Preventing Postpartum Depression: A Dyadic Approach Adjunctive to Obstetric Care

NCT03283254

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STUDY PROTOCOL

CONSENT:

Consent is obtained by those study staff with a Bachelor's degree or higher, who passed all necessary CITI training, and are IRB-approved to obtain consent. A link to the consent form is sent to the participant prior to the consent session. Consent forms are either signed in-person on paper copies or are signed electronically via REDCap by both the potential participant and the research staff obtaining consent. Potential participants are emailed the link to the electronic consent form prior to the virtual consent session, which they can access with any device that can connect to the internet. The Redcap consenting record is updated to contain the most recent IRB-approved and stamped Consent and HIPAA forms. All potential participants are asked if they give additional, optional consent to have their participation in the study filmed for use in front of a professional audience. If participants give consent to be filmed, they are provided with an additional consent form addendum. An informed Consent Form is sent via an alert which is logged, time-stamped & encrypted when the "protect mode" is turned on. The risks related to a loss of confidentiality when using electronic devices to transmit, store, and/or access the Consent Form and HIPAA forms are outlined in the Consent Form and discussed during the consent process. Additionally, the possibility that data could be accessed by others, should the participant lose their electronic device, lend the device to other people, or if the device is subject to a search warrant or subpoena, is described to the participant during the consenting session. All participants who sign via REDCAp, are offered the option to receive the consent and HIPAA forms as hard copies via the mail if requested.

SCREENING

PHASE 1 OF SCREENING

Phase 1 of screening is conducted via telephone by a CITI trained research assistant to determine if participants meet the initial inclusion and exclusion criteria listed below. The results are entered in REDCap, an online secure database. All information entered in Redcap is de-identified using a screen ID. Any identifying information is entered in a password-protected Excel document on our server.

Inclusion and Exclusion Criteria: Participants are screened at 20-29 weeks gestation

Inclusion:

1. Healthy pregnant women between 18-45 years old [phone screen, self report]:
2. A healthy, singleton pregnancy [phone screen, self report]
3. Fluent English speaker [phone screen, self report]
4. Receiving standard prenatal care [phone screen, self report]
5. A score of 19 or greater on the Predictive Index of Postnatal Depression (PIPD), indicating risk for developing postpartum depression; or score of 7 or greater on the Edinburgh Postnatal Depression Scale (EPDS). [phone screen, assessment administered by trained staff]

Exclusion:

1. Multi-fetal pregnancy [phone screen, self report]
2. Illicit drug use, alcohol use during pregnancy [phone screen, self report]
3. Acute medical illness or significant pregnancy complication [phone screen, self report]
4. Currently in weekly, individual psychotherapy, including psychopharmacology [phone screen, self report]
5. Psychotic d/o; Bipolar I; Major Depressive Disorder [phone screen, MINI assessment and clinical interview administered by trained clinicians] (Determined in Phase 2 of Screening)

If eligible based on the initial phone screen, participants are asked to participate in a follow-up screening session, either by telephone or via HIPAA compliant video call to assess the final IRB approved exclusion Criteria (which are determined by the clinical interview and MINI assessment, which is administered by a licensed clinician or an unlicensed clinician under licensed supervision.

PHASE 2 OF SCREENING

The potential participant is first consented for this screening session. If consented, the potential participant undergoes a screening conducted by both the research assistant and a licensed clinician or an unlicensed clinician under licensed supervision.

The potential participant then meets virtually with a licensed clinician or an unlicensed clinician under licensed supervision who conducts a clinical interview and a standardized assessment

(MINI) to screen for psychosis, major depressive disorder, and bipolar disorder. Participants that meet criteria for any of those disorders are not enrolled in the study, but the clinician is to proceed by: (1) making an immediate appropriate referral, or (2) arranging for an immediate psychiatric evaluation.

Information collected during the screening procedure was used to confirm eligibility based on the IRB approved inclusion and exclusion criteria. The screening and the screening results were reviewed and approved by the PI.

Baseline Assessment (20-29 weeks gestation):

A trained research worker will administer the Hamilton Anxiety Scale (HAM-A) and Hamilton Depression Scale (HAM-D) to the participant.

Prenatal Session 1 (28-32 weeks gestation)

At this time point, if the individual agrees to participate in this session and gives consent, the individual is randomly assigned to one of two groups: Intervention vs. Enhanced Treatment As Usual (ETAU). When the participants are 28-32 weeks pregnant, they participate in an in-person session (pre-COVID) or in a virtual session (during COVID), either by phone or video call, and are asked to complete mood assessments, a cognitive assessments and answer questionnaires about feelings, life events, and sleep. Participants are asked a questionnaire about the effect of COVID-19 on their lives. In total, these questionnaires take about 90 minutes. All questionnaire results are entered in Redcap, an online secure database. All information entered in REDCap is de-identified using a screen ID. At home, we ask participants to wear an activity monitor for 7 full 24-hour days. We ask participants to complete a sleep diary noting sleep times and durations for the seven consecutive days they are wearing the activity monitor.

Prenatal Session 2 (34-39 weeks)

At 34-39 weeks gestation, participants have another session (in-person if pre-COVID or virtual if during COVID), and complete mood assessments, a cognitive assessment, and answer more questions about feelings and sleep. This session takes about 75 minutes. They are asked to wear the activity monitor again for 7 days and complete a sleep diary (5-10 minutes to complete).

All participants are provided with psychoeducation (and an information sheet) that highlights the warning signs of depression and the risks of depression and contact information for research staff so that they can access help and referrals if they begin to experience depression. All participants (regardless of group assignment) are encouraged to contact the study clinician at any point during the study if they are interested in a referral for treatment.

Newborn Session (18-36 hours post-delivery)

Participants are invited to have their newborn participate in an EEG sleep study that occurs between 18-36 hours after birth in the newborn nursery. We will examine variation in EEG left/right power asymmetry in relation to potential group differences in the effectiveness of the intervention in helping mothers function as a social "buffer" and modulate infant reactivity. The newborn EEG sleep protocol takes place in the newborn nursery while the baby is sleeping. This is a non-clinical EEG recording. A cap with EEG sensors is placed on the newborn's head by a trained member of the research team. The research team then waits for the baby to enter a state of quiet sleep. This allows the research team time to measure brain activity while the baby sleeps. The participant is reassured by the research team that although the sensors may leave a slight red mark for a brief time after they are removed, this procedure is completely painless and does not harm the newborn.

The EEG session takes approximately 30 minutes. This session is video recorded to allow the researchers to collect information about newborn behavior during the session. In total, including setup of materials and video-recording, the session is approximately 1.5 hours in duration.

The participant is allowed extra time to pick up, feed, comfort, or change the newborn to accommodate fussiness or discomfort at any time during the EEG. If the participant is uncomfortable with the EEG, they were free to stop the session.

If the participant gives birth prior to 37 weeks, they do not complete this EEG session with their newborn. The participant is still be able to proceed with the rest of the study. Participants did not complete this session during the COVID pandemic.

6-Week Postpartum Session

At 6 weeks postpartum, participants are asked to participate in another session (in-person if pre-COVID or virtual if during COVID), to complete mood assessments. This session is about an hour. During this session, participants are videotaped as they engage in a standard routine of infant care. This takes about 5 minutes to complete.

If the session is completed in-person (not virtually), participants are invited to complete the infant EEG. We will examine variation in EEG left/right power asymmetry in relation to potential group differences in the effectiveness of the intervention in helping mothers function as a social "buffer" and modulate infant reactivity. The 6-week postpartum EEG sleep protocol takes place while the baby is sleeping. This is a non-clinical EEG recording. A cap with EEG sensors is placed on the newborn's head by a trained member of the research team. The research team then waits for the baby to enter a state of quiet sleep. This allows the research team time to measure brain activity while the baby sleeps. The participant is reassured by the research team that although the sensors might may leave a red mark briefly after they are removed, this procedure is completely painless and does not harm the newborn.

The EEG session takes approximately 30 minutes. This session is video recorded to allow the researchers to collect information about infant behavior during the session. In total, including setup of materials and video-recording, the 6-week EEG session is approximately 1.5 hours in duration.

The participant is allowed extra time to pick up, feed, comfort, or change the infant to accommodate fussiness or discomfort at any time during the EEG. If the participant is uncomfortable with the EEG, they are free to stop the session.

Participants wear an activity monitor again for 7 full days. While wearing the monitors, participants complete a sleep diary noting sleep times and durations, which takes about 5-10 minutes. Participants in the treatment group are asked to complete a diary entry that asks them the frequency and duration of their utilization of the skills learned from PREPP (i.e., carrying/holding baby, accentuation of day/night cues, focal feeding, use of swaddling,

mindfulness techniques). These questions take about 10 minutes to complete. Infant sleep is assessed using a Smart Sleep Sensor worn by the infant. The Sensor detects day and night sleep activity by recording activity patterns during the time intervals in which it is worn. Infants wear the Sensor for four days (24- hour periods).

12-Week Phone Session

At 12 weeks postpartum, participants complete mood assessments over the phone. This takes about an hour to complete.

16-Week Postpartum Session

At 16 weeks postpartum, participants are asked to participate in a final session (in-person if pre-COVID or virtual if during COVID) to complete mood assessments and other questions related to feelings, life events, and sleep. Participants are asked again to complete a questionnaire about the effect of COVID-19 on their lives (if during COVID pandemic).

All together, these questionnaires take an hour to complete. Participants are asked to sit on the floor and play with their baby using a set of toys they usually use at home. They are asked to engage in free play for 10 minutes, and their play interaction is videorecorded and later coded using the Emotional Availability (EA) Scales. Mothers and infants are also asked to participate in a modified 'double' Still Face Protocol (SFP), an A-B-A-B-A design with alternating free-play (A) and still-face (B) periods. The entire SFP session is videotaped for later behavioral coding. The session begins with five minutes of face-to-face free play, followed by a two-minute still-face episode. Two additional free-play periods and a second still-face episode, each lasting two minutes, follows. A study coordinator signals transitions by saying "Switch". If the infant cries for more than 30 seconds or intensely for over five seconds, the session is stopped so the mother can comfort the infant. The full procedure lasts about 20 minutes. Frequency of infant positive affect, signs of avoidance (infant head turn and back arch), and duration of infant distress/crying and neutral/positive vocalizations will be coded. Mothers will be coded for duration of vocalizations to the infant, touching the infant, and positive/negative affect.

During this session, participants are also videotaped as they engage in a standard routine of infant care. This takes about 5 minutes to complete.

For a final time, participants wear the activity monitor again for 7 days. Participants complete a sleep diary noting sleep times and durations, which takes them 5-10 minutes to complete. Participants in the treatment group complete a diary entry asking them about the frequency and duration of their utilization of PREPP skills. Infant sleep is assessed using a Smart Sleep Sensor worn by the infant. The Sensor detects day and night sleep activity by recording activity patterns during the time intervals in which it is worn. Infants wear the Sensor for four days (24- hour periods).

Table

Session	**Task**	**Time Commitment**
Prenatal: 28-32 weeks	Questions about mood and COVID-19, cognitive assessment	90 minutes
Prenatal: 34-39 weeks	Questions about mood, cognitive assessment	75 minutes
Newborn: 18-36 hours	Infant EEG	1.5 hours
Postpartum: 6 weeks	Questions about mood, cognitive assessment, infant care routine, Infant EEG	2.5 hours
Postpartum: 12 weeks (on the phone)	Questions about mood and cognitive assessment	60 minutes
Postpartum: 16 weeks	Questions about mood and COVID-19, cognitive assessment, Infant care routine, Mom/Baby play	2.5 hours

Baby Day Diaries

At 6 and 16 weeks postpartum, mothers are asked to complete four consecutive days of 24-hour diaries describing infant and parental behavior (the Baby Day Diary). The diaries allow for notation of infant cry, fuss, and awake-content, feeding and sleeping activity. Caregiving behavior is also noted, including; changing, bathing, dressing, holding/carrying and playing/talking behaviors as well as their own sleep periods. Baby diaries take about 30 minutes to complete.

List of Instruments and Standardized Protocols:

Data Collection Instrument	Screening (20-29 weeks)	Prenatal 1 (28-32 weeks)	Prenatal 2 (34-39 weeks)	Newborn	6 week	12 week	16 week
Demographics		X	X		X	X	X
Newborn Delivery Data				X			
Pregnancy Medical History	X						

Predictive Index of Postnatal Depression (PIPD)	X						
Mini International Neuropsychiatric Interview (MINI)	X						
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X		X	X	X
Edinburgh Postnatal Depression Scale (EPDS)	X	X	X		X	X	X
Hamilton Anxiety Scale (HRSA)	X	X	X		X	X	X
Hamilton Depression Scale (HRSD)	X	X	X		X	X	X
Personal Health Questionnaire-9 (PHQ-9)		X	X		X	X	X
Pittsburgh Sleep Quality Index (PSQI)		X	X		X	X	X
Pregnancy Physical Activity Questionnaire (PPAQ)		X	X				
Family History Screen (FHS)			X				
Adverse Childhood Experiences Questionnaire (ACE)		X					
Benevolent Childhood Experiences scale (BCEs)		X					
The Hunger Vital Sign (HVS)		X	X		X		X
Experiences in Close Relationships (ECR)		X					
Childhood Trauma Questionnaire (CTQ)		X					
Multidimensional Scale of Perceived Social Support Questionnaire (MSPSS)		X			X		
Maternal Antenatal Attachment Scale (MAAS)			X				
Abbreviated Brief Infant Sleep Questionnaire (BISQ)					X		X
Childcare Arrangement Scale (CAS)					X		X
Infant Intentionality Questionnaire (IIQ)					X		X
Infant Nutrition Questionnaire (INQ)					X		X
Karitane Parenting Confidence Scale (KPCS)					X		X
Short Acculturation Scale for Hispanics (SASH)			X				
Experiences of Discrimination (EOD)			X				

Adult Attachment Questionnaire (AAQ)		X	X				
Maternal Postnatal Attachment Scale (MPAS)					X		X
Being a Mother (BaM-13)							X
Parental Bonding Instrument for Mothers (PBI-M)		X	X				
Parental Bonding Instrument for Fathers (PBI-F)		X	X				
Rejection Sensitivity Questionnaire (RSQ)		X					
Difficulties in Emotion Regulation Scale (DERS)		X	X		X		
Interpersonal Support Evaluation List (ISEL)		X					
COVID-19 Questionnaire		X					X
Utilization of PREPP Skills		X	X		X		X
Infant EEG				X	X		
Adult Activity Monitor		X	X		X		X
Sleep Log		X	X		X		X
Infant Smart Sleep Sensor					X		X
Baby Day Diary					X		X
Infant Care Routine, video					X		X
Modified 'double' Still Face Protocol, video (SFP)							X
Free Play, Video							X

Treatment Protocols:

Experimental Arm: PREPP Intervention

The intervention is carried out at 5 timepoints, Session 1 at 28-32 gestational weeks, Session 2 at 34-39 gestational weeks, Session 3 at 6 weeks postpartum, Check-In Session 1 within 3 days of the birth and at Check 2 Session at 2 weeks postpartum. These sessions are scheduled to coincide with standard medical visits (3rd trimester ultrasounds and 6-Week Well Baby visit), which enable us to test the feasibility of incorporating these sessions into routine medical care. A licensed trained clinician or an unlicensed trained clinician under licensed supervision provide the intervention. The sessions of this preventive psychotherapy are comprised of three

components: (a) mindfulness and self-reflection skills, (b) parenting skills and (c)psycho-education. The intervention protocol encompasses the following 5 specific established behavioral techniques: (1) feeding the infant between 10 pm and midnight, even if s/he must be awakened (‘a focal feed’); (2) accentuating differences between day and night cues so that there are higher levels of stimulation during the former than the latter; (3) assuming adequate weight gain is reached by 3 weeks, lengthening the latency to feeding time in the middle of the night by engaging in other attentive activities such as walking with the baby and diapering; the goal is to lengthen the nighttime feeding intervals by extinguishing the association between night time waking and feeding; (4) carrying infants for a minimum of 3 hours a day, throughout the day, independent of responding to crying, carrying during feeding, and whether the baby is awake; and (5) learning to swaddle the baby as a possible soothing intervention. Mindfulness-based tools are provided with the aim to (1) aid them to return to sleep after waking at night, (2) help them to cope better when their babies are distressed or unsoothable. These mindfulness exercises are provided as audio files via an App.

Active Comparator: Enhanced Treatment As Usual (ETAU):

ETAU comprises Postpartum Depression psychoeducation, mood assessments, and referral for treatment if needed or requested by the participant. Three sessions are delivered by licensed trained clinician or an unlicensed trained clinician under licensed supervision. Participants receive "usual care" along with Postpartum Depression psychoeducation and enhanced support for finding perinatal mental healthcare treatment when appropriate by meeting with a study clinician specifically assigned to provide ETAU in this study at three times that are aligned with PREPP sessions that span from pregnancy to 6 weeks postpartum. At the first contact, participants meet with their assigned ETAU clinician and are given information about PPD, a brief clinical mental health assessment, and a referral for treatment if warranted or requested; the second session is a follow-up mental health clinical assessment with the study clinician and a referral for treatment if warranted or requested; at the third session, participants meet again with their study clinician and receive a mental health assessment, review relevant psychoeducation on PPD and are referred to treatment when appropriate.

Statistical Analysis Plan

Overall. Based on preliminary data, we anticipate minimal attrition (≤5%) during the first two assessment sessions (pre-delivery), and up to 33% attrition postpartum across both groups in the worst-case scenario. All participants with data available for a given study phase (pre- or postpartum) will be included in the primary analyses. Before conducting hypothesis tests, we will screen all variables at all time points for out-of-range values, outliers, and data inconsistencies. Means, standard deviations, interquartile range, minima, and maxima for continuous variables and proportions for categorical variables will be reported.

Following CONSORT guidelines, the primary analyses for all aims will follow an intention-to-treat (ITT) approach, including all randomized participants regardless of treatment adherence or dropout. If significant imbalances in baseline covariates (e.g., maternal age, BMI, birth order, infant sex) are observed despite randomization, these variables will be included as covariates in the models. Additional exploratory models will examine relevant biological factors, such as maternal BMI, fetal/infant sex, maternal age, infant gestational age at birth, and birthweight corrected for birth age, as potential covariates.

Aim 1. Reduce women's distress during pregnancy. We hypothesize that PREPP will be associated with: (A) Diminished depressive symptoms using interviewer-rated and self-report questionnaires; (B) Improved perception of sleep quality relative to objective changes in sleep duration (per self report and actigraphy).

Analysis for Aim 1A: For depressive symptom outcomes (HRSD, PHQ-9, HRSA, PSQI, EPDS), we will fit linear mixed-effects models with fixed effects for Treatment (PREPP vs. ETAU), Time (2nd and 3rd assessments), and birth order, along with subject-specific random intercepts. For EPDS, we will adjust for the screening score and test a Treatment × Screening Score interaction as a secondary analysis. Additional moderators will also be tested.
Analysis for Aim 1B: Two ActiGraph-derived measures, total sleep time (TSTact) and sleep efficiency (SEact), will serve as outcomes in separate mixed-effects models with fixed effects for time and day (within the ActiGraph epoch) and subject-specific random intercepts, assuming an AR(1) correlation structure. We will assess whether adjustment for weekday/weekend is warranted. Subject-specific means of these measures will be used as predictors of their subjective

counterparts (TSTact, SEact) in additional mixed models testing for treatment group differences in the association between objective and subjective sleep measures. Moderation by trauma history and attachment will be explored.

Aim 2. Determine the maintenance of improved maternal mood and differences in infant behavior. We hypothesize that PREPP will be associated with: (A) Lower rates of PPD and distress, including poor sleep efficiency, assessed by interviewer-rated and self-report questionnaires as well as sleep actigraphy. (B) Less infant fuss/cry behavior and longer nocturnal sleep bouts based on maternal report and actigraphy.

Analysis for Aim 2A: Separate linear mixed-effects models will be used for each maternal mood outcome (PHQ-9, HRSD, EPDS, HRSA, PSQI) and ActiGraph-derived sleep measures. Models will include Treatment, Time (6, 12, and 16 weeks postpartum), and their interaction, with baseline (pregnancy) values as covariates. Subject-specific random intercepts will be included. The primary parameter of interest is the Treatment × Time interaction; if non-significant, the main effect of Treatment will be tested. PPD diagnosis will be modeled using mixed-effects logistic regression with analogous fixed effects.
For infant outcomes (6 and 16 weeks), linear mixed-effects models will assess Treatment effects without Time × Treatment interaction. Sleep data will be processed as in Aim 1B. Covariates include time-varying factors such as weaning, solid food introduction, maternal return to work, and social support. Moderators (infant sex, trauma history, attachment) will also be assessed.
Analysis for Aim 2B: Infant sleep and cry behavior at 6 and 16 weeks will be compared using mixed-effects models with Treatment, Time, and their interaction as fixed effects. Covariates and secondary analyses will be same as those in Aim 2A.

Aim 3. Identify some of the pathways by which PREPP positively affects the dyad. We hypothesize that PREPP-associated: (A) Lower depression scores postpartum will be mediated by concurrent and/or temporally earlier maternal reports of less infant fuss/cry behavior and higher parenting competence; (B) Less infant fuss/cry behavior will be mediated by fewer concurrent and/or temporally earlier negative infant attributions and higher concurrent observed maternal sensitivity; (C) More positive perceptions and objective assessments of maternal

postpartum sleep efficiency will be mediated by greater infant left frontal EEG power reflecting sleep spindle activity and associated longer average durations of infant nocturnal sleep per maternal report and actigraphy.

Analysis for Aim 3: Structural equation models will be used to test multiple-mediation. The mediation and Lavaan R packages will be used for this modeling as it can accommodate both continuous and ordered categorical (including dichotomous) variables. Indirect effects (i.e. combined mediational pathways) will be tested using the bootstrapping with 10000 resampling. Specifically for Aim 3A, we will test whether the effect of PREPP on maternal depressive symptoms at week 16 is mediated by infant fuss/cry behavior and higher parenting competence assessed at 6 and 16 weeks after delivery. A model without inclusion of week 16 mediators will also be considered (due to the contemporaneousness of week 16 with the outcome). For Aim 3B, the primary outcome is infant fuss/cry behavior at week 16 and mediators are the maternal reports of negative infant attribution assessed at 6 and 16 weeks after delivery and maternal sensitivity at week 16 after delivery. Because of the concurrently observed mediators and outcomes, alternative mediational pathways will be evaluated and compared. For Aim 3C, a mediation model with EEG power at week 6 and avg. infant sleep (actigraphy) quality will be assessed as mediators of the treatment effect on maternal sleep at week 16, controlling for EEG power at birth as a covariate.

Power analysis We adjusted for multiple comparisons (five primary outcomes across Aims 1 and 2) using Bonferroni correction, resulting in a significance threshold of 0.01. For Aim 1, with N = 214 and an assumed 5% attrition, our mixed-effects model analysis is powered to detect a minimum effect size of d = 0.48 (assuming within-subject correlation r = 0.2). Prior research has shown larger effects (e.g., d = 0.85 for EPDS in mindfulness-based therapy), indicating our design has ample power. For Aim 2, assuming 33% attrition and five primary outcomes, power calculations show that N = 107 per group is sufficient to detect interactions as small as d = 0.087 with 80% power at a Bonferroni-adjusted $\alpha = 0.01$. Our preliminary data support this assumption. For Aim 3, based on tabulated recommendations 184 for sample sizes needed to test mediation effects, with N=142 completers (assuming 33% attrition for assessments), we have more than 80% power to detect a significant mediation effect with moderate effect sizes (d=0.54,

r=0.26) of both paths (i.e. the paths from treatment to the mediator(s) and the mediator(s) to outcomes). Since the full sample (N = 214) will be used in mediation models, the actual power will exceed this estimate.