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Original Article

Upper-airway flow limitation and transcutaneous carbon dioxide during sleep in normal pregnancy

Ville Rimpilä [a, b, *], Riina Jernman [c], Katariina Lassila [a], Jukka Uotila [c], Heini Huhtala [d], Johanna Mäenpää [a, c], Olli Polo [b, e]

[a] Faculty of Medicine and Life Sciences, University of Tampere, PL 100, 33014, Tampere, Finland
[b] Unesta Research Center, Näsilinnankatu 48 D, 4th Floor, 33520, Tampere, Finland
[c] Department of Obstetrics and Gynaecology, Tampere University Hospital, PL 2000, 33521, Tampere, Finland
[d] Faculty of Social Sciences, University of Tampere, PL 100, 33014, Tampere, Finland
[e] Department of Pulmonary Diseases, Tampere University Hospital, PL 2000, 33521, Tampere, Finland

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ABSTRACT

Objective: Sleep during pregnancy involves a physiological challenge to provide sufficient gas exchange to the fetus. Enhanced ventilatory responses to hypercapnia and hypoxia may protect from deficient gas exchange, but sleep-disordered breathing (SDB) may predispose to adverse events. The aim of this study was to analyze sleep and breathing in healthy pregnant women compared to non-pregnant controls, with a focus on CO_2 changes and upper-airway flow limitation.
Methods: Healthy women in the third trimester and healthy non-pregnant women with normal body mass index (BMI) were recruited for polysomnography. Conventional analysis of sleep and breathing was performed. Transcutaneous carbon dioxide ($TcCO_2$) was determined for each sleep stage. Flow-limitation was analyzed using the flattening index and $TcCO_2$ values were recorded for every inspiration.
Results: Eighteen pregnant women and 12 controls were studied. Pregnancy was associated with shorter sleep duration and more superficial sleep. Apnea–hypopnea index, arterial oxyhemoglobin desaturation, flow-limitation, snoring or periodic leg movements were similar in the two groups. Mean SaO_2 and minimum SaO_2 were lower and average heart rate was higher in the pregnant group. $TcCO_2$ levels did not differ between groups but variance of $TcCO_2$ was smaller in pregnant women during non-rapid eye movement (NREM). $TcCO_2$ profiles showed transient $TcCO_2$ peaks, which seem specific to pregnancy.
Conclusions: Healthy pregnancy does not predispose to SDB. Enhanced ventilatory control manifests as narrowing threshold of $TcCO_2$ between wakefulness and sleep. Pregnant women have a tendency for rapid CO_2 increases during sleep which might have harmful consequences if not properly compensated.

1. Introduction

Pregnancy is a challenge for the cardiorespiratory system, particularly during sleep when the body needs to rest without compromising fetal oxygen supply and carbon dioxide removal. In normal pregnancy, breathing during sleep is well preserved [1]. Plasma concentrations of progesterone are elevated during pregnancy and contribute to the increased ventilatory responses to hypoxia [2] and hypercapnia [3]. Factors compromising breathing during pregnancy are the growing uterus that elevates the diaphragm, resulting in decreased functional residual capacity of the lung. The decreased tracheal traction in turn predisposes to upper-airway narrowing, and hormonal changes increase the upper-airway edema. Obesity during pregnancy is an additional factor predisposing to obstructive sleep apnea (OSA) or snoring [4]. Breathing abnormalities are purported to be common during pregnancy, with partial upper-airway obstruction rather than OSA usually observed [5]. Sleep-disordered breathing (SDB) in pregnant women is associated with intrauterine growth retardation [6,7].

In sleep studies, CO_2 is rarely measured, and little is known about CO_2 control during SDB, but we have previously shown the effect of progressively developing flow-limitation as well as steady flow-limitation on transcutaneous CO_2 ($TcCO_2$) increase [8–10]. CO_2 has been suggested to play a role in hypertension in pre-

* Corresponding author. Unesta Research Center, Näsilinnankatu 48 D, 4th floor, 33520 Tampere, Finland.
E-mail address: rimpila.ville.p@student.uta.fi (V. Rimpilä).

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eclampsia [11]. Central chemoreceptor sensitivity to CO_2 is also increased during pregnancy [3], which could destabilize the ventilation when operated near threshold values.

The purpose of this study was to evaluate the differences in SDB and $TcCO_2$ parameters during normal pregnancy compared to non-gravid controls. It was hypothesized that pregnant women may have more flow-limitation and snoring compared to non-pregnant women (1). In addition, flow-limitation in pregnant women may cause greater $TcCO_2$ increase (2), and consequently, $TcCO_2$ values during sleep should differ between pregnant and non-pregnant women (3).

2. Methods

2.1. Participants

We recruited 18 pregnant women from maternity clinics in Tampere and its nearby regions and from the antenatal outpatient clinic and antenatal ward of Tampere University Hospital. Inclusion criteria were 18–45 years of age, singleton pregnancy without fetal demise, and gestational age 33 ± 1 weeks. Women with pre-eclampsia or other complications warranting constant monitoring and/or induction of labor were excluded.

Twelve non-pregnant women with body mass index similar to that of pregnant women in the beginning of pregnancy were chosen as controls. These women were recruited from Tampere University of Applied Sciences, Medical School of University of Tampere, and Tampere University Hospital, Department of Obstetrics and Gynecology, using recruitment posters. The study was approved by the local Ethics Committee (Identification Number R12102), and all women received oral and written information on the trial and signed a consent form before attending.

2.2. Obstetrical examination

The patients were first seen by an obstetrician (R.J.) at the antenatal outpatient clinic or ward. From the maternity card the following baseline information (standard recordings of the first maternity clinic visit in early pregnancy) was obtained: initial weight, height, body mass index (BMI), initial blood pressure, and the results of the oral glucose tolerance test if performed. Fetal ultrasound was performed using Voluson ultrasound equipment (Voluson S6 ultrasound, GE Healthcare, CT, USA) to record a fetal weight estimate, amniotic fluid index (AFI), fetal movements, and to assess the flow of the umbilical artery (uA). After a minimum of 15 min rest in a supine position in the examination room, blood pressure was measured from the right arm using a validated oscillometric technique (Omron automated manometer, M4-I Intellisense, Omron Corporation, Japan) with medium cuff-size. Weight was measured on a regular weighing scale. Urine dip stick test was analyzed for protein and glucose (Combur3 Test, Roche Diagnostics, Germany).

2.3. Sleep recordings

An overnight polysomnography was performed at Unesta Research Centre within a week after the obstetrical examination in the pregnant group. Controls visited the sleep laboratory once and all the information needed was then gathered. Recording montage contained electroencephalogram (EEG) with eight channels (A1, A2, O1, O2, F3, F4, C3, C4), electrooculogram (EOG), submental electromyography (EMG), anterior tibial EMG, nasal flow (prongs/cannula), body position, and inductance plethysmography (RIP) belts, which reflect the respiratory effort of the abdomen and thorax (Somnologica, Medcare Flaga hf, Reykjavik, Iceland). The sleep investigations included also nocturnal measurement of transcutaneous partial pressure of carbon dioxide ($TcCO_2$) and transcutaneous partial pressure of oxygen (TcO_2). A parasternally fixed dual sensor ($TcCO_2$ and TcO_2) warmed up to 43.0 °C was used (TCM4, Radiometer, Copenhagen, Denmark).

2.4. Data analysis

Sleep was scored according to AASM (American Academy of Sleep Medicine) criteria [12], and former stages S3–S4 were used in the breath-by-breath analysis. Proprietary scoring function of Somnologica was used to score flow limitation and snoring (default flattening index of 0.13 was used) and reported as percentage of total sleep time. Episodes of apnea were scored according to AASM rules [13], hypopnea was scored when a 30% reduction of flow was observed for a minimum of 10 s and apnea-hypopnea index (AHI) was calculated. Oxyhemoglobin desaturations of 3% (ODI3) or more were tabulated. $TcCO_2$ values were sampled with the frequency of 1 Hz and the data values during each sleep stage were pooled to calculate the statistics, including the median and quartiles for each sleep stage. This means that each epoch produced 30 data points to the corresponding sleep stage data pool. $TcCO_2$ values were also determined separately during inspirations with and without flow-limitation in each sleep stage. For this respiratory analysis, the $TcCO_2$ data was advanced 30 s in order to correct the physiological delay between breathing and the CO_2 reading on the skin. In addition, to avoid the disproportionately marked effect of individuals with low levels of flow-limited breathing on overall data, the $TcCO_2$ data was excluded from this analysis if less than 75 data points were available in a given sleep stage. One to two data points were available from each inspiration. Accordingly, short episodes (less than 3–5 min, depending on respiratory rate) of flow-limitation were not included. Poor quality $TcCO_2$ data (missing, unphysiological behavior and drift more than 1 kPa between evening and morning wakefulness for sleep stage analysis) as well as data during calibrations were omitted. $TcCO_2$ drift corrections were not done. Technical drift occurs both upwards and downwards, which results in a reduced effect of signal drift on a group level, but at the same time increases the variance of the sample which affects statistical analysis.

2.4.1. Peak analysis

The overnight profile revealed $TcCO_2$ fluctuations, which have not been reported or identified earlier in any other patient population or healthy controls. Based on initial visual observation, a set of rules to identify and numerically characterize these events were established. A $TcCO_2$ peak was scored when a sudden $TcCO_2$ increase followed by decrease to baseline was observed. Since no guidelines exist for scoring this type of event, $TcCO_2$ increase of more than 0.1 kPa was chosen as a loose criterion to score a $TcCO_2$ peak. For exclusion of clear episodes of apnea and hypopnea, minimum event duration was set to 1 min and 30 s. Peaks during rapid eye movement (REM) sleep were excluded due to normal ventilatory instability and fluctuating $TcCO_2$ that is commonly seen. Sleep state was required for the peak to be scored and peak events containing two or more consecutive epochs of wakefulness were excluded. Association to arousal or respiratory arousal was also scored. Respiratory arousal was scored when inspiratory flow shape improved simultaneously with arousal. The start of the peak was marked when $TcCO_2$ slope started to increase. The end of the event was marked when $TcCO_2$ returned to starting value or slope returned near zero (applied when the peak ended at higher $TcCO_2$). Signal drift was considered insignificant during these shorter events.