Mommy-Baby Treatment for Perinatal Depression

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A Randomized Controlled Trial of IPT-Dyad treatment for Perinatal Depression
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Overview

Perinatal depression is a major public health problem, affecting 15 % of women during pregnancy through the postpartum period, with adverse consequences for the mother, the fetus, the infant, and the family. Despite increasing evidence of the importance of this critical risk interval, there is a paucity of research investigating the effects of depression treatment initiated during pregnancy on infant outcomes. Recent findings suggest the need for robust, integrated peripartum depression treatments that target maternal depressive symptoms, parenting skills, and the mother-infant relationship.

A treatment manual for a new intervention, Interpersonal psychotherapy for the mother-infant dyad (IPT-Dyad), was developed based upon an established psychotherapeutic treatment for depression (Interpersonal Psychotherapy). This intervention begins during pregnancy and continues with the mother and infant until one year post-partum. The purpose of this study is to test the feasibility, acceptability, and effectiveness of this new intervention in a small randomized controlled trial. We will enroll approximately 40 patients aged 18 and older, pregnant, with depressive disorders. We will treat them with 20-22 sessions of psychotherapy for a period of 14-18 months (depending on gestational weeks at enrollment).

We will assess acceptability and feasibility of the intervention. Maternal depressive symptoms, psychosocial functioning, parenting self-efficacy will be assessed as well as mother-infant relationship quality and infant emotional development. A small subsample (n=10) of infants will participate in a MRI brain scan to generate pilot data regarding mechanisms of psychotherapy effectiveness on infant outcomes.

Background:

Perinatal depression is a major public health concern: Perinatal depression refers to depressive disorders that occur during pregnancy through the first postpartum year. As many as 18% of pregnant women experience depressive symptoms and 13-15% develop a major depressive episode during pregnancy through the first three months postpartum. Incidence of perinatal depression is higher in low income, minority populations, with rates ranging from 24% to 47%. Depression during pregnancy is associated with increased risk of miscarriage, pre-term birth, low birth weight, small for gestational age babies, gestational hypertension, and preeclampsia. It may also lead to poor adherence to prenatal care, poor self care, and other unhealthy lifestyle choices, including nicotine, alcohol, and drug use. At least 50% of women who are depressed antenatally remain depressed postpartum: detection and treatment that integrates pre

and postnatal periods is imperative to decrease the burden of illness on mothers and their children.

Consequences of Perinatal Depression on Infant Development: The effects of maternal depression are evident in early infancy across a range of domains. Infants of depressed mothers display more negative affect, show less secure attachment relationships, and experience difficulties in emotion regulation. Such infants show abnormalities in frontal EEG patterns and neurotransmitter levels, patterns which remain stable from one week to at least three years of age. An important potential mechanism for intergenerational risk transmission of depression is the infant's inability to regulate emotions. This involves a combination of innate and environmental elements, with parenting behaviors a key factor. Infants may be particularly vulnerable to the effects of maternal depression because of their immature neuroregulatory abilities and reliance on mother for external emotional regulation. The mother's inability to model self-regulatory strategies and to provide external regulation for the infant may increase the stress of the maternal-infant interaction while also not providing the infant with the needed comfort and support. Therefore, treatment for maternal depression should address these impairments in the mother-infant dyad to enhance infant emotion development and decrease risk for later psychopathology.

Early intervention is critical: There is substantial evidence that the developmental trajectory towards health or disease is encoded during the fetal stage. Prenatal stress via maternal depression is one such stressor thought to alter the intrauterine environment. Processes underlying emotion regulation and attention seem to be particularly sensitive to prenatal stressors. Given these recent developments in both animal and human models, there is increasing evidence of the need for the earliest possible intervention or prevention efforts.

The overall level of "exposure" to depressive symptoms over the course of pregnancy is the most robust predictor of neonatal behavior. Maternal depressive symptoms in the first few months of an infant's life have greater developmental consequences than maternal depressive symptoms experienced during toddler or later stages. Therefore, an integrated treatment of depression during the perinatal continuum has the potential to influence prenatal psychosocial risk factors (health behaviors, social support), prenatal physiological risk factors (HPA-axis regulation), and postnatal risk (parenting, health behaviors, social support). Despite increasing evidence of the importance of this critical risk interval, there is a paucity of research investigating the effects of depression treatment initiated during pregnancy on infant outcomes.

Effective interventions for perinatal depression: Few randomized trials have investigated the efficacy of antenatal treatment of maternal depression. Use of antidepressant medications during pregnancy involves risks and many women prefer psychotherapy. Cognitive Behavioral Therapy (CBT) has been used successfully to treat or prevent postpartum depression. Few studies have investigated CBT for treatment of depression during pregnancy.

Another evidence-based treatment, Interpersonal Psychotherapy (IPT), is recognized as an ideal psychosocial treatment for depression during the perinatal period. IPT focuses on four problem areas that are related to disruptions in social support networks and communications with others: grief, role disputes, role transitions, and interpersonal deficits. As perinatal depression is often associated with lack of social

support from partner or families, as well as life changes resulting from pregnancy and parenthood, IPT is well suited to address perinatal depression and has been shown to be an efficacious treatment of peri and postpartum depression. It can be difficult to engage pregnant women, especially low-income or minority women, into treatment for depression. In an effort to address some of the barriers associated with psychotherapy, Swartz and colleagues developed a brief eight-session form of IPT (IPT-B). Building upon this model, Grote and colleagues developed a multicomponent model of depression care, "Enhanced IPT-B", which includes a pre-treatment engagement interview (designed to address psychological and cultural barriers to care), 8 prenatal sessions of IPT, and pragmatic case management (i.e., bus passes, child care, and free baby supplies). In a recent RCT with low-income, depressed, pregnant women, those who received Enhanced IPT-B were more likely to show improvements in depressive symptoms and social functioning than women in usual care. These results suggest that this is an effective treatment for perinatal depression in a difficult to engage, non-treatment seeking population.

Parent-Infant Psychotherapies: One of the best-known mother-infant psychotherapies, Infant-Parent Psychotherapy (IPP) focuses on identifying negative experiences of being parented that may be influencing a mother's ability to be emotionally available to her child and to parent effectively – often referred to as the "ghosts in the nursery". Examples of other interventions designed to improve parent-child relationships are Watch, Wait, and Wonder, Keys to Caregiving, and Circle of Security. Although these interventions are effective in improving the quality of the mother-infant relationship, they were not designed to address maternal depression. For example, IPP alone had no effect on maternal depression scores in a study of toddlers of depressed mothers. Recently, interventions have been developed to improve maternal depressive symptoms as well as the mother-infant relationship. For example, M-ITG, a multicomponent group intervention for postpartum depression focused on mother-infant and family relationships, was effective in treating maternal depressive symptoms and increasing positive affective involvement with infants. Van Doesum and colleagues developed a home-visiting intervention that included cognitive restructuring, education, and infant massage; however, there were no significant reductions in depressive symptoms in comparison to the telephone support control group. Currently, Toth and colleagues are investigating the efficacy of IPT plus Infant-Parent Psychotherapy (beginning at one year of age) in preventing emergent psychopathology in the offspring of low-income depressed mothers. Altogether, these results suggest that dyadic interventions hold promise in reducing maternal depressive symptoms and enhancing mother-infant relationships. Much work remains as these treatments have not been initiated in the potentially critical interval of pregnancy or the immediate postpartum period, and applicability to newborns or young infants is unknown. The intervention proposed in the current project would begin during pregnancy thereby improving the new mother's ability to engage in effective mother-infant interactions and enhance the infant's emotion development.

Providing for the Needs of Mother and Infant with IPT: While some studies suggest postpartum depression treatment benefits mother-infant interactions, others have failed to find such benefits or beneficial effects on attachment security, cognitive development, or emotionality. These findings support the need for a more robust, integrated

peripartum depression treatment that targets parenting skills and the parent-infant dyad in addition to maternal depressive symptoms. Therefore, integrating principles of infant-parent psychotherapy into IPT, during a key window of risk, represents a novel and efficient approach to perinatal depression care. This type of dyadic therapy can be readily incorporated into IPT. Primary goals of IPT treatment are to help restore self-esteem by developing a sense of mastery over a new role and improving communication strategies and skills, thus making it an ideal treatment for reducing maternal insecurity and isolation. Interpersonal communication skills are the foundation of mother-infant relationship development and infant emotional regulation. By enriching IPT in the postpartum phase of the perinatal period with interactive mother-infant exercises, the IPT therapist is able to explore and directly target this new mother-infant dyad *in vivo*. Enhancements specific to the maternal-infant relationship and maternal attunement to the infant will advance our abilities to treat perinatal depression and prevent intergenerational transmission.

Research Objectives:
The purpose of this study is to examine feasibility, acceptability, and effectiveness of Interpersonal Psychotherapy for the Mother-Infant Dyad (IPT-Dyad) for women who experience depression during the perinatal period. We will assess maternal depressive symptoms, psychosocial functioning, and mother-infant relationships before, during, and after a course of IPT-Dyad. Data will be utilized to further refine and subsequently perform a large scale trial of this adapted psychotherapeutic intervention for perinatal depression.

Primary Aims:

1) Conduct a preliminary RCT comparing IPT-Dyad versus enhanced treatment as usual (TAU) in 40 women with antenatal depression to establish feasibility.
    Hypothesis: IPT-Dyad will be better than TAU in:
        a) Reducing antenatal depressive symptoms
        b) Preventing postpartum depression relapse
        c) Improving psychosocial functioning
        d) Reducing parenting stress and improving parenting self-efficacy
        e) Increasing maternal sensitivity and responsiveness, enhancing mother-infant relationship quality, and improving infant social and emotional regulation

A secondary aim of this study is to investigate potential mechanisms of psychotherapy treatment response on infant brain development.

Potential Contribution:
Perinatal depression is a major public health concern for both the mother and her infant. Even mild depression in new mothers has been shown to negatively impact mother-child bonding. Effective treatment for depression can significantly improve outcomes for both the mother and child. The perinatal period is a window of opportunity in which to

address depression in women because they are more likely to come in contact with the health care system.

Methods

Timeline:

April 2012-October 2012	October 2012-December 2014	December 2014-October 2015
Set-up, train clinicians	Accrue and randomize 40 patients	Complete follow-up data collection
Obtain HRPO approval	Take participants through study protocol	Data analysis and dissemination of findings
Establish recruiting, consenting, and scheduling procedures	Gather treatment outcome data, including depressive symptoms and functioning	
Establish data management system	Gather treatment process data, including model fidelity, patient acceptability, feedback from ObGyn physicians and clinical staff	Estimated end date is December 2015

General Inclusion Criteria (women):

1) Pregnant women ages 18 and older
2) Between 12 and 30 weeks gestation
3) Score greater than or equal to 10 on the Edinburgh Depression Scale
4) Meet diagnostic criteria for a depressive disorder (MDD, dysthymia, Depressive Disorder NOS, or Bipolar -depressed) based on the SCID-IV
5) English speaking.

General Exclusion Criteria (women):

1) Substance abuse or dependence in the previous 3 months
2) Active suicidal or homicidal ideation such as to preclude safety in an outpatient settings
3)Current mania (Young Mania Rating Scale >12), psychotic disorder, or organic mental disorder
4) Unstable medical condition (i.e. untreated hypertension) or other medical/obstetrical complications (multiple gestation, history of prior pre-term birth)
5) Evidence of severe intimate partner violence
6) Ongoing psychosocial therapy or pharmacotherapy for depression. Patients taking psychopharmacologic medications for depression will be included on a case by case basis decided after consultation with the PI, Dr. Luby, and the prescribing provider.

General Inclusion Criteria for babies:

1) Those born to participants in the study during their enrollment in the study.

General Exclusion Criteria for babies:
1) None

For the Neuroimaging subset:
Inclusion (women):
1) Must be enrolled in the general study
Exclusion (women):
1) absence of major maternal medical illness
2)chronic maternal medication treatment (e.g., insulin, steroids, thyroid replacement, antidepressants, and anticonvulsants)
3) history of maternal substance abuse (including alcohol or tobacco) at any time during the pregnancy

Inclusion (infants):
1) Must be enrolled in the general study
2) 5-minute APGAR score >8
3) Weight and head circumference at birth appropriate for gestational age (between 10th and 90th percentile)

Exclusion (infants):
1)pre-term delivery (prior to 37 weeks gestation)
2) admission to neonatal or special care nursery
3) congenital or chromosomal abnormality, congenital or acquired infection (e.g., HIV, sepsis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex)
4) known prenatal brain lesions (e.g., cysts or malformations) or neonatal seizures
5) absence of prenatal care

Recruitment and Informed Consent:
Participants will be recruited from the Barnes-Jewish Hospital outpatient ObGyn Clinics and community providers. Recruitment strategies will include the use of IRB approved flyers and pamphlets, referrals by community providers and word of mouth, and referrals by ObGyn providers. Interested patients will be interviewed individually by research clinicians trained in the protection of human subjects. Recruitment procedures will protect participant confidentiality and no cold calling will occur. No individually identifiable health information will be shared with the research investigators until a potential participant signs a HIPAA authorization for sharing health information consent form, if applicable. If the referring entity is Washington University, then the referring entity will document verbal permission of the participant to share protect health information with the researchers. To ensure that the risk to the privacy of the involved participant remains minimal: 1) the potential participant's recorded contact information will be stored by the researchers in a secure manner accessible only to the relevant members of the research team, and 2) the potential participant's recorded contact information will be destroyed immediately after the researchers have contacted the participant to discuss the research study for which this information was provided; unless, upon such contact, the potential participant indicates further interest in study participation.

For potential participants who indicate further interest in study participation, the participant will be engaged in an informed consent process to further determine research study eligibility and/or study interest. The recorded participant contact information will not be reused or re-disclosed to any other person or entity (other than the members of the research team) except as required by law or for authorized oversight of the study.

Potential participants will complete an informed consent procedure and provide written consent to participate. The informed consent procedure will include a discussion of study risks, measures to protect against risks, and possible benefits. Participants will be informed of their right to refuse to answer questions. They will also be informed of their right to refuse participation at any time without penalty. All participants will sign separate HIPAA consent documents, medical release forms, and videotaping release forms as required. Per Federal regulations: 1) no inducements will be offered to terminate the pregnancy 2) no member of the research team will have any part in decisions as to timing, method, or procedures used to terminate pregnancy, and 3) no member of the research team will have any part in determining the viability of the neonate. As assent for participation in research cannot be obtained from infants, upon the birth of the baby informed consent procedures will be re-initiated with the mother for continued participation in the study. Participants will be asked to provide written consent to continue with the intervention and to include the infant in the study. Per Missouri state law, any suspected case of child abuse or neglect must be reported to the Missouri Department of Social Services Children's Division. All participants will be informed of this risk during the informed consent procedures.

The PI or trained study staff will be responsible for discussing the components of the study and the risks and benefits of participation. Written informed consent will be obtained from all participants prior to their involvement in the study.

Procedures:

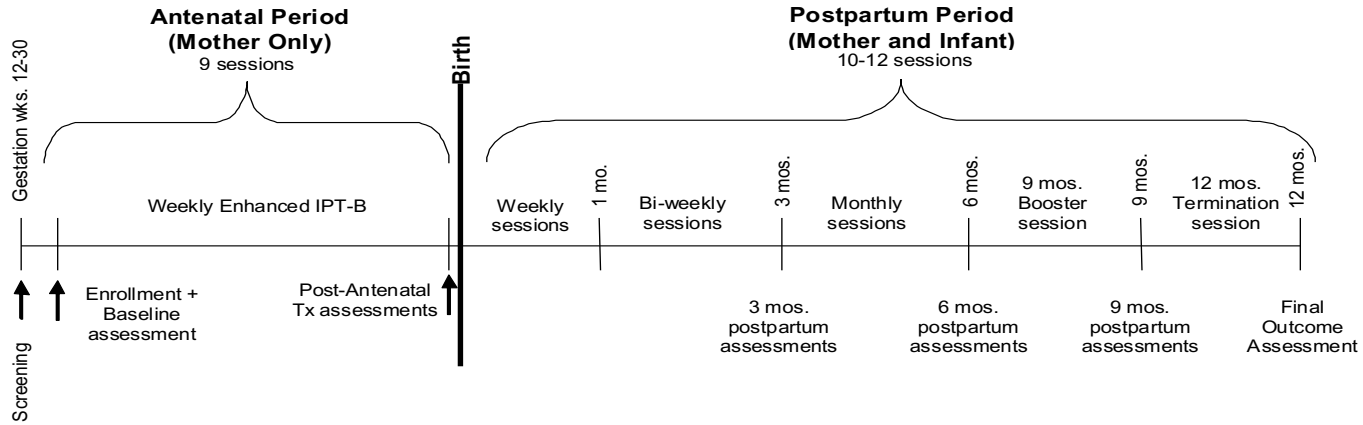
Approximately 40 pregnant (between 12-30 weeks gestation) women with scores $\geq$10 on the Edinburgh Depression Scale will be asked to participate. Women meeting all inclusion and exclusion criteria who provide written informed consent will be randomized to receive IPT-Dyad or enhanced treatment as usual (TAU).

A small subsample (n=10) of women and infants may be eligible to participate in a MRI scan of the newborn's brain. Participation in the study is not contingent upon consenting to the MRI. If the participant and her baby meet eligibility criteria and consent to participation in the scan, the scan will take place during their postpartum hospitalization post delivery of the baby. The infant will be fed within an hour of the scan. Infants will be wrapped with blankets and be accompanied by a research nurse or physician at all times. The infant will be gently restrained in the standard manner, and will receive continuous monitoring by a research nurse present throughout the entire scan. The neuroimaging takes about one-hour to complete. No narcotic or sedative agents will be administered to the infant for study purposes. After completion of the scan, the infant will be returned to the postpartum nursery or the infant's mother.

Enhanced TAU: Participants randomized to receive treatment as usual will be informed of any psychiatric diagnosis revealed during the clinical and diagnostic assessments and will be given psychoeducation about depression. The clinician will give the woman a referral to appropriate treatment, ensure that an appointment is scheduled within 2 weeks, and help to problem solve any practical barriers to care. Material supports (i.e., free diapers, bus passes) will be provided at regular intervals. Assessments will be completed (in home or via telephone) every two weeks or on the same assessment schedule as the IPT-Dyad group to monitor depressive symptoms and suicidality. This extra contact by trained clinicians is greater than is usually incurred during routine care and may help to retain these women in the study. Results from the assessments will be available to the woman's treatment provider if she provides a written authorization for release of research information.

IPT-Dyad: Figure 1 illustrates the study timeline for participants randomized to the IPT-Dyad intervention. All sessions will be video or audiotaped for supervision and treatment fidelity monitoring. In the current project, adequate indicators of acceptability will include attendance to at least 80% of treatment sessions, less than 20% attrition in the IPT-dyad group, and scores and feedback obtained from the Client Satisfaction Questionnaire. Indicators of feasibility will include therapist adherence ratings. A treatment fidelity checklist will be modified that will be used to monitor adherence to the model.

Figure 1. IPT-Dyad participant flow through the study.



The IPT-Dyad intervention consists of the engagement session plus eight 60-minute sessions of weekly treatment during the antenatal period followed by 4 weekly, 4 bi-weekly and 3 monthly 60-minute sessions conducted with the infant during the postnatal period for the first six post-birth months plus one 60-minute booster session at month 9. A brief description of the intervention is provided in the following sections.

Antepartum Sessions:

Engagement Session (session 1): The engagement session, based on Grote and colleagues, is designed to elucidate the woman's view on several factors related to treatment engagement, including: the woman's experience of depression, acute and chronic stressors, practical or psychological barriers to receiving care, goals/hopes for treatment or therapist, and health related beliefs or practices (i.e. importance of spirituality). The overall effect of the engagement session personalizes the treatment to the woman's views about depression and depression treatment and barriers to receiving care. The engagement session will be conducted by the same therapist who will conduct the remaining phases of treatment.

Initial Sessions (sessions 2-3): As in IPT-B, the next two sessions of treatment are dedicated to completing the interpersonal inventory (a careful review of all interpersonal relationships) and agreeing upon the IPT focus or problem area (role transitions, role disputes, or grief).

Middle Sessions (sessions 4-9): The middle sessions of treatment are based on IPT-B and maintain the essential features and strategies of standard IPT treatment. Specific techniques used include communication analysis, decision analysis, and role playing. Behavioral activation strategies, including using a graded approach to challenging the patient to re-engage in pleasurable activities and promoting self-mastery are also used.

Protocol Guidelines for Antepartum Sessions: The goal is to complete 9 sessions prior to delivery of the baby (1 engagement session and 8 IPT sessions). We need to balance the therapeutic ideal of weekly sessions with the reality that patients have conflicts that arise and other barriers that may prevent regular attendance. Therefore, patients have 16 weeks to complete the antepartum sessions or they will be withdrawn from the study and provided referrals. More than 9 sessions will be provided if the patient has completed all 9 sessions and has not given birth yet.

Sessions will be provided once weekly. Session 7 to the postpartum phase can be provided bi-weekly if PHQ-9 scores <10 and there is sufficient time to complete all 9 sessions prior to delivery.

Emergency sessions may be added to a max of 2 sessions/week. Referral for additional treatment or withdrawal from the study will be considered for any patient needing >2 consecutive emergency sessions.

Patients not achieving at least partial response as evidenced by at least 2 point decrease from baseline in PHQ-9 score by session #4 or response as evidenced by a 5 point decrease from baseline in PHQ-9 score by session #8 will discuss with the therapist the possible need for psychiatric consultation or referral for alternative treatment. Patients necessitating in-patient psychiatric hospitalization may be withdrawn from the study at the PI's discretion. This will be reviewed on a case by case basis.

Postpartum Sessions:

Postpartum Sessions (approximate sessions 12-22): The postpartum focus of IPT-Dyad is based on traditional IPT strategies that were developed to prevent depression relapse and enhance interpersonal functioning. The goal is to help the patient to develop more effective strategies to cope with interpersonal problems that might arise following remission of depression. For example, patients are encouraged to develop stronger social networks, refine social skills, enhance existing relationships with others, or modify maladaptive communication skills. Drawing from the model of infant mental health risk transmission and infant emotional development theories discussed in the background and significance sections, the postpartum sessions of IPT-Dyad will also include several techniques designed to specifically target the mother-infant relationship. Table 2 highlights essential elements of infant emotional development and how IPT-Dyad will address these elements. Techniques used will include: modeling, coaching, floor play, gaze and contact exercises, and education.

Table 2. Potential elements of infant emotion development targeted by IPT-Dyad.

Element *	Impact of maternal depression on element **	IPT-Dyad Approach
Maternal availability, sensitivity, responsivity	Withdrawn and/or decreased responsiveness to infant cues.	• Treatment of Depressive Symptoms • Education • Coaching during face-to-face interactions
Social play	Decreased time spent in positive play.	• Floor play in session with toys • Coaching during face-to-face play • Play homework
Gaze/touch	Decreased time spent gazing at infant. Decreased amount of positive & nurturing touch.	• Hold infant during sessions • Education • Modeling • Gaze and touch homework
Maternal affect	Negative, withdrawn, & flat	• Treatment of depressive symptoms
Gestures, postures, & vocalization	Hostile, intrusive, and/or withdrawn & avoidant	• Treatment of depressive symptoms • Education • Modeling
Mutual regulation, reciprocity, & synchrony	Increased time spent in mismatch states. Less time, ability, and/or effort to repair mismatch	• Modeling • Coaching during face-to-face interactions • Practice repairs after stress (i.e. still face exercises)

Protocol Guidelines for Postpartum Sessions:

The goal is to complete 10 sessions in the first year postpartum (8 sessions by 3 months, 11 sessions by 6 months, and 12 sessions by 12 months). Patients may complete more or less depending on individual therapeutic needs. All sessions will be terminated at 12 months postpartum. Patients needing additional treatment will be provided with an appropriate referral.

Up to 3 months postpartum

Weekly sessions are indicated for all patients in the first month postpartum. After the first month, weekly sessions are indicated for patients with PHQ-9 scores $\geq$ 15. Alternative treatment should be considered for any patient whose scores do not decrease below 15 or increase 3 consecutive weeks. Weekly sessions are also indicated for patients who did not complete all 9 sessions of antepartum therapy (i.e. due to premature delivery). Weekly sessions can continue until 9 sessions have been completed and/or PHQ-9 scores $\leq$ 14.

Bi-weekly sessions are indicated for patients with PHQ-9 scores $\leq$ 14.

Emergency sessions may be added to a max of 2 sessions/week. Referral for additional treatment or withdrawal from the study will be considered for any patient needing >2 consecutive emergency sessions.

3 to 6 months postpartum
Weekly sessions are indicated for patients with PHQ-9 scores ≥ 15. Alternative treatment should be considered for any patient whose scores do not decrease below 15 or increase 3 consecutive weeks. Emergency sessions may be added to a max of 2 sessions/week. Referral for additional treatment or withdrawal from the study will be considered for any patient needing >2 consecutive emergency sessions.

Bi-weekly sessions are indicated for patients with PHQ-9 scores ≤ 14 but the clinician determines more intensive mother-infant relationship work is needed (the Parent Infant Relationship-Global Assessment Scale should be used to help make this determination in suspected cases).

Monthly sessions are indicated for patients with PHQ-9 scores ≤ 10 or there has been at least a 50% reduction from baseline scores for 4 consecutive weeks and the mother-infant relationship is functioning in the optimal range.

6 to 12 months postpartum
Weekly sessions are indicated for patients with PHQ-9 scores ≥ 15. However, alternative treatment should be discussed with the patient and withdrawal from the study considered. Emergency sessions may be added to a max of 2 sessions/week. Referral for additional treatment or withdrawal from the study will be considered for any patient needing >2 consecutive emergency sessions.

Bi-weekly sessions are indicated for patients with PHQ-9 scores ≤ 14 but the clinician determines more intensive mother-infant relationship work is needed (the Parent Infant Relationship-Global Assessment Scale should be used to help make this determination in suspected cases).

Monthly sessions are indicated for patients with PHQ-9 scores ≤ 10 or there has been at least a 50% reduction from baseline scores for 4 consecutive weeks and the mother-infant relationship is functioning in the optimal range. Patients with 8 consecutive weeks of PHQ-9 scores ≤ 10 and solid mother-infant relationship functioning may extend time between sessions up to 12 weeks.

Remuneration: Participants will receive $15 at the screening visit, $30 at baseline assessments, $20 at 37-39wks gestation assessments, $20 at 3 month postpartum assessment, $30 at 6 month postpartum assessment, $20 at 9 month postpartum assessment, and $45 at the 12 month postpartum assessment. Participants whose newborns receive a brain MRI scan will be paid $25. Additionally, women will be provided with material supports such as free diapers, developmentally appropriate toys and books on a regular basis. Parking reimbursement or bus passes will be available for assistance with transportation to and from appointments if needed.

Measures:
Regular assessments will be conducted throughout the course of treatment. The frequency of assessments was chosen to minimize participant burden while still maximizing the ability to capture treatment-related changes. The measure and rationale for the measures are described below. Table 3 describes the measures and the timeline for administration. *It should be noted that the Patient Health Questionnaire, Depression, Anxiety and Stress Scale and the Brief State Trait Anxiety Inventory will be administered at each psychotherapy session in addition to the assessment schedule below. The Hypomania Symptom Checklist will be administered as needed if the clinician suspects onset of hypomanic symptoms.

Table 3. Measures Administered and Assessment Timeline

	Antenatal		Postnatal			
	Enrollment	37-39wks gestation	3 mos.	6 mos.	9 mos.	12 mos.
Obstetrical Chart Review –prenatal complications	X	X				
Structured Clinical Interview for the Diagnosis for DSM-IV (SCID) -evaluates for psychopathology and provides broad coverage for psychiatric diagnosis	X					
Inventory of Interpersonal Problems -25 item (IIP-25) -self report measure of interpersonal functioning	X					X
Edinburgh Depression Scale (EDS) -self report scale for measuring pre and postnatal depressive symptoms	X	X	X	X	X	X
Young Mania Rating Scale (YMRS) -brief interview to assess manic symptoms	x	x	x	x	x	x
Hypomania Symptom Checklist-32 (HCL32)* -self-report checklist to measure manic symptoms	x					
State Trait Anxiety Inventory - Brief -Self report scale measuring transient anxiety symptoms	X	X	X	X	X	X
Depression Anxiety and Stress Scale (DASS21) -Self report scale measuring negative emotionality	X	X	X	X	X	X
Patient Health Questionnaire -9 item (PHQ-9)* -Self report measures of depressive symptoms	X					
Social Support Questionnaire (SSQ) -self report measure of social network size and satisfaction	X	X		X		X
Abuse Assessment Screen	X					

-self report assessment of risk for current physical, emotional, or sexual abuse while pregnant						
Experiences in Close Relationships –Revised (ECR-R) -self report measure of attitudes towards close relationships with intimate partners	X					X
Difficult Life Circumstances (DLC) -self-report measure of stressful life events	X	X	X	X	X	X
Postpartum Adjustment Questionnaire (PPAQ) -self report assessment of social role adjustment postpartum			X	X	X	X
Parenting Stress Index (PSI) -questionnaire evaluating seven domains of parenting including attachment, competence, support, isolation, and health status				X		X
Infant Behavior Questionnaire (IBQ) -assesses six domains of infant temperament				X		X
Mullen Scales of Early Learning (MSEL) -brief assessment of infant motor, perceptual, and language abilities			X			
Still-Face Paradigm -structured paradigm used to characterize parent-infant interactions				X		X
Emotional Availability Scales -structured paradigm used to characterize maternal sensitivity and responsiveness			X	X	X	X
Infant-Toddler Social and Emotional Assessment (ITSEA) -parent questionnaire used to assess competencies and difficulties across a range of social and emotional developmental domains					X	X
Community Life Skills Scale (CLS) -measures ability to negotiate for self and family in the community	X					X
Client Satisfaction Questionnaire (CSQ) -measures satisfaction with psychological treatment		X	X	X	X	X
Emotion Regulation Questionnaire (ERQ) -measures emotion regulation	X	X	X	X	X	X

<u>Protocol Guidelines for Assessments:</u>
Assessments must be completed no more than 10 days prior to the assessment due date and within 4 weeks after the assessment due date. If infants are not able to participate in the observational assessments (due to fussiness, sleeping, or other reasons), they should be rescheduled within 2 weeks.

Participants may drop out of therapy by still participate in assessments.

Procedures for Maintaining Confidentiality
There is a potential risk of breach of confidentiality that is inherent in all research protocols. Procedures have been established, and will be followed to minimize the risk of breach of confidentiality. Data will be entered into password-secured databases by staff authorized by the PI to do this, and they will abide by the confidentiality regulations of the IRB. Participant anonymity will be preserved by the use of a code number (not related to name, social security number, or date of birth) on all questionnaires and reports. A list of participant names will be kept in a separate locked cabinet will access only to study personnel authorized by the PI. No participant names will be identified by name in any published reports.

Assessment of Risks and Benefits
Risk to Participants: The anticipated risks to participants are few, as IPT-Dyad is an adaptation of an empirically supported treatment for depression. Some participants may experience emotional discomfort when discussing interpersonal problems or emotionally laden material. Some emotional discomfort may be associated with the clinical assessments conducted in the study. All clinical assessors will make every effort to conduct interviews and administer questionnaires in a sensitive and supportive manner. Participants may be stressed or uncomfortable about being separated from their infants during the MRI scan. There is slight risk for breach of confidentiality. There are no known adverse effects of psychotherapy to the fetus. Risks to infants may include frustration, boredom, or fatigue. Infants might experience transient discomfort or distress during the infant observational paradigm, but nothing more than is experienced routinely on a daily basis. The MRI scan may cause the infant to experience discomfort from the pillow restraint device if he/she awakes during the MRI. There may be abnormalities detected on the MRI. If this is the case, the participant and pediatrician will be notified. The overall benefit to the infant is thought to clearly outweigh the risk.

Possible Benefits: Participants who receive IPT-Dyad may benefit in terms of reduced depression. Participants will be informed that there are no guarantees that they will benefit from IPT-Dyad. Participants will receive a comprehensive mental health assessment at no charge, which they otherwise may not receive at all. Receiving a psychosocial intervention administered by a highly trained and supervised Master's level or higher clinician at no cost may be beneficial. Participants may benefit by learning new communication skills, improve social support, and effectively manage interpersonal problems, which may result in a decrease in depressive symptoms and increase day to day functioning. Results from this study may inform long-term treatment strategies for perinatal depression. These benefits, both to the participants and to others, outweigh the minor risks to study participants.

Alternative Procedures/Therapies: Participants may choose to receive treatment from their ObGyn, primary care doctor, or other mental health care provider.

Revised Data Monitoring Plan (11/2014)
I. Study Overview

A. **Brief Description of the Purpose of the Study**: In this clinical trial we test the feasibility and acceptability of Interpersonal Psychotherapy for the Mother-Infant Dyad (IPT-Dyad), a new intervention for perinatal depression. This intervention proposes a novel integration of ante- and postnatal depression treatment based on an evidence-based treatment for depression (IPT) and infant emotional developmental theory to address both maternal depressive symptoms and infant emotion development.
B. **Adherence Statement**: The Data Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the NIMH and the Washington University IRB.
C. **General description of monitoring plan:** This is a single-site study. Dr. Lenze will be the primary monitoring entity. She will have primary responsibility for the monitoring of participants during the entire time they participate in the study, both with respect to their safety (including confidentiality) and the integrity of their research data.

The study PI will maximize the safety and privacy of all study participants and ensure the integrity, validity, and confidentiality of data collection procedures through regular monitoring of clinical and research activities during weekly (and additional as needed) project meetings with the study staff. Areas of particular concern will be 1) the number of subjects in each phase of the protocol and the number who have completed the protocol; 2) the amount of data lost, including subject withdrawal, reason for loss, and steps taken to avoid loss in the future; 3) presence of any adverse consequences (whether minor or severe) to any subject, together with the short- and long-term remedies to the problem; and 4) the presence of any new information, especially from this study or from other sources, regarding the expected efficacy and safety of any therapy or procedure used in this study. The agenda for protocol meetings will include tracking of subject recruitment, enrollment, and retention, including assessment of diversity; data collection and entry; accuracy and/or issues with the implementation of the intervention; documentation and review of any subject symptoms, concerns, or adverse effects. The PI and her mentor will use this information to monitor whether the research progress is satisfactory, whether the participant's risk/benefit ratio has changed (in which the IRB will be informed), and whether any changes need to be made to any protocol procedures. The PI will also ensure that data archives and quality control procedures are in place and working well. The PI will report any serious and unexpected adverse events, unexpected problems that involve risks to the participants or others, and any breeches of confidentiality to the IRB. An adverse event (AE) will be defined as any undesirable experience of a nature likely to require medical attention that occurs after informed consent for the study has been obtained, without regard to treatment group assignment. A serious adverse event (SAE) will be defined as any event that precipitates or prolongs hospitalization, is potentially life threatening, or results in chronic disability or significant chronic discomfort. If an AE or SAE occurs, the treating clinician will immediately take appropriate clinical action and contact the PI, who will immediately consult with her mentors. Adverse events will be reported to the local IRB as soon as possible per IRB policy. SAE's will be reported to mentors, local IRB, and NIMH project officer within 24 hours. More detailed information regarding this process is outlined below.

II. Confidentiality

A. **Protection of Participant Confidentiality**

The PI and her staff will provide adequate safeguards for the protection of confidentiality of all research records. Procedures designed to maintain confidentially include: (1) training for all research staff emphasizing the importance of confidentiality; (2) specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants. Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number, assigned by the research coordinator at the time of initial contact will represent participants during data entry, data transfer, data analysis, or other file management procedures. To facilitate tracking, a password-protected computer file will be maintained containing the identity of participants, their ID numbers, and information about how they can be reached. This file, however, will contain no clinical data. Only members of the investigative group will have access to secured files or to master lists for participant code numbers and will be well informed regarding the protection of patients' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project.

Videotaping permission and confidentiality: participants will be videotaped for the purposes of observing the therapists and providing training material. Participants will sign a consent which indicates the use of the videotaping, who may have access to the videotaping, and the length of time that the videotape will be kept by investigators. Videotapes will be kept with the same confidentiality procedures as other research data.

B. **Database Protection**
All participant research data is stored separate from participant contact information, which is stored on our secure servers with network and database level passwords, only accessible to research staff who need contact with the participants.

C. **Confidentiality During Adverse Event (AE) Reporting**
AE reports and annual summaries will not include participant- or group-identifiable material. Each report will only include the identification code.

III. Adverse Event Information

A. **Definition**

An adverse event (AE) is any untoward medical occurrence in a participant temporally associated with participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

A Serious Adverse Event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment

B. **Classification of AE Severity**

AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed “mild” if it does not have a major impact on the patient, “moderate” if it causes the patient some minor inconvenience, and “severe” if it causes a substantial disruption to the patient’s well being.

C. **AE Attribution Scale**

AEs will be categorized according to the likelihood that they are related to the study intervention or other study procedures. Specifically, they will be labeled definitely unrelated, definitely related, probably related, or possibly related to the study intervention or procedures.

D. **Expected Risks**

Study assessments: The assessments to be conducted as part of this study are non-invasive and carry with them no more than minimal risk. The most significant risks to the participants related to assessments are those that would follow a breach of confidentiality and the disclosure of clinical information or video recordings.

IPT-Dyad Psychotherapy: Participants assigned to IPT-Dyad may feel uncomfortable disclosing private and/or emotional experiences. This risk is minimized by using well-trained and supervised staff.

Enhanced Treatment as Usual (ETAU): Participants assigned to ETAU may also feel uncomfortable disclosing private and/or emotional experiences. This risk is minimized by using well-trained and supervised staff.

Because this study involves participants with depression, there is a risk of suicidal behavior. However, these are risks associated with the illness not the study.

Risks in relation to benefits: No participants will be denied interventions; participants receive either standard of care in the community or the IPT-Dyad intervention. No risks other than possible emotional distress exist from the study assessments. Thus, the risks involved in participating in this study are deemed low, which justifies the data and safety monitoring plan described here.

Protections for mother (both pre- and postnatal)

Potential risks:

Potential risks to the mother during her participation in the study include worsening of depressive symptoms, decrease in self or prenatal care due to worsening of symptoms, suicidal ideation or behaviors, homicidal ideation or behaviors, and the development of manic or psychotic symptoms.

Protections in place to manage risks:

1) Research clinicians will be clinically experienced and will receive additional training in delivering IPT-Dyad and the research assessments. Clinicians will be closely supervised by Drs. Lenze and Luby. Participants in the study will be provided with 24-hour access to Dr. Lenze or a back-up on-call clinician.
2) Depressive symptoms are monitored at every contact via the Edinburgh Depression Scale and/or the Patient Health Questionnaire -9 item scales. Per protocol, emergency sessions may be added to a max of 2 sessions/week. Referral for additional treatment or withdrawal from the study will be considered for any patient needing >2 consecutive emergency sessions. Patients not achieving at least partial response as evidenced by at least 2 point decrease from baseline in PHQ-9 score by session #4 or response as

evidenced by a 5 point decrease from baseline in PHQ-9 score by session #8 will discuss with the therapist the possible need for psychiatric consultation or referral for alternative treatment. Alternative treatment should be considered for any patient whose PHQ-9 scores do not decrease below 15 or increase 3 consecutive weeks. Patients necessitating in-patient psychiatric hospitalization may be withdrawn from the study at the PI's discretion. This will be reviewed on a case by case basis by Drs. Lenze and Luby. If Drs. Lenze or Luby have any concerns about the appropriateness of continuation, Dr. Lenze will arrange for the patient to have an independent consultation from a psychiatrist not associated with the study.

3) All research clinicians will be trained to assess suicidality and homicidality, including thoughts about harming the fetus or baby, and to take appropriate steps. Suicide risk will be probed at each assessment via several mechanisms, including the Edinburgh Depression Scale or the Patient Health Questionnaire (9-item), and clinical interview. For those who endorse suicidal ideation, severity of suicidal ideation will be assessed using the Scale for Suicidal Ideation, which assesses the extent of suicide risk (i.e. wish to live vs. die, plans, intent). If a patient endorses suicidal ideation, intent, or plan, the clinician will follow an operationalized protocol developed to manage high-risk depressed participants in clinical research (Pearson et al., 2001). This plan, and its implications with respect to the need to balance safety with confidentiality and autonomy, will be explained to the participant at the time of consent. Suicidal or homicidal attempts or hospitalizations are considered serious adverse events and are reported to the IRB and to NIMH program staff as per their guidelines.

4) Other mental health crises (e.g., onset of psychosis, mania or other behavioral disturbance, infanticidal ideation) will be managed similarly. The decision to withdraw any patient from the trial will be made on a case by case basis with regard to safety for outpatient management and appropriateness of IPT-Dyad as an intervention (i.e. IPT-Dyad is not appropriate for patients with mania or psychosis).

Protections for Fetus

Potential Risks:

There are no known risks to the fetus from maternal participation in psychotherapy.

Protections for Infant

Potential Risks:

Infants engaged in mother-infant psychotherapy may become bored, fussy, or overstimulated.

Protection against risks:

1) Research staff and clinicians will be trained and closely supervised by Drs. Lenze and Luby to monitor the infant's response to study interventions. The infant's mother will always be allowed to comfort her baby or otherwise attend to the baby's needs. In cases where the infant clearly is too distressed to continue, study sessions will be rescheduled.

Participants will be reviewed at baseline with Dr. Lenze; exclusion criteria (e.g., psychosis, unstable medical conditions, suicidal ideation that precludes outpatient treatment) will reduce the

risk to participants. Dr. Macones, a Maternal-Fetal Medicine specialist, will provide advice regarding medical stability for this study. Depressive symptoms are monitored throughout the study using the Patient Health Questionnaire-9 item.

E. **AE Reporting and Follow-Up**
Study staff will systematically collect AEs and summarize them in a running table throughout the study, including date of onset/offset, type of AE, severity, and interventions if any. Per Washington University IRB policy, reportable AEs are those that are possibly, probably, or definitely related to the study intervention or procedures.

F. **SAE Reporting**
SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IRB, and NIMH in accordance with requirements.

- Unexpected fatal or life-threatening SAEs related to the intervention will be reported to the NIMH Program Officer within 24 hours. Other serious and unexpected AEs related to the intervention will be reported to the NIMH Program Official within 15 days.

V. Data Quality and Safety Review Plan and Monitoring

A. Data Quality and Management

Research staff and participants will provide data through paper forms. Tracking forms will document that procedures were followed and completed at each visit. A closed and password-protected data-entry system will track data in real time as they are entered. This will allow continuous checks on data completion and integrity (e.g., errors). Range checks, review screens, and error trapping routines will be built into the system as quality control procedures to minimize the chance of data entry errors. Hard copy data summaries of all active and recent participants will be provided to the PI who will review them for any apparent errors, missing data, or discrepancies. The frequency of this formal review of the integrity of the accumulating study data will be approximately weekly. This information will be reviewed with Dr. Luby monthly, or more frequently if errors are detected.

B. Participant Accrual and Compliance

1) Measurement and Reporting of Participant Accrual, Compliance with Inclusion/Exclusion Criteria: Review of the rate of participant accrual and compliance with inclusion/exclusion criteria will occur weekly at PI/study staff meetings during the recruitment phases of the project, to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria and the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table). Dr. Lenze and all research study staff will be present at these meetings. This information will be reviewed with Dr. Luby on a bi-weekly basis during the progress and safety meeting.

2) Measurement and Reporting of Participant Adherence to Treatment Protocol

Data on participant adherence to the protocol (i.e., therapy participation, completion of research measures) will be collected in real time by study staff, and reviewed (weekly if nonadherence is detected, so that study staff can intervene) by the PI.

C. **Safety Review Plan**
Study progress and safety will be reviewed at weekly meetings with Drs. Lenze and Luby and all study staff (and more frequently if needed). Progress reports will be provided to the NIMH on a yearly basis. The IRB will review progress of this study on an annual basis.

VI. Informed Consent

Written informed consent will be obtained from each participant at entry into the study. Informed consent is obtained by the following process:

1. The participant will be asked to review the study consent form.
2. Study staff will confirm the participant's understanding of the study using a formal scale to assess understanding of consent, and to answer any questions the participant might have.
3. Once the participant demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of study staff.

VII. Reporting Changes in Study Status

During the funding of this study, any action by an IRB or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NIMH Program Official within 1 business day of notification.