

PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Title:

Incidence of sleep-disordered breathing and upper airway collapsibility in postpartum patients and its intervention

I. BACKGROUND AND SIGNIFICANCE

Post-partum airway obstruction is a main cause of anesthesia related maternal death in North America.¹ A significant decrease in oral volume and pharyngeal area after labor and delivery, as well as a potential impairment of upper airway dilator muscle control are mechanisms that likely contribute to a decrement in upper airway patency during and after labor. We aim to conduct a randomized controlled study to evaluate the effects of posture during the first post partum night on the incidence and severity of sleep apnea. In addition, we will further examine the anatomical and physiological risk factors that contribute to post-partum upper airway obstruction.

Sleep-disordered breathing has been identified as an issue of national interest; the NIH has recently decided to request RO1 applications related to this topic (effective as of May 2011).

The function of the upper airway

The upper (supralaryngeal) airway is the pathway located between the nose/mouth and the base of the epiglottis². Its main function is not only to conduct air, but also to take part in other processes such as air conditioning (through warming and humidification), swallowing, speech and smell. The muscles in the upper airway comprise those of the external nares, soft palate, pharynx and larynx. Their function is to promote patency of the upper airway during inspiration, when the respiratory pump muscles evoke a negative pharyngeal pressure that puts the upper airway at risk of collapse in its retropalatal and retroglossal segments. The genioglossus, a fan-shaped muscle that runs dorsally from the ventral portion of the mandible to the tongue and protrudes the tongue when it contracts, protects the retroglossal part of the airway from collapsing during inspiration.

While the activity in the chest-wall muscles increases progressively during inspiration and reaches its peak at or near the cessation of inspiratory flow, activity in the alae nasi, genioglossus and posterior cricoarytenoid starts rather abruptly, reaches its peak early after the onset of inspiration and declines well before cessation of

inspiratory flow. Furthermore, the activity onset of these muscles usually precedes the diaphragmatic activity and, when negative pressure is applied selectively to the upper airway, a reflex increase in peak inspiratory activity and a greater lead time relative to the onset of diaphragmatic activity occurs. This pattern of contraction allows the upper airway to stabilize or dilate throughout the period when it is subjected to the negative intraluminal pressure produced by contraction of the inspiratory chest wall muscles. If the forces generated by the upper airway dilating muscles are not sufficient to oppose the negative intraluminal pressure, the upper airway will decrease in size and may collapse during sleep.

Problems of airway change in parturients

Dynamic changes in respiratory anatomy and physiology occur in the parturient ³. Mucosal edema, hyperemia, capillary congestion, and fragility of the upper airway begin in the first trimester, persist throughout pregnancy, and peak in the third trimester. There is also gestational weight gain and decreased functional residual capacity in pregnant women. With labor, there is a significant increase in Mallampati airway classification score ⁴ and there is a well-documented reduction in the oropharyngeal volume following delivery ³. These anatomic and physiologic changes may place the parturient at increased risk for sleep-disordered breathing and upper airway obstruction. Sleep-disordered breathing and upper airway collapsibility ⁵ are important causes of respiratory distress. Peripartum patients may be at particular risk for these complications. A review of anesthesia-related maternal deaths in Michigan from 1985 to 2003 identified five deaths resulting from airway obstruction or hypoventilation after general anesthesia, and this was the leading cause of anesthesia-related maternal mortality ¹.

While it is recognized that parturients may have an elevated risk for sleep-disordered breathing and upper airway obstruction ³, there is little data regarding the incidence and risk factors for these disorders during the peripartum period. Parturient are frequently exposed to neuraxial and systemic narcotics, both of which may interact synergistically with sleep-disordered breathing to cause respiratory complications. Therefore, understanding the magnitude of the risk of airway obstruction and respiratory failure has important implications for monitoring in the peri-delivery period. We have previously conducted a research study evaluating the postoperative upper airway obstruction by quantifying its incidence ⁶.

The absolute risk of death particularly without general anesthesia is low, but

airway size is decreased in parturients, increasing the risk for temporary sleep apnea during pregnancy in some patients.

Posture strongly predicts airway collapsibility during sleep and anesthesia.^{7,8} Recently it has been observed that postural changes from supine to sitting significantly improve collapsibility of the pharyngeal airway. Therefore, we hypothesize that a 45 degrees bed head elevation in parturients after delivery stabilizes the airway patency and consequently prevents nocturnal deoxygenation. We believe that the insights gained from these studies may lead to novel strategies to improve the safety of peri-partum patients presenting with airway obstruction, and eventually reduce the morbidity and mortality of postpartum patients.

II. SPECIFIC AIMS

Aim 1 To compare respiratory outcomes in post-partum women on 45 degrees bed head elevation or supine (flat) position to determine its association with changes on the Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI) within 48 hours and after 3-6 months post-partum.

Aim 2 To further elucidate the anatomical and physiological risk factors that contribute in the upper airway obstruction in post-partum patients compared with healthy female volunteers.

III. SUBJECT SELECTION

Inclusion criteria:

Postpartum mothers within 24 hours of delivery, over 18 years old.

Inclusion Criteria for Control Group:

Healthy female volunteers, between 20- 40 years

Exclusion criteria:

1. Age under 18 years.
2. History of pre-existing pulmonary and cardiac diseases, including bronchial asthma, cystic fibrosis, chronic obstructive lung disease, neck and chest tumors (thyroid, mediastinal, etc.), and congenital airway deformities.
3. Stillbirth, child in NICU or maternal ICU admission, remaining on “Labor and Delivery” floor for bleeding monitoring or preeclampsia.

4. In case of C-section delivery, mother will be excluded from the tests involving respiratory effort monitoring through abdominal belt.

IV. SUBJECT ENROLLMENT

We anticipate recruiting a total of 260 subjects. Written, informed consent will be obtained by co-investigators after subjects/health care proxy have considered the study consent form and detailed explanation of the study purpose, procedures, risks and discomforts. Consent will be obtained not earlier than 2 hours after delivery and until 10 PM of the same day. We will enroll patients from Ellison 13 and Blake 13.

V. STUDY PROCEDURES

In the first part of the study, upper airway patency during inspiration was assessed by spirometry, with the ratio of the maximum expiratory and inspiratory flow at 50% vital capacity (MEF₅₀/MIF₅₀ ratio). This variable that can be used to detect dynamic inspiratory flow limitation, defined as MEF₅₀/MIF₅₀ ratio greater than one⁹⁻¹¹. In addition, pharyngometry was used to assess upper airway cross sectional area (CSA). Finally, apnea-hypopnea index (AHI) was evaluated with a standard monitor for conducting ambulatory PSG; this non-invasive monitor (Alice PDX, Respiration, Inc) measures pulse oximetry, respiratory flow, and respiratory effort (respiratory belt movements). Spirometry and pharyngometry were measured on the evening, and on the morning after the first post-partum night. PSG was taken during the first night post-partum. If the patient is deemed to have significant sleep apnea, a letter was written to inform the patient of this result and to consider further testing by her primary care provider. The first part of the study has been already finished.

In the second stage of this study, we will test an additional group of 100 subjects with a wrist worn pulse oximeter to calculate their Oxygen Desaturation Index (ODI) and estimate the content of oxygen in their blood while they are sleeping either in a supine position or at 45 degree bed head elevation.

Experimental design:

Patient condition (Table 1)

The information listed in Table 1 will be obtained at the time of enrolment, which is during 2-8 h after delivery.

Table 1

Demographic details	Age
	Race
	Weight (on the day of admission)
	Pre-pregnancy weight
	Height
	BMI
	ASA physical status score
Anatomical airway inspections	Inter-incisor gap
	Thyromental distance
	Sternomental distance
	Neck Circumference
Physical examination	Vital Signs at 28-32weeks
	Vital Signs at admission
Gestational age at delivery	
Allergies	Latex, drugs, food, other allergies
Social history	Smoking (patient, family)
Medications	Tocolysis
	Magnesium therapy
	Beta blockers
	Betamethasone

	Other medications
Mother complications	HELLP
	Eclampsia
	Preeclampsia
	Gestational DM
	Anemia
	Recent upper respiratory infection
Labor	Length of labor (hours)
	<p>The first stage begins with the onset of contractions that cause progressive changes in the cervix and ends when the cervix is fully dilated. This stage is divided into two phases: early (or latent) and active labor.</p> <p>During early labor, the cervix gradually effaces (thins out) and dilates (opens). During active labor, the cervix begins to dilate more rapidly and contractions are longer, stronger, and closer together. People often refer to the last part of active labor as "transition."</p>
	<p>The second stage of labor begins once the cervix is fully dilated and ends with the birth of the baby. This is sometimes referred to as the "pushing" stage.</p>
	<p>The third and final stage begins right after the birth of the baby and ends with the separation and subsequent delivery</p>

	of the placenta.
	Induction
	CS following labor vs. CS without labor vs. vaginal
Anesthetic management	Neuraxial anesthetic (epidural vs. spinal vs. CSE)
	Neuraxial narcotics (medication, dose, route, time)
	General anesthesia
	Other
Postoperative pain management	Narcotics (medication, dose, route, time)
	Other
Newborn outcome	Gender
	APGAR scores at 0 and 5 min
	NICU admission
	IUGR
Number of days hospitalized	

Methods:

Aim 1: To compare respiratory outcomes in post-partum women on 45 degrees bed head elevation or supine (flat) position to determine its association with changes on the Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI) within 48 hours and after 3-6 months post-partum.

This study will be performed in two stages. In the first part, a cross-over study was performed. Patients were randomly assigned to at least 2.5 hours on supine position or at 45 degrees bed head elevation during the first postoperative night.

An overnight polysomnography (PSG) to measure the apnea-hypopnea index (AHI) was conducted. The AHI estimated the incidence of sleep disordered breathing in the night following delivery, and is calculated from pulse oximetry and capnography, a waist-bound respiratory belt to determine respiratory effort, and an EEG study. An ambulatory PSG device that has been designed to be self-applied by the patient prior to going to sleep will estimate the above-mentioned parameters. A research fellow, an anesthesia resident or Staff member set the device on the patient. All members of the obstetric anesthesia team were briefed on the study and a study team member will always be immediately available to answer any questions that the patient or the nursing staffs have about the study or the monitor. Whenever an obstruction in the upper airway was found, a letter to her primary care physician was mailed from Dr. Matthias Eikermann (see submitted document: OSA letter).

In the second stage of this study, we will assess the Oxygen Desaturation Index (ODI) by means of a wrist-worn pulse oximeter (WristOx2 3150). The device probe will be placed on the index finger to measure the amount of oxygen in the blood during the night while the patient is sleeping supine or at 45 degree bed head elevation. The device will be placed by a research fellow, anesthesia resident, or an anesthesia staff member and it will not interfere with medical care, childcare, or self-care.

Aim 2: To elucidate the anatomical and physiological risk factors that contribute in the upper airway obstruction in post-partum patients compared to healthy female volunteers.

1. Upper airway patency during forced inspiration (MEF₅₀/MIF₅₀):

MEF₅₀/MIF₅₀ is the ratio of maximal expiratory flow and maximal inspiratory flow at 50% vital capacity. MEF₅₀/MIF₅₀ is a variable derived from spirometry that can be used to detect dynamic inspiratory flow limitation^{6,11 9-10}). Upper airway obstruction will be defined as MEF₅₀/MIF₅₀ ratio greater than one ($[MEF_{50}/MIF_{50}] > 1$)⁶. Within 48 hours following delivery, we will measure three valid spirometric readings via face mask/mouth-piece; FEV1, FVC and MEF₅₀/MIF₅₀ will also be done at that time. Patients will be instructed to take deep breaths and forcefully exhale into the measuring device.

2. Upper airway cross sectional area:

To measure cross section area (CSA) of the pharynx, we will perform acoustic

pharyngometry (EccoVision Acoustic Pharyngometer-E. Benson Hood laboratories, Pembroke, MA^{13 14,15}) after the pulmonary function tests are completed. The device will be positioned in the mouth using a mouthpiece designed to secure the tongue in place. The pulse emitter will produce five pulses per second. Two microphones will detect the amplitude and temporal changes of the reflected pulse. Data will be collected and analyzed by a single investigator (research fellow). During the measurements, the subject's head position will be fixed.

Upper airway-cross sectional area will be determined at end expiration as the mean area between the nasal and oropharyngeal junction (velum) and the glottis¹⁶. A standard adult mouthpiece will be used. Acoustic pharyngometry has been validated against CT scanning¹⁷ and MRI¹⁸ for assessment of the cross-sectional area in non-snorers and in snorers with and without OSA in both the supine and upright positions¹⁹⁻²². At least 4 curves will be obtained and will be considered valid if the CSA differed by 10% or less.

VI. BIOSTATISTICAL ANALYSIS

Continuous variables will be compared by a two-sample, and paired-measurements t-test, as appropriate. Categorical variables will be compared by using Fisher's exact test or Pearson's chi-square test. Data will be reported as mean (\pm SD), and P<0.05 will be considered statistically significant. The primary criterion is AHI, and comparisons will be made within an individual between two body positions. We powered the study for detecting changes AHI between body positions. As for power analysis, we expect based on the finding of Tagaito Y, and co-workers⁸. Accordingly, a sample size of 50 patients will provide a 90 per cent power to identify a difference between groups. We plan to conduct an interim analysis on 25 patients to make sure a potentially helpful intervention (elevated body position) will be provided to all patients in the case of clinical significance.

VII. RISKS AND DISCOMFORTS

There are no significant risks from the tests on this study. The investigation of the ability to swallow normally is part of the routine care in these patients. In addition, we will perform pulmonary function tests, grip strength measurement, and an acoustic pharyngometry test.

1. Spirometry is not associated with any notable risk.
2. Acoustic pharyngometry, overnight oximetry and respiratory effort monitoring are

not associated with any notable risk.

3. Intervention (bed head positioning) is not associated to any notable risk, but the pre-defined body position may induce some discomfort. In addition, the patient will be woken up once during the night in order to change the upper body position between supine and 45 degrees elevated.

VIII. POTENTIAL BENEFITS

Understanding the risk of sleep-disordered breathing associated with the peripartum period may help clinicians to determine which patients need monitoring following delivery with pulse-oximetry or other assessments to prevent respiratory complications. By investigating the beneficial effect of intervention (i.e. bed head positioning), we aim to eventually improve upper airway patency in our patient population.

IX. MONITORING AND QUALITY ASSURANCE

As our study is observational in nature, no formal quality assurance program needs to be implemented. In addition, any adverse events will be reported to the Human Research Committee for review.

X. Flow sheet

Stage 1:

Part 1 (2-8 h after delivery): enrollment, vital signs recording.

Part 2 (48 hours post-delivery): AHI, PSG and pharyngometry:

	On the day after delivery, 5-10 PM ***	From 10 pm to 1:30 am	From 1:30 am to 5 am	Morning after delivery
**Group A	MEF ₅₀ /MIF ₅₀ and upper airway cross sectional area	PSG, 45° elevated*	PSG Supine	MEF ₅₀ /MIF ₅₀ and upper airway cross sectional area
**Group B		PSG, Supine	PSG, 45° elevated *	
Control Group	MEF ₅₀ /MIF ₅₀ and upper airway cross sectional area	-----	-----	-----
Follow up Group	-----	PSG	PSG	-----

*For the intervention we will apply a supine (flat)²³ or 45° semi-recumbent position²⁴.

**For the determination of AHI, overnight pulse oximetry, nasal pressure, abdominal wall motion and electroencephalography (EEG) will be measured in both Group A and Group B patients.

*** After enrollment (for the control group)

Stage 2:

	On the day after delivery, 5-10 PM ***	From 10 pm to 7 am	Morning after delivery
Group A	Screening for eligibility and consent form. Questionnaires (Epworth	ODI evaluation with wrist-worn pulse oximeter, 45° bed head elevation*	Removal of the device, questionnaire (Quality of sleep score).

Group B	Sleepiness Scale, Pittsburgh Sleep Quality Index)	ODI evaluation with wrist-worn pulse oximeter, Supine	<hr/> <hr/> <hr/>
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Version 5

XI. REFERENCES

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