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Original Article

Increased plasma levels of inflammatory markers and upper airway resistance during sleep in pre-eclampsia ☆,☆☆

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Abstract

Objectives: To evaluate pregnancy-associated sleep disorders, pregnancy outcomes and inflammatory markers in pre-eclampsia and normal pregnancy (control).
Patients and methods: We studied 15 consecutive pre-eclamptic women and 14 controls. Pre-eclamptic women underwent overnight pulse oximetry and nasal pressure measurements at a university teaching hospital, and the sleep study for the controls was performed at home. Mean gestation was 31 weeks. Nasal airflow was carefully analyzed visually, and the time with flow limitation was calculated as a percentage of total recording time. At the time of the sleep study, the subjects were clinically evaluated, they answered sleep questionnaires, and fasting blood samples were drawn for tumor necrosis factor alpha TNF-α, interleukin 6 (IL-6) and sensitive C-reactive protein. Pregnancy outcomes were collected after delivery.
Results: Pre-eclampsia patients spent significantly more time with flow limitation (mean ± SD: 21 ± 18% vs. 4 ± 9%), had higher plasma levels of TNF-α (6.2 ± 2.3 ng/l vs. 4.1 ± ng/l) and IL-6 (4.4 ± ng/l vs. 1.2 ± 0.4 ng/l), had more generalized edema, had increased fatigue and snoring, and had poorer pregnancy outcomes than did controls. Age, gestational age, mean SpO_2 and body mass index did not differ between the groups.
Conclusions: Pregnant women with pre-eclampsia showed significantly more nasal flow limitation during the night, higher fasting IL-6 and TNF-α plasma levels, more edema and worse pregnancy outcomes than did healthy pregnant women.

Keywords: Pre-eclampsia; Pregnancy; Upper airway resistance; Snoring; Tumor necrosis factor alpha; Interleukin 6

1. Introduction

Pregnancy-associated physiological changes lead to sleep complaints that include snoring, insomnia, nocturnal awakenings, parasomnias and daytime sleepiness [1–4]. Pregnancy rhinitis, which is associated with a high level of pregnancy hormones, is relieved by nasal decongestants but not by nasal steroids. This indicates mucosal hyperemia/congestion during pregnancy [5,6]. The etiology of increased snoring and upper airway resistance during sleep with pregnancy remains under investigation.

Pre-eclampsia is a hypertensive disorder of pregnancy and a leading cause of fetal and maternal morbidity and

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mortality [7]. It is usually associated with generalized edema and an increase in inflammatory mediators [8], both of which may play a role in sleep-related breathing disorders. Despite major advances in our understanding of the pathophysiology of pre-eclampsia, its cause remains unknown [8]. Studies of patients with pre-eclampsia have suggested that patients experience a narrowing of the upper airway in both the upright and supine postures [9] and increased upper airway resistance during sleep [10,11]. Moreover, snoring itself is associated with hypertension and represents a risk factor for pre-eclampsia and intra-uterine growth restriction [12].

Since inflammation is believed to play a role in the pathogenesis of cardiovascular events, the measurement of inflammation markers [C-reactive protein (CRP), interleukin 6 (IL-6)] has been proposed as a method to improve the prediction of the risk of these events [13–15]. Moreover, pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), have been shown to contribute to the pathogenesis of sleep apnea, and neutralizing TNF-α activity is associated with a significant reduction in objective sleepiness in obese patients with obstructive sleep apnea [16].

Both sleep apnea and pre-eclampsia are associated with similar adverse medical effects, such as cardiovascular problems, diabetes and poor pregnancy outcomes [12,17,18]. The strong connection between these two disorders appears to be complex, so examining it in order to understand the nature of sleep apnea is crucial. Data on sleep-disordered breathing during pregnancy are lacking, and given the association between sleep apnea and hypertension [19], the investigation of sleep-disordered breathing in pre-eclampsia is clinically relevant.

The purpose of this study was to identify an association between sleep-disordered breathing, inflammatory markers and clinical findings in pre-eclamptic women with no previous history of sleep-disordered breathing. We, therefore, compared data from sleep studies, clinical findings and blood inflammatory markers collected from pre-eclamptic and healthy pregnant women during the third trimester of pregnancy.

2. Methods

2.1. Subjects and study design

We studied 17 women with pre-eclampsia and 15 healthy pregnant women (controls). We included subjects with no history of regular snoring, chronic sleep complaints, or psychiatric disease, or who had been receiving medication regularly prior to pregnancy. We expected the control women to present normal pregnancy until delivery. We excluded one woman initially considered healthy but who developed pre-eclampsia one week after the sleep study. We used the definition of pre-eclampsia established by the American College of Obstetricians and Gynecologists [20]. Pre-eclmaptic women were recruited through the Department of Obstetrics and Gynecology at the Helsinki University Hospital after their admission for pre-eclampsia. Control females were recruited from among colleagues of the research team. All subjects provided their written informed consent for the study, which had the approval of the Local Ethics Advisory Committee. The characteristics of the pre-eclamptic and control women appear in Table 1.

2.2. Sleep studies

In order to increase the acceptance of the study protocol, the sleep study included only nasal airflow and a pulse oximeter. The sleep studies for pre-eclamptic women were carried out at the Department of Obstetrics and Gynecology, whereas the controls were examined at home. The sleep studies were performed between 23 and

Table 1
Characteristics of pre-eclamptic ($n = 15$) and control ($n = 14$) women

	Pre-eclampsia		Control		p
	Mean	SD	Mean	SD	
Age, years	33.7	6.3	31.7	5.7	n.s.
BMI, kg/m^2	24.3	5.1	24.2	2.2	n.s.
Neck circumference, cm	35.2	2.8	34.2	1.9	n.s.
Systolic blood pressure, mmHg	152	14	115	12	0.001
Diastolic blood pressure, mmHg	96	10	72	6	0.001
Fatigue, 0 = none, 3 = severe	1.4	0.5	0.1	0.5	0.001
ESS	4.7	1.6	4.6	3.2	n.s.
Coffee consumption, cups/day	1.3	1.3	2.8	1.5	0.01
Smoking, *n*	1		1		n.s.
Napping, times/week	4.9	2.6	2.4	2.7	0.02
Napping, min/week	62	42	68	30	n.s.
Difficulties in falling asleep, nights/week	1.2	1.6	0.6	1.1	n.s.
Wake-ups after sleep onset, episodes/night	2.7	1.1	2.3	0.9	n.s.
Wake-ups after sleep onset, nights/week	6.2	1.7	5.9	2.3	n.s.

Abbreviations: BMI, body mass index; ESS, Epworth sleepiness scale; n.s., not significant.