Sleep and Breathing (2019) 23:687–693
https://doi.org/10.1007/s11325-018-1758-8

EPIDEMIOLOGY • ORIGINAL ARTICLE

Obstructive sleep apnea as a risk factor for preeclampsia–eclampsia

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Received: 18 June 2018 / Revised: 10 November 2018 / Accepted: 14 November 2018 / Published online: 27 November 2018

Abstract

Purpose Preeclampsia–eclampsia remains one of the leading causes of maternal and perinatal morbidity and mortality. Emerging evidence suggests that obstructive sleep apnea (OSA), which has been linked to hypertension in the general population, may play role in hypertensive disorders in pregnancy, including preeclampsia–eclampsia. However, little research has been conducted in Asia (no data in Thailand) on the effects of OSA on preeclampsia–eclampsia. We aimed to examine the association between OSA and preeclampsia–eclampsia among Thai pregnant women.

Methods We conducted a large prospective cohort study among Thai pregnant women who were in the second trimester of singleton pregnancy. The Berlin Questionnaire was administered to evaluate the risk for OSA. Preeclampsia–eclampsia was diagnosed by standard clinical assessment. Multivariate models were applied in adjustment for confounding factors.

Results Enrolled were 1345 pregnant women. The overall prevalence of high risk for OSA was 10.1% (95% confidence intervals [CIs] 8.5–11.7), and it was significantly associated with pre-pregnancy body mass index and score on the Perceived Stress Scale. An adjusted odds ratio (OR) for preeclampsia–eclampsia in women with high risk for OSA was 2.72 (95% CI 1.33–5.57).

Conclusions Pregnant women with high risk for OSA are at increased risks for preeclampsia–eclampsia compared to those with low risk for OSA. Our results support a role for screening for OSA by BQ during antenatal care.

Keywords Obstructive sleep apnea · Pregnancy · Preeclampsia–eclampsia · Berlin Questionnaire

Introduction

Preeclampsia–eclampsia is a hypertensive, multiple-organ disorder of pregnancy, which occurs in 3–5% of pregnancies in developed countries and in up to 7.5% worldwide [1–3]. It remains one of the leading causes of maternal and perinatal mortality and morbidity [2, 3]. Moreover, women with preeclampsia–eclampsia are at increased risk of cardiovascular diseases [2]. Preventing preeclampsia–eclampsia appears to be one of the most significant challenges in obstetrics, and one area of investigation of interest relates to obstructive sleep apnea (OSA).

OSA is a sleep-related breathing disorder characterized by repeated episodes of upper airway occlusion that results in brief periods (at least 10 s) of breathing cessation (apnea) or a marked reduction in tidal volume (hypopnea). These mechanisms lead to intermittent hypoxia and sympathetic overactivation [4, 5]. OSA has been identified as an important risk factor for cardiovascular complications, including hypertension [5, 6].

Although several risk factors for hypertension in pregnancy have been recognized for decades [7], OSA has been recently discovered as a novel risk factor. Literature has shown that the presence of habitual snoring, snoring for three or more nights a week, and other hallmark symptoms of OSA increase in frequency during pregnancy and affect up to one third of women by late pregnancy [8–10]. OSA is now recognized

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as a common condition that is associated with maternal and neonatal outcomes [10–12]. Sleep apnea and its risk among Thai pregnant women has not been widely evaluated, partly because of the lack of awareness of the impact of OSA in pregnancy and the limited availability of polysomnography (PSG). The Berlin Questionnaire (BQ) is a screening tool widely used to identify patients with OSA, including pregnant women [13]. It is a useful and practical method of screening for OSA and can easily be incorporated into routine antenatal care. Studies have demonstrated that the BQ has different predictive values, depending on the trimester of pregnancy when it is administered [14]. The BQ appears to be most advantageous during the second trimester of pregnancy [14]. During the first trimester, the amount of sleep increases, coinciding with the subjective worsening of sleep quality. General sleep disturbance and fatigue are more common with advancing gestation, particularly during the third trimester [15–17], whereas during the second trimester, normal characteristics of sleep, such as sleep duration or sleep quality, prevail [18, 19]. We aimed to examine the association between OSA and preeclampsia–eclampsia among Thai pregnant women. We hypothesized that Thai pregnant women with high risk for OSA would have an increased risk of preeclampsia–eclampsia.

Methods

Study population

We conducted a large prospective cohort study at five antenatal care clinics affiliated with Maharat Nakhon Ratchasima Hospital, a large tertiary hospital, in Nakhon Ratchasima Province, Thailand, between July 2013 and December 2014. Sample size was calculated based on literature available at the time of this study initiation [9]. With the sample size of 1350, using an α error of 0.05 and a power of 0.80, the lowest detectable risk ratio was 2.3 for preeclampsia–eclampsia, compared to that of pregnant women with low risk and high risk for OSA.

Eligible participants were pregnant women who were in the second trimester of singleton pregnancy, started visiting the hospital for antenatal care before 20 weeks of gestation, and completed follow-up until delivery at the participating hospitals. Pregnant women with asthma, chronic kidney disease, chronic hypertension, or multiparity were excluded. Participants who had fetal loss or were lost to follow-up were also excluded from primary analysis.

The protocol was approved by the Faculty Ethical Committee at the Faculty of Medicine, Chulalongkorn University and Maharat Nakhon Ratchasima Hospital. Written informed consent was obtained from each participant.

Data collection

We used a self-administered questionnaire to collect demographic data including maternal age, marital status, and education level. Questions were also related to behavioral risk factors such as smoking and alcoholic consumption. In addition, we used BQ to evaluate the risk for OSA [13, 14], and Perceived Stress Scale-10 (PSS-10) questionnaire to measure the perceived stress [20, 21].

After delivery, clinical data which consisted of maternal height, pre-pregnancy weight, total weight gain during pregnancy, gravidity, parity, history of preterm delivery (PTD), pre-gestational diabetes mellitus, and prior preeclampsia–eclampsia were collected from medical records by well-trained research personnel using standardized abstraction form.

Preeclampsia and eclampsia

Preeclampsia and eclampsia were defined by the American College of Obstetricians and Gynecologists definitions at the time of study (2013–2014) [22].

Berlin Questionnaire

The BQ was developed in 1996, consisting of three categories designed to illicit information regarding snoring (category 1), daytime somnolence (category 2), and the presence of obesity and/or hypertension (category 3). In category 1, high risk for OSA is defined as persistent symptoms (more than three to four times per week) in two or more questions about their snoring. In category 2, high risk for OSA is defined as persistent (more than three to four times per week) wake-time sleepiness, drowsy driving, or both. In category 3, high risk for OSA is defined as the history of high blood pressure and/or the body mass index (BMI) of greater than 30 kg/m^2. Because we excluded all participants with known chronic hypertension at the time of screening, a positive response in the category 3 was based on the presence of the BMI criteria. Consideration for high risk for OSA (high-risk group) required the presence of at least two symptom categories, otherwise it would be considered as low risk for OSA (low-risk group) [13].

Statistical analysis

All data were analyzed using STATA software, version 11.0 (Stata Corp., College Station, TX, USA). Histograms, boxplots, and descriptive methods were used to examine data for errors and outliers. Between-group comparisons of continuous variables (perceived stress score) were conducted with *t* tests (high-risk group vs low-risk group). Dichotomized variables were compared with Fisher exact test. Logistic regression was used to determine associations between risk of OSA and

preeclampsia–eclampsia after adjusting for potential covariates where appropriate. We considered the following covariates as possible confounders: maternal age, parity, marital status, maternal educational attainment, pre-pregnancy weight and BMI, total weight gain, alcohol consumption, and smoking status during pregnancy. Confounders were defined as those factors which altered unadjusted odds ratios by at least 10%. Variables of a prior interest (e.g., prior history of preterm delivery and prior preeclampsia–eclampsia) were forced into final models. Statistical hypotheses were tested using two-tailed, odds ratios (OR), and 95% confidence intervals (CIs), and $p < 0.05$ was considered statistically significant.

Results

We initially recruited 1500 pregnant women; however, only 1345 participants were included in the primary analysis. Two recruited cases with fetal loss, 153 cases with delivery at non-participating hospitals, and cases with incomplete data were excluded from primary analysis. Among 1345 participants who completed screening questionnaires for symptoms of OSA at a mean gestational age of 18.1 (SD 3.29) weeks, 136 (10.1%, 95% CI 8.5–11.7) met the criteria for high risk for OSA and were classified as high-risk group, while the others were classified as low-risk group. Of the 136 participants in the high-risk group, 65 (47.8%) had a positive score in category 1 of BQ, 95 (69.9%) had a positive score in category 2, and 32 (23.5%) had a positive score in category 3, because their BMI was > 30 kg/m^2. Among 1209 participants in the low-risk group, 464 (38.4%) had positive score in category 1 of BQ, 80 (6.6%) had a positive score in category 2, and 39 (3.2%) had a positive score in category 3, because their BMI was > 30 kg/m^2.

As shown in Table 1, the maternal baseline characteristics were comparable between the two risk groups for OSA. Clinical data including total weight gain during pregnancy, gravidity, parity, history of preterm delivery, pre-gestational diabetes mellitus, and prior preeclampsia–eclampsia were not significantly different between the two groups with exception of pre-pregnancy overweight–obesity which was higher in the high-risk group. The average score of PSS-10 was also higher in the high-risk group (Table 2).

Preeclampsia–eclampsia was found among 15 of 136 pregnant women with high risk for OSA (11%), but in only 2.9% women who had low risk for OSA (35 of 1174) (Table 3). The risk for preeclampsia–eclampsia was higher in the high-risk group than the low-risk group (unadjusted OR = 4.16, 95% CI 2.21–7.83). After adjustment for confounding factors by maternal age, pre-pregnancy BMI, number of previous abortions, prior history of preterm delivery, and prior preeclampsia–eclampsia, the high-risk group was still associated with higher risk for preeclampsia–eclampsia (adjusted OR = 2.72, 95% CI 1.33–5.57) (Table 3). In the low-risk group, preeclampsia–eclampsia was found among 13 of 464 pregnant women with a history of snoring (11%), and in 22 of 745 women without history of snoring (3%) ($p > 0.05$).

Discussion

This is the first prospective cohort study to evaluate the occurrence of preeclampsia–eclampsia among Thai pregnant women, comparing between those with high and low risk for OSA. Although preeclampsia–eclampsia and OSA share common risk factors such as increased maternal age and obesity, we found that high risk for OSA, screened by BQ during the second trimester of pregnancy, remained the independent risk factor for preeclampsia–eclampsia after adjustment for confounders. Interestingly, our study demonstrated that snoring history alone was not useful to estimate the risk for OSA in pregnant women.

These findings are consistent with those of previous studies which noted an association between preeclampsia–eclampsia and OSA. According to the study of Antony et al. among predominantly Hispanic pregnant women, it was found that 15.5% of subjects at any gestational age were screened as high risk for OSA on BQ [23]. The investigators further noted that pregnant women with high risk for OSA were associated with a 2.45-fold (95% CI 1.84–3.26) and 2.02-fold (95% CI 1.37–2.99) increased risk ratio of preeclampsia and severe preeclampsia, respectively, when compared with pregnant women with low risk for OSA. Olivarez et al. also found that pregnant women with high risk for OSA, who had BMI < 30 kg/m^2 during the second and third trimesters of pregnancy, were at increased risk of preeclampsia of 6.58-fold (95% CI 1.04–38.5) after adjustment for gravidity, gestational age, and maternal age [24]. Interestingly, increased risk for preeclampsia among pregnant women with OSA and obesity did not reach statistical significance (adjusted OR = 1.48, 95% CI 0.35–6.64). In the study of Louis et al. among 175 pregnant women who underwent an overnight sleep study using a portable home monitor, OSA was significantly associated with preeclampsia (adjusted OR = 3.55, 95% CI 1.12–11.3) after adjustment for maternal age, chronic hypertension, prior preeclampsia, BMI, and pre-gestational diabetes mellitus [25]. Facco et al. enrolled 3705 nulliparous women who underwent an in-home sleep-disordered breathing assessment. The authors reported that, in early and mid-pregnancy, the adjusted odds ratios for preeclampsia when sleep disordered breathing was present were 1.94 (95% CI 1.07–3.51) and 1.95 (95% CI 1.18–3.23), respectively; hypertensive disorders of pregnancy, 1.46 (95% CI 0.91–2.32) and 1.73 (95% CI 1.19–2.52); and GDM, 3.47 (95% CI 1.95–6.19) and 2.79 (95% CI 1.63–4.77) [26]. Despite screening for OSA using BQ in our study, our

Table 1 Socio-demographic and behavioral characteristics of study participants according to high risk and low risk for OSA, Nakhon Ratchasima Province, Thailand, 2013–2014

Characteristic	Low risk for OSA ($n = 1209$)[a]		High risk for OSA($n = 136$)[a]		p
	n	%	n	%	
Maternal age, years					0.567
< 20	117	9.7	10	7.4	
20–24	282	23.3	38	27.9	
25–29	317	26.2	33	24.3	
30–34	294	24.3	29	21.3	
≥ 35	199	16.5	26	19.1	
Maternal education, years					0.682
≤ 6	93	7.7	13	9.6	
7–12	818	67.7	88	64.7	
> 12	297	24.6	35	25.7	
Marital status					0.564
Married	975	81.1	109	80.7	
Unmarried	199	16.6	21	15.6	
Separated	28	2.3	5	3.7	
Smoked during pregnancy					0.230
Yes	7	0.6	2	1.5	
No	1199	99.4	134	98.5	
Alcohol use during pregnancy					0.123
Yes	37	3.1	8	5.9	
No	1172	96.9	127	94.1	

OSA, obstructive sleep apnea

[a] Number may not be added to the total number due to missing data

findings were similar to those using standard tests (polysomnography) or portable home monitoring systems.

The association between OSA and preeclampsia–eclampsia has biological plausibility and is likely to be multifactorial [27]. OSA causes inflammation, autonomic dysfunction, oxidative stress, and altered hormonal regulation of energy expenditure [28]. These pathways are also found to be associated with adverse pregnancy outcomes [29, 30]. However, no prior research has directly examined the relationship between OSA, levels of pro-inflammatory markers, autonomic dysfunction, oxidative stress, altered hormonal regulation, and risk of preeclampsia–eclampsia. Further research is warranted to enhance our understanding of the effect of OSA on preeclampsia–eclampsia and the pathophysiological mechanisms underlying this relationship.

Our study provided several strengths. First, this is a large prospective cohort with a high rate of complete follow-up (89.7% of participants) with less than 5% missing data. We also compared the baseline characteristics of enrollees lost to follow-up to those who completed the study and noted that all variables were comparable, suggesting that the few women lost to follow-up would not have affected the outcomes disproportionately, therefore providing sufficient statistical power to detect differences and would likely increase data validity. Second, we excluded such cases with chronic hypertension which might lead to adverse maternal and perinatal outcomes, including preeclampsia–eclampsia [31, 32]. The results of this study also add to the overall limited existing literature on OSA of pregnant women, especially in the Thai population.

Nevertheless, there were some limitations in our study which may have affected our conclusion validity. First, we screened for OSA risk using BQ instead of the gold standard polysomnography. However, BQ has been widely used, including in pregnancy, and when used during the second trimester, has proved predictive of adverse pregnancy outcomes [14, 33, 34]. Second, we did not measure some potentially confounding factors such as urinary tract infection and pre-existing OSA, which might affect the outcomes. Long-standing or pre-existing OSA and newly diagnosed OSA may affect the cardiovascular system to different degrees which, in turn, pose different risks for preeclampsia–eclampsia. However, we did not have this information as awareness of OSA has been very limited, especially in rural areas, thus we could not estimate the actual prevalence of pre-existing OSA by this questionnaire.

These observations, when coupled with previous reports, have important clinical and public health implications because pregnant women with symptoms of OSA are at higher risk of

Table 2 Reproductive and medical characteristics of study participants according to high risk and low risk for OSA, Nakhon Ratchasima Province, Thailand, 2013–2014

Characteristic	Low risk for OSA ($n = 1209$)[a]		High risk for OSA ($n = 136$)[a]		p
	%	Mean (SD)	%	Mean (SD)	
Total gestational weight gain, kg		14.7 (4.44)		14.9 (5.56)	0.699
Perceived Stress Scale score		15.8 (5.30)		16.9 (5.24)	0.024
Parity					0.854
Nulliparous	40.0		41.2		
Multiparous	60.0		58.8		
Prior history of PTD					0.157
Parous-no-prior PTD	91.2		86.2		
Parous-prior PTD	8.8		13.8		
Number of previous abortions					0.176
0	80.2		77.9		
1	16.5		15.4		
≥ 2	3.4		6.6		
Prior preeclampsia–eclampsia					0.338
Yes	1.4		2.5		
No	98.6		97.5		
Pre-pregnancy body mass index[b]					<0.001
Underweight (< 18.5)	20.6		7.4		
Normal (18.5–24.9)	64.0		41.2		
Overweight (25.0–29.9)	12.2		27.9		
Obesity (≥ 30.0)	3.2		23.5		
Pre-gestational diabetes mellitus	8.8		11.8		0.270

OSA, obstructive sleep apnea; *PTD*, preterm delivery; *SD*, standard deviation

[a] Number may not be added to the total number due to missing data

[b] Weight (kg)/height $(m)^2$

preeclampsia–eclampsia. However, even in the absence of a clinically positive OSA diagnosis, our results suggest that the higher risk of preeclampsia–eclampsia detected by the BQ screening tool indicates a far more complex relationship that requires further study. Our study illustrates the need for further studies to assess mechanisms for the association or causal relationship between OSA and preeclampsia–eclampsia. Likewise, further study should include those participants who were excluded from this study (i.e., hypertensive patients) and the use of other questionnaires and screening tools.

Conclusion

Pregnant women with high risk for OSA as estimated using the BQ have an increased risk for preeclampsia–eclampsia. It is important to increase awareness of OSA among pregnant women, and more importantly, among physicians. Our results support the routine screening for OSA during antenatal care. BQ may be a useful screening modality, since it has high predictive values in detecting OSA in pregnancy. It is also cost-effective, widely available, and non-invasive. Early diagnosis and effective

Table 3 Odds ratio and 95% confidence interval of preeclampsia–eclampsia according to the risk group for OSA, Nakhon Ratchasima Province, Thailand, 2013–2014

Risk of OSA	No PE/E ($n = 1295$)		PE/E ($n = 50$)		Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
	No.	%	No.	%				
Low risk	1174	97.1	35	2.9	1.00	Reference	1.00	Reference
High risk	121	89.0	15	11.0	4.16	2.21, 7.83	2.72	1.33, 5.57

OSA, obstructive sleep apnea; *PE*, preeclampsia; *E*, eclampsia; *CI*, confidence interval; *OR*, odds ratio

[a] Adjusted for maternal age, pre-pregnancy body mass index, number of previous abortions, previous preterm, and prior preeclampsia–eclampsia

management may significantly diminish adverse outcomes associated with OSA during pregnancy. Further study to evaluate the benefits of screening and treating OSA during pregnancy in reducing preeclampsia–eclampsia is recommended.

Acknowledgments The authors would like to thank the staff of the Research Center of Maharat Nakhon Ratchasima Hospital for their assistance in data collection.

Funding This study was supported by grants from the 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund) and Ratchadaphiseksomphot Fund (RA 57/001), Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. The funders had no influence on study design or analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Comment

This is an important addition to the field in focusing on the potential role of SDB in adverse pregnancy outcomes. While such a link has been suspected for a long time, there have been remarkably few studies of the problem, which is suprising considering the potential clinical significance in which there have been very few clinical advances in terms of predicting and managing the problem. However, recent studies have confirmed a link for both GHT and GDM (i.e., the Facco NuMoM2B studies).
This work makes several important additions to this nascent area. First, the study hints at a high prevalence of SDB in pregnant women in an Asian country where obesity does not dominate (unlike the USA and Australia—where high BMIs are now markedly increased in women of child-bearing age—with the result that many clinicians simply think of SDB as the result of obesity). An estimate of 10% is very high and suggests that an Asian population might be more susceptible. This might relate to the higher prevalence of GHT in some Asian countries. The study confirms the link between likely SDB and GHT and provides further support for bringing clinical attention to the potential for a treatable problem of pregnancy.

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