevalence and severity.

The gold standard to assess OSA is *attended* full polysomnography, i.e. monitored at the bedside by a sleep study technician. I used *unattended* full polysomnography for logistics and security reasons, since some participants-especially those with pre-eclampsia- required direct overnight observation by the obstetrical team. This contributed to a number of inadequate polysomnographic studies, as some women removed or dislodged the monitoring equipment during the recording period. If unsuccessful polysomnographic recording was related to the presence of OSA (e.g.: more agitated sleep with OSA increased the chances dislodging the recording wires) then the strength of the association might again have been underestimated.

The cross-sectional design of this study prevents inference about causality. However, in the non-pregnant population, it has now been established that OSA is an independent risk factor for subsequent incident hypertension, implying a causal link. Furthermore, in a case series, treatment with CPAP in 11 pre-eclamptic women with inspiratory airflow limitation reduced nocturnal blood pressure by a mean of 18 mmHg, without any change in antihypertensive medication (74) which suggests that OSA may cause or aggravate gestational hypertension. Prospective cohort studies of OSA in pregnancy are needed to establish OSA as an independent causal risk factor for gestational hypertension. Similarly, benefits of treatment and absence of harm will need to be addressed in randomized controlled trials with concealed allocation of treatment prior to recommending CPAP use in this population. Design of such randomized trials will be facilitated and justified by the results of cohort studies.

In summary, this study demonstrates a strong association between obstructive sleep apnea and gestational hypertension in women with singleton pregnancies. The association is even stronger after adjustment for multiple known confounders, and is consistent across several definitions of OSA. Further studies are required to address the natural history and the best management of OSA and gestational hypertension among pregnant women, which could include cohort studies of pregnancy outcomes in women with and without underlying OSA, and potentially a randomized intervention trial of CPAP for pregnant women in this context.

Appendix 1

Accepted for publication April 1999
Comments and Reprint Requests to: AASM in conjunction with: The European Respiratory Society, The Australasian Sleep Association, The American Thoracic Society

Sleep–Related Breathing Disorders in Adults: Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research

The Report of an American Academy of Sleep Medicine Task Force

4.1 Obstructive sleep apnea-hypopnea syndrome (OSAHS)

4.1.2 Diagnostic criteria

The individual must fulfill criterion A or B, plus criterion C.

A. Excessive daytime sleepiness that is not better explained by other factors;

B. Two or more of the following that are not better explained by other factors:

-choking or gasping during sleep,
-recurrent awakenings from sleep,
-unrefreshing sleep,
-daytime fatigue,
-impaired concentration; and/or

C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep.[1,4] These events may include any combination of obstructive apneas/hypopneas or respiratory effort related arousals, as defined below.

4.1.2.1 Obstructive apnea/hypopnea event

An event characterized by a transient reduction in, or complete cessation of, breathing. In routine clinical practice it is not considered necessary to distinguish obstructive hypopneas from apneas because both types of events have similar pathophysiology. These events must fulfill criterion 1 or 2, plus criterion 3 of the following:

1. A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).
2. A clear amplitude reduction of a validated measure of

breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of >3% or an arousal.
3. The event lasts 10 seconds or longer.[2]

4.1.2.2 Respiratory effort-related arousal (RERA) event

A sequence of breaths characterized by increasing respiratory effort leading to an arousal from sleep, but which does not meet criteria for an apnea or hypopnea. These events must fulfill both of the following criteria:
1. Pattern of progressively more negative esophageal pressure, terminated by a sudden change in pressure to a less negative level and an arousal
2. The event lasts 10 seconds or longer[1]

4.1.2.3 Justification for the diagnostic criteria

The use of an event frequency of five per hour as a minimal threshold value was based on epidemiological data that suggest minimal health effects such as hypertension, sleepiness, and motor vehicle accidents,[10-12] may be observed at an apnea-hypopnea index (AHI) threshold of five. Additionally, limited data from intervention studies suggest treatment associated improvements in vitality, mood, and fatigue in subjects with AHIs between 5 and 30[13] and improvements in sleepiness and neurocognitive function in subjects with AHI levels of 5 to 15.[14,15]

4.1.3 Severity criteria

Severity of the OSAHS has two components: severity of daytime sleepiness and of overnight monitoring. A severity level should be specified for both components. The rating of severity for the syndrome should be based on the most severe component.
A. Sleepiness [Level of Evidence - 3]
1. Mild: Unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. Examples include sleepiness that is likely to occur while watching television, reading, or traveling as a passenger. Symptoms produce only minor impairment of social or occupational function.
2. Moderate: Unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention. Examples include uncontrollable sleepiness that is likely to occur while attending activities such as concerts, meetings, or presentations. Symptoms produce moderate impairment of social or occupational function.
3. Severe: Unwanted sleepiness or involuntary sleep episodes occur during activities that require more active attention. Examples include uncontrollable sleepiness while eating, during conversation, walking, or driving. Symptoms produce marked impairment in social or occupational function.
B. Sleep Related Obstructive Breathing Events [Level of Evidence - 2]

1. Mild: 5 to 15 events per hour
2. Moderate: 15 to 30 events per hour
3. Severe: greater than 30 events per hour

4.1.3.2 Justification for the severity criteria

There are currently no adequate prospective studies that have validated severity criteria for sleepiness. The criteria are suggested by the task force as an operational definition. The data to justify a severity index based on event frequency are derived from the Wisconsin Sleep Cohort data that show an increased risk of hypertension that becomes substantial at an AHI of approximately 30.[10] Currently there is no data available to indicate an appropriate distinction between mild and moderate degrees of obstructed breathing events during sleep. The recommended level of 15 reflects a consensus opinion of the Task Force (level 3). Additional data are needed to characterize changing risk profiles with changing frequency of hypopneas/apneas.

4.1.5 Predisposing factors

1. Obesity, particularly upper body adiposity
2. Male gender
3. Craniofacial abnormalities including mandibular/maxillary hypoplasia
4. Increased pharyngeal soft or lymphoid tissue including tonsillar hypertrophy
5. Nasal obstruction
6. Endocrine abnormalities: hypothyroidism, acromegaly
7. Familial history

4.1.6 Prevalence

OSAHS encompasses a wide spectrum of airflow obstruction and associated morbidity. Prevalence varies with levels of severity. Snoring is reported by 40-60% of adults.[16,17] The combination of snoring and "breathing pauses during sleep" have been reported in 2.5% of adults.[18] Using AHI threshold values to define prevalence is problematic because of the previous use of disparate definitions of hypopneas, limiting both comparisons among studies and estimation of prevalence based on the current recommended procedures for measuring hypopneas. AHI levels >5, based on identifying hypopneas using a breathing amplitude criteria in conjunction with desaturation, may be present in 24% of men and 9% of women.[19] Similarly measured AHI levels of >15 may be found in 9% and 4% of men and women, respectively.[19] Using that definition of AHI and requiring sleepiness as another disease defining criterion reduces prevalence estimates to 2 and 4% for women and men respectively. Prevalence may be higher among racial and ethnic minorities.[20,21]

8.0 REFERENCES

1. Gould GA, Whyte KF, Rhind GB, Douglas D, et al. The sleep hypopnea syndrome. Am Rev Respir Dis 1988;137:895-8.
2. Guilleminault, C., R. Stoohs, A. Clerk, M. Cetel, and P. Maistros. A

cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest 1993;104:781-7.
3. Burwell C, Robin E, Whaley R, Bickelmann A. Extreme obesity associated with alveolar hypoventilation - a pickwickian syndrome. Am J Med 1956;21:811-8.
4. White, DP. Central sleep apnea. Med Clin N America 1985;69:1205-19.
5. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. Annu Rev Med 1976;27:465-484
6. Block AJ, Boysen PG, Wynne JW, Hunt LA. Sleep apnea, hypopnea, and oxygen desaturation in normal subjects. N Engl J Med 1979;300:513-7.
7. Guilleminault C. Obstructive sleep apnea: the clinical syndrome and historical perspective. Med Clin N America 1985;69:1187-1203.
8. Bradley TD, Young T, Strohl K. American Thoracic Society/American Academy of Sleep Medicine Statement on health outcomes research in sleep apnea. Am J Respir Crit Care Med 1998.
9. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1986;89:2S-3S.
10. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med 1997;157:1746-52.
11. Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. Sleep 1997;20:608-13.
12. Young T, Finn L, Hla KM, Morgan B, Palta M. Snoring as part of a dose-response relationship between sleep-disordered breathing and blood pressure. Sleep 1996;19:S202-5.
13. Redline S, Adams N, Strauss M, Winters M, Roebuck T, Rosenberg C. Improved Outcomes After CPAP Treatment in Mild Sleep Disordered Breathing. Am J Respir Crit Care Med 1998; In Press.
14. Engleman HM, Martin SE, Dreary IJ, Douglas NJ. Effect of CPAP therapy on daytime function on patients with mild sleep apnoea/hpopnoea syndrome. Thorax 1997;52:114-9.
15. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled trial of CPAP for mild sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med; In press.
16. Kump K, Whalen C, Tishler PV et al. Assessment of the validity and utility of a sleep-symptom questionniare. Am J Respir Crit Care Med 1994;150:735-41.
17. Norton PG, Dunn EV. Snoring as a risk factor for disease: an epidemiologic survey.
BM J 1985;291:630-3.
18. Ohayon MM, Guilleminault C, Priest RG, Caulet M. Snoring and breathing pauses during sleep: telephone interview survey of a United Kingdom population sample. BMJ. 1997;314:860-3.
19. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Bader S. The occurrence of sleep disordered breathing in middle-aged adults . New Engl J Med 1993;328:1230-5.
20. Redline S, Tishler PV, Hans M, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep disordered breathing in African Americans and Caucasians. Am J Respir Crit Care Med 1997;155:186-92.
21. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40-64 years: A population-based survey. Sleep 1997;20:65-76.

Extracted from the full recommendations published in Sleep August 1999.

Appendix 2 Systematic Review on the Association of Sleep Apnea during Pregnancy and Fetomaternal Complications.

I conducted a systematic review to search for evidence of a potential link between sleep apnea in pregnancy and GH. Searches were performed independently by a librarian specialized in systematic searches and by me in the 2nd week of March 2006 using Ovid Embase 1980-10th week 2006, Ovid Medline 1950-2006 including Medline ® (in process and other non indexed citations), and Ovid All EBM Reviews (Cohrane Database of systematic reviews, ACP Journal Club, Database Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials). The search was conducted without restriction using: « sleep apnea syndromes », « hypoventilation », « central sleep apnea syndrome », « snoring » as exploded MeSH words, « sleep » combined with « apnea », « hypopnea », « sleep disordered breathing », « sleep related respiratory disorder », « ondine », « hypoventilation » (textwords). These terms were combined with « pregnancy », « preeclampsia », « toxemia », «maternal hypertension » (exploded MeSH words), « pregnant », « parturient » (textwords) with an exclusion of articles focusing on « infant ».

References cited in the retrieved articles were checked for any additional articles that might have been missed. Papers were included if they pertained to apnea during sleep in pregnant women, and were published in English, French, German, Italian, or Spanish. I excluded articles on unrelated topics, animals, apneas induced either pharmacologically or during anesthesia, apneas in fetuses or infants, reviews or commentaries, and those which related to pregnant women without OSA who were followed for the subsequent development of either snoring or OSA during pregnancy.

Three quality criteria were required for inclusion of articles in this review. First, a clear diagnosis of sleep apnea was required, supported either by polysomnography or peripartum oximetry or by a clear description of sleep apnea as assessed independently by two sleep experts (R. John Kimoff and KC); second, data on obstetrical outcomes including at least maternal blood pressure or infant birth weight were required; third, information was required as to whether any sleep apnea treatment was initiated during pregnancy. Data were extracted using standardized forms, then summarized using appropriate denominators.

Results

The search strategy yielded 371 articles. I rejected 35 papers on animals, 10 commentaries/editorials, 46 on apneas induced pharmacologically or during anesthesia, 109 covering a different topic, 109 on fetal or child apnea. I rejected 18 narrative reviews with primary or secondary focus on sleep apnea in pregnancy (95-112). I excluded 21 studies on incidence and prevalence of clinical markers of OSA in pregnancy.

One study compared pregnant women with and without hypertension, but all had OSA. This study was excluded as participants were selected specifically based on blood pressure values, and no information was provided as to how many were approached (to estimate prevalence of GH in OSA) and no fetal weight data were provided (113). One article in Japanese (114) and two without information on obstetrical outcomes (115;116) were excluded. A total of 19 papers remained for this review. One case report with a narrative review of 8 other cases reported in the literature was included. These were published between 1978 and 2006.

There were 15 reports (75;77;79;117-128) of single cases, and one report of two pregnancies in the same woman with and without treatment of OSA (78). One reported on two women (129), one on three women (130) whereas two case series described 8 (131) and 12 women (76) respectively.

Baseline characteristics

A total of 42 pregnancies occurred in 41 women diagnosed with sleep apnea. Mean age was 28.5 (minimum 22, maximum 38). 72% (28/39) were primiparous. All pregnancies were singleton. Based on body mass index (BMI) when provided, 56% (21/39) were obese (BMI>30), 15% (6/39) were overweight (BMI 25-30), 26% (10/39) had a normal weight (BMI 20-25), 5% (2/39) were underweight (BMI<20).

Sleep characteristics

Diagnosis of SA was made on clinical grounds alone in 13 pregnancies (especially in the reports from 1980s). In 13 pregnancies, the diagnosis was based on polysomnography and clinical features prior to pregnancy. Based on the same elements, diagnosis was ascertained during the first trimester in 5, in the last trimester in 5, and postpartum in 6. All but three had OSA. Two had exclusively central apneas (121;128). One had mixed (central and obstructive) sleep apnea presenting in the context of hypothyroidism combined with a lingual thyroid (124). Based on the polysomnography results (132), OSA was severe in 14, moderate in 8, mild in 4, and of unspecified severity in three.

Information on maternal oxygenation was available for 25 women. The nadir of saturation was below 90% in those 25 parturients, below 80% in 12, and below 50% in 4. The baby whose mother had the lowest saturation (20%) died in utero at 26 weeks. The

nadir of saturation had a Pearson's correlation of 0.3 with the adjusted birth weight percentile.

Twenty women received no treatment for sleep apnea during pregnancy, one was intubated for apnea and delivered immediately at 29 weeks (133), one had a tracheostomy at 22 weeks (134), while 20 others used positive airway pressure (continuous or bilevel). Positive airway pressure was initiated prior to pregnancy in 10 women, during the first trimester in 5, and in the third trimester in 5.

Reported risk factors for OSA include BMI>25 in 70% (27/39), asthma or respiratory allergies in 17% (7/42) but in 50% (6/12) of women where this was systematically explored (135), and narrow upper airway (micrognathia, retrognathia, crowded oropharynx, ogival hard palate, narrow nasal passage) in 92% (24/26). (Note that denominators vary because of inconsistent ascertainment/documentation).

Sleep apnea likely preceded pregnancy in half of the women. In 14 women, sleep apnea was documented prior to pregnancy. An additional 5 women had clinical history and physical description compatible with sleep apnea pre-pregnancy but were not investigated. Ten had documented persistence of sleep apnea post partum and were therefore likely to have had sleep apnea antepartum. In only one woman, absence of symptoms prior to pregnancy was reported. In the remaining 11 women, no information was reported.

OSA worsened in pregnancy in 13 women based on an increase in snoring, sleepiness, apnea-hypopnea index, or CPAP requirements. Post partum, severity of sleep apnea was decreased clinically or on repeat polysomnography when done though it did not disappear. Similarly, in a case-series, ten women diagnosed with OSA during

pregnancy had a second polysomnography three months postpartum. The median AHI decreased from 54 in pregnancy to 18 postpartum, suggesting marked improvement post partum (55).

Obstetrical complications

Fourteen of the 42 pregnancies were preceded or complicated by increased blood pressure. Ten developed a hypertensive disorder during pregnancy. Six were labelled as pre-eclampsia, although not all met unequivocal criteria for this diagnosis. Two additional women had borderline blood pressure : one at term (140/88) (75) and one from the onset of pregnancy (138-142/90-91) (76). Two had chronic hypertension (77;78). There were no reported cases of HELLP syndrome or eclampsia. One woman had severe pulmonary hypertension with right heart failure during pregnancy (79). Treatment was initiated at 29 weeks gestation. She lost 104 lbs with CPAP at night and supplemental oxygen during the daytime. She corrected her right heart failure and improved her pulmonary hypertension prior to delivery. One completely reversed her severe pulmonary hypertension (systolic blood pressure of 100 mmHg by right heart catheterization) and polycythemia with BiPAP prior to pregnancy (121).

Fetal outcomes

Several reports documented acute fetal distress in response to maternal apneas. Five fetuses had either low scalp pH, decelerations or decreased fetal heart rate variability associated with maternal desaturating apneas. Four of the five fetuses with documented acute distress had an adjusted birth weight below the 10^{th} percentile. For 7 other pregnancies where acute fetal distress was evaluated but found to be absent, 3 infants had

birth weights below the 10th percentile, 2 were at the 25th, and 2 were above the 75th percentile for birth weight.

Birth weight in grams or percentiles were available for 25 infants, out of the 42 pregnancies reviewed. I adjusted birth weights for gestational age, race, sex and parity and expressed them in percentiles according to American population charts (136). Of these 25 infants, the mean birth weight percentile was 19%; 16/25 had birth weights below the 10th percentile, 4/25 were between the 10th and 25th percentiles, 1/25 was at the 50th percentile, 2/25 were between the 75th and 90th percentiles, and 2/25 were above the 90th percentile. This distribution is dramatically different from normal expected weights adjusted for race, parity, sex, and gestational age, and is even more striking when one considers that these mostly obese women might be expected to have large, not small babies (137). These observations suggest that SA is associated with chronic compromise of maternal-placental-fetal circulation.

Pregnancy complications for the mother or the fetus

Overall, pregnancy with maternal sleep apnea was complicated for the mother (GH, pre-eclampsia or right heart failure/pulmonary hypertension) in 31% (13/42) and for the child (birth weight below 10th percentile) in 64% (16/25) where reported.

Complications for either the mother or the child as defined above occurred at most, in 86% (25/29) of pregnancies for whom clear data were available. An additional 13 normotensive women gave birth to « healthy » babies (76;123) or had « successful pregnancies » (124). Assuming those babies were all of normal birthweight, then the frequency of complications for either the mother or the child was 60% (25/42).

Among the 25 pregnancies with complications (GH, preeclampsia, pulmonary hypertension or small for gestational age babies), 18 women (72%) were not treated at all. Among the 7 who developed complications despite treatment, treatment was initiated late in the third trimester in 6, at a time where maternal complications were already present in all 6.

Among the 17 uncomplicated pregnancies, 88% (15) received treatment. Treatment was initiated prior to or during the first trimester in 13 (76%). Treatment of SA was associated with fewer fetomaternal complications.

Limitations of the literature

Inference is limited by the relatively small number of reported cases, the absence of relevant controls, the non-randomized assignment of treatment, and the probability of substantial publication bias. Specifically, pregnancies with severe complications are most likely to be reported as are those with apparent successes of treatment. In addition, the articles I reviewed did not use a consistent format for collection and reporting of obstetrical and fetal data, and used varying definitions of hypertension, pre-eclampsia, and sleep apnea. Also technology used, if any, to document sleep-related events varied over the 28-year span of this review. Because very few cases were available and because physiologic responses are similar, we included cases of central sleep apnea despite differences from OSA with respect to pathophysiology. However, their exclusion would be unlikely to change the conclusions of this review.

We conclude that systematic, prospective investigations addressing the impact of sleep apnea on pregnancy outcomes are clearly needed. A prospective cohort study of women with and without sleep apnea who become pregnant would address the risk of

obstetrical complications. Similarly, a carefully designed randomized, controlled trial of treatment for sleep apnea during pregnancy would address the question of benefits and absence of harm for the mother and baby.

Reference List for the Systematic Review

(1) Feinsilver SH, Hertz G, Feinsilver SH, Hertz G. Respiration during sleep in pregnancy. [Review] [40 refs]. Clin Chest Med 1992 Dec;13(4):637-44.

(2) Brown LK. Dyspnea during pregnancy and sleep-disordered breathing in pregnancy. Seminars in Respiratory & Critical Care Medicine 1998;19(3):209-21.

(3) Edwards N, Middleton PG, Blyton DM, et al. Sleep disordered breathing and pregnancy. [Review] [43 refs]. Thorax 2002 Jun;57(6):555-8.

(4) Meurice JC, Paquereau J, Neau JP, et al. [Respiratory disorders during sleep in the pregnant woman]. [Review] [15 refs] [French]. Rev Neurol (Paris) 2003 Nov;159(11 Suppl):6S91-4.

(5) Shaver JL, Shaver JLF. Women and sleep. [Review] [36 refs]. Nurs Clin North Am 2002 Dec;37(4):707-18.

(6) Moline ML, Broch L, Zak R, et al. Sleep in women across the life cycle from adulthood through menopause. [Review] [119 refs]. Sleep Med Rev 2003 Apr;7(2):155-77.

(7) Moline ML, Broch L, Zak R. Sleep in women across the life cycle from adulthood through menopause. Medical Clinics of North America 2004;88(3):705-36.

(8) Moline M, Broch L, Zak R. Sleep problems across the life cycle in women. Current Treatment Options in Neurology 2004;6(4):319-30.

(9) Sharma S, Franco R. Sleep and its disorders in pregnancy. WMJ 2004;103(5):48-52.

(10) Pien GW, Schwab RJ, Pien GW, Schwab RJ. Sleep disorders during pregnancy. [Review] [149 refs]. Sleep 2004 Nov 1;27(7):1405-17.

(11) Santiago JR, Nolledo MS, Kinzler W, et al. Sleep and sleep disorders in pregnancy. [Review] [136 refs]. Ann Intern Med 2001 Mar 6;134(5):396-408.

(12) Sahota PK, Jain SS, Dhand R, Sahota PK, Jain SS, Dhand R. Sleep disorders in pregnancy. [Review] [54 refs]. Curr Opin Pulm Med 2003 Nov;9(6):477-83.

(13) Young T, Peppard PE, Gottlieb DJ, Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. [Review] [275 refs]. Am J Respir Crit Care Med 2002 May 1;165(9):1217-39.

(14) Collop NA, Adkins D, Phillips BA, Collop NA, Adkins D, Phillips BA. Gender differences in sleep and sleep-disordered breathing. [Review] [126 refs]. Clin Chest Med 2004 Jun;25(2):257-68.

(15) Otake K, Shinobe R, Sato K, et al. [Sleep apnea syndrome]. [Review] [30 refs] [Japanese]. Nippon Rinsho 2005 Jul;63(7):1221-6.

(16) Saaresranta T, Polo O, Saaresranta T, Polo O. Sleep-disordered breathing and hormones. [Review] [185 refs]. Eur Respir J 2003 Jul;22(1):161-72.

(17) Harding SM. Complications and consequences of obstructive sleep apnea. Curr Opin Pulm Med 2000;6(6):485-9.

(18) Douglas NJ. Recent advances in the obstructive sleep Apnoea/Hypopnoea syndrome. Annals of the Academy of Medicine, Singapore 2002;31(6):697-701.

(19) Edwards N, Blyton DM, Kirjavainen TT, Sullivan CE. Hemodynamic responses to obstructive respiratory events during sleep are augmented in women with preeclampsia. Am J Hypertens 2001 Nov;14(11 Pt 1):1090-5.

(20) Adachi H, Mukai E, Okuda S, Kawada T. [A severe case of acute autonomic and sensory neuropathy]. Rinsho Shinkeigaku 1998 Jul;38(7):663-8.

(21) Sritippayawan S, Hamutcu R, Kun SS, Ner Z, Ponce M, Keens TG. Mother-daughter transmission of congenital central hypoventilation syndrome. Am J Respir Crit Care Med 2002 Aug 1;166(3):367-9.

(22) Funada Y, Nishimura Y, Kamemura K, et al. Familial adult onset primary alveolar hypoventilation syndrome. Intern Med 2001 Jun;40(6):526-31.

(23) Conti M, Izzo V, Muggiasca ML, Tiengo M. Sleep apnoea syndrome in pregnancy: a case report. Eur J Anaesthesiol 1988 Mar;5(2):151-4.

(24) Kowall J, Clark G, Nino-Murcia G, Powell N. Precipitation of obstructive sleep apnea during pregnancy. Obstet Gynecol 1989 Sep;74(3 Pt 2):453-5.

(25) Hastie SJ, Prowse K, Perks WH, Atkins J, Blunt VA. Obstructive sleep apnoea during pregnancy requiring tracheostomy. Aust N Z J Obstet Gynaecol 1989 Aug;29(3 Pt 2):365-7.

(26) Sherer DM, Caverly CB, Abramowicz JS. Severe obstructive sleep apnea and associated snoring documented during external tocography. Am J Obstet Gynecol 1991 Nov;165(5 Pt 1):1300-1.

(27) Charbonneau M, Falcone T, Cosio MG, Levy RD. Obstructive sleep apnea during pregnancy. Therapy and implications for fetal health. Am Rev Respir Dis 1991 Aug;144(2):461-3.

(28) Pieters T, Amy JJ, Burrini D, Aubert G, Rodenstein DO, Collard P. Normal pregnancy in primary alveolar hypoventilation treated with nocturnal nasal intermittent positive pressure ventilation. Eur Respir J 1995 Aug;8(8):1424-7.

(29) Lefcourt LA, Rodis JF. Obstructive sleep apnea in pregnancy. Obstet Gynecol Surv 1996 Aug;51(8):503-6.

(30) Singh D, Mills GH, Caunt JA, Alderson JD. Anaesthetic management of labour in two patients with Klippel-Feil syndrome. Int J Obstet Anesth 1996 Jul;5(3):198-201.

(31) Oleszczuk J, Leszczynska-Gorzelak B, Mierzynski R, Kaminski K, Oleszczuk JJ. Pregnancy in obstructive sleep apnoea syndrome under treatment with nCPAP. Zentralbl Gynakol 1998;120(2):71-4.

(32) Taibah K, Ahmed M, Baessa E, Saleem M, Rifai A, al-Arifi A. An unusual cause of obstructive sleep apnoea presenting during pregnancy. J Laryngol Otol 1998 Dec;112(12):1189-91.

(33) Lewis DF, Chesson AL, Edwards MS, Weeks JW, Adair CD. Obstructive sleep apnea during pregnancy resulting in pulmonary hypertension. South Med J 1998 Aug;91(8):761-2.

(34) Shiomi T, Guilleminault C, Izumi H, Yamada S, Murata K, Kobayashi T. Obstructive sleep apnoea in a puerperal patient with Hallermann-Streiff syndrome. Eur Respir J 1999 Oct;14(4):974-7.

(35) Rai N, Masson EA, Lindow SW. Sleep apnoea syndrome in pregnancy without fetal compromise. J Obstet Gynaecol 2000 Jan;20(1):84.

(36) Roush SF, Bell L. Obstructive sleep apnea in pregnancy. J Am Board Fam Pract 2004 Jul;17(4):292-4.

(37) Ochoa-Sepulveda JJ, Ochoa-Amor JJ. Ondine's curse during pregnancy. J Neurol Neurosurg Psychiatry 2005 Feb;76(2):294.

(38) Brain KA, Thornton JG, Sarkar A, Johnson AO. Obstructive sleep apnoea and fetal death: successful treatment with continuous positive airway pressure. BJOG 2001 May;108(5):543-4.

(39) Domingo C, Latorre E, Mirapeix RM, Abad J. Snoring, obstructive sleep apnea syndrome, and pregnancy. Int J Gynaecol Obstet 2006 Mar 9;.

(40) Joel-Cohen SJ, Schoenfeld A. Fetal response to periodic sleep apnea: a new syndrome in obstetrics. Eur J Obstet Gynecol Reprod Biol 1978 Apr;8(2):77-81.

(41) Schoenfeld A, Ovadia Y, Neri A, Freedman S. Obstructive sleep apnea (OSA)-implications in maternal-fetal medicine. A hypothesis. Med Hypotheses 1989 Sep;30(1):51-4.

(42) Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med 2004 Jan;5(1):43-51.

(43) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999 Aug 1;22(5):667-89.

(44) Ochoa-Sepulveda JJ, Ochoa-Amor JJ. Ondine's curse during pregnancy [5]. J Neurol Neurosurg Psychiatry 2005;. 76(2).

(45) Hastie SJ, Prowse K, Perks WH, Atkins J, Blunt VAW. Obstructive sleep apnoea during pregnancy requiring tracheostomy. Aust N Z J Obstet Gynaecol 1989;. 29(3 II).

(46) Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med 2004;. 5(1).

(47) Edwards N, Blyton DM, Hennessy A, Sullivan CE. Severity of sleep-disordered breathing improves following parturition. Sleep 2005 Jun 1; 8(6):737-41.

(48) Zhang J, Bowes WAJr. Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. Obstet Gynecol 1995 Aug;86(2):200-8.

(49) Jensen D, Damm P, Sorensen B, et al. Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. Am J Obstet Gynecol 2005;189(1):239-44.

Appendix 3 Questionnaire

Questionnaire to be filled by the participant and a research assistant

(1)Code Number_____(2)Date(YYMMDD)_____

Below is a list of symptoms that some pregnant women may experience. Please score how much of a problem this has been over the last 2 weeks. Use the scale provided.

	Very large(1)						no problem(7)
3 Decreased energy	1	2	3	4	5	6	7
4 Waking up in the morning feeling unrefreshed or tired	1	2	3	4	5	6	7
5 Feeling that ordinary activities require an extra effort	1	2	3	4	5	6	7
6 Falling asleep at inappropriate times	1	2	3	4	5	6	7
7 Falling asleep if not active	1	2	3	4	5	6	7
8 Sore throat upon awakening	1	2	3	4	5	6	7
9 Waking more than twice during the night	1	2	3	4	5	6	7
10 Concern about the times you stop breathing at night	1	2	3	4	5	6	7
11 Waking up feeling you were choking	1	2	3	4	5	6	7
12 Waking up with a headache	1	2	3	4	5	6	7
13 Excessive fatigue	1	2	3	4	5	6	7
14 Waking up more than once a night to go to the bathroom	1	2	3	4	5	6	7
15 A feeling that your sleep is restless	1	2	3	4	5	6	7
16 Difficulty staying awake when reading	1	2	3	4	5	6	7
17 Difficulty staying awake when carrying on a conversation	1	2	3	4	5	6	7
18 Difficulty staying awake when watching TV	1	2	3	4	5	6	7
19 Fighting the urge to fall asleep when driving	1	2	3	4	5	6	7
20 Sweating at night	1	2	3	4	5	6	7
21 Discomfort in legs preventing you from sleeping	1	2	3	4	5	6	7
22 Discomfort in back preventing you from sleeping	1	2	3	4	5	6	7
23 Discomfort related to heartburn preventing you from sleeping	1	2	3	4	5	6	7
24 Being awakened by young children	1	2	3	4	5	6	7
25 Grinding your teeth at night	1	2	3	4	5	6	7
26 Blocked nose	1	2	3	4	5	6	7

Add your own symptoms or complaints.

27	1	2	3	4	5	6	7
	1	2	3	4	5	6	7

Appendix 3 Questionnaire-continued

28 Put an X corresponding to your overall rating of sleep quality in pregnancy on this line

poor _____ excellent

29 Do you have discomfort in your legs? Yes No

If yes

30 Is it worse in the evening? Yes No

31 Is it worse if you are still (not moving)? Yes No

32 Is it worse if standing up? Yes No

33 Is is better if you move? Yes No

Please fill this section after discussion with someone who has been a witness **of your sleep.**

34 How many nights a week did you snore before pregnancy?	0 1 2 3 4 5 6 7 NA
35 Did you snore in the last 2 weeks?	Yes No I do not know If No or I do not know, skip to 39
36 Is the snoring louder than someone talking?	Never, rarely, occasionnally, sometimes, often, most of the time, I don't know
37 How many nights a week do you snore?	0 1 2 3 4 5 6 7
38 If you began snoring in this pregnancy, when did the snoring begin?	

39 Circle the most appropriate answer concerning the sleep witness:
bed partner; shares the house; nurse; hospital roommate; no witness; _____

Have you ever had any problems with	If yes describe problem
40 Breathing	No Yes Describe:
41 Nose (including fracture, surgery)	No Yes Describe:
42 Allergies with sneezing, blocked nose	No Yes Circle known allergies: unknown cat dog feather animal pollens molds weeds ragweed trees_____
43 If yes to question 42, did you have sneezing, blocked nose for at least 7 days during pregnancy	No Yes Specify trimester(s) of pregnancy: **1**(0-12wks) **2**(13-26wks) **3**(26wks+)
44 Heart	No Yes Describe:
45 Diabetes	No Yes
46 Bleeding (easy bleeding, blood clots)	No Yes Describe:
47 Kidney	No Yes Describe:
48 Lupus, arthritis, thyroid (specify)	No Yes Describe:
49 Tonsils, head and neck, face fracture or surgery	No Yes Describe:

Appendix 3 Questionnaire-continued

If you **never** smoked, go to question 55

50 At what age did you begin smoking?	
51 In the 3 months prior to pregnancy, how much were you smoking?	In average_____packs per day
52 How much are you smoking now?	In average_____packs per day
53 Have you ever quit for more than 6 months?	No Yes how long in total
54 How much are you usually smoking when not pregnant?	In average_____packs per day

If this is your first pregnancy, go to question 58. Pre-eclampsia occurs at different frequencies if a woman changes partners or if she has some health conditions.

55 Did you have high blood pressure or pre-eclampsia in previous pregnancies?	No Yes Specify high blood pressure pre-eclampsia
56 Was the father of this child the same as in the other pregnancies?	No Yes I don't know I don't want to answer
57 Did you have diabetes (high sugar) in previous pregnancies?	No Yes

To your knowledge, has anyone related to you by blood had any of the following. Report who this is relative to you

58 High blood pressure in pregnancy (pre-eclampsia)	No Yes Specify: mother sister grandmother
59 Bleeding (easy bleeding, blood clots)	No Yes Specify problem: Specify: mother father brother sister grandmother grandfather child
60 Snoring	No Yes Specify: mother father brother sister grandmother grandfather child
61 Allergies with sneezing, blocked nose	No Yes Specify: mother father brother sister grandmother grandfather child

We would like to know your

62 Weight just before pregnancy	
63 Height	

We would like to know which products, puffers you **used,** if any, during this pregnancy while at home. Add the names of what you used even if not frequently used. Omit quantity and frequency.

64 Vitamins	
65 Lung medication including puffers	
66 Nasal sprays	
67 Aspirin, ASA	
68 Over-the-counter	
69 Others	
70 Did you participate in the Antioxidant trial	No Yes

Appendix 3 Questionnaire-continued

On average, how often a week did you exercise for at least 30 minutes

71 From 0 to 13 weeks of pregnancy	0	1	2	3	4	>=5days/wk
72 From 13 to 26 weeks of pregnancy	0	1	2	3	4	>=5days/wk

Pre-eclampsia and sleep apnea occur at different frequencies depending on the country of origin. We would like to know where you and your parents were born and the year of your arrival if born elsewhere.

73 My country of birth		
74 The year I arrived in Canada		
75 Country of birth of parents	Father	Mother

Pre-eclampsia may occur at different frequencies depending on years at school.
76 Check the highest level of school completed.

- ❑ Elementary school
- ❑ Some high school
- ❑ Completed high school
- ❑ Some college or vocational education
- ❑ Completed college or vocational education
- ❑ Some university studying
- ❑ Completed Bachelor's degree
- ❑ Some Master degree training
- ❑ Completed master degree
- ❑ Some PhD training
- ❑ PhD

Pre-eclampsia could occur at different frequencies depending on work. Check all that may apply
77 What was your work during this pregnancy.

- ❑ Homemaker
- ❑ Sick leave or preventive withdrawal
- ❑ Work:_____

Comments (you may use the other side of this sheet)

_____

_____

_____

Thank you for your time.
Charlene Barber, research nurse, Naftaly Naor, research assistant, Katéri Champagne MD, John Kimoff MD, K Schwartzman MD

78 Data collected with the assistance of CB NN

SCORING

1. a very large problem
2. a large problem
3. a moderate to large problem
4. a moderate problem
5. a small to moderate problem
6. a small problem
7. no problem

Appendix 4 Research scoring criteria for the MUHC Sleep Lab

The American Academy of Sleep Medicine (AASM) published in 1999 recommendations on technology to use and definition of respiratory events for research purposes (Appendix 1). I elaborated the MUHC research criteria in collaboration with the Sleep Lab director and chief technologist following closely those recommendations except for more detailed description of the events (apneas/hypopneas are not distinguished and sub classifications are not part of the AASM recommendations). I added the autonomic obstructive hypopneas to acknowledge more subtle events with physiological translation. Those would normally require an esophageal probe to be diagnosed as Respiratory Events Related Arousals (RERA) something that was not ethically acceptable in our population because of the risk of epistaxis in women with severe facial swelling as may be seen in pre-eclampsia. The sub classifications were introduced to better describe respiratory events from a mechanistic point of view, to allow flexibility for different research settings where needs for either more sensitive or more specific criteria arise in addition to allowing sensitivity analysis.

Using ambulatory polysomnogram with EEG technology Suzanne, Tyco, Ottawa

1. Respiratory Events:

Baseline flow amplitude is defined as the mean amplitude of stable breathing and oxygenation in the 2 minutes preceding onset of the event (in those with stable breathing pattern)
Or the mean amplitude of the 3 largest breaths in the preceding 2 minutes (in those with unstable breathing pattern)

Epochs are the standard 30-second windows.

Apnea (9 possibilities):
Absence of airflow (≥90% decrease in airflow)
lasting ≥ 10 seconds
Type

Obstructive:	with continued respiratory effort.
Mixed:	>50% central, ≥ 3 obstructed efforts at end-apnea.
Central:	No respiratory effort on the respiratory bands.

Sub classify

Desaturating	if terminating >3% desaturation
Arousal	if terminated with EEG arousal
Neither	if no >3% desaturation or arousal associated

Note: If an apnea is associated with both a desaturation and an EEG arousal, score as desaturating event.

Appendix 4 Research scoring criteria-continued

Hypopnea (11 possibilities):

A clear decrease from baseline airflow amplitude
lasting $\geq$ 10 seconds,
associated with a > 3% decrease in O_2 saturation,
or terminated with an arousal.

Type
Obstructive: inspiratory flow limitation, rib cage paradox or snoring.
Indeterminate: no evidence of inspiratory flow limitation, rib cage paradox or snoring.

Sub classify
"Big" 50-90% decrease in airflow;
(Corresponds to rule 1 of the Chicago criteria)
- **Desaturating** if terminating with >3% desaturation
- **Arousal** if terminated with EEG arousal
- **Neither** if no >3% desaturation or arousal associated

"Small" <50% but clear decrease in airflow;
(Corresponds to rule 2 of the Chicago criteria)
- **Desaturating** if terminating >3% desaturation
- **Arousal** if terminated with EEG arousal
- **Autonomic** only for obstructive hypopneas, if associated with brady-tachycardia* in the absence of >3%-desaturation and EEG arousal

*(absolute difference in heart rate of 6/minute between the slowest and fastest heart rate)
Notes:
1. For obstructive events with small airflow reduction, don't score if neither an EEG arousal, a >3% desaturation nor brady-tachycardia is present
2. For indeterminate events with small airflow reduction, don't score if neither an EEG arousal, a >3% desaturation regardless of brady-tachycardia
2. If a hypopnea is associated with both an arousal and a desaturation, classify as a **desaturating hypopnea**

Appendix 4 Research scoring criteria-continued

RERA (Respiratory Event Related Arousal)
(Scored only on polysomnography with EEG and esophageal probe).

Pattern of progressively more negative esophageal pressure,
Terminated by a sudden change in pressure to a less negative level
And an arousal
Lasting $\geq$10 seconds.

Summary of respiratory (both central and obstructive) events

1. **ODI** (Oxygen Desaturation Index)
   Mean number of >3%-saturation dips per hour of sleep (total sleep time TST) calculated as the sum of the 7 indices associated with desaturations ; this includes apneas (obstructive, central and mixed) and hypopneas (big and small, obstructive and indeterminate).

2. **AHI** (Apnea- Hypopnea Index)
   Mean number of apneas + hypopneas + RERAs per hour of sleep

References:
Sleep 1999; 22(5) 663- 689 Sleep-related breathing disorders in adults American Academy Sleep Medicine (AASM) Task Force "Chicago criteria" Sleep Medicine 2003; 4: 537-42 Clinical significance of pulse rate rise during sleep as a screening marker (sic) for the assessment of sleep fragmentation in sleep-disordered breathing. Hiroyoshi Adachi, A Mikami T Kumano-go, N Suganuma H Matsumoto Y Shigedo Y Sugita M Takeda

2. Sleep-Wake State
Allan Rechstschaffen and Anthony Kales, A Manual of Standard Terminology, Techniques and Scoring System for Sleep Stages of Human Subject, Los Angeles: UCLA BIS/BIR Publications 1968.

3. Arousal
The Atlas Task Force of the American Sleep Disorders Association. EEG Arousals: scoring rules and examples. SLEEP 1992; 16:174-84

Appendix 4 Research scoring criteria-continued

4. Periodic Limb Movements

The Atlas Task Force of the American Sleep Disorders Association. Recording and scoring leg movements. SLEEP 1993; 16:749-59

Note: PLM associated with the termination of apnea and hypopnea events are not included in the PLM score but their presence in association with respiratory events should be reported in the comment section.

As approved by John Kimoff, Allen Olha, and Kateri Champagne

Appendix 5 Odds of having pre-eclampsia in presence of OSA

Odds ratio estimate, based on Franklin paper
Assumptions: OSA = 50% of snorers and 2% of non snorers
Using Minitab version 13

Tabulated Statistics: osa, pe(pre-eclampsia)

```
 Rows: osa     Columns: pe

           0        1      All

 0       422       16      438
      415.31    22.69   438.00

 1        54       10       64
       60.69     3.31    64.00

 All     476       26      502
      476.00    26.00   502.00

Chi-Square = 16.297, DF = 1, P-Value = 0.000
1 cells with expected counts less than 5.0

  Cell Contents --
                 Count
                 Exp Freq
```

Binary Logistic Regression: pe versus osa

```
Logistic Regression Table
                                                    Odds        95% CI
Predictor       Coef    SE Coef        Z      P    Ratio    Lower    Upper
Constant     -3.2724     0.2547   -12.85 0.000
osa
 1            1.5860     0.4282     3.70 0.000     4.88     2.11    11.31

Log-Likelihood = -96.396
Test that all slopes are zero: G = 11.784, DF = 1, P-Value = 0.001

* NOTE * No goodness of fit tests performed.
       * The model uses all degrees of freedom.

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs           Number  Percent     Summary Measures
Concordant        4220    34.1%     Somers' D                0.27
Discordant         864     7.0%     Goodman-Kruskal Gamma    0.66
Ties              7292    58.9%     Kendall's Tau-a          0.03
Total            12376   100.0%
```

Appendix 6 Nine Scenarios with case-control ratio 1, 2-tailed alpha

9 scenarios of distribution of disease (pre-eclampsia) in those exposed and non-exposed to OSA at 3 levels of confounder (gestational age), using an **odds ratio of 4.88**, 2-tailed alpha, case-control ratio of 1, a probability of exposure in the population of 7%, for different levels of power and 2-sided alpha.

Scenario 1

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.100	.400	.500
Non-Exposed	.100	.200	.700
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	78	78	75	75
	.025	60	60	65	65	62	62
	.050	50	50	54	54	**52**	**52**
	.100	40	40	43	43	41	41
.90	.010	96	96	103	103	99	99
	.025	81	81	87	87	83	83
	.050	70	70	75	75	**72**	**72**
	.100	58	58	62	62	59	59

The population exposure probability is .070.
No interaction effects assumed.

Appendix 6. Nine Scenarios with case-control ratio 1, 2-tailed alpha- continued

Scenario 2

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.100	.400	.500
Non-Exposed	.200	.200	.600
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	76	76	73	73
	.025	60	60	63	63	60	60
	.050	50	50	53	53	**50**	**50**
	.100	40	40	42	42	40	40
.90	.010	96	96	100	100	95	95
	.025	81	81	85	85	80	80
	.050	70	70	73	73	**69**	**69**
	.100	58	58	60	60	57	57

The population exposure probability is .070.
No interaction effects assumed.

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.100	.400	.500
Non-Exposed	.300	.200	.500
Rc(i)	1.00	4.00	5.00

Scenario 3

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	75	75	71	71
	.025	60	60	61	61	59	59
	.050	50	50	51	51	**49**	**49**
	.100	40	40	41	41	39	39
.90	.010	96	96	98	98	93	93
	.025	81	81	83	83	78	78
	.050	70	70	71	71	**67**	**67**
	.100	58	58	59	59	55	55

The population exposure probability is .070.
No interaction effects assumed.

Appendix 6. Nine Scenarios with case-control ratio 1, 2-tailed alpha-continued

Scenario 4

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.200	.600	.200
Non-Exposed	.100	.200	.700
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	96	96	89	89
	.025	60	60	79	79	73	73
	.050	50	50	66	66	**61**	**61**
	.100	40	40	53	53	49	49
.90	.010	96	96	126	126	116	116
	.025	81	81	106	106	98	98
	.050	70	70	91	91	**84**	**84**
	.100	58	58	75	75	70	70

The population exposure probability is .070.
No interaction effects assumed.

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.200	.600	.200
Non-Exposed	.200	.200	.600
Rc(i)	1.00	4.00	5.00

Scenario 5

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	92	92	83	83
	.025	60	60	76	76	68	68
	.050	50	50	63	63	**57**	**57**
	.100	40	40	51	51	46	46
.90	.010	96	96	121	121	109	109
	.025	81	81	102	102	92	92
	.050	70	70	87	87	**79**	**79**
	.100	58	58	72	72	65	65

The population exposure probability is .070.
No interaction effects assumed.

Appendix 6. Nine Scenarios with case-control ratio 1, 2-tailed alpha- continued

Scenario 6

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.200	.600	.200
Non-Exposed	.300	.200	.500
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	89	89	80	80
	.025	60	60	73	73	66	66
	.050	50	50	61	61	**55**	**55**
	.100	40	40	49	49	44	44
.90	.010	96	96	116	116	104	104
	.025	81	81	98	98	88	88
	.050	70	70	84	84	**75**	**75**
	.100	58	58	69	69	62	62

The population exposure probability is .070.
No interaction effects assumed.

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.300	.400	.300
Non-Exposed	.100	.200	.700
Rc(i)	1.00	4.00	5.00

Scenario 7

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	91	91	84	84
	.025	60	60	75	75	69	69
	.050	50	50	63	63	**58**	**58**
	.100	40	40	50	50	47	47
.90	.010	96	96	120	120	111	111
	.025	81	81	101	101	94	94
	.050	70	70	87	87	**81**	**81**
	.100	58	58	72	72	67	67

The population exposure probability is .070.
No interaction effects assumed.

Appendix 6. Nine Scenarios with case-control ratio 1, 2-tailed alpha- continued

Scenario 8

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.300	.400	.300
Non-Exposed	.200	.200	.600
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	87	87	77	77
	.025	60	60	71	71	64	64
	.050	50	50	60	60	**54**	**54**
	.100	40	40	48	48	43	43
.90	.010	96	96	114	114	103	103
	.025	81	81	96	96	87	87
	.050	70	70	82	82	**75**	**75**
	.100	58	58	68	68	62	62

The population exposure probability is .070.
No interaction effects assumed.

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.300	.400	.300
Non-Exposed	.300	.200	.500
Rc(i)	1.00	4.00	5.00

Scenario 9

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.88,
FOR VARIOUS POWER AND 2-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 1.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	73	73	83	83	74	74
	.025	60	60	69	69	61	61
	.050	50	50	57	57	**51**	**51**
	.100	40	40	46	46	41	41
.90	.010	96	96	109	109	97	97
	.025	81	81	92	92	82	82
	.050	70	70	79	79	**71**	**71**
	.100	58	58	65	65	59	59

The population exposure probability is .070.
No interaction effects assumed.

Appendix 7. Nine Scenarios with case-control ratio 2, 1-tailed alpha

Modeling 3 possible distributions of pre-eclampsia in those with and without exposure to OSA for a total of 9 scenarios, at 3 levels of confounder levels (gestational age strata) using an **odds ratio of 4, 1-sided alpha, a control to case ratio of 2,** a proportion of exposure (OSA) of 8% in the population, no interaction, for different alpha and beta, using Edwardes' software.

Scenario 1

P(Ci|E), P(Ci|not E) at Confounder Levels

	1	2	3
Exposed	.100	.400	.500
Non-Exposed	.100	.200	.700
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	69	138	64	128
	.025	51	101	54	108	**51**	**101**
	.050	40	80	43	85	40	80
	.100	29	58	31	62	29	58
.90	.010	84	168	89	178	84	167
	.025	68	135	72	144	68	135
	.050	55	110	59	117	**55**	**110**
	.100	42	84	45	90	43	85

The population exposure probability is .080.
No interaction effects assumed.

Appendix 7. Nine Scenarios with case-control ratio 2, 1-tailed alpha- continued

Scenario 2

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.100	.400	.500
Non-Exposed	.200	.200	.600
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	66	132	63	126
	.025	51	101	52	103	**50**	**99**
	.050	40	80	41	81	39	78
	.100	29	58	30	59	29	57
.90	.010	84	168	86	171	82	163
	.025	68	135	69	138	66	132
	.050	55	110	56	112	**54**	**107**
	.100	42	84	43	86	41	82

The population exposure probability is .080.
No interaction effects assumed.

Scenario 3

	P(Ci|E), P(Ci|not E) at Confounder Levels		
	1	2	3
Exposed	.100	.400	.500
Non-Exposed	.300	.200	.500
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	63	126	63	126
	.025	51	101	50	99	**49**	**98**
	.050	40	80	39	78	39	77
	.100	29	58	29	57	28	56
.90	.010	84	168	82	164	81	162
	.025	68	135	67	133	65	130
	.050	55	110	54	108	**53**	**106**
	.100	42	84	42	83	41	81

The population exposure probability is .080.
No interaction effects assumed.

Appendix 7. Nine Scenarios with case-control ratio 2, 1-tailed alpha- continued

Scenario 4

P(Ci|E), P(Ci|not E) at Confounder Levels	1	2	3
Exposed	.200	.600	.200
Non-Exposed	.100	.200	.700
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	84	167	74	148
	.025	51	101	65	130	**58**	**116**
	.050	40	80	52	103	46	92
	.100	29	58	38	75	34	68
.90	.010	84	168	108	216	97	193
	.025	68	135	87	174	79	157
	.050	55	110	71	142	**65**	**129**
	.100	42	84	55	109	50	100

The population exposure probability is .080.
No interaction effects assumed.

Scenario 5

P(Ci|E), P(Ci|not E) at Confounder Levels	1	2	3
Exposed	.200	.600	.200
Non-Exposed	.200	.200	.600
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	79	158	70	139
	.025	51	101	62	123	55	109
	.050	40	80	49	97	**44**	**87**
	.100	29	58	36	71	32	64
.90	.010	84	168	102	204	91	182
	.025	68	135	83	165	74	147
	.050	55	110	68	135	**61**	**121**
	.100	42	84	52	103	47	93

The population exposure probability is .080.
No interaction effects assumed.

Appendix 7. Nine Scenarios with case-control ratio 2, 1-tailed alpha- continued

Scenario 6

P(Ci|E), P(Ci|not E) at Confounder Levels

	1	2	3
Exposed	.200	.600	.200
Non-Exposed	.300	.200	.500
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	75	149	68	135
	.025	51	101	59	117	**53**	**106**
	.050	40	80	46	92	42	84
	.100	29	58	34	67	31	61
.90	.010	84	168	97	194	88	176
	.025	68	135	79	157	71	142
	.050	55	110	64	128	**58**	**116**
	.100	42	84	49	98	45	89

The population exposure probability is .080.
No interaction effects assumed.

Scenario 7

P(Ci|E), P(Ci|not E) at Confounder Levels

	1	2	3
Exposed	.300	.400	.300
Non-Exposed	.100	.200	.700
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	81	162	69	137
	.025	51	101	64	127	**54**	**108**
	.050	40	80	50	100	43	86
	.100	29	58	37	73	32	64
.90	.010	84	168	105	210	91	181
	.025	68	135	85	169	74	148
	.050	55	110	69	138	**61**	**121**
	.100	42	84	53	106	47	94

The population exposure probability is .080.
No interaction effects assumed.

Appendix 7. Nine Scenarios with case-control ratio 2, 1-tailed alpha-continued

Scenario 8

P(Ci|E), P(Ci|not E) at Confounder Levels

	1	2	3
Exposed	.300	.400	.300
Non-Exposed	.200	.200	.600
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	76	152	63	126
	.025	51	101	60	119	**50**	**100**
	.050	40	80	47	94	40	79
	.100	29	58	35	69	30	59
.90	.010	84	168	99	197	84	167
	.025	68	135	80	159	68	136
	.050	55	110	65	130	**56**	**112**
	.100	42	84	50	100	44	87

The population exposure probability is .080.
No interaction effects assumed.

Scenario 9

P(Ci|E), P(Ci|not E) at Confounder Levels

	1	2	3
Exposed	.300	.400	.300
Non-Exposed	.300	.200	.500
Rc(i)	1.00	4.00	5.00

SAMPLE SIZE REQUIRED TO DETECT AN ODDS RATIO = 4.00,
FOR VARIOUS POWER AND 1-TAILED SIGNIFICANCE LEVELS, ADJUSTING & NOT ADJUSTING FOR A CONFOUNDER WITH 3 LEVELS, GIVEN 2.0 CONTROLS PER CASE

		Unadjusted		Adjusted		Adjusted & Matched	
Power	Type I Error	Cases	Controls	Cases	Controls	Cases	Controls
.80	.010	65	130	72	144	61	122
	.025	51	101	57	113	**48**	**96**
	.050	40	80	45	89	38	76
	.100	29	58	33	65	28	56
.90	.010	84	168	94	187	80	160
	.025	68	135	76	151	65	130
	.050	55	110	62	123	**53**	**106**
	.100	42	84	48	95	41	82

The population exposure probability is .080.
No interaction effects assumed.

Appendix 8 Co-authors' copyright waiver form

June 15, 2006

Author's copyright waiver form

The thesis submitted by Dr Kateri Champagne on June 19, 2006 to McGill University contains a systematic review on Obstructive Sleep Apnea and materno-fetal implications in pregnancy. We, undersigned, have contributed to the realization of this manuscript and agree to its publication as part of her thesis. This manuscript has not yet been accepted for publication and as such, its final version in a journal might differ from the thesis version.

R John Kimoff

Lucie Morin

Peter C Barriga

Kevin Schwartzman

Appendix 9 Ethics Review Board documents November 27, 2003

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

KATERI

November 27, 2003

Dr. John Kimoff
Respiratory Division
L4.08

REB No. MED-B 03-084

RE: **The Potential Contribution of Sleep Apnea to Pre-eclampsia. A Case-control Study of Sleep Apnea in Pregnant Women with and without Pre-eclampsia**

Dear Dr. Kimoff:

Thank you for submitting the above named study for review by the Research Ethics Board of the Royal Victoria Hospital.

The Medicine-B Committee at their meeting of November 18, 2003 reviewed the protocol and consent forms (consent for cases and consent for control subjects) both dated October 31, 2003 and the study was found acceptable for conduct at the McGill University Health Centre. However, the questionnaire was missing, and must be provided. The following comments were made:

1. In the protocol, item "h." of the Exclusion Criteria-Cases, the committee questions the "*less or more than*" 4 hours of sleep anticipated before delivery. Which is it? in my version, this is already >4h and it's j-
2. The Introduction sections of both consent forms must be modified to invite the subjects to participate and the second paragraph should start by "We have a theory that....." instead of "We believe that ...". In addition, the condition "*leaking kidneys*" should be explained as having "*protein in the urine*".
3. In the Subject Rights section, replace "To withdraw, "*the mother*" may call...." by "To withdraw, "*you*" may call..."
4. The Liability Clause is missing.
5. Information on who the subject should call regarding questions about the study must be included.
6. Delete the witness clause.

It was agreed that Dr. L. Moroz, Chairman of the Medicine-B Committee, will review your response, the questionnaire and the revised consent forms and if found to be satisfactory, he will provide approval. Therefore, please submit your response, the questionnaire and the revised consent forms in duplicate and it would be appreciated if all changes are highlighted to facilitate review.

Sincerely,

Lilian Fateen
Ethics Review Coordinator
RVH Research Ethics Board

Appendix 9 Ethics Review Board documents March 20, 2004 page 1

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

March 10, 2004

Dr. John Kimoff
Respiratory Division
L4.08

REB No. MED-B 03-084

RE: The Potential Contribution of Sleep Apnea to Pre-eclampsia. A Case-control Study of Sleep Apnea in Pregnant Women with and without Pre-eclampsia

Dear Dr. Kimoff:

The above-named protocol received Full Board review at the convened meeting of November 18, 2003 by the Royal Victoria Hospital Research Ethics Board, was found to be within ethical guidelines for conduct at the McGill University Health Centre, and was entered into the minutes of the Research Ethics Board meetings. At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840. Final approval for the research protocol study, the patient questionnaire as well as for the English and French consent forms for cases and for control subjects dated January 19, 2004, was provided on January 24, 2004.

Below is a list of the Research Ethics Board members responsible for the review of the above named study. The names of the members are not disclosed for reasons of confidentiality. Dr. J. Kimoff, Principal Investigator, Drs. K. Champagne and K. Schwartzman, Co-investigators as well as the members of his research staff were not involved in the review or voting process. The reviewing committee is comprised of:

1 chair, MD
2 physicians
1 ethicist
1 legal member (non-affiliated)
2 patient community (non-affiliated)
1 member of multidisciplinary committee (MDC)
1 nurse
1 pharmacist

All research involving human subjects requires review at a recurring interval and the current study approval is in effect until November 18, 2004. An Application for Continuing Review must be submitted to the REB prior to the expiration of approval to comply with the regulation for continuing review of "at least once per year".

Appendix 9 Ethics Review Board documents March 20, 2004 page 2

Dr. J. Kimoff
REB No. MED-B 03-084
Page 2

Validation for the translated versions of the consent documents were certified by an MUHC translator. As the translated text was potentially modified, it must be reviewed by the study sponsor and any modification to the REB approved and certified consent document must be identified by a revised date in the document footer, and re-submitted for review prior to its use.

The Research Ethics Boards (REBs) of the McGill University Health Centre are registered REBs working under the published guidelines of the Tri-Council Policy Statement, in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998) and the Food and Drugs Act (7 June 2001); and acting in conformity with standards set forth in the (US) Code of Federal Regulations governing human subjects research, function in a manner consistent with internationally accepted principles of good clinical practice.

We wish to advise you that this document completely satisfies the requirement for Research Ethics Board Attestation as stipulated by Health Canada.

Should any revision to the research or other unanticipated development occur prior to the next required review, please advise the REB promptly and prior to initiating any revision.

Sincerely.

L. Moroz, MD
Chair, Medicine-B Committee
RVH Research Ethics Board

Appendix 9 Ethics Review Board documents October 22, 2004

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

October 22, 2004

Dr. John Kimoff
Respiratory Division
L4.08

REB No. MED-B 03-084

RE: The Potential Contribution of Sleep Apnea to Pre-eclampsia. A Case-control Study of Sleep Apnea in Pregnant Women with and without Pre-eclampsia

Dear Dr. Kimoff:

Thank you for submitting the Amendment dated September 17, 2004 to the above referenced study for review by the Research Ethics Board of the Royal Victoria Hospital.

The Biomedical-B Committee at their meeting of October 19, 2004 reviewed the above mentioned amendment which included the protocol, consent form and an advertisement. The amendment to the protocol dated October 1, 2004 and the revised consent forms for cases and for control subjects dated September 3, 2004 were approved. However, the consent form for cases in the second page at the end of the first paragraph, insert "*in pregnancy*" following the highlighted word "hypertension". In addition, please paginate all the consent forms. A copy of all the modified consent forms is required for the REB file.

The advertisement/poster was also reviewed and the committee found the ad missing information, i.e. the title/MUHC logo, where the study is being conducted and a brief information on the study. Also, replace the statement "who gave birth lately" by "*who recently delivered*".

It was agreed that Dr. L. Moroz, Chairman of the Biomedical-B Committee will review the revised advertisement and if found satisfactory, he will provide approval. Therefore, please forward the revised advertisement in duplicate and it would be appreciated if all changes are highlighted to facilitate review.

Sincerely,

Lilian Fateen
Ethics Review Coordinator
RVH Research Ethics Board

Appendix 9 Ethics Review Board documents November 9, 2004

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

November 9, 2004

Dr. John Kimoff
Respiratory Division
L4.08

REB No. MED-B 03-084

RE: The Potential Contribution of Sleep Apnea to Pre-eclampsia. A Case-control Study of Sleep Apnea in Pregnant Women with and without Pre-eclampsia

Dear Dr. Kimoff:

Thank you for your response dated October 27, 2004 to the REB's letter of October 22, 2004 regarding the revised consent forms and the advertisement for recruitment of subjects into the above referenced study for review by the Research Ethics Board of the Royal Victoria Hospital.

Dr. L. Moroz, Chairman of the Biomedical-B Committee reviewed your response and the revised advertisement/poster and found them satisfactory. Therefore, Dr. Moroz provided approval for the use of the advertisement/poster dated July 2004 – September 2005.

In addition, this is to acknowledge receipt of the French and English approved paginated consent forms dated September 3, 2004 for the Cases and Control subjects for the REB file.

Please take note that all research involving human subjects requires review at a regular interval and it is the responsibility of the principal investigator to submit an Application for Continuing Review before the expiration of the study approval. Should any revision to the research or other unanticipated development occur prior to the next required review, please advise the REB promptly and prior to initiating any revision.

Sincerely,

Lilian Fateen
Ethics Review Coordinator
RVH Research Ethics Board

Appendix 9 Ethics Review Board documents November 17, 2004

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

November 17, 2004

Dr. John Kimoff
Respiratory Division
L4.08

REB No. MED-B 03-084

RE: The Potential Contribution of Sleep Apnea to Pre-eclampsia. A Case-control Study of Sleep Apnea in Pregnant Women with and without Pre-eclampsia

Dear Dr. Kimoff:

Thank you for submitting the Application for Continuing Review for the research study referenced above. The report was presented for Full Board review at the convened meeting of the Biomedical-B Committee of the Research Ethics Board on November 16, 2004 was found to be acceptable for ongoing conduct at the McGill University Health Centre, and was entered accordingly, into the minutes of the meeting. The re-approval for the study was provided until November 17, 2005 and no revision to the approved consent document is required at this time.

At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840.

All research involving human subjects requires review at a recurring interval. It is the responsibility of the investigator to submit an Application for Continuing Review to the REB prior to expiration of approval to comply with the regulation for continuing review of "at least once per year".

However, should the research conclude for any reason prior to the next required review, you are required to submit a Termination Report to the Committee once the data analysis is complete to give an account of the study findings and publication status. Should any revision to the study, or other unanticipated development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

Sincerely,

Leonard Moroz, MD.
Chair, Biomedical-B Committee
RVH Research Ethics Board

Appendix 9 Ethics Review Board documents October 20, 2005

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

October 20, 2005

Dr. John Kimoff
Respiratory Division
L4.08

REB No. MED-B 03-084

RE: The Potential Contribution of Sleep Apnea to Pre-eclampsia. A Case-control Study of Sleep Apnea in Pregnant Women with and without Pre-eclampsia

Dear Dr. Kimoff:

Thank you for submitting the Amendment dated September 12, 2005 to the above referenced study for review by the Research Ethics Board of the Royal Victoria Hospital.

The Biomedical-B Committee at their meeting of October 18, 2005 reviewed and approved the above mentioned amendment, the amended English and French consent forms for controls and cases dated September 12, 2005 as well as the revised advertisements.

However, the name of Dr. Lucie Opatrny as co-investigator of this study should be added to the consent forms. A final copy is required for the REB file.

Please take note that all research involving human subjects requires review at a regular interval and it is the responsibility of the principal investigator to submit an Application for Continuing Review before the expiration of the study approval. Should any revision to the research or other unanticipated development occur prior to the next required review, please advise the REB promptly and prior to initiating any revision.

Sincerely,

Lilian Fateen
Research Ethics Coordinator
RVH Research Ethics Board

Appendix 9 Ethics Review Board documents October 20, 2005

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

October 20, 2005

Dr. John Kimoff
Respiratory Division
L4.08

REB No. MED-B 03-084

RE: **The Potential Contribution of Sleep Apnea to Pre-eclampsia. A Case-control Study of Sleep Apnea in Pregnant Women with and without Pre-eclampsia**

Dear Dr. Kimoff:

Thank you for submitting the Application for Continuing Review for the research study referenced above. The report was presented for Full Board review at the convened meeting of the Biomedical-B Committee of the Research Ethics Board on November 18, 2005 was found to be acceptable for ongoing conduct at the McGill University Health Centre, and was entered accordingly, into the minutes of the meeting. The re-approval for the study was provided until November 17, 2006 and no revision to the approved consent document is required at this time.

At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840.

All research involving human subjects requires review at a recurring interval. It is the responsibility of the investigator to submit an Application for Continuing Review to the REB prior to expiration of approval to comply with the regulation for continuing review of "at least once per year".

However, should the research conclude for any reason prior to the next required review, you are required to submit a Termination Report to the Committee once the data analysis is complete to give an account of the study findings and publication status. Should any revision to the study, or other unanticipated development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

Sincerely,

Leonard Moroz, MD.
Chair, Biomedical-B Committee
RVH Research Ethics Board

Appendix 9 Director Professional Services, September 15, 2005

Centre universitaire de santé McGill
McGill University Health Centre

September 13, 2005

Dr. John Kimoff
Director, MUHC Sleep Lab
Respiratory Department
RVH – L4.08

Dr. Kateri Champagne
Respiratory Department
RVH – L4.08

RE: AUTHORIZATION TO ACCESS MEDICAL RECORDS FOR A RESEARCH PROTOCOL ENTITLED: "The potential contribution of sleep apnea to pre-eclampsia. A case-control study of sleep apnea in pregnant women with and without pre-eclampsia"

Dear Drs Kimoff & Champagne:

In accordance with Article 19 of the Act Respecting Health Services and Social Services, permission has been granted to Ms Kathryn Riches – research nurse, Ms. Charlene Barber – research nurse and Dr. Kateri Champagne, to examine the medical records of patients for research purposes without the user's prior consent. The purpose is to pre-screen charts for eligibility.

In general, the practice of photocopying part of the medical chart is not recommended. However, if this is necessary, the confidentiality requirements must be strictly followed and the Medical Records Department will clarify the specific modalities that apply.

We have included the McGill University Health Centre "Policy & Procedure" entitled "Cost of Retrieving Medical Records for Research" which specifies the conditions, procedures and cost, if applicable, for retrieving medical records.

We wish you well in your endeavours.

Yours truly,

Dr. Mathias (Maciej) Kalina
Associate Director Professional Services
McGill University Health Centre

MK/cp

c.c. D. Pothier/S. Molsan – medical records

HÔPITAL ROYAL VICTORIA HOSPITAL

Reference List

(1) Forest JC, Girouard J, Masse J, Moutquin JM, Kharfi A, Ness RB et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. Obstet Gynecol 2005 June;105(6):1373-80.

(2) Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ 2003 April;19;326(7394):845.

(3) Dekker G, Sibai B. Primary, secondary, and tertiary prevention of pre-eclampsia. Lancet 2001 January;20;357(9251):209-15.

(4) Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000 April 12;283(14):1829-36.

(5) Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 2004 September 15;160(6):521-30.

(6) Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier NF et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001 January;163(1):19-25.

(7) Gabbe. Hypertension. Obstetrics- Normal and Problem pregnancies. 4th ed. 2002. p. 945.

(8) Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. CMAJ 1997 September 15;157(6):715-25.

(9) Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005 March 12;330(7491):565.

(10) Mittendorf R, Lain KY, Williams MA, Walker CK. Preeclampsia. A nested, case-control study of risk factors and their interactions. J Reprod Med 1996 July;41(7):491-6.

(11) Martel MJ, Rey E, Beauchesne MF, Perreault S, Lefebvre G, Forget A et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. BMJ 2005 January 29;330(7485):230.

(12) Moore LG, Hershey DW, Jahnigen D, Bowes W, Jr. The incidence of pregnancy-induced hypertension is increased among Colorado residents at high altitude. Am J Obstet Gynecol 1982 October 15;144(4):423-9.

(13) Palmer SK, Moore LG, Young D, Cregger B, Berman JC, Zamudio S. Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 meters) in Colorado. Am J Obstet Gynecol 1999 May;180(5):1161-8.

(14) Roberts JM, Pearson G, Cutler J, Lindheimer M. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension 2003 March;41(3):437-45.

(15) Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005 June 10;308(5728):1592-4.

(16) Dekker GA, Sibai BM. The immunology of preeclampsia. Semin Perinatol 1999 February;23(1):24-33.

(17) Williams DJ, de SM. The pathophysiology of pre-eclampsia. Intensive Care Med 1997 June;23(6):620-9.

(18) Martin JN, Jr., Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. Am J Obstet Gynecol 1999 June;180(6 Pt 1):1373-84.

(19) Roberts JM, Gammill HS. Preeclampsia: recent insights. Hypertension 2005 December;46(6):1243-9.

(20) Milne F, Redman C, Walker J, Baker P, Bradley J, Cooper C et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005 March 12;330(7491):576-80.

(21) Shennan AH. Recent developments in obstetrics. BMJ 2003 September 13;327(7415):604-8.

(22) Bashiri A, Zmora E, Sheiner E, Hershkovitz R, Shoham-Vardi I, Mazor M. Maternal hypertensive disorders are an independent risk factor for the development of necrotizing enterocolitis in very low birth weight infants. Fetal Diagn Ther 2003 November;18(6):404-7.

(23) Impey L, Greenwood C, Sheil O, MacQuillan K, Reynolds M, Redman C. The relation between pre-eclampsia at term and neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed 2001 November;85(3):F170-F172.

(24) Lewit EM, Baker LS, Corman H, Shiono PH. The direct cost of low birth weight. Future Child 1995;5(1):35-56.

(25) Shennan AH, Bewley S. Why should preterm births be rising? BMJ 2006 April 22;332(7547):924-5.

(26) Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001 November 24;323(7323):1213-7.

(27) Dunger DB, Ong KK. Endocrine and metabolic consequences of intrauterine growth retardation. Endocrinol Metab Clin North Am 2005 September;34(3):597-615, ix.

(28) Ruano R, Fontes RS, Zugaib M. Prevention of preeclampsia with low-dose aspirin -- a systematic review and meta-analysis of the main randomized controlled trials. Clinics 2005 October;60(5):407-14.

(29) Villar J, Abalos E, Nardin JM, Merialdi M, Carroli G. Strategies to prevent and treat preeclampsia: evidence from randomized controlled trials. Semin Nephrol 2004 November;24(6):607-15.

(30) Ray JG, Vermeulen MJ, Burrows EA, Burrows RF. Use of antihypertensive medications in pregnancy and the risk of adverse perinatal outcomes: McMaster Outcome Study of Hypertension In Pregnancy 2 (MOS HIP 2). BMC Pregnancy Childbirth 2001;1(1):6.

(31) von DP, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet 2000 January 8;355(9198):87-92.

(32) Sibai BM, Gonzalez AR, Mabie WC, Moretti M. A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. Obstet Gynecol 1987 September;70(3 Pt 1):323-7.

(33) Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005 February 26;365(9461):785-99.

(34) Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. Am J Obstet Gynecol 2004 June;190(6):1520-6.

(35) Kryger MH, Roth T., Dement WC. Principles and Practice of Sleep Medicine.Philadelphia: WB Saunders; 2000. p. 835.

(36) Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2003 May 1;167(9):1181-5.

(37) Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 1997 September;20(9):705-6.

(38) Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab 2001 February;86(2):517-20.

(39) Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002 May 1;165(9):1217-39.

(40) Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000 May 11;342(19):1378-84.

(41) 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 March 19;365(9464):1046-53.

(42) Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of Sleep-disordered Breathing and the Occurrence of Stroke. Am J Respir Crit Care Med 2005 December 1;172(11):1447-51.

(43) Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005 November 10;353(19):2034-41.

(44) Malhotra A, White DP. Obstructive sleep apnoea. Lancet 2002 July 20;360(9328):237-45.

(45) Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000 March;85(3):1151-8.

(46) Saaresranta T, Polo O. Sleep-disordered breathing and hormones. Eur Respir J 2003 July;22(1):161-72.

(47) Morrell MJ, Finn L, Kim H, Peppard PE, Badr MS, Young T. Sleep fragmentation, awake blood pressure, and sleep-disordered breathing in a population-based study. Am J Respir Crit Care Med 2000 December;162(6):2091-6.

(48) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999 August 1;22(5):667-89.

(49) EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992 April;15(2):173-84.

(50) Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993 April 29;328(17):1230-5.

(51) Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev 2006 January 25;(1):CD001106.

(52) White J, Cates C, Wright J. Continuous positive airways pressure for obstructive sleep apnoea. Cochrane Database Syst Rev 2002;(2):CD001106.

(53) Ellegard E, Hellgren M, Toren K, Karlsson G. The incidence of pregnancy rhinitis. Gynecol Obstet Invest 2000;49(2):98-101.

(54) Ellegard E, Oscarsson J, Bougoussa M, Igout A, Hennen G, Eden S et al. Serum level of placental growth hormone is raised in pregnancy rhinitis. Arch Otolaryngol Head Neck Surg 1998 April;124(4):439-43.

(55) Edwards N, Blyton DM, Hennessy A, Sullivan CE. Severity of sleep-disordered breathing improves following parturition. Sleep 2005 June 1; 8(6):737-41.

(56) Izci B, Vennelle M, Liston WA, Dundas KC, Calder AA, Douglas NJ. Sleep-disordered breathing and upper airway size in pregnancy and post-partum. Eur Respir J 2006;27(2):321-7.

(57) Izci B, Riha RL, Martin SE, Vennelle M, Liston WA, Dundas KC et al. The upper airway in pregnancy and pre-eclampsia. Am J Respir Crit Care Med 2003 January 15;167(2):137-40.

(58) Hoffstein V, Zamel N, Phillipson EA. Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. Am Rev Respir Dis 1984 August;130(2):175-8.

(59) White DP. Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med 2005 December 1;172(11):1363-70.

(60) Badr MS, Toiber F, Skatrud JB, Dempsey J. Pharyngeal narrowing/occlusion during central sleep apnea. J Appl Physiol 1995 May;78(5):1806-15.

(61) O'Hare JA, Abuaisha F, Cotter T. Experiences with octreotide in acromegaly. Ir J Med Sci 1993 February;162(2):40-2.

(62) Bondanelli M, Ambrosio MR, gli Uberti EC. Pathogenesis and prevalence of hypertension in acromegaly. Pituitary 2001 September;4(4):239-49.

(63) Molitch ME. Pituitary tumors and pregnancy. Growth Horm IGF Res 2003 August;13 Suppl A:S38-44.:S38-S44.

(64) Molitch ME. Evaluation and management of pituitary tumors during pregnancy. Endocr Pract 1996 July;2(4):287-95.

(65) Millman RP, Carlisle CC, McGarvey ST, Eveloff SE, Levinson PD. Body fat distribution and sleep apnea severity in women. Chest 1995 February;107(2):362-6.

(66) Ijuin H, Douchi T, Nakamura S, Oki T, Yamamoto S, Nagata Y. Possible association of body-fat distribution with preeclampsia. J Obstet Gynaecol Res 1997 February;23(1):45-9.

(67) Anand A, Remsburg-Sailor S, Launois SH, Weiss JW. Peripheral vascular resistance increases after termination of obstructive apneas. J Appl Physiol 2001 November;91(5):2359-65.

(68) Samet JM, Nieto FJ, Punjabi NM. Sleep-disordered breathing and hypertension: more research is still needed. Am J Respir Crit Care Med 2000 May;161(5):1409-11.

(69) Portaluppi F, Provini F, Cortelli P, Plazzi G, Bertozzi N, Manfredini R et al. Undiagnosed sleep-disordered breathing among male nondippers with essential hypertension. J Hypertens 1997 November;15(11):1227-33.

(70) Edwards N, Blyton CM, Kesby GJ, Wilcox I, Sullivan CE. Pre-eclampsia is associated with marked alterations in sleep architecture. Sleep 2000 August 1;23(5):619-25.

(71) Connolly G, Razak ARA, Hayanga A, Russell A, McKenna P, McNicholas WT. Inspiratory flow limitation during sleep in pre-eclampsia: Comparison with normal pregnant and nonpregnant women. Eur Respir J 2001; 18(4):672-6.

(72) Bar A, Pillar G, Dvir I, Sheffy J, Schnall RP, Lavie P. Evaluation of a Portable Device Based on Peripheral Arterial Tone for Unattended Home Sleep Studies. Chest 2003 March 1;123(3):695-703.

(73) Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia -- A State of Sympathetic Overactivity. N Engl J Med 1996 November 14;335(20):1480-5.

(74) Edwards N, Blyton DM, Kirjavainen T, Kesby GJ, Sullivan CE. Nasal continuous positive airway pressure reduces sleep-induced blood pressure increments in preeclampsia. Am J Respir Crit Care Med 2000;162(1):252-7.

(75) Charbonneau M, Falcone T, Cosio MG, Levy RD. Obstructive sleep apnea during pregnancy. Therapy and implications for fetal health. Am Rev Respir Dis 1991 August;144(2):461-3.

(76) Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med 2004 January;5(1):43-51.

(77) Oleszczuk J, Leszczynska-Gorzelak B, Mierzynski R, Kaminski K, Oleszczuk JJ. Pregnancy in obstructive sleep apnoea syndrome under treatment with nCPAP. Zentralbl Gynakol 1998;120(2):71-4.

(78) Brain KA, Thornton JG, Sarkar A, Johnson AO. Obstructive sleep apnoea and fetal death: successful treatment with continuous positive airway pressure. BJOG 2001 May;108(5):543-4.

(79) Lewis DF, Chesson AL, Edwards MS, Weeks JW, Adair CD. Obstructive sleep apnea during pregnancy resulting in pulmonary hypertension. South Med J 1998 August;91(8):761-2.

(80) Franklin KA, Holmgren PA, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest 2000 January;117(1):137-41.

(81) Loube DI, Poceta JS, Morales MC, Peacock MD, Mitler MM, Loube DI et al. Self-reported snoring in pregnancy. Association with fetal outcome.[see comment]. Chest 1996 April;109(4):885-9.

(82) Guilleminault C, Querra-Salva M, Chowdhuri S, Poyares D. Normal pregnancy, daytime sleeping, snoring and blood pressure. Sleep Med 2000 October 1;1(4):289-97.

(83) Zarnke KB, Levine M, McAlister FA, Campbell NR, Myers MG, McKay DW et al. The 2000 Canadian recommendations for the management of hypertension: part two--diagnosis and assessment of people with high blood pressure. Can J Cardiol 2001 December;17(12):1249-63.

(84) A Manual of Standardized Terminology, Technique and Scoring System for Sleep Stages of Human Sleep. Brain Information Service UCLA ed. Los Angeles: 1968.

(85) Edwardes M. Sample size requirements for case-control study designs. BMC Medical Research Methodology 2001;1(1):11.

(86) Rothman KJ, Sander G. Modern Epidemiology. 2nd edition ed. Philadelphia: Lippincott-Raven; 1998.

(87) Lee-Chiong Jr TL. Sleep Disorders. Philadelphia, Penn: 2004.

(88) American Academy of Sleep Medicine. The International Classification of Sleep Disorders, Diagnostic and Coding Manual.Westchester, illinois: 2005. p. 177-96.

(89) Haas DC, Foster GL, Nieto FJ, Redline S, Resnick HE, Robbins JA et al. Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. Circulation 2005 February 8;111(5):614-21.

(90) Edwards N, Wilcox I, Sullivan C. Haemodynamic responses to obstructive sleep apnoeas in premenopausal women. J Hypertens 1999 May;17(5):603-10.

(91) Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 2001 December;19(12):2271-7.

(92) Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep 2005 March 1;28(3):309-14.

(93) Yinon D, Lowenstein L, Suraya S, Beloosesky R, Zmora O, Malhotra A et al. Pre-eclampsia is associated with sleep-disordered breathing and endothelial dysfunction. Eur Respir J 2006;27(2):328-33.

(94) Martinez-Garcia MA, Gomez-Aldaravi R, Gil-Martinez T, Soler-Cataluna JJ, Bernacer-Alpera B, Roman-Sanchez P. [Sleep-disordered breathing in patients with difficult-to-control hypertension]. Arch Bronconeumol 2006 January;42(1):14-20.

(95) Feinsilver SH, Hertz G, Feinsilver SH, Hertz G. Respiration during sleep in pregnancy. [Review] [40 refs]. Clin Chest Med 1992 December;13(4):637-44.

(96) Brown LK. Dyspnea during pregnancy and sleep-disordered breathing in pregnancy. Seminars in Respiratory & Critical Care Medicine 1998;19(3):209-21.

(97) Edwards N, Middleton PG, Blyton DM, Sullivan CE, Edwards N, Middleton PG et al. Sleep disordered breathing and pregnancy. [Review] [43 refs]. Thorax 2002 June;57(6):555-8.

(98) Meurice JC, Paquereau J, Neau JP, Pourrat O, Pierre F, Meurice JC et al. [Respiratory disorders during sleep in the pregnant woman]. [Review] [15 refs] [French]. Rev Neurol (Paris) 2003 November;159(11 Suppl):6S91-4.

(99) Shaver JL, Shaver JLF. Women and sleep. [Review] [36 refs]. Nurs Clin North Am 2002 December;37(4):707-18.

(100) Moline ML, Broch L, Zak R, Gross V, Moline ML, Broch L et al. Sleep in women across the life cycle from adulthood through menopause. [Review] [119 refs]. Sleep Med Rev 2003 April;7(2):155-77.

(101) Moline ML, Broch L, Zak R. Sleep in women across the life cycle from adulthood through menopause. Medical Clinics of North America 2004;88(3):705-36.

(102) Moline M, Broch L, Zak R. Sleep problems across the life cycle in women. Current Treatment Options in Neurology 2004;6(4):319-30.

(103) Sharma S, Franco R. Sleep and its disorders in pregnancy. WMJ 2004;103(5):48-52.

(104) Pien GW, Schwab RJ, Pien GW, Schwab RJ. Sleep disorders during pregnancy. [Review] [149 refs]. Sleep 2004 November 1;27(7):1405-17.

(105) Santiago JR, Nolledo MS, Kinzler W, Santiago TV, Santiago JR, Nolledo MS et al. Sleep and sleep disorders in pregnancy. [Review] [136 refs]. Ann Intern Med 2001 March 6;134(5):396-408.

(106) Sahota PK, Jain SS, Dhand R, Sahota PK, Jain SS, Dhand R. Sleep disorders in pregnancy. [Review] [54 refs]. Curr Opin Pulm Med 2003 November;9(6):477-83.

(107) Young T, Peppard PE, Gottlieb DJ, Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. [Review] [275 refs]. Am J Respir Crit Care Med 2002 May 1;165(9):1217-39.

(108) Collop NA, Adkins D, Phillips BA, Collop NA, Adkins D, Phillips BA. Gender differences in sleep and sleep-disordered breathing. [Review] [126 refs]. Clin Chest Med 2004 June;25(2):257-68.

(109) Otake K, Shinobe R, Sato K, Shiomi T, Otake K, Shinobe R et al. [Sleep apnea syndrome]. [Review] [30 refs] [Japanese]. Nippon Rinsho 2005 July;63(7):1221-6.

(110) Saaresranta T, Polo O, Saaresranta T, Polo O. Sleep-disordered breathing and hormones. [Review] [185 refs]. Eur Respir J 2003 July;22(1):161-72.

(111) Harding SM. Complications and consequences of obstructive sleep apnea. Curr Opin Pulm Med 2000;6(6):485-9.

(112) Douglas NJ. Recent advances in the obstructive sleep Apnoea/Hypopnoea syndrome. Annals of the Academy of Medicine, Singapore 2002;31(6):697-701.

(113) Edwards N, Blyton DM, Kirjavainen TT, Sullivan CE. Hemodynamic responses to obstructive respiratory events during sleep are augmented in women with preeclampsia. Am J Hypertens 2001 November;14(11 Pt 1):1090-5.

(114) Adachi H, Mukai E, Okuda S, Kawada T. [A severe case of acute autonomic and sensory neuropathy]. Rinsho Shinkeigaku 1998 July;38(7):663-8.

(115) Sritippayawan S, Hamutcu R, Kun SS, Ner Z, Ponce M, Keens TG. Mother-daughter transmission of congenital central hypoventilation syndrome. Am J Respir Crit Care Med 2002 August 1;166(3):367-9.

(116) Funada Y, Nishimura Y, Kamemura K, Nakajima T, Tsuchiya T, Nishiuma T et al. Familial adult onset primary alveolar hypoventilation syndrome. Intern Med 2001 June;40(6):526-31.

(117) Conti M, Izzo V, Muggiasca ML, Tiengo M. Sleep apnoea syndrome in pregnancy: a case report. Eur J Anaesthesiol 1988 March;5(2):151-4.

(118) Kowall J, Clark G, Nino-Murcia G, Powell N. Precipitation of obstructive sleep apnea during pregnancy. Obstet Gynecol 1989 September;74(3 Pt 2):453-5.

(119) Hastie SJ, Prowse K, Perks WH, Atkins J, Blunt VA. Obstructive sleep apnoea during pregnancy requiring tracheostomy. Aust N Z J Obstet Gynaecol 1989 August;29(3 Pt 2):365-7.

(120) Sherer DM, Caverly CB, Abramowicz JS. Severe obstructive sleep apnea and associated snoring documented during external tocography. Am J Obstet Gynecol 1991 November;165(5 Pt 1):1300-1.

(121) Pieters T, Amy JJ, Burrini D, Aubert G, Rodenstein DO, Collard P. Normal pregnancy in primary alveolar hypoventilation treated with nocturnal nasal intermittent positive pressure ventilation. Eur Respir J 1995 August;8(8):1424-7.

(122) Lefcourt LA, Rodis JF. Obstructive sleep apnea in pregnancy. Obstet Gynecol Surv 1996 August;51(8):503-6.

(123) Singh D, Mills GH, Caunt JA, Alderson JD. Anaesthetic management of labour in two patients with Klippel-Feil syndrome. Int J Obstet Anesth 1996 July;5(3):198-201.

(124) Taibah K, Ahmed M, Baessa E, Saleem M, Rifai A, al-Arifi A. An unusual cause of obstructive sleep apnoea presenting during pregnancy. J Laryngol Otol 1998 December;112(12):1189-91.

(125) Shiomi T, Guilleminault C, Izumi H, Yamada S, Murata K, Kobayashi T. Obstructive sleep apnoea in a puerperal patient with Hallermann-Streiff syndrome. Eur Respir J 1999 October;14(4):974-7.

(126) Rai N, Masson EA, Lindow SW. Sleep apnoea syndrome in pregnancy without fetal compromise. J Obstet Gynaecol 2000 January;20(1):84.

(127) Roush SF, Bell L. Obstructive sleep apnea in pregnancy. J Am Board Fam Pract 2004 July;17(4):292-4.

(128) Ochoa-Sepulveda JJ, Ochoa-Amor JJ. Ondine's curse during pregnancy. J Neurol Neurosurg Psychiatry 2005 February;76(2):294.

(129) Domingo C, Latorre E, Mirapeix RM, Abad J. Snoring, obstructive sleep apnea syndrome, and pregnancy. Int J Gynaecol Obstet 2006 March 9;.

(130) Joel-Cohen SJ, Schoenfeld A. Fetal response to periodic sleep apnea: a new syndrome in obstetrics. Eur J Obstet Gynecol Reprod Biol 1978 April;8(2):77-81.

(131) Schoenfeld A, Ovadia Y, Neri A, Freedman S. Obstructive sleep apnea (OSA)-implications in maternal-fetal medicine. A hypothesis. Med Hypotheses 1989 September;30(1):51-4.

(132) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999 August 1;22(5):667-89.

(133) Ochoa-Sepulveda JJ, Ochoa-Amor JJ. Ondine's curse during pregnancy [5]. J Neurol Neurosurg Psychiatry 2005;. 76(2).

(134) Hastie SJ, Prowse K, Perks WH, Atkins J, Blunt VAW. Obstructive sleep apnoea during pregnancy requiring tracheostomy. Aust N Z J Obstet Gynaecol 1989;. 29(3 II).

(135) Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med 2004;. 5(1).

(136) Zhang J, Bowes WAJr. Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. Obstet Gynecol 1995 August;86(2):200-8.

(137) Jensen D, Damm P, Sorensen B, Molsted-Pedersen L, Westergaard J, Ovesen P et al. Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. Am J Obstet Gynecol 2005;189(1):239-44.