Neuropathic Pain in Pregnancy

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Abbreviations:

a) AED = anti-epileptic drugs
b) BDI = Beck Depression Inventory
c) CGI-I = Clinical Global Impression-Global Improvement Scale
d) EFNS = European Federation of Neurological Societies
e) IASP = International Association for the Study of Pain
f) neuPSIG = Neuropathic Pain Special Interest Group
g) NP = neuropathic pain
h) NSAID = non-steroidal anti-inflammatory drug
i) PCP = phencyclidine
j) PCS = Pain Catastrophizing Scale
k) PDQ = painDETECT Questionnaire
l) PGIC = Patients' Global Impression of Change scale
m) PRI = Psychiatric Research Institute
n) PROMIS = Patient Reported Outcomes Measurement Information System
o) rTMS = repetitive transcranial magnetic stimulation
p) TCA = tricyclic antidepressant
q) THC = tetrahydrocannabinol
r) TMS= transcranial magnetic stimulation
s) UAMS = University of Arkansas for Medical Sciences
t) UWC = University of Arkansas for Medical Sciences Women's Clinic
u) VAS = Visual Analogue Scale
v) WMHP = Women's Mental Health Program

Introduction – Background

Neuropathic pain (NP), defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' according to The International Association for the Study of Pain (IASP), affects up to 8% of the population (IASP Task Force; Dieleman *et al* 2008). Compared to other chronic pain conditions, NP is associated with higher pain severity, poorer health, and greater disability (Smith *et al* 2007). In addition, depression and anxiety are common comorbidities of NP (Radat *et al* 2013). As NP affects more women than men (Dieleman *et al* 2008), women's health practitioners need to be familiar with both acute and chronic neuropathic pain conditions. Acquired nerve compressions are common in pregnancy, and consensus exists regarding their management (Sax and Rosenbaum 2006). However, knowledge regarding chronic NP (and other chronic pain conditions) in pregnancy is scarce. **The overall goal of this project is to better define the course, management, and obstetrical/neonatal outcomes of chronic neuropathic pain in pregnancy and the acute postpartum period.**

Acquired nerve compressions peak in the third trimester and the majority resolve by six months postpartum. The trend of chronic NP as well as chronic pain in pregnancy is unknown. **This study will characterize the course of neuropathic pain in pregnancy and the postpartum period using longitudinal measures of pain characteristics.**

Pharmacological management of NP is suboptimal as those with NP report greater disability and less effective pain relief despite receiving more pain medication prescriptions compared to those with non-neuropathic pain (Torrance *et al* 2007; Smith *et al* 2007). In addition, pharmacological treatment fails to relieve symptoms at the costs of side effects (e.g., constipation, dry mouth, sedation, risks of falls). Thus, alternative pharmacological treatments or non-pharmacological options are needed.

Neurostimulation modalities are efficacious in the management of NP but are not included in current treatment guidelines (O'Connor and Dworkin 2009; Attal *et al* 2010; Moulin *et al* 2007). In particular, rTMS is one technique that has shown effectiveness in the management of NP and is recognized as having level B evidence (Hosomi *et al* 2013; Khedr *et al* 2005; Mhalla *et al* 2011; Passard *et al* 2007; Onesti *et al* 2013; Cruccu *et al* 2007). Transcranial magnetic stimulation uses electromagnetic induction to influence underlying cortical neurons and trigger action potentials. This non-invasive and localized mechanism of action makes it attractive for use in special populations, such as pregnancy.

Pain management in pregnancy relies on conservative strategies and pharmacological monotherapy to minimize the risk to benefit ratio of fetal exposure; thus, the management of NP in pregnancy is challenging as evidence of teratogenicity limits options. In addition, little is known of other treatment options, such as pregabalin and duloxetine (Hoog *et al* 2013; Winterfield *et al* 2015). Also, pharmacological monotherapy is always recommended to minimize fetal exposure in pregnancy, and this limits the use of combination therapies.

Transcranial magnetic stimulation may be an acceptable alternative to pharmaceuticals for the management of NP in pregnancy. Repetitive transcranial magnetic stimulation is acceptable as a treatment option for depression in pregnancy (Kim *et al* 2011). Two studies effectively applied rTMS in pregnancy for depression with no adverse fetal or obstetrical outcomes (Sayar *et al* 2014; Kim *et al* 2011). According to a follow-up study, rTMS is not associated with poorer cognitive, motor, or language development in children of mothers who were treated with rTMS in pregnancy

for depression (Eryilmaz *et al* 2014). **This will be the first pilot study to investigate the use of rTMS in the treatment of neuropathic pain in pregnancy**.

The application of rTMS in pregnancy for the treatment of depression has resulted in two cases of inferior vena cava compression syndrome (also referred to as supine hypotensive syndrome) and one episode of dizziness without hypotension (Kim and Wang 2014). This condition typically occurs after 24 weeks gestation and is managed by placing the pregnancy women onto the left lateral position if they are going to be supine for an extended period of time. Thus, it has been recommended to avoid the supine position when applying rTMS to the pregnant women (Kim and Wang 2014). To decrease the likelihood of inferior vena cava compression syndrome, all subjects beyond 24 weeks gestation will be positioned on their left side using a wedge cushion.

Seizures can adversely affect pregnancy, and the use of high frequency stimulation, defined as greater than or equal to 10-Hz, in rTMS increases the risk of seizures. The general risk of seizures with rTMS is low (1/10,000), and rTMS has been used in pregnancy at high frequency (I.e. 25-Hz) stimulation without any adverse effects (Sayar *et al* 2014). The proposed study will utilize 5-Hz as it is the lowest, effective frequency stimulation reported for the treatment of neuropathic pain (Hosomi *et al* 2013). We believe this will minimize seizure risk, and in efforts to further decrease seizure risk with rTMS, the study is applying rTMS in trains of pulses interspersed with periods of rest and excluding those with risk factors for seizures. The results of the current study will provide data supporting the acceptability and feasibility of rTMS of the treatment of neuropathic pain in pregnancy and will support larger studies to determine the most effective and safe frequency stimulation for the treatment of neuropathic pain in pregnancy.

The management of chronic pain conditions in pregnancy has a direct effect on neonatal outcomes through fetal exposure. For example, neonatal abstinence syndrome is a drug withdrawal disorder of neonates that is secondary to in utero exposure to opioids, antidepressants, and muscle relaxants – all which are used to treat NP. Given the current limited knowledge of teratogenicity regarding pharmacological agents, we aim to better define the association of neonatal outcomes with chronic neuropathic conditions in pregnancy. **We aim to compare obstetrical and neonatal outcomes of pregnant women with neuropathic pain, non-neuropathic pain, and no pain.**

Objectives

To further define the impact of NP in the peripartum period, we propose the following objectives:

I. Characterize the course and pharmacological management of neuropathic pain in pregnancy and the postpartum period. We will define descriptive statistics of the use of analgesic medications in pregnancy and the postpartum period for the treatment of neuropathic pain.
II. Compare obstetrical and neonatal outcomes of pregnant women with chronic neuropathic pain, non-neuropathic chronic pain, and pregnant women without chronic pain.
III. Determine the acceptability and tolerability of rTMS for the treatment of neuropathic pain in pregnancy, and describe the impact of rTMS on neuropathic pain in pregnancy.

Subject Selection

Subjects will be enrolled through the Women's Mental Health Program (WMHP) at the University of Arkansas for Medical Sciences (UAMS) at the following clinical spaces: Psychiatric Research Institute (PRI); UAMS Women's Clinic (UWC); the Psychiatric Research Institute (PRI) inpatient units (PRI floors 5&6); and the UAMS Obstetrics & Gynecology units (UAMS floors 5,6, and 7A).

Study visits can occur at all of the above locations. For those subjects in part B, study visits will occur in a designated room designed for rTMS in the PRI. We aim to actively recruit and enroll 60 pregnant women and up to 70 infants (to allow for multiple gestation pregnancies) for Part A of this study and enroll 10 pregnant women and up to 15 infants (to allow from multiple gestation pregnancies) (from Part A) for Part B.

Compensation: Mothers participating in the study will receive a $10 in cash for each visit. All participants will be given a token or voucher to pay for parking at each outpatient study visit when applicable.

Inclusion of Women, Minorities and Children
Women and adolescents between 18-45 years of age are eligible for participation in the current study. Every effort will be made to recruit a diverse population of women along racial and ethnic categories residing in underserved areas.

Eligibility Criteria
All women will provide consent and HIPAA authorization prior to enrollment in the study.

Part A:
Maternal Inclusion Criteria
- Age 18-45 years old,
- Ability to give informed consent,
- Viable pregnancy, and
- Enrollment prior to or equal to 24 weeks gestation

Maternal Exclusion Criteria
- Active or history of substance use disorder within the past year
- Non-English speaking

Part B:
Maternal Inclusion Criteria
- Subjects enrolled in Part A and willing to consent to Part B of this protocol
- Pregnant with current chronic neuropathic pain
- Subjects failed treatment with amitriptyline or nortriptyline as defined by one of the following:
  - no clinical improvement following a four week trial of amitriptyline or nortriptyline (i.e., CGI-I score ≥4)
  - an inability to tolerate the medication (i.e., side effects)
- Subjects must pass the TMS Safety Checklist Adult Safety Screen (TASS).
- Subjects should be off medication, which can lower seizure thresholds (e.g., amitriptyline and nortriptyline) for at least two weeks prior to study entry.
- Subjects with neuropathic pain including those with diagnosis of spinal cord injury, fibromyalgia, compression neuropathies (including diabetic peripheral neuropathy), post stroke pain, and multiple sclerosis
- Subjects with a baseline VAS score greater than 30

Maternal Exclusion Criteria

- Current or past history of a seizure disorder (e.g., epilepsy)
- Current history of preeclampsia
- Current or history of brain lesions (e.g., aneurysm)
- History of major head trauma (e.g., stroke; previous cranial neurosurgery)
- Ferromagnetic metal in the head, neck, or chest (e.g., plates or pins, bullets, shrapnel)
- Microprocessor implants in the head (e.g., cochlear implants) or life-sustaining microprocessor implants anywhere in the body (e.g., prosthetic cardiac valves)
- Cardiac pacemaker
- Active or inactive implants (e.g., deep brain stimulators, vagus nerve stimulators)
- Active treatment with medications that lower seizure threshold (e.g., bupropion, amitriptyline, nortriptyline, or other TCA)
- Increased intracranial pressure (which lowers seizure threshold)
- Implanted medication pumps
- Intracardiac lines
- Significant heart disease defined as heart disease that causes moderate to severe symptoms and/or is characterized by moderate to severe pathology, including a recent history of myocardial infarction and heart failure with an ejection fraction of less than 30% or with a New York Heart Association Functional Classification of Class III or IV.
- Bipolar disorder (to reduce the risk of mania)
- History of suicide attempt(s)
- Family history of epilepsy
- Heavy alcohol consumption within the past 48 hours
- Permanent makeup or tattoos with metallic dyes

Investigational Plan

The study will involve two phases - initially focusing on identification and course, followed by treatment paradigm assessment (Part A), and culminating in a pilot trial of rTMS (Part B).

***Part A**:*

Study visits will occur approximately every 4-6 weeks during pregnancy until approximately 3 months postpartum for a maximum of 12 visits. Table 1 provides an overview of study procedures. Figure 1 illustrates subject participation and flow. In order to optimize diagnostic clarity for group assignment, we will employ a valid tool, the painDETECT Questionnaire (PDQ), for diagnostic purposes (written permission for use of PDQ has been obtained and is available upon request). The PDQ has been validated and shown high sensitivity (85%), specificity (80%), and positive predictive value (83%) (Freynhagen *et al* 2006). At study entry, subjects will complete the PDQ. Based on their scores, subjects will be separated into three groups: Group 1) subjects with NP in pregnancy (score ≥13); Group 2) subjects with non-neuropathic pain in pregnancy (1≥score≤12; and Group 3) subjects without any type of pain in pregnancy (score=0).

Other measures collected at entry include a general biographical form (WMHP Intake Form). Subjects will complete pain measures and the Beck Depression Inventory (BDI) (Beck *et al* 1960) at study entry and at each study visit. Pain measures include the Visual Analogue Scale (VAS), Pain Catastrophizing Scale (PCS) (Sullivan *et al* 1995), and measures of pain intensity, pain interference, pain behavior - all three derived from Patient Reported Outcomes Measurement Information System (PROMIS) (Amtmann *et al* 2010; Revicki *et al* 2009; Cella *et al* 2010). At each visit, the exposure tracking form will record the timing (weeks of gestation) and dosage of all

prescription and non-prescription medications used in pregnancy and the postpartum period. A urine drug screen will also be obtained at each visit testing for the presence or absence of the following: amphetamines/methamphetamines, barbiturates, benzodiazepines, THC, cocaine, methadone, opiates, PCP, and cotinine. For all visits following entry visit, subjects will complete the Patients' Global Impression of Change scale (PGIC) (Hurst and Bolton 2004); and the clinician will complete the Clinical Global Impression-Global Improvement scale (CGI-I) (Guy 1976). At all study visits, weight and vital signs will be collected. For all subjects who delivered at UAMS, medical records for labor and delivery and neonatal outcome will be obtained following birth. All subjects will participate in Part A. All subjects will receive treatment as usual within each group.

***Part B**:*
Subjects in group 1 will be invited to participate in part B of the study following their enrollment in part A. This pilot study will aim to enroll 10 subjects (of Group A).

Subjects will undergo daily rTMS, defined as Monday through Friday, for a total of 10 consecutive sessions with the exception of weekends and holidays (i.e., Monday to Friday only). Typically, a stimulation period will start on Monday (day 1) and end on Friday (day 12). In the case that a stimulation period does not start on Monday, day 1 will begin on the day of the subject's first rTMS session. Subjects will be followed daily until day 29, following their last session of rTMS (day 12). Table 2 provides an overview of study procedures. For each session (days 1-5 and 8-12), subjects will complete a VAS prior, immediately following, and 60 minutes post. Adverse events will also be recorded prior to and immediately following and 60 minutes after each session. They will complete a BDI on Days 1, 5, 12, 22, and 29. Subjects will complete VAS also on days 22 and 29. For days 5, 12, 22, and 29; subjects will complete the PGIC; and clinicians will complete the CGI-I. Subjects will have a maximum of 12 visits for Part B (10 rTMS sessions plus days 22 and 29). Either study visit for days 22 or 29 may occur in conjunction with a study visit for Part A.

Repetitive transcranial magnetic stimulation will be applied using the NeuroStar TMS Therapy System with the XPLOR System in the PRI. For all subjects beyond 24 weeks gestation, they will be positioned on their left side using a wedge cushion to minimize the occurrence of inferior vena cava compression syndrome. Repetitive TMS will be applied through a figure-8 coil connected to a magnetic stimulator, which provides a biphasic pulse. The coil is applied to the primary motor cortex, M1, contralateral to the painful side. The optimal stimulus site, motor hot spot, will be determined according to visual detection of muscle twitches, and a resting motor threshold is defined as the minimal intensity necessary to induce at least one visible muscle twitch. At each rTMS treatment, study staff will determine resting motor threshold by stimulating the primary motor cortex (functional assessment of the primary motor cortex). To find the optimal stimulation site, study staff will measure the halfway distance between the nasion and inion and the halfway distance between the right tragus and left tragus. From the intersection of these two points, the optimal stimulation site is approximately 5cm lateral on the contralateral side. Study staff may need to adjust positioning to find the optimal site by moving in all angles by approximately 1 cm. To begin, study staff will set the TMS intensity to 35% stimulator output and deliver a single pulse over the optimal site with handle 45 degrees to the sagittal plane. Intensity will be increased progressively by 5% increments until a muscle evoked potential is seen as determined by relative visual inspection. Study staff will wait 6-10 seconds between stimuli to avoid cumulative effects. Once a muscle evoked potential is seen as determined by relative visual inspection, several stimuli will be delivered to ensure a consistent response. The stimulus intensity will then be lowered in 1% stimulator output until 50% positive responses are recorded (5 out of 10). This stimulus intensity plus 1% is then defined as the resting motor threshold.

An rTMS session consists of 10 trains at 90% intensity of resting motor threshold. One train consists of 50 pulses at 5 Hz for a 10s duration. There is a 50s intertrain interval. A total of 500 pulses are applied in a session for a cumulative exposure of 5000 pulses over 10 sessions. Each session lasts about one hour.

All rTMS treatments will be administered by the PI (Dr. Ray-Griffith) or study staff who have been adequately trained to perform rTMS. Dr. Ray-Griffith will receive training for rTMS through the intensive course in TMS offered by the Berenson-Allen Center for Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center – a teaching facility of Harvard Medical Center and device specific training from the device manufacturer, Neuronetics, Inc. Device specific training from the device manufacturer, Neuronetics, Inc., will also be provided for study staff. If potential adverse events occur during the treatments, the PI will follow the data and safety monitoring plan, as stated below. All participants will receive prompt medical treatment. As treatments are completed in an outpatient setting, emergency services will be utilized in the event of a series adverse event prompting emergency medical treatment.

Table 1: Data Information for All Study Participation (Part A)

MEASURES	ENTRY (≤24 weeks gestation)	PREGNANCY VISITS (EVERY 4-6 WEEKS)	POSTPARTUM VISITS (weeks postpartum)		
			0-4	5-8	9-12
SELF-REPORT MEASURES					
PDQ	X				
General Biographical Form (WMHP Intake Form)	X				
PCS	X	X	X	X	X
Pain Interference-Short Form 4A	X	X	X	X	X
Pain Behavior-Short Form 7A	X	X	X	X	X
Pain Intensity-Short Form 3A	X	X	X	X	X
VAS	X	X	X	X	X
BDI	X	X	X	X	X
PGIC		X	X	X	X
CLINICIAN-RATED MEASURES					
CGI-I		X	X	X	X
OTHER MEASURES					
Maternal Weight and Vital Signs	X	X	X	X	X
Exposure Tracking Form	X	X	X	X	X
OB/Delivery Records			X		
Neonatal Records			X		
Urine Drug Screen	X	X	X	X	X

Table 2: Data Information for rTMS Study Participation (Part B)

MEASURE	Days with rTMS			Day 1	Day 5	Day 12	Day 22	Day 29
	Pre	Immediately Post	60 mins Post					
VAS	X	X	X				X	X
Adverse Events		X	X					
BDI				X	X	X	X	X
PGIC					X	X	X	X
CGI-I					X	X	X	X
TASS	X							

Initial Screening
Subjects will be identified by clinical staff based on current pregnancy status to identify potential subjects for the study. Once referred, initial screening by research personnel will include reviewing inclusion and exclusion criteria (as described in Eligibility Criteria) discussing the study, obtaining informed consent, completing the TASS questionnaire and initiating enrollment. These assessments and health related information will be collected on a paper form. All personnel will be qualified to administer all questionnaires.

Access to Medical Records: As a part of the informed consent for this protocol, individuals will allow the investigative team access to medical records. Any information acquired from medical records will be de-identified (no PHI, only subject ID code) and stored with the de-identified records obtained for this study.

The medical record will be utilized to gather obstetrical information regarding gestation and delivery of the infant, which may include but not limited to infant weight, height, APGAR scores, gender, head circumference, method of delivery and maternal or infant complications. Collection of health information will occur shortly following delivery of infant. Infants will only be assessed via medical records. There will be no direct assessment of infants within the scope of this study.

Questionnaires and Surveys for Parts A and B:
- Pain Interference Scale-Short Form 4a (Part A): This 4-item self-report scale measures the consequences of pain on relevant aspects of the subject's life. It includes impairment in the subject's social, cognitive, emotional, physical, and recreational activities. It also incorporates items about sleep and enjoyment of life. The short form is not disease specific and assesses pain interference over the past 7 days.
- Pain Behavior Scale-Short Form 7a (Part A): This 7-item, self-report scale measures behaviors that typically indicate to others that an individual is experiencing pain. These measures include observations (sighing, crying), behaviors (resting, guarding, facial expressions, asking for help), and verbal reports of pain. The short form is not disease specific and assesses pain interference over the past 7 days.
- Pain Intensity Scale-Short Form 3a (Part A): This 3-item, self-report scale assesses how much a person hurts. The first 2 items assess pain intensity over the past 7 days and the last item asks the subject to rate their pain intensity "right now." The short form is not disease specific.
- Pain Catastrophizing Scale (PCS) (Part A): The PCS is a 13-item self-report scale. It asks subjects to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales with the end points (0) not at all and (4) all the time. The PCS yields a total score and three subscale scores assessing rumination, magnification, and helplessness.
- painDETECT Questionnaire (PDQ) (Part A): This self-report questionnaire consists of 7 questions that address the quality of neuropathic pain syndromes. The first 5 questions ask about the gradation of pain, question 6 asks about the pain course pattern and question 7 asks about radiating pain. There are 4 additional questions which asks the subject to rate their pain now and over the last 4 weeks and to mark on a body chart if there is pain radiating into other parts of the body. These last questions are not counted in the total score.
- Exposure Tracking Form (Part A): This is a customized form used by study staff to document all exposures on a weekly basis during pregnancy and the postpartum period.
- General Biographical Form (WMHP Pain Intake Form) (Part A): All subjects will complete a WMHP-Pain intake packet, which will be composed of several sections including: 1) general

information or demographics; 2) gynecological history; 3) genetic history; 4) obstetrical history; 5) current/most recent pregnancy; 6) surgical history; 7) drug and alcohol history; 8) family medical history; 9) medical history; and 10) current status. The intake form is used at baseline and may be updated as appropriate at follow up visits.

- Beck Depression Inventory (BDI) (Part A and B): The BDI is a widely used instrument that has been used in both clinical and non-clinical setting measuring depressive symptoms. It is a 21 item questionnaire with 4-5 responses for each question. Responses are coded 0-3 for the 4 point scales. The 5 point scales include an additional 2a and 2b response code. The symptom categories reflect overt behavioral manifestations of depression. The instrument has both a high degree of reliability and validity (Beck, Ward, Mendelson, Mock & Erbaugh, 1961). This scale will be performed at every subject visit.
- Patient's Global Impression of Change Scale (PGIC) (Part A and B): The PGIC gives a global rating of change in symptoms, activities, emotion, and overall quality of life related to the subject's pain condition. This is a self-rated scale.
- Clinical Global Impression-Global Improvement Scale (CGI-I) (Part A and B): The CGI-I gives a global rating of the improvement/change in the symptoms since the last study visit. This is administered by the MD.
- Visual Analog Scale (Part A and B): 100 mm line scale that is subject administered to subjectively rate current pain symptoms. The subject will be instructed to draw a single vertical line that best describes current state. The VAS will be administered at every subject visit.
- TASS: TASS is the Transcranial magnetic stimulation Adult Safety Screen that is used to alert investigators to factors in potential subjects that may be predisposed to adverse events during rTMS. The decision to proceed with rTMS is entirely up to the investigator's judgment. TASS compliments history-taking and is not meant to exclude or replace the investigator's judgment.

Maternal Labs

We will obtain maternal urine collection for research analysis at every subject visit for urine drug screen and cotinine analysis. Urine will be collected and processed in a designated research space at PRI/UWC or in the subject's room in PRI/UAMS and will be sent to an outside laboratory. WMHP research personnel process the research lab. All research samples will be temporarily stored in a dedicated -20 degrees freezers in the Psychiatric Research Institute (PRI) 4th floor laboratory. Access to the samples will be restricted to WMHP research personnel.

Cotinine/Nicotine

Many women may continue to use tobacco during pregnancy and may or may not inform their obstetrical care about such use. Given the well documented untoward effects on pregnancy outcome, each subject will be provided information about available smoking discontinuation programs in their geographic area and encouraged to discuss tobacco use with their obstetrical care provider. Obstetricians will not be informed of a positive cotinine/nicotine screen by the investigative team.

Illicit Drugs

Urine drug analysis is important in identifying exposure to substances; however, they are not done routinely during pregnancy. In reference to the current study, the urine drug screen is important to confirm exposure to prescription and non-prescription medications that may confound study results. Not surprising, some women taking medications choose not to inform their obstetrical care about such use or the extent of such use. These medications may include both prescription medications, medications obtained through other sources (e.g. internet), and illicit substances. We view this as highly problematic and not indicative of a collaborative clinical care plan to

minimize obstetrical complications. Our experience has been that with effective education and supportive interactions, the majority of women will inform both their obstetrical and pediatric care providers. In the event that the subject refuses to notify their obstetrical care provider, this is viewed as a potential hazard to the pregnancy and infant, and in the opinion of the investigative team constitutes a 'duty to warn' – since the fetus cannot be warned, the subject will be asked to meet to discuss how to best inform their obstetrical care provider. The details regarding how to handle such medication use in pregnancy is not covered under the auspices of the social service offices in the Little Rock area. The subject's obstetrical care provider will be notified by phone with the subject in the office to permit them to hear how the information is communicated. If the subject declines such a meeting, the obstetrical care provider will be notified. The study investigators are experienced with the treatment of substance abuse in pregnancy, and the study participants will be offered care for their substance abuse problem. Given the importance of providing these women optimal clinical care, we have found that having an office visit to discuss the results and treatment planning, as well as making contact with their obstetrical care provider in their presence has been remarkably successful at keeping the women engaged in care.

Statistical Methods and Data Management

All data will be kept either in locked file cabinets or password-protected computers accessible to only investigators or designated study staff. Trained study staff will enter data and original source documents will be stored in locked file cabinets in offices with limited access. A database will also be created to input subject information and only designated study staff will have access. Periodic reviews will occur to ensure that data is accurately entered and if needed, corrections can be made. The database will generate queries to account for missing information. Every subject enrolled in this study will be given a unique ID number that will be used for tracking purposes. The key linking the unique study ID number to identifiable information will also be stored in the password-protected computers accessible to only investigators or designated study staff.
Each subject's name, SSN, birth date, address, phone number, and email address will be obtained for purposes of payment and follow-up. We will ask for each subject's drug use history, medical history, and current drug use.

Part A:
Descriptive statistics will be calculated for all measures obtained.

For the first hypothesis, primary outcome measures include VAS and pain assessments. Secondary outcome measures include BDI, PGIC, and CGI-I. For each outcome measure, scatter plots will be constructed for visual inspection across time by group. As outcome measures will be obtained at multiple time points, mixed models will be used to account for the correlations among the measurements within the subjects.

Table 3 provides a list of specific outcome data of interest for the second hypothesis. The occurrence of obstetrical outcomes will be compared between the three groups. If measures are normally distributed, we will use ANOVA to test the differences among the three groups. Otherwise, we will use a non-parametric method, such as Kruskal Wallis test, to test the difference among the groups.

Table 3: Specific Outcome Data

Obstetrical Records	Neonatal Records
• Preterm labor • Preterm birth • Premature rupture of membranes • Mode of delivery	• 1 minute and 5 minute APGAR Scores • Length of Hospitalization • Neonatal Intensive Care Unit Admission • Neonatal Abstinence Syndrome • Birth weight and length • Gender

Part B (rTMS):
We will determine the acceptability of rTMS as a treatment option by determining the percentage of subjects who accept the treatment when offered. Tolerability will be determined by the reporting of adverse events. The primary outcome measure is VAS. Secondary outcome measures include BDI, PGIC, and CGI-I. For each outcome measure, scatter plots will be constructed for visual inspection across treatment. Using previous studies of rTMS for the treatment of neuropathic pain, we will determine an effect size and complete a power analysis. This information will help guide future studies of the effectiveness of rTMS in the treatment of neuropathic pain in pregnancy.

Neonatal outcomes will be analyzed between the following groups: 1. Subjects participating in rTMS (Part B); 2. Subjects with neuropathic pain who participated in Part A but did not participate in Part B; 3. Subjects with chronic non-neuropathic pain who participated in Part A; and 4. Subjects without chronic pain who participated in Part A. Specific endpoints of interest include neonatal intensive care unit admission, length of hospitalization, birth weight and length, and 1-min and 5-min APGAR scores. The occurrence of obstetrical outcomes will be compared between the groups. If measures are normally distributed, we will use ANOVA to test the differences among the three groups. Otherwise, we will use a non-parametric method, such as Kruskal Wallis test, to test the difference among the groups.

Neonatal outcomes will be scrutinized after each delivery and neonatal period. The investigator team will convene and review all neonatal outcomes to determine if any complication occurred that could be attributed to the study, participation in the study, and/or treatment received. If any complication is identified (i.e. preterm delivery with all subjects who participated in rTMS), we will cease all current and potential study procedures related to part B of the study.

All statistical analysis will be completed using SAS 9.4. Significance will be set at $p<0.05$.

Data Safety and Monitoring Plan

A trained study staff member will perform the consenting in a quiet and private room. This person will review the consent with the subject and aid in the discussion. The consent discussion time will be determined based on the subjects' questions and understanding of the consent form. Subjects will be informed of their rights and that by participating in this research will not impact their treatment now or in the future at UAMS. It will be emphasized that the research is voluntary. The person obtaining consent will carefully explain each element of the document and outline the risks and benefits, alternate treatment(s), and any follow-up requirements of the study. Participation privacy will be maintained and questions regarding participation will be answered. The language for the consent is in English and only those who comprehend English will be allowed to provide consent for this study.

No coercion or undue influence will be used in the consent process. The steps that will be taken to minimize the possibility of coercion or undue influence include:

1. Stressing that the study is of voluntary nature.
2. Telling subjects they can leave the study anytime they choose.
3. Assuring the subjects that there are no consequences to leaving the study and that acceptance or refusal to be in the study will not affect any treatment.

We want to stress that the subject will be INFORMED of all the rights that go along with signing an informed consent to be in a voluntary study. The language used by those obtaining consent is English and the language understood by the prospective subject or the legally authorized representative will also be English. No research related procedures will be performed prior to obtaining informed consent. All signatures and dates will be obtained. A copy of the signed consent will be given to the subject. The informed consent process will be documented in each subjects' research record.

Data Handling and Recordkeeping

The PI is responsible for monitoring data confidentiality and the safety of our subjects. Quality assurance will be monitored through a set of standard operating procedures that will be compiled and placed in binders. Our safety monitoring plan includes the following:

1. The PI is the designated responsible entity;
2. Immediately following stimulation, subjects will be inspected for signs of twitching and movement indicative of seizure by the study physician.
3. In the event of seizure, the plan outlined under protection against risk will be followed by study personnel;
4. The PI will report any adverse events to the IRB, Sponsor and funding agency as appropriate.

Independent Study Monitoring

The sponsor will conduct independent data safety and monitoring according to the ORRA Monitoring Plan.

1. The Data and Safety Monitoring Plan describes operating procedures that will be in place to monitor compliance, study data validity and integrity, subject safety, individuals and/or entities (e.g., IRB) that will be involved in monitoring these procedures, and the frequency/regularity of this monitoring.
2. For Part B, the PI will meet with the medical monitor after each 3 enrollments to review adverse events.
3. UAMS IRB regulations will be strictly adhered to in the conduct of the proposed research. Specifically, prior to implementation of any protocol changes, amendments will be submitted to the IRB for approval.
4. In terms of subject safety, if an adverse event occurs during the course of a study, guidelines in the UAMS IRB Investigator's Handbook for adverse event and serious adverse event reporting will be followed. The PI will report all such activities to the IRB and the Sponsor. Additionally, the PI will inform the sponsor of any actions taken by the IRB resulting from its continuing review of this study.
5. Monitoring of the aforementioned procedures will also be overseen by the PI, study coordinator, and the IRB.
6. Data will be stored on a secure server only accessible to study staff members. Any breaches in the data integrity or confidentiality of subject information will immediately be reported to the PI and then, if necessary, to the IRB. All study staff will be trained in the protocol and

study procedures. All staff on this study has completed Human Subjects and HIPAA training. Any deviations to the protocol will be reported to the PI and to the IRB.

Termination of Study Participation:
Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Principal Investigator also has the right to withdraw subjects from the study for any of the following reasons:

- In the event of a seizure or other AE
- Non-compliance
- Protocol violation
- Study terminated
- At discretion of PI

Risks and Benefits
Identification of Adverse Events:
An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered drug/device-related by the investigator.

Adverse Event Reporting
All adverse events occurring during the course of the study, whether related to Part A or Part B or otherwise, will be recorded on the Adverse Event Case Report Form. For all adverse events, the Investigator will provide an assessment of the adverse event, its treatment and resolution, and its relationship to the study. Special reporting procedures are required for certain adverse events.

Relationship of Adverse Events to the Investigational Device
The investigator will assess the relationship of the adverse event to the investigational device. The relationship will be assessed using the following categories:

- Definitely Related: A direct cause and effect relationship between the investigational drug or device/experimental treatment and the adverse event exists.
- Possibly Related: A direct cause and effect relationship between the investigational drug or device/experimental treatment and the adverse event has not been clearly demonstrated, but is likely or very likely.
- Unlikely Related: A direct cause and effect relationship between the investigational drug or device/experimental treatment and the adverse event is improbable, but not impossible.
- Unrelated: The adverse event is definitely not associated with the investigational drug or device/experimental treatment.

Unanticipated Adverse Device Effects
An unanticipated adverse device effect is defined as “any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.” If an unanticipated adverse effect occurs, the investigator will promptly notify the sponsor of such an event within 24 hours of first learning of the event using the FDA MedWatch 3500A form. The form can be found online at: https://www.fda.gov/media/69876/download.

Serious Adverse Events

Each adverse event will be assessed for its seriousness using the criteria outlined below. The term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experienced by the subject. An adverse event will be classified as serious if it meets any of the following criteria:

- Results in, or contributes to, a death
- Life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death)
- Results in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
- Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure)
- Requires in-subject hospitalization or prolongs hospitalization
- Necessitates medical or surgical intervention to preclude a permanent disability or incapacity
- Results in a congenital anomaly or birth defect

Non-serious adverse events are all events that do not meet criteria for a "serious" adverse event.

If serious adverse event occurs, the investigator will promptly notify the sponsor of such an event within 24 hours of first learning of the event using the FDA MedWatch 3500A form. The can be found on-line at: https://www.fda.gov/media/69876/download

The investigator will also promptly notify the IRB of such an event as soon as possible, but no later than ten (10) working days after first learning of the event.

Severity

Each adverse event will be assessed for its severity, or the intensity of an event experienced by the subject, using the following.

- Mild: Discomfort noticed, but no disruption to daily activity.
- Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Severe: Inability to work or perform normal daily activity.

Deaths

The investigator will notify the sponsor and IRB as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of subject's death, regardless of whether the death is related or unrelated to the investigational drug or device. The investigator will attempt to determine, as conclusively as possible, whether the death is related to the drug or device. The cause of death and the investigator's discussion regarding whether or not the death was drug- or device-related will be described in a written report.

Pre-existing conditions

Pre-existing conditions will not be reported as an adverse event unless there has been a substantial increase in the severity or frequency of the problem, which has not been attributed to natural history.

Eliciting and Reporting Adverse Events
The investigator will assess subjects for the occurrence of adverse events at each study visit. All adverse events (serious and non-serious) reported by the subject will be recorded on the source documents and CRFs.

Abuse of illicit or licit substances during pregnancy poses a potential risk to the subject and their pregnancy that their obstetrical and pediatric care provider should be aware. As a policy, we strongly encourage subjects to communicate this information to their obstetrical and pediatric care providers. We will only share this information with other care providers with subject's signed release of information. To the best of our knowledge, participation in part A of this study poses no risk to pregnancy and/or the infant. There may be risks, discomforts, or side effects that are not known yet. There is also the possibility of loss of confidentiality.

Risks Associated with Part A
No real risks are associated with Part A of this study other than possible loss of confidentiality. Subjects may decline to answer any questions that may make subjects uncomfortable.

Risks Associated with rTMS (Part B)
Likely: Subjects may feel anxious about participation. This typically abates after the first one or two sessions.

Less likely: Subjects may experience minor discomfort associated with head and hand muscle twitching, headache, local (head and neck), and dental pain. Head and neck pain related to stimulation of underlying muscle and nerves occurs in approximately 10% of subjects. The incidence and severity is a function of stimulus site and intensity but is most common over frontal-temporal regions. The symptoms are typically mild and limited to the time of stimulation and can be treated with acetaminophen if necessary. Subjects typically tolerate the discomfort better as session's progress. The coil position is adjusted if pain occurs. Subjects will be advised to take acetaminophen for treatment if necessary. The study physician or nurse will monitor subjects during and after each rTMS for twitching of a hand muscle, such as the abductor pollicis brevis or the first dorsal interosseous muscle, on the side of the body that is contralateral to the rTMS treatment site.

Rare: Seizure and hearing loss. The risk of having a single seizure is small, estimated at ≤1/10,000 (Rossi *et al* 2009). In order to decrease this risk, subjects with preeclampsia, brain lesions, head trauma, a history of seizures (e.g., epilepsy), or taking medications known to lower seizure threshold are precluded from participating in rTMS. Study staff administering rTMS are trained in the treatment and management of an acute seizure. Life-support equipment is also readily available. All subjects will be visually monitored for signs of a seizure and/or muscle twitching throughout each rTMS treatment.

Another risk is hearing loss (temporary or permanent). To minimize this risk, subjects will wear ear plugs during rTMS. Subjects will be asked to immediately report any loosening or detachment of an earplug during treatment. Study staff will immediately stop rTMS if a subject reports or if an investigator observes that a subjects' ear plug has loosened or has fallen out.

Rare: A specific, but rare, risk of rTMS in pregnancy is inferior vena cava syndrome (or supine hypotensive syndrome). This syndrome happens in pregnancy after 24 weeks pregnant and usually occurs after laying down for about 5-10 minutes. Common symptoms are feeling dizzy

and/or upset to your stomach and having low blood pressure and/or high heart rate. The symptoms do not last long and usually go away when you change your position, such as lay on your left side. To decrease the chance of this happening, you will have a cushion placed under you right side during treatments when you are 24 weeks pregnant or greater.

Temporary changes in vision may be noticed immediately after rTMS. These visual changes are not thought to be actual problems with the eyes, but, rather changes in brain functioning as a result of rTMS. Things like blurred vision and/or eye floaters normalize in time. The risk will be minimized by using conservative stimulation parameters.

Facial numbness and facial nerve stimulation may also occur. Some sources estimate that 1 out of 3 individuals experience “facial twitching” during and/or after rTMS sessions. This twitching in the facial muscles is caused by intense electrical stimulation that penetrates the cortex. We will minimize this risk by using as conservative stimulation parameters as possible to meet the goals of the study.

Some patients may have fainted (syncopal/convulsive syncopal) or become lightheaded and nauseous during rTMS. We would stop TMS in case of suspected syncope. Such symptoms have been brief and resolved completely. In order to minimize risks the study doctor or nurse will use the following procedures to minimize the risks of convulsive syncope:

- Request information regarding a history of syncope during your screening process
- Monitor blood pressure during rTMS
- Monitor you for signs and symptoms of syncope appearing during rTMS and stop stimulation if signs and/or symptoms occur
- Immediately place you in a reclining position elevating your legs if signs or symptoms of syncope appear

Temporary changes in mood, such as mania and hypomania, have been caused by rTMS with high frequency stimulation. There are no reports of lasting changes in mood using the rate of stimulation that will be used in this study. To minimize this risk, subjects with a history of bipolar disorder have been excluded from participation in the study. In addition, subjects will be assessed clinically by the PI daily after each rTMS session for the development of mania or hypomania. If they develop during the study, the subject will be withdrawn from the study and referred for appropriate treatment as indicated. The PI is trained in the assessment and treatment of hypomania and mania.

Ferromagnetic pigments may interfere with rTMS treatments, and some forms of eye make-up, especially eyeliner, eye shadow and mascara, may contain ferromagnetic pigments. To minimize this occurrence, all subjects will be asked to remove all forms of eye makeup before each rTMS treatment.

The long-term effects of rTMS are unknown.

There may be benefit to subjects in this study who are participating in rTMS. For all others, taking part in this research study may not benefit the subjects personally, but we may learn new things that may be of benefit to women and children in the future.

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