Sleep-Disordered Breathing and PAP in Perinatal Depression

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Sleep and Perinatal Depression

Objectives

1. *Assess the impact of positive airway pressure (PAP) on depressive symptoms in women with prenatal sleep-disordered breathing (SDB) and depression.*
Hypothesis: The PAP group, in comparison to the non-PAP group, will demonstrate improvements in depressive symptoms and more frequent remission of depression, as well as improved sleep quality, reduced sleep fragmentation, and increased sleep duration.

2. *Characterize the effect of PAP on the HPA axis in women with prenatal SDB and depression.*
Hypothesis: Use of PAP will reduce levels of cortisol, a marker of HPA axis functioning, and reductions in cortisol will correlate with improvements in mood.

3. *An additional, exploratory aim is to assess associations between PAP treatment and adverse pregnancy and neonatal outcomes.*
We hypothesize that the PAP group in comparison to the non-PAP group will show better delivery outcomes (lower rates of preterm birth, shorter hospitalization) and their infants will demonstrate greater neurodevelopment relative to those born to the non-PAP group.

Design and Outcomes

The study is a randomized trial to test the efficacy of PAP on sleep and depression symptoms in perinatal women. Mood and sleep assessments will be completed at baseline, after 1 week of enrollment, and monthly thereafter through 12 weeks postpartum. Cortisol will be measured using saliva collection at baseline and again 8 weeks later. Blood will be drawn at baseline and again eight weeks later.

Interventions and Duration

Participants will be randomly assigned to PAP or treatment as usual.

Participants assigned to the PAP arm of the study will be offered PAP therapy using an auto-titrating device. Participants will receive the first night of therapy in the Sleep Laboratory. Participants will use PAP at home for the remainder of their pregnancy and through 12 weeks postpartum.

Participants in the treatment as usual arm will continue their clinical care as usual through obstetrics. Note that PAP is not part of treatment as usual/standard care through obstetrics.

Sample Size and Population

The study is a randomized controlled trial with 50 participants, 25 per group. Participants will be pregnant women with SDB and major depressive disorder. Women will be randomly assigned to either PAP (PAP group) or treatment as usual (SDB group).

1. STUDY OBJECTIVES

1.1 Primary Objectives

Assess the impact of positive airway pressure (PAP) on depressive symptoms in women with prenatal sleep-disordered breathing (SDB) and depression. The PAP group, in comparison to the non-PAP group, will demonstrate improvements in depressive symptoms and more frequent remission of depression, as well as improved sleep quality, reduced sleep fragmentation, and increased sleep duration.

Characterize the effect of PAP on the HPA axis in women with prenatal SDB and depression. Use of PAP will reduce levels of cortisol, a marker of HPA axis functioning, and reductions in cortisol will correlate with improvements in mood.

1.2 Secondary Objectives

An additional, exploratory objective is to assess associations between PAP treatment and adverse pregnancy and neonatal outcomes. We hypothesize that the PAP group in comparison to the non-PAP group will show better delivery outcomes (lower rates of preterm birth, shorter hospitalization) and their infants will demonstrate greater neurodevelopment relative to those born to the non-PAP group.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Sleep-disordered breathing (SDB) represents a spectrum of breathing disturbances during sleep, ranging from habitual snoring to obstructive sleep apnea. Between 3-17% of the population experiences SDB of at least moderate severity (Peppard et al., 2013). Consequences of SDB include cardiovascular and behavioral morbidity and mortality (T. Young et al., 2009). An estimated 9% of women of childbearing age have SDB; however, this figure is likely an underestimate, as 90% are undiagnosed (Peppard et al., 2013; T. Young et al., 1993). Furthermore, risk increases during pregnancy (Izci et al., 2006; Pien, Fife, Pack, Nkwuo, & Schwab, 2005). Published data, including our own, show that by the third trimester >30% of women demonstrate habitual snoring, the hallmark symptom of SDB (Bourjeily, Raker, Chalhoub, & Miller, 2010; Hutchison et al., 2012; O'Brien, Bullough, Owusu, et al., 2012).

Perinatal depression affects nearly 20% of women (Gavin, 2005). Highly recurrent (Di Florio et al., 2013), severe cases can precipitate psychosis, suicide, and infanticide (Yonkers, 2011). Despite the high prevalence, 50% of women with perinatal depression do not receive treatment (Ko, Farr, Dietz, & Robbins, 2012)and even with antidepressant treatment >40% remain depressed (Sit et al., 2011), conferring serious risk to themselves and their offspring. It is well-established that offspring born to depressed mothers as compared to healthy mothers have poorer proximal (e.g., shorter gestation, lower birth weight (Field et al., 2004)) and distal outcomes (e.g., childhood cognitive impairment (Hollins, 2007), self-regulation difficulties (Maughan, Cicchetti, Toth, & Rogosch, 2007)). A critical need exists for interventions that could improve these outcomes.

2.2   Study Rationale

Depression is a frequent morbidity of SDB. SDB of moderate severity increases the prospective risk for depression 2-fold, equivalent to the increase in risk for hypertension (T. Young et al., 2009). Estimates of the comorbidity between SDB and depression range from 18-58% (Mosko et al., 1989; Ohayon, 2003). SDB is associated with treatment-resistant depression (Roest et al., 2012). Notably, treatment of SDB with positive airway pressure (PAP) significantly reduces depressive symptoms in patients with depression (El-Sherbini, 2011), including treatment-resistant depression (Habukawa et al., 2010).

A new line of inquiry indicates that SDB is a risk factor for a variety of adverse pregnancy outcomes (Bourjeily et al., 2010; Facco et al., 2012; Louis et al., 2012; O'Brien, Bullough, Owusu, et al., 2012; O'Brien, Bullough, et al., 2013; Poyares et al., 2007). However, the relationship between SDB and perinatal depression, one of the leading causes of maternal morbidity (Colvin, Slack-Smith, Stanley, & Bower, 2013), is not well understood.

Importantly, accumulating evidence now strongly indicates that maternal sleep disturbance is a key modifiable risk factor for depressive illness. Studies demonstrate that poor sleep quality (Dørheim, Bondevik, Eberhard-Gran, & Bjorvatn, 2009; Jomeen & Martin, 2007) and sleep fragmentation (Okun et al., 2011) are robustly associated with perinatal depressive symptoms. Poor sleep quality in early pregnancy directly predicts later depressive symptoms (Helen Skouteris, Germano, Wertheim, Paxton, & Milgrom, 2008; H. Skouteris, Wertheim, Germano, Paxton, & Milgrom, 2009). Furthermore, poor sleep quality in late pregnancy predicts postpartum depression (Okun et al., 2011; Wolfson, Crowley, Anwer, & Bassett, 2003). One of the most common, yet undiagnosed, causes of poor sleep quality is sleep disordered breathing (SDB). Notably, our own data show significant overlap between SDB and depressive symptoms in pregnancy; 43% of pregnant women who snore report significant depressive symptoms, relative to 23% of non-snorers (O'Brien, Owusu, & Swanson, 2013). Our findings, the first in a pregnant population, are consistent with other studies that show high comorbidity between SDB and depression. This raises the distinct possibility that treatment of SDB will improve perinatal depression. Importantly, PAP is a non-invasive, non-pharmacological intervention that can be readily implemented in pregnant women, as our own data demonstrate. However, the impact of SDB treatment on perinatal depression has not been investigated to date.

Sleep fragmentation, a consequence of SDB, is associated with HPA axis hyperactivity (Follenius, Brandenberger, Bandesapt, Libert, & Ehrhart, 1992; Spath-Schwalbe, Gofferje, Kern, Born, & Fehm, 1991). Chronic activation of the HPA axis is a hypothesized pathway by which SDB may cause, and increase vulnerability to, depression. Hyperactivity of the axis is observed in both prenatal depression (Parcells, 2010; Rich-Edwards et al., 2008) and SDB (Vgontzas et al., 2007), and, importantly, predicts resistance to antidepressants (E. A. Young et al., 2004). The axis is normalized with PAP (Henley et al., 2009; Schmoller et al., 2009; Vgontzas et al., 2007). Maternal HPA axis functioning is implicated in fetal programming (Weinstock, 2005).

PAP is the standard treatment for sleep-disordered breathing in the non-perinatal population. However, it has not been studied in pregnancy, and the effects of PAP treatment on SDB, health, and mental health in pregnant and postpartum women remains unknown. Participants will use PAP nightly through 12 weeks postpartum.

Justification of Randomized Design

We have proposed a randomized design – in which participants are assigned to either PAP therapy or treatment as usual -- only after careful consideration of ethical and safety issues,

and consultation with numerous leaders in the field. Conclusions from a panel discussion (held during the 2009 Annual Meeting of the Associated Professional Sleep Societies) regarding ethical issues in obstructive sleep apnea clinical trials were also utilized (Brown et al., 2011). Dr. Chervin, a co-investigator on this study, was a member of this panel, and he has conducted randomized, controlled trials in obstructive sleep apnea treatment. A randomized design was proposed for the study because in a non-randomized protocol many factors could influence acceptance or refusal of CPAP, and these confounding variables might obscure our ability to draw conclusions about effects of CPAP.

We believe a randomized design is ethical based on several main points. First, there is a notable lack of published data and therefore significant clinical equipoise exists regarding the risks of SDB in pregnancy, the effects of PAP treatment in this population, and the ability of pregnant women to use PAP. The little evidence that does exist on risks of untreated SDB during pregnancy are conflicting. Importantly, there is no published evidence that treatment of SDB in pregnancy has any impact on maternal, obstetric, or neonatal outcomes. No guidelines have been published for treatment of SDB during pregnancy. Second, screening for SDB is not standard of care in pregnancy, and most pregnant women are never referred for sleep studies. Thus, the vast majority of pregnant women with SDB do not know they have this condition, and are untreated. Third, several large studies of SDB have assessed participants' SDB status and followed them across many years without providing treatment, or randomizing participants to receive PAP or standard care (e.g., Sleep and Heart Health Study; Sleep Apnea cardioVascular Endpoint study). We also wish to reference a recent study of sleep apnea in pregnancy conducted by Facco and colleagues (Facco et al., 2014), wherein pregnant women were assessed for SDB and those diagnosed with SDB were not offered PAP treatment. Fourth, we have established a plan to protect participants from the most likely risk of untreated SDB, motor vehicle crash due to daytime sleepiness, further delineated in the Data Safety Monitoring Plan. This approach and the focus for safety purposes on sleepiness rather than other features of SDB follows published recommendations for SDB randomized trials (Brown et al. 2011). Finally, all participants will be offered referrals for SDB treatment upon conclusion of the study. In short, some individuals could benefit by participation in this trial; no participant will be prevented from seeking clinical care for SDB on their own accord; and participation in this research is not anticipated to impose incremental harm that would have been avoided absent participation.

3. STUDY DESIGN

This 5-year study is a randomized trial of PAP therapy in pregnant women with SDB and depression. The main objectives of the study are to (1) assess the impact of PAP on depression symptoms in women with prenatal SDB and depression and (2) characterize the effect of PAP on the HPA axis in women with prenatal SDB and depression. A secondary objective is to assess associations between PAP treatment and adverse pregnancy and neonatal outcomes.

Fifty pregnant women who have comorbid SDB and depression will be enrolled in the study. Participants will be screened for depression using methodologies established by our group (Swanson, Flynn, Adams-Mundy, Armitage, & Arnedt, 2013). a Participants will be randomly assigned to PAP (n=25) or treatment as usual (n=25). Participants will complete assessments of sleep and mood at enrollment through 12 weeks postpartum.

Participants will complete most aspects of the study in their home, including telephone-based

assessments. They will undergo an in-person eligibility interview, and complete an in-home sleep study to determine SDB   Those assigned to the PAP group will also complete their first night of PAP therapy in the sleep laboratory. Length of participation will vary depending on gestational age at enrollment and the length of each participant's pregnancy. We anticipate that most women will participate for 4-6 months.

Women who meet eligibility for the study will be randomized to either PAP or treatment as usual using the minimization method (Schulz, Altman, & Moher, 2010). In this CONSORT-approved method, the first participant is truly random, and thereafter participants are allocated to condition to minimize between-group imbalance of selected characteristics. Minimization is a viable alternative to true randomization, arguably superior as it allows for balanced groups even in smaller samples (Treasure & MacRae, 1998). We will balance assignment to group based on the following characteristics: race, gestation week, depression severity, SDB severity, socioeconomic status, partnered status, 1st trimester BMI. Participants will not be blind to condition. The study clinician, who will complete clinician-rated assessments of participants' mood, will be blind to group assignment.

Participants randomized to PAP treatment will be asked to use PAP nightly through 12 weeks postpartum. Participants will use PAP at home for the remainder of their pregnancy, through 12 weeks postpartum.

Participants randomized to the treatment as usual group will not be offered PAP, and will continue to receive care as usual within obstetrics (SDB group).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Recruitment will occur through multiple sites at UM, leveraging the existing research infrastructure of the Women's Mental Health and Infants Program (WMHIP). The WMHIP maintains an IRB-approved research recruitment registry at obstetrics clinics. Briefly, all women who present for care at the clinics complete a screen consisting of a demographic form, perinatal depression measure (EPDS), a question regarding habitual snoring, and consent to be contacted for research. A research assistant inspects all forms for study eligibility and eligible women are contacted.

Other sources of recruitment include the Women and Infants Mental Health Clinic at UMHS, UMClinicalstudies.org website, and fliers posted in the community and UMHS clinics.

Subjects may be identified from the M-STRIDES database - the clinical database of the Department of Psychiatry, based on their Edinburgh Postnatal Depression Scale score. They may also be identified from the UMHS Obstetrics Clinic appointment list; those patients who have documentation of depression or an Edinburgh Postnatal Depression Scale score ≥8 in their medical record may be contacted. Finally, we may also use Emerse to identify potential participants across UMHS. For these recruitment sources, we will send participants a letter to introduce the study, including information for how to opt out of follow-up contact regarding the study. Participants who do not opt out of contact may be contacted by telephone or email to discuss their interest in the study.

4.1 Inclusion Criteria

Females 18-45 years and: (1) 20-32 weeks gestation with a single, live fetus, (2) meet criteria for major depressive disorder per the Structured Clinical Interview for DSM-V (SCID), (3) apnea symptoms (snoring, witnessed apnea, daytime sleepiness, sleep disturbance, snort arousals), (4) and if taking an antidepressant, dose must be stable (for ≥8 weeks); if not using an antidepressant medication, participant must be free of all antidepressants for the past 4 weeks.

4.2 Exclusion Criteria

(1) Diagnosis of bipolar disorder, posttraumatic stress disorder, schizophrenia or psychosis, dissociative disorders, eating disorder, obsessive-compulsive disorder, somatic symptom and related disorders, substance use disorder, panic disorder, agoraphobia per DSM-V, (2) diagnosis of, or suspicion for, narcolepsy or REM behavior disorder, (3) current SDB treatment, (4) medical conditions for which PAP is contraindicated (e.g., pneumothorax, pneumocephalus, recent trauma, recent surgery), and (5) evidence of risk for drowsy driving (excessive daytime sleepiness plus history of motor vehicle accident or near miss due to sleepiness, fatigue, or inattention in past 12 months).

4.3 Study Enrollment Procedures

Potential participants identified from the research recruitment registry will be contacted and those who agree to participate will be invited to complete an interview to assess eligibility. All participants will complete written informed consent before they complete the eligibility interview. The eligibility interview will consist of self-report and clinician rated measures of mood and sleep, the SCID, Hamilton Rating Scale for Depression (HRSD), and Pittsburgh Sleep Quality Index (PSQI), as well as information regarding demographics.. A study Screening Log will be maintained to document reasons for ineligibility and reasons for declined participation in eligible participants.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Positive Airway Pressure (PAP)

Positive airway pressure therapy entails use of a machine that blows pressurized room air through the airway (via a mask or nasal pillows, worn on the face) at a sufficient pressure to keep the upper airway open. The pressurized air acts as a splint. Participants randomized to PAP treatment will be offered PAP therapy using an auto-titrating device. The initial trial night of PAP will be conducted in a monitored, technologist-attended sleep laboratory. Heated humidification will be used in this study, to minimize nasal symptoms and optimize adherence. The auto-titrating PAP delivers a minimum effective pressure with the result that the mean pressure over the course of the night is often lower than the fixed pressure delivered by continuous PAP, and therefore tolerance of PAP may be improved. This device is ideal for pregnant women, as it automatically adjusts pressure settings to optimally treat SDB by adapting to the fluctuations in weight and edema typically experienced through pregnancy and into postpartum without additional laboratory visits for re-titration. As in our other protocols of PAP in pregnancy, participants will receive the first night of therapy in the sleep laboratory. Treating obstetricians and psychiatrists will be informed of their patient's enrolment in the study and will

be informed if any issues arise with use of PAP. Subjects will have almost daily contact initially with the research team, which typically tapers to a weekly telephone call to discuss any problems or questions. This greatly exceeds generally available standard of care, but is successfully used in our pregnancy protocols and will optimize safety and yet remain generalizable to clinical settings where high-risk obstetric clinic personnel probably could replicate these frequent contacts, in person or by phone, when necessary. Women will use the PAP device for the remainder of their pregnancy and through 12 weeks postpartum. In comparison, people in the general population who use PAP for SDB often use it for many years.

Risks of PAP therapy are minor, typically discomfort as the participant adjusts to PAP therapy, and other minor risks related to mask problems or nasal symptoms. There is a rare risk of pneumothorax or pneumocephalus. All documented events of pneumothorax or pneumocephalus occurred in women who had previous trauma and/or nasal surgery. Therefore, participants with recent head trauma or surgery (pituitary or nasal) that may have produced cranio-nasopharyngeal fistula (risk of entry of air or other material into the cranial cavity) will be excluded from the study. The most frequent risks, all minor, and interventions to minimize these risks are as follows:

Mask problem:
Air leaks   Proper mask fitting and application
Skin irritation   Avoid over tightening of headgear; use of nasal pillows
Mouth dryness   Chin strap to eliminate mouth leak; heated humidity
Mask claustrophobia   Nasal pillows-type of interface

Nasal symptoms:
Congestion   Chin strap; heated humidity; nasal saline
Nose bleed   Chin strap; heated humidification; nasal saline rinses
Rhinitis   Nasal saline rinses

Treatment as Usual

In this condition, participants will continue their care through obstetrics. Positive airway pressure therapy is not provided as part of usual care in obstetrics.

5.2 Concomitant Interventions

The clinical care of participants will not be altered or affected in any way by their participation in the study. No interventions will be prohibited. Use of medications, including those for depression (eg, SSRIs), and other depression treatments (eg, psychotherapy), will be monitored and documented throughout the study, but participants will not be prevented or prohibited from accessing such care, or in making changes to their medications or clinical care.

5.3 Adherence Assessment

Use of PAP will be monitored using web-based software, which will provide real-time, web-based notification of nightly use. Adherence is defined as four hours or more of PAP use on 70% or more of nights. Participants who use PAP for <4 hours will be contacted the same day by telephone to address barriers to use and enhance motivation. Early intervention is crucial to maximize adherence (Budhiraja et al., 2007).

6. STUDY PROCEDURES

6.1   Schedule of Evaluations

Assessment	Screening: Eligibility interview	In-lab PAP trial (PAP group)	Baseline	Week 1	Monthly through pregnancy	Week 8	After delivery	Postpartum follow-up 1 (Month 1)	Postpartum follow-up 2 (Month 2)	Final Visit (12 weeks postpartum)
Informed Consent Form	X									
Demographics, medical history, & ACE	X									
Inclusion/Exclusion Criteria	X									
In-home sleep monitoring			X							X
In-lab PAP therapy night		X								
Blood draw			X			X				
Depression measures (HRSD, EPDS, C-SSRS)			X	X	X	X		X	X	X
Sleep measures (PSQI, ISI, ESS)			X	X	X	X		X	X	X
Relationship measures (RQS; PBI or MFA)			X							X
Cortisol (saliva collection)			X			X				
Sleep diary			X			X				
Actigraphy and SF12			X			X				X
Medical record abstraction (pregnancy & infant)							X			
Neonatal development assessment							X			
Ages and Stages Questionnaire-3										X
Adverse Events	X	X	X	X	X	X	X	X	X	X

6.2   Description of Evaluations

6.2.1   Screening Evaluation

Consenting Procedure

A waiver of consent is sought to allow access to potential participants' medical records prior to the eligibility interview to determine initial eligibility based on pregnancy status, current health, medical history, and medications.

Written informed consent will be obtained prior to the eligibility interview. Informed consent will be conducted by the PI or study coordinator. The informed consent document will be reviewed in detail with the potential participant, and any questions will be answered. A hard copy of the signed informed consent document will be maintained in the study's records, which will be stored in a locked cabinet in a locked office accessible only by study staff.

Screening

An initial screen will occur prior to the full eligibility interview. This screen will involve examination of potential participants' medical records and a telephone screen to determine preliminary eligibility.

The full eligibility interview includes

- Structured Clinical Interview for DSM-V (SCID)

    o Standardized, structured clinical interview to obtain information regarding current and past mental health history necessary to for diagnosis. Diagnostic criteria are based on the DSM-V. Information to be obtained includes mental health symptoms, frequency, and duration of symptoms of mood disorders, anxiety disorders, substance use disorders, eating disorders, and psychosis.

- Columbia-Suicide Severity Rating Scale (C-SSRS)

    o Structured clinician-administered interview to obtain information regarding risk for suicide.

- Medical history

    o Participants will complete a questionnaire indicating their history of medical conditions. They will also list their current medications.

    o Corroborating information will also be abstracted from participants' medical records.

- Sleep

    o Participants will complete questionnaires to assess their sleep patterns and to determine risk for sleep disorders. Questionnaires will include the Stop-Bang for SDB symptoms and questions about RLS symptoms. They will also complete a questionnaire (the Pregnancy

and Sleep Questionnaire) to characterize their sleep before and during pregnancy.

6.2.2   Enrollment, Baseline, and/or Randomization

Enrollment

Participants who meet study criteria based on the eligibility interview will be enrolled in the study. They will be randomized to condition at the time of enrollment.

Baseline Assessments

- In-home <u>overnight sleep monitoring (Watch-PAT)</u>
  - <u>Baseline sleep and sleep-disordered breathing characteristics will be assessed in participants' homes.</u> Participants will wear a watch-like device worn on the wrist (Watch-PAT) will measure sleep/wake times and blood volume changes (monitored via sensor worn on the finger).
- Participants randomized to the PAP group will complete a pre/post sleep questionnaire the night they sleep in the lab.
- Hamilton Rating Scale for Depression (HRSD)
  - The HRSD is a clinician-rated assessment of depression symptoms.
- Edinburgh Postnatal Depression Scale (EPDS)
  - The EPDS is a self-report scale of perinatal depression symptoms.
- Relationship Quality Scale (RQS)
  - The RQS is a measure of relationship quality, and assesses several different relationship domains, including love, conflict, and ambivalence.
- Maternal-Fetal Attachment Scale (MFA)
  - The MFA is a measure of maternal attachment during pregnancy. It yields several subscales, including giving of self, differentiation of self from fetus, role taking, nesting, attributing characteristics to the fetus, and interaction with the fetus.
- Pittsburgh Sleep Quality Index (PSQI)
  - The PSQI is a self-report scale of sleep quality. It assesses 7 domains of sleep (duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, medication use), in addition to a global sleep quality score.
- Insomnia Severity Index (ISI)
  - The ISI is a self-report measure of insomnia symptoms.
- Epworth Sleepiness Scale (ESS)
  - The ESS measures daytime sleepiness to assess for excessive daytime sleepiness.
- ACE – Adverse Childhood Experience Questionnaire
  - This questionnaire assesses history of adverse childhood experiences.

- SF12
  - This questionnaire measures functioning and functional impairment.
- Actigraphy
  - Sleep-wake and activity patterns will be measured using wrist actigraphy. Wrist actigraphy data are collected using a wrist-worn, watch-like device that measures light and motion.
- Daily sleep diary
  - Participants will complete approximately one week of daily sleep diaries at baseline. The diary will collect information regarding self-reported bed and wake times, sleep onset latency, wake after sleep onset, frequency of nighttime awakenings, and sleep quality. Information regarding daytime behaviors which may affect sleep, such as napping and caffeine use, will also be collected.
- Blood draw
- Cortisol
  - Salivary cortisol will be assessed in participants' homes. They will be provided with a salivary cortisol collection kit. They will use the kit to collect saliva by chewing on a salivette upon awakening, 30-45 minutes after awakening, in the afternoon (3-4 pm), and within 45 minutes before bedtime on 3 consecutive days. The kit will include an alarm system that will alert them to each saliva sample collection time. Participants will also complete a measure of daily hassles (The Hassles and Uplifts Scale) on each day of saliva collection.

6.2.3   Blinding

The study clinician will be responsible for completing the clinician rated study assessments with participants. The study clinician will be blind to participant condition. Participants will be reminded at the outset of each assessment that the study clinician is blind to their group assignment, and ask them to not reveal any information which may indicate their group.

6.2.4   Follow-up Visits

The first follow-up visit will occur roughly 1 week after study enrollment. Subsequent follow-up visits will occur at roughly monthly intervals thereafter through approximately 12 weeks postpartum. The HRSD and C-SSRS will be administered via telephone by the study clinician. The remaining measures will be completed by the participant by internet; in cases where participants do not have internet access, the measures may also be completed by mail.

Follow-up visits will include the following measures:

- Hamilton Rating Scale for Depression (HRSD)

  - The HRSD is a clinician-rated assessment of depression symptoms.
- Columbia-Suicide Severity Rating Scale (C-SSRS)

  - Structured clinician-administered interview to obtain information

regarding risk for suicide.

- Edinburgh Postnatal Depression Scale (EPDS)
  - The EPDS is a self-report scale of perinatal depression symptoms.
- Pittsburgh Sleep Quality Index (PSQI)
  - The PSQI is a self-report scale of sleep quality. It assesses 7 domains of sleep (duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, medication use), in addition to a global sleep quality score.
- Epworth Sleepiness Scale (ESS)
  - The ESS is a self-report measure of excessive daytime sleepiness.
- Insomnia Severity Index (ISI)
  - The ISI is a self-report measure of insomnia symptoms.
- Driving questions
  - To assess safety, participants will be asked if they have experienced any motor vehicle accidents or near-misses since the last assessment. Participants who report such an event will be further queried regarding the circumstances of the event to determine whether drowsiness or inattention was a factor.
- Current medications
- Breastfeeding
  - After a participants delivers their baby, we will ask them if they are breastfeeding.

The follow-up visit conducted around week 8 of the study, approximately two months after enrollment(conducted between 6-9 weeks after enrollment), will also include these additional measures:

- Actigraphy
  - Sleep-wake and activity patterns will be measured using wrist actigraphy. Wrist actigraphy data are collected using a wrist-worn, watch-like device that measures light and motion.
- Daily sleep diary
  - Participants will complete approximately one week of daily sleep diaries at baseline. The diary will collect information regarding self-reported bed and wake times, sleep onset latency, wake after sleep onset, frequency of nighttime awakenings, and sleep quality. Information regarding daytime behaviors which may affect sleep, such as napping and caffeine use, will also be collected.
- SF12 Questionnaire
- Blood draw
- Cortisol
  - Salivary cortisol will be assessed in participants' homes. They will be provided with a salivary cortisol collection kit. They will use the kit to collect saliva by chewing on a salivette upon awakening, 30-45 minutes after awakening, in the afternoon (3-4 pm), and within 45 minutes before bedtime on 3 consecutive days. The kit will include an

alarm system that will alert them to each saliva sample collection time. Participants will also complete a measure of daily hassles (The Hassles and Uplifts Scale) on each day of saliva collection.

Prior to hospital discharge following birth, participants' infants will complete a non-invasive, simple assessment focused on the infant's neurodevelopment. Following delivery, medical records of the participant and their infant will also be accessed to abstract data regarding their health; specific information to be obtained from the participant's record includes delivery type (e.g., operative or vaginal), gestational length, birth complications, and days of hospitalization. Information to be obtained from the medical record of the participant's infant include length, gender, weight, head circumference, transfer to NICU, length of hospital stay.

We will send the participant a congratulations card after the baby has been born.

6.2.5 Completion/Final Evaluation

At the final evaluation, the following measures will be completed:

- Hamilton Rating Scale for Depression (HRSD)

  - The HRSD is a validated clinician-rated assessment of depression symptoms.
- Edinburgh Postnatal Depression Scale (EPDS)
  - The EPDS is a validated self-report scale of perinatal depression symptoms.
- Brockington Postpartum Bonding Instrument (PBI)
  - The PBI is a validated self-report measure of parent-infant bonding and attachment.
- Pittsburgh Sleep Quality Index (PSQI)
  - The PSQI is a validated self-report scale of sleep quality. It assesses 7 domains of sleep (duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, medication use), in addition to a global sleep quality score.
- Insomnia Severity Index (ISI)
  - The ISI is a self-report measure of insomnia symptoms.
- Epworth Sleepiness Scale (ESS)
  - The ESS is a validated, self-report measure of excessive daytime sleepiness.
- SF12 Questionnaire
- Current medications and medical history
- Ages and Stages Questionnaire-3 (ASQ-3)
  - The ASQ-3 is a valid, brief, parent-rated measure of infant development. The measure assesses communication, gross motor, fine motor, problem-solving, and adaptive skills.
- Wear the Watch-PAT device one night at home.
- Actigraphy

- o Sleep-wake and activity patterns will be measured using wrist actigraphy. Wrist actigraphy data are collected using a wrist-worn, watch-like device that measures light and motion.
- Daily sleep diary
  - o Participants will complete approximately one week of daily sleep diaries at baseline. The diary will collect information regarding self-reported bed and wake times, sleep onset latency, wake after sleep onset, frequency of nighttime awakenings, and sleep quality. Information regarding daytime behaviors which may affect sleep, such as napping and caffeine use, will also be collected.
- Infant's medical history
  - o Information regarding the infant's medical history, including any hospitalizations. If they have been hospitalized we will get the reason why.

Participants will be offered referrals for clinical care for both depression and sleep-disordered breathing upon completion of the study.

7. STATISTICAL CONSIDERATIONS

7.1   Data Analyses

Data analysis plan for objective 1:
Linear mixed models using a repeated measures group X time (weeks of study) will be used to assess main effects and interactions for intervention and treatment week on HRSD, EPDS, PSQI, ESS scores. Logistic regression will assess for the odds of remission by treatment group. Covariates to be included in the models proposed in the analysis include maternal age, marital relationship quality, bonding, pregnancy and delivery complications, and SSRI dosage. Should other demographic characteristics differ between groups despite the minimization assignment method, these will be included as covariates.

Data analysis plan for objective 2:
Cortisol values for each time point will be averaged across the 3-day period to obtain an average for pre and post-treatment assessments. Linear mixed models using a repeated measures group X time (weeks of study) will be used to assess main effects and interactions for intervention and treatment week on cortisol. Correlations will assess the relationship between change in depression scores (HRSD, EPDS) and cortisol. Covariates to be included in the models include gestational week at assessment, marital relationship quality, BMI, and pregnancy and delivery complications.

Data analysis for secondary objective:
The effects of treatment group on gestational age at delivery, type of delivery, length of hospitalization, and neurodevelopmental score will be conducted using linear regression. Logistic regression, covaried for gestational age, will assess for the odds of failing domains on the ASQ-3 by treatment group. Covariates may include maternal education, baseline EPDS score, SSRI dose, bonding, and maternal health.

8. DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board has been established for the study. The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. Please see the DSMB's charter and Data Safety Monitoring Plan for more detail.

9. REFERENCES

Bourjeily, G., Raker, C. A., Chalhoub, M., & Miller, M. A. (2010). Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. *Eur Respir J, 36*(4), 849-855. doi: 10.1183/09031936.00021810

Brown, D. L., Anderson, C. S., Chervin, R. D., Kushida, C. A., Lewin, D. S., Malow, B. A., . . . Goldman, E. B. (2011). Ethical issues in the conduct of clinical trials in obstructive sleep apnea. *J Clin Sleep Med, 7*(1), 103-108.

Budhiraja, R., Parthasarathy, S., Drake, C. L., Roth, T., Sharief, I., Budhiraja, P., . . . Hudgel, D. W. (2007). Early CPAP use identifies subsequent adherence to CPAP therapy. *Sleep, 30*(3), 320-324.

Colvin, L., Slack-Smith, L., Stanley, F. J., & Bower, C. (2013). Are women with major depression in pregnancy identifiable in population health data? *BMC Pregnancy Childbirth, 13*, 63. doi: 10.1186/1471-2393-13-63

Di Florio, A., Forty, L., Gordon-Smith, K., Heron, J., Jones, L., Craddock, N., & Jones, I. (2013). Perinatal episodes across the mood disorder spectrum. *JAMA Psychiatry, 70*(2), 168-175. doi: 10.1001/jamapsychiatry.2013.279

Dørheim, S., Bondevik, G., Eberhard-Gran, M., & Bjorvatn, B. (2009). Sleep and depression in postpartum women: a population-based study. *Sleep, 32*(7), 847-855.

El-Sherbini, A. M. (2011). Association between obstructive sleep apnea (OSA) and depression and the effect of continuous positive airway pressure (CPAP) treatment. *Neuropsychiatric disease and treatment, 7*, 715-721. doi: 10.2147/ndt.s26341

Facco, F. L., Liu, C. S., Cabello, A. A., Kick, A., Grobman, W. A., & Zee, P. C. (2012). Sleep-disordered breathing: a risk factor for adverse pregnancy outcomes? *Am J Perinatol, 29*(4), 277-282. doi: 10.1055/s-0031-1295658

Facco, F. L., Ouyang, D. W., Zee, P. C., Strohl, A. E., Gonzalez, A. B., Lim, C., & Grobman, W. A. (2014). Implications of sleep-disordered breathing in pregnancy. *Am J Obstet Gynecol, 210*(6), 559 e551-556. doi: 10.1016/j.ajog.2013.12.035

Field, T., Diego, M., Dieter, J., Hernandez-Reif, M., Schanberg, S., Kuhn, C., . . . Bendell, D. (2004). Prenatal depression effects on the fetus and the newborn. *Infant Behavior and Development, 27*(2), 216-229. doi: http://dx.doi.org/10.1016/j.infbeh.2003.09.010

Follenius, M., Brandenberger, G., Bandesapt, J. J., Libert, J. P., & Ehrhart, J. (1992). Nocturnal cortisol release in relation to sleep structure. *Sleep, 15*(1), 21-27.

Gavin, N. I. (2005). Perinatal depression: a systematic review of prevalence and incidence. *Obstetrics and gynecology (New York. 1953), 106*(5), 1071-1083. doi: 10.1097/01.AOG.0000183597.31630.db

Habukawa, M., Uchimura, N., Kakuma, T., Yamamoto, K., Ogi, K., Hiejima, H., . . . Matsuyama, S. (2010). Effect of CPAP treatment on residual depressive symptoms in

patients with major depression and coexisting sleep apnea: Contribution of daytime sleepiness to residual depressive symptoms. *Sleep Medicine, 11*(6), 552-557. doi: 10.1016/j.sleep.2010.02.007

Henley, D. E., Russell, G. M., Douthwaite, J. A., Wood, S. A., Buchanan, F., Gibson, R., . . . Lightman, S. L. (2009). Hypothalamic-pituitary-adrenal axis activation in obstructive sleep apnea: the effect of continuous positive airway pressure therapy. *J Clin Endocrinol Metab, 94*(11), 4234-4242. doi: 10.1210/jc.2009-1174

Hollins, K. (2007). Consequences of antenatal mental health problems for child health and development. *Current opinion in obstetrics & gynecology, 19*(6), 568-572.

Hutchison, B. L., Stone, P. R., McCowan, L. M., Stewart, A. W., Thompson, J. M., & Mitchell, E. A. (2012). A postal survey of maternal sleep in late pregnancy. *BMC Pregnancy Childbirth, 12*, 144. doi: 10.1186/1471-2393-12-144

Izci, B., Vennelle, M., Liston, W. A., Dundas, K. C., Calder, A. A., & Douglas, N. J. (2006). Sleep-disordered breathing and upper airway size in pregnancy and post-partum. *Eur Respir J, 27*(2), 321-327. doi: 10.1183/09031936.06.00148204

Jomeen, J., & Martin, C. R. (2007). Assessment and relationship of sleep quality to depression in early pregnancy. *Journal of Reproductive & Infant Psychology, 25*(1), 87-99.

Ko, J. Y., Farr, S. L., Dietz, P. M., & Robbins, C. L. (2012). Depression and treatment among U.S. pregnant and nonpregnant women of reproductive age, 2005-2009. *J Womens Health (Larchmt), 21*(8), 830-836. doi: 10.1089/jwh.2011.3466

Louis, J., Auckley, D., Miladinovic, B., Shepherd, A., Mencin, P., Kumar, D., . . . Redline, S. (2012). Perinatal Outcomes Associated With Obstructive Sleep Apnea in Obese Pregnant Women. *Obstetrics & Gynecology, 120*(5), 1085-1092 http://1010.1097/AOG.1080b1013e31826eb31829d31828.

Maughan, A., Cicchetti, D., Toth, S. L., & Rogosch, F. A. (2007). Early-occurring maternal depression and maternal negativity in predicting young children's emotion regulation and socioemotional difficulties. *Journal of abnormal child psychology, 35*(5), 685-703.

Mosko, S., Zetin, M., Glen, S., Garber, D., DeAntonio, M., Sassin, J., . . . Warren, S. (1989). Self-reported depressive symptomatology, mood ratings, and treatment outcome in sleep disorders patients. *J Clin Psychol, 45*(1), 51-60.

O'Brien, L. M., Bullough, A. S., Owusu, J. T., Tremblay, K. A., Brincat, C. A., Chames, M. C., . . . Chervin, R. D. (2012). Pregnancy-onset habitual snoring, gestational hypertension, and preeclampsia: prospective cohort study. *Am J Obstet Gynecol, 207*(6), 487 e481-489. doi: 10.1016/j.ajog.2012.08.034

O'Brien, L. M., Bullough, A. S., Owusu, J. T., Tremblay, K. A., Brincat, C. A., Chames, M. C., . . . Chervin, R. D. (2013). Snoring during pregnancy and delivery outcomes: a cohort study. *Sleep, 36*(11), 1625-1632. doi: 10.5665/sleep.3112

O'Brien, L. M., Bullough, A. S., Shelgikar, A. V., Chames, M. C., Armitage, R., & Chervin, R. D. (2012). Validation of Watch-PAT-200 against polysomnography during pregnancy. *J Clin Sleep Med, 8*(3), 287-294. doi: 10.5664/jcsm.1916

O'Brien, L. M., Owusu, J. T., & Swanson, L. M. (2013). Habitual snoring and depressive symptoms during pregnancy. *BMC Pregnancy Childbirth, 13*(1), 113.

Ohayon, M. M. (2003). The effects of breathing-related sleep disorders on mood disturbances in the general population. *J Clin Psychiatry, 64*(10), 1195-1200; quiz, 1274-1196.

Okun, M. L., Luther, J., Prather, A. A., Perel, J. M., Wisniewski, S., & Wisner, K. L. (2011). Changes in sleep quality, but not hormones predict time to postpartum depression

recurrence. *Journal of affective disorders, 130*(3), 378-384. doi: 10.1016/j.jad.2010.07.015

Parcells, D. A. (2010). Women's mental health nursing: depression, anxiety and stress during pregnancy. *Journal of Psychiatric and Mental Health Nursing, 17*(9), 813-820. doi: 10.1111/j.1365-2850.2010.01588.x

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased Prevalence of Sleep-Disordered Breathing in Adults. *Am J Epidemiol*. doi: 10.1093/aje/kws342

Pien, G. W., Fife, D., Pack, A. I., Nkwuo, J. E., & Schwab, R. J. (2005). Changes in symptoms of sleep-disordered breathing during pregnancy. *Sleep, 28*(10), 1299-1305.

Poyares, D., Guilleminault, C., Hachul, H., Fujita, L., Takaoka, S., Tufik, S., & Sass, N. (2007). Pre-eclampsia and nasal CPAP: part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention. *Sleep Med, 9*(1), 15-21. doi: 10.1016/j.sleep.2007.04.019

Rich-Edwards, J. W., Mohllajee, A. P., Kleinman, K., Hacker, M. R., Majzoub, J., Wright, R. J., & Gillman, M. W. (2008). Elevated midpregnancy corticotropin-releasing hormone is associated with prenatal, but not postpartum, maternal depression. *J Clin Endocrinol Metab, 93*(5), 1946-1951. doi: 10.1210/jc.2007-2535

Roest, A. M., Carney, R. M., Stein, P. K., Freedland, K. E., Meyer, H., Steinmeyer, B. C., . . . Rubin, E. H. (2012). Obstructive sleep apnea/hypopnea syndrome and poor response to sertraline in patients with coronary heart disease. *J Clin Psychiatry, 73*(1), 31-36.

Schmoller, A., Eberhardt, F., Jauch-Chara, K., Schweiger, U., Zabel, P., Peters, A., . . . Oltmanns, K. M. (2009). Continuous positive airway pressure therapy decreases evening cortisol concentrations in patients with severe obstructive sleep apnea. *Metabolism, 58*(6), 848-853. doi: 10.1016/j.metabol.2009.02.014

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med, 7*(3), e1000251. doi: 10.1371/journal.pmed.1000251

Sit, D., Perel, J. M., Wisniewski, S. R., Helsel, J. C., Luther, J. F., & Wisner, K. L. (2011). Mother-infant antidepressant concentrations, maternal depression, and perinatal events. *J Clin Psychiatry, 72*(7), 994-1001. doi: 10.4088/JCP.10m06461

Skouteris, H., Germano, C., Wertheim, E., Paxton, S., & Milgrom, J. (2008). Sleep quality and depression during pregnancy: a prospective study. *Journal of sleep research, 17*(2), 217-220.

Skouteris, H., Wertheim, E. H., Germano, C., Paxton, S. J., & Milgrom, J. (2009). Assessing sleep during pregnancy: a study across two time points examining the Pittsburgh Sleep Quality Index and associations with depressive symptoms. *Womens Health Issues, 19*(1), 45-51. doi: 10.1016/j.whi.2008.10.004

Spath-Schwalbe, E., Gofferje, M., Kern, W., Born, J., & Fehm, H. L. (1991). Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. *Biol Psychiatry, 29*(6), 575-584.

Swanson, L. M., Flynn, H., Adams-Mundy, J. D., Armitage, R., & Arnedt, J. T. (2013). An open pilot of cognitive-behavioral therapy for insomnia in women with postpartum depression. *Behav Sleep Med, 11*(4), 297-307. doi: 10.1080/15402002.2012.683902

Treasure, T., & MacRae, K. D. (1998). Minimisation: the platinum standard for trials?. Randomisation doesn't guarantee similarity of groups; minimisation does. *BMJ, 317*(7155), 362-363.

Vgontzas, A. N., Pejovic, S., Zoumakis, E., Lin, H. M., Bentley, C. M., Bixler, E. O., . . . Chrousos, G. P. (2007). Hypothalamic-pituitary-adrenal axis activity in obese men with and without sleep apnea: effects of continuous positive airway pressure therapy. *J Clin Endocrinol Metab, 92*(11), 4199-4207. doi: 10.1210/jc.2007-0774

Weinstock, M. (2005). The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain Behav Immun, 19*(4), 296-308. doi: 10.1016/j.bbi.2004.09.006

Wolfson, A., Crowley, S., Anwer, U., & Bassett, J. (2003). Changes in sleep patterns and depressive symptoms in first-time mothers: last trimester to 1-year postpartum. *Behavioral sleep medicine, 1*(1), 54-67.

Yonkers, K. A. (2011). Diagnosis, pathophysiology, and management of mood disorders in pregnant and postpartum women. *Obstetrics and gynecology (New York. 1953), 117*(4), 961-977. doi: 10.1097/AOG.0b013e31821187a7

Young, E. A., Altemus, M., Lopez, J. F., Kocsis, J. H., Schatzberg, A. F., DeBattista, C., & Zubieta, J. K. (2004). HPA axis activation in major depression and response to fluoxetine: a pilot study. *Psychoneuroendocrinology, 29*(9), 1198-1204. doi: 10.1016/j.psyneuen.2004.02.002

Young, T., Palta, M., Dempsey, J., Peppard, P. E., Nieto, F. J., & Hla, K. M. (2009). Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. *WMJ, 108*(5), 246-249.

Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S., & Badr, S. (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med, 328*(17), 1230-1235. doi: 10.1056/nejm199304293281704