

Title: Obstructive sleep apnea and its association with gestational hypertension

Subtitle : Sleep apnea and gestational hypertension

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Hypertension develops in 10% of pregnancies. Snoring, a marker for obstructive sleep apnea, is a newly identified risk factor for gestational hypertension. Moreover, obstructive sleep apnea is an independent risk factor for incident hypertension in the non-pregnant population.

Research question: Test the hypothesis that obstructive sleep apnea is associated with new onset of hypertension among pregnant women.

Materials/patients and methods Case-control study involving 17 pregnant women with gestational hypertension and 33 pregnant women without hypertension, frequency-matched for gestational age, recruited in a tertiary obstetrical centre. Obstructive sleep apnea was ascertained by polysomnography, and defined by an apnea-hypopnea index ≥ 15 events per hour, without a requirement for desaturation.

Results: The mean apnea-hypopnea index for normotensive pregnant women was 18.2 ± 12.2 (SD) events/h compared with 38.6 ± 36.7 events/h for women with hypertensive pregnancies ($p=0.005$). 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 3.5-16.2), based on a logistic regression model with adjustment for maternal age, gestational age, pre-pregnancy body mass index, prior pregnancies, and previous live births.

Conclusions: Gestational hypertension appears to be strongly associated with the presence of obstructive sleep apnea.

Keywords: hypertension, obstructive sleep apnea, pre-eclampsia, pregnancy, sleep-disordered breathing

Abbreviations:

OR	Odds Ratio
95% CI	95% confidence interval
SD	Standard Deviation
BMI	Body Mass Index

Introduction

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

Snoring, a marker for obstructive sleep apnea, was recently demonstrated to be associated with gestational hypertension with an odds ratio (OR) 2.03 (95% CI 1.01-4.01) after adjustment for maternal weight, age, and smoking habits(8). We hypothesized that obstructive sleep apnea was associated with new onset of hypertension in pregnancy. To address this hypothesis, we performed polysomnography on women with and without gestational hypertension.

Methods

Study setting

We recruited subjects at a tertiary obstetrical centre with fertility and high-risk obstetrics services, serving a multiethnic population. Health care is covered by public insurance. Women with significant gestational hypertension, or suspected preeclampsia, are ordinarily admitted for observation and treatment.

Participants

From May 1, 2004 through April 30, 2006, a research nurse screened charts to identify potential cases on the antenatal ward once per weekday. All women diagnosed with gestational hypertension by an obstetrician were approached for participation. During the same period, the research nurse recruited control subjects from antenatal clinics, obstetrical ultrasound clinics and the antenatal ward approximately once weekly. Before clinics, the research nurse reviewed charts to identify all pregnant normotensive women. All women who agreed to be approached were then contacted for participation. To avoid preferential booking of women with sleep complaints, the research nurse did not provide advance notice of her attendance. All women were recruited while pregnant.

Case definition

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

Controls

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

Exclusion Criteria

Women with known pre-gravid hypertension, treated obstructive sleep apnea, neuromuscular disease, or previous stroke were excluded, as were women who lived > 30

km from the study center or who were unable to communicate in English or French. The study protocol was approved by the Royal Victoria Hospital's Research Ethics Board. Participants provided written informed consent.

Measurements

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

A certified technologist scored the polysomnogram according to standard sleep-wake(10) arousal(11), and respiratory criteria(12). Apneas were ≥ 10 -second events with $\geq 90\%$ decrease in airflow. Hypopneas were ≥ 10 -second events with either 1) a 50-90% decrease from baseline airflow amplitude or 2) $< 50\%$ decrease in airflow associated with $\geq 4\%$ -desaturation or arousal. Obstructive sleep apnea was defined as an apnea-hypopnea index ≥ 15 . All studies were reviewed by a sleep physician; both the physician and technician were blinded to the clinical status of subjects.

The criteria used to define respiratory events can substantially alter the apnea-hypopnea index(13), and there is some variability in the literature with respect to the apnea-hypopnea index threshold used to define obstructive sleep apnea. Therefore, we

conducted a sensitivity analysis where we considered alternate event definitions and thresholds, in order to assess the robustness of any association between gestational hypertension and obstructive sleep apnea. Specifically, we re-did the analysis using 1) a stricter definition for hypopneas, discounting events with <50% reduction in airflow and 2) a threshold of 10 apnea-hypopnea events per hour of sleep. The apnea-hypopnea index calculated using all respiratory events was referred to as AHI₁, while the more conservative index excluding hypopneas with <50% reduction in airflow was termed AHI₂.

Statistical analysis

We generated standard summary descriptive statistics, odds ratio (OR) estimates using logistic regression for the association between gestational hypertension and obstructive sleep apnea, and for the relationship between gestational hypertension and potential predictors and confounders that were determined a priori. We used Stata version 8 (College Station, TX) for all statistical analyses.

Results

Between May 2004 and April 2006, 135 hypertensive pregnant women and 150 normotensive pregnant women were screened for inclusion.

Inclusions and exclusions for the cases are shown in **Figure 1** and for controls, in **Figure 2**. The mean ages of participating and non participating women were similar, 33.9 SD 5.5 and 32.8 SD 5.8 years, respectively.

Among the 17 cases, 7 had at least 300 mg proteinuria on a 24-hour urine collection, 9 had proteinuria on spot urinalysis without completion of a 24-hour urine collection and one had no proteinuria on spot urinalysis and did not complete a urine

collection. Six cases had their polysomnographic studies postpartum only, at a median of 4 days.

Cases and controls frequently had other obstetrical, medical or psychiatric conditions as shown in **Table 1**, most frequently gestational diabetes, asthma or allergic rhinitis. As shown in **Table 2**, hypertensive women were slightly older with slightly higher reported pre-gravid body mass index (BMI) than normotensive controls.

At the time of polysomnography, 2 hypertensive women were taking magnesium sulfate, 5 were taking alpha-methyl dopa (3 in combination with labetalol, 1 in combination with hydralazine), and 4 were taking labetalol alone. One normotensive woman was taking nifedipine for preterm labor, and one was taking paroxetine at the time of the polysomnography.

Prevalence of obstructive sleep apnea among hypertensive and normotensive pregnant women

Sleep-related breathing indices are described in **Table 3**. The mean and nadir of nocturnal oxygen saturation were similar in the 2 groups but respiratory event indices were significantly worse in the hypertensive group. The prevalence of obstructive sleep apnea was 14/17 (82%, 95% CI 57-96%) among the hypertensive women compared to 15/33 (45%, 95% CI 26-64%) among the normotensive pregnant women, based on a definition of ≥ 15 apneas or hypopneas per hour of sleep, as described in the Methods section.

Association of obstructive sleep apnea with gestational hypertension

Obstructive sleep apnea was associated with gestational hypertension with a crude OR 5.6, 95% CI 1.4-23.2, $p = 0.018$. After adjustment for maternal age, gestational age,

pre-gravid BMI, previous pregnancies, and previous live births, the OR was 7.5 (95% CI 3.5-16, $p < 0.0001$). Each of these variables was found to be a significant confounder, and was thus kept in the final model. In this multivariable model, obstructive sleep apnea, past pregnancy without live births, and BMI were the strongest predictors of gestational hypertension, as shown in **Table 4**. Compared to women with previous live births, women with only previous abortions (spontaneous or induced) were at increased risk of gestational hypertension. The size of our dataset prevented adjustment for smoking, pre-existing diabetes and ethnic origin.

A sensitivity analysis examined alternative definitions for respiratory events as well as alternative thresholds for the number of respiratory events needed to diagnose obstructive sleep apnea. The results consistently support the association of gestational hypertension with obstructive sleep apnea (**Table 5**).

Four normotensive and three hypertensive women completed both antepartum and postpartum polysomnographies, at a median of 8 days postpartum. All had a reduction in the apnea-hypopnea index postpartum, by an average of 32%.

The 6 hypertensive women who were only able to complete polysomnography postpartum (at a median of 4 days postpartum) had more severe sleep apnea and more severe obstetrical conditions than the hypertensive women who completed antepartum studies. Four had gestational hypertension with adverse events [eclampsia and HELLP (n=1), HELLP with blurred vision (n=1), placental abruption (n=1), diastolic blood pressure > 110 (n=1)]. Among these six women studied only postpartum, the mean apnea-hypopnea index was 53; 5 of the 6 met our definition for obstructive sleep apnea. In comparison, among the 11 hypertensive women who were able to complete an

antenatal study, the mean apnea-hypopnea index was 31; 9 had obstructive sleep apnea and 3 had similar obstetrical adverse events [HELLP(n=1), diastolic blood pressure >110(n=2)].

Discussion

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

Despite our best efforts, only a small number of participants successfully completed the study (**Figures 1 and 2**). We believe this reflects the poor sleep of pregnant women in their third trimester, potentially compounded by hospitalization for unstable blood pressure, attendant interventions, and related psychological distress. Some withdrew consent after fetal death or their infant's admission to the intensive care unit. Similar difficulties in completing full polysomnography among hypertensive pregnant women were reported by other researchers, who adopted a tonometry approach(14).

The requirements for intensive nursing and medical surveillance of both the mothers and the fetus precluded the use of in-lab polysomnography. While the use of portable complete polysomnography provided a more feasible alternative, our inclusion criteria had to be modified to permit postpartum polysomnography, because the instability of the hypertensive women precluded a delay of one night for polysomnography before delivery. This study therefore included six women with gestational hypertension who were studied postpartum. If the urgency to deliver was

related to difficult blood pressure control in women with obstructive sleep apnea, as is observed in the non-pregnant population(15), the exclusion of those women would have led to an underestimation of the association. Based on previous case-series, obstructive sleep apnea tends to worsen during pregnancy(16) and improve postpartum(17). Similarly, in our small subset with both ante and postpartum data, the apnea-hypopnea index decreased by a third after delivery. Thus, postpartum polysomnography is likely to have underestimated the severity of obstructive sleep apnea during pregnancy among these six women, thereby attenuating the potential association between gestational hypertension and obstructive sleep apnea.

There are several potential mechanisms which may link obstructive sleep apnea to pregnancy. These include changes in body habitus mimicking truncal obesity, reduced upper airway calibre(18) secondary to lung volume effects(19), fluid retention, pregnancy-related rhinitis(20), increased soft tissue mass (related to placental growth hormone secretion), and increased airway collapsibility because of muscle relaxation (due to relaxin and other hormones). Obstructive sleep apnea is thought to predispose to hypertension in the non-pregnant population through endothelial dysfunction, oxidative stress, sympathetic activation enhanced by hypoxia, flow limitation, sleep fragmentation and arousals(21;22). The pathophysiology of gestational hypertension includes endothelial dysfunction, oxidative stress, and sympathetic activation enhanced by hypoxia(23). We believe that similar mechanisms promote hypertension among pregnant women with obstructive sleep apnea.

It has been proposed that pregnancy is a physiological stress test, unmasking women most likely to develop metabolic and cardiovascular complications later in life, as

documented by several cohort studies(2;3). In parallel fashion, we hypothesize that pregnancy is a physiological stress test that identifies women with either unrecognized obstructive sleep apnea or those who are at risk for obstructive sleep apnea should predisposing conditions, including truncal obesity, reappear later in life.

The high prevalence of obstructive sleep apnea in our control group may relate to the inclusion of normotensive controls with obstetrical and medical complications, which is a representative sample of the population serviced in our tertiary obstetrical center; normal pregnant women (no co-morbidities, low-risk pregnancies) are managed in non-tertiary institutions. If any of the medical or obstetrical complications described is also associated with obstructive sleep apnea, the inclusion of those women as controls would bias the association of gestational hypertension with sleep apnea towards the null. In addition, polysomnography was performed in the mid- to late- third trimester, which previous studies have identified as the time of peak snoring and obstructive sleep apnea-related symptoms among pregnant women(8;24). We believe that the high proportion of controls with obstructive sleep apnea in pregnancy is related to the high-risk population and the timing of polysomnography, and reduces the observed association between gestational hypertension and obstructive sleep apnea.

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

larger than previously described in the non-pregnant population, where reported OR have ranged from 1.4 to 2.9(5;25;26).

We believe this may reflect two potential mechanisms: the rapid evolution of both obstructive sleep apnea and hypertension among pregnant women, as well as the relatively young population studied.

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

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

Our observation that obstructive sleep apnea among women with gestational hypertension is characterized predominantly by obstructive hypopneas without $\geq 4\%$ oxygen desaturation (**Table 3**) is in keeping with previous work. Connolly and colleagues reported increased periods of inspiratory flow limitation among 15 pre-eclamptic women compared with normotensive pregnant women, although the apnea-hypopnea index based

on the $\geq 50\%$ reduction in airflow, did not differ between study groups(29). Edwards and colleagues reported similar findings, although the flow limitation episodes were not quantified(30). Yinon and colleagues used oximetry with arterial tonometry; they reported an increased respiratory disturbance index among women with pre-eclampsia compared to women with normotensive pregnancies, but nearly 50% of events were not associated with $\geq 4\%$ oxygen desaturation(14). Unlike these earlier studies, we ascertained obstructive sleep apnea by polysomnography including electroencephalography, we defined obstructive sleep apnea as a binary variable, we included hypopneas with arousal in the apnea-hypopnea index, and we corrected for several confounders.

We chose not to distinguish between gestational hypertension and pre-eclampsia for several reasons. First, our own unpublished systematic review of the literature on pre-eclampsia and sleep apnea demonstrated some cases previously labelled as pre-eclampsia actually involved gestational hypertension according to current diagnostic criteria. Second, the Canadian guidelines for hypertensive disorders of pregnancy(9) acknowledge a continuum of disease between gestational hypertension, gestational hypertension with proteinuria (pre-eclampsia in other countries) and complicated gestational hypertension with proteinuria. There were major logistical obstacles to obtaining a 24-hour urine collection prior to polysomnography in an unstable group of patients, as those who had reached 37 weeks of gestation were rapidly delivered. All the hypertensive pregnant women did reach a systolic blood pressure > 140 prior to delivery, fulfilling most international criteria for gestational hypertension. Classification of women according to blood pressure was performed by the obstetrician, reflecting current Canadian clinical

management. Finally, the mistaken inclusion of normotensive women as hypertensive cases in our study would tend to obscure any true underlying association between gestational hypertension and obstructive sleep apnea.

The cross-sectional design of this study prevents inference about causality. However, a possible causal role for obstructive sleep apnea in the development of gestational hypertension is congruent with other observations. In a case series, treatment (continuous positive airway pressure) administered to 11 pre-eclamptic women with inspiratory airflow limitation reduced nocturnal blood pressure by a mean of 18 mmHg, without any change in antihypertensive medication(31). In a randomized controlled study of 16 women with chronic hypertension and newly documented obstructive sleep apnea in early pregnancy, CPAP treatment was associated with less requirement for anti-hypertensive drugs and better control of blood pressure in the third trimester(32). In the non-pregnant population, it has clearly been established that obstructive sleep apnea is an independent risk factor for incident hypertension(25). However, prospective cohort studies of women with and without obstructive sleep apnea who become pregnant are needed to establish a causal role for obstructive sleep apnea in the development of gestational hypertension.

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

management of obstructive sleep apnea and gestational hypertension among pregnant women.

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Figure 1: Inclusion and exclusion of potential participants with gestational hypertension.

Among the women excluded, 8 were judged by the treating team to be too unstable (intensive care unit admission, fetal loss) to be approached for participation. The two main exclusion criteria were chronic hypertension and multiple pregnancies. Rare exclusions were treated obstructive sleep apnea, language barrier, age < 18 years, distant residence. Among women who had consented, 5 withdrew prior to the polysomnography whereas failed polysomnographies were due to intolerance of the equipment (7) and failure to sleep (3).

Figure 2: Inclusion and exclusion of potential participants without gestational hypertension.

14 were excluded because the treating team judged them too unstable for recruitment (intensive care unit, fetal loss). Polysomnography recording failed because of lack of sleep or difficulty tolerating the equipment in 7. Six withdrew consent prior to the polysomnography.

Table 1: Co-morbidities of women with and without gestational hypertension

	Gestational hypertension (n=17)	Normotensive pregnancy (n=33)
No co-morbidities	1	12
Gestational diabetes	7	1
Preterm labor	0	4
Premature rupture of membrane	0	1
Pre-existing diabetes mellitus, type I or II	1	1
Asthma	5	9
Allergic rhinitis	7	14
Past depression	1	5
Coagulopathy	1	3
≥2 Previous spontaneous abortions	4	4
Other	1*	7†

Among the 17 cases, 16 had co-morbidities, mainly gestational diabetes, allergic rhinitis and asthma. Among the 33 controls, 21 had co-morbidities, most commonly allergic rhinitis, asthma and past depression.

*One case had hyperthyroidism.

†Infrequent co-morbidities among controls included hypothyroidism (2), past fertility treatment (2 including one woman whose current pregnancy was medically assisted), and micro-prolactinoma (1). Controls were newly diagnosed during the current pregnancy with pancreatitis due to hyperlipoproteinemia type III (1 subject), hepatolenticular

degeneration (1 subject), cardiomyopathy secondary to adriamycin administered remotely for lymphoma (1 subject).

Table 2**Baseline demographics**

	Gestational hypertension (n=17)*	Normotensive pregnancies (n=33)
Age (years)	35.4 ± 4.3	32.7 ± 5.5
Pre-gravid body mass index (kg/m ²)	26.7 ± 4.6	23.8 ± 3.9
Gestational age at polysomnography (weeks)	33.4 ± 4.7	32.4 ± 4.6
First pregnancy	5/17 (29%)	7/33 (21%)
No previous live birth	11/17 (65%)	16/33 (48%)

Values are mean ± SD for age, body mass index and gestational age

*Six cases were respectively 2, 3, 3, 5, 14, and 29 days postpartum at the time of the polysomnography.

Table 3 Sleep-related breathing indices

	Gestational hypertension (n=17)	Normotensive pregnancies (n=33)	P-values
Respiratory events			
AHI ₁ * (#events/h sleep)	38.6 ± 36.7	18.2 ± 12.2	0.0053
AHI ₂ † (#events/h sleep)	21.6 ± 35.2	5.6 ± 5.6	0.013
ODI‡ (#events/h sleep)	4.0 ± 9.7	0.2 ± 0.7	0.028
Central+indeterminate event index (#events/h)	1.9 ± 2.4	1.3 ± 2.0	0.37
Oximetry data			
Mean oxygen saturation (%)	96.7 ± 1.2	97.0 ± 1.1	0.33
Nadir oxygen saturation (%)	90.2 ± 4.8	92.4 ± 3.0	0.061

Values are mean ± SD

*AHI₁: apnea-hypopnea index including all apneas and hypopneas per hour of sleep

†AHI₂: apneas plus hypopneas restricted to 50-90% reduction in airflow, per hour of sleep

‡ODI ≥ 4%-oxygen desaturating apneas and hypopneas per hour of sleep

Table 4 Adjusted odds ratio for each variable and its association with gestational hypertension

Variables	Adjusted OR	95% CI	P- values
Sleep apnea* vs no sleep apnea	7.5	3.5-16.2	<0.0001
Body mass index, per 1 kg/m ² increase	1.2	1.1-1.4	0.001
Maternal age, per 1 year increase	1.2	0.95-1.4	0.14
Previous live birth (reference)	1		
Previous pregnancy but no live birth	12.8	3.5-46.0	<0.0001
First pregnancy	3.4	0.25-45.5	0.35
Gestational age, reference >34 wks	1		
20-27 weeks	1.1	0.4-3.2	0.80
27-34 weeks	0.8	0.5-1.2	0.32

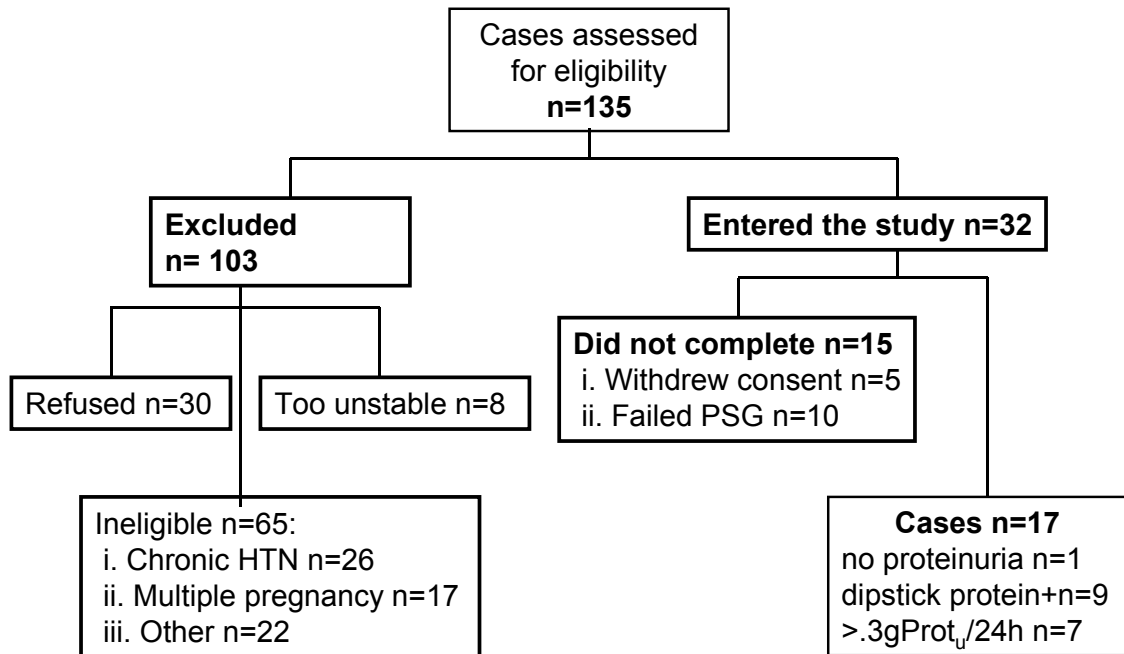
*Sleep apnea was defined by an apnea-hypopnea index ≥ 15 .

Table 5 Sensitivity analysis, adjusted odds ratio for the association of obstructive sleep apnea and gestational hypertension

Apnea-hypopnea index	Threshold	OR adjusted	95% CI	P-values
AHI ₁	10	4.3	2.8-6.7	< 0.001
AHI ₁	15	7.5	3.5-16.2	< 0.0001
AHI ₂	10	5.4	1.3-23.0	0.04
AHI ₂	15	8.4	1.1-66.2	0.02

Abbreviations: AHI₁ , AHI₂ as in Table 3; OR: Odds Ratio

Figure 1



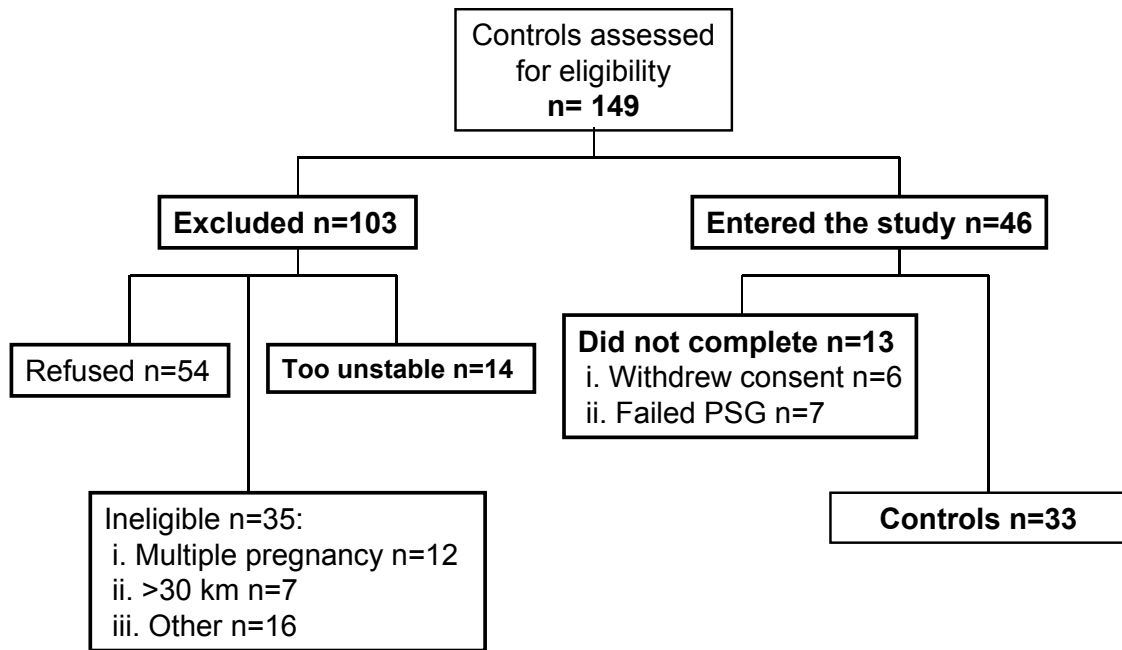
PSG = Polysomnography.

>30km = Living further than 30 km from the research site.

HTN = Hypertension.

>.3g Prot_u/24h = Proteinuria > 300mg in the 24h urine sample.

Figure 2



PSG = Polysomnography.

>30km = Living further than 30 km from the research site.

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