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An Open Label Pilot Study of Transcranial Magnetic Stimulation for Pregnant Women with Major Depressive Disorder

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Abstract

Objective: Despite the data that major depressive disorder (MDD) is common during pregnancy and that pregnant women prefer nonmedication treatment options, there is a paucity of research examining alternative treatments for this special population. We present the results of an open label pilot study examining treatment with transcranial magnetic stimulation (TMS) in pregnant women with MDD.
Methods: Ten women with MDD in the second or third trimester of pregnancy were treated with 20 sessions of 1-Hz TMS at 100% of motor threshold (MT) to the right dorsolateral prefrontal cortex. The total study dose was 6000 pulses. Antenatal monitoring was performed during treatment sessions 1, 10, and 20.
Results: Seven of ten (70%) subjects responded (decrease $\geq$50% in Hamilton Depression Rating Scale [HDRS-17] scores). No adverse pregnancy or fetal outcomes were observed. All infants were admitted to the well baby nursery and were discharged with the mother. Mild headache was the only common adverse event and was reported by 4 of 10 (40%) subjects.
Conclusions: TMS appears to be a promising treatment option for pregnant women who do not wish to take antidepressant medications.

There are roughly 4 million live births each year in the United States. With approximately 13% of pregnant women meeting criteria for major depressive disorder (MDD),[1,2] about 0.5 million pregnancies are complicated by depression per year. Women who are depressed during pregnancy are less likely to get prenatal care and more likely to abuse drugs and alcohol.[3–5] In addition, depression during pregnancy is associated with poorer obstetrical outcomes, such as preterm birth,[6,7] preeclampsia,[8] lower birth weight,[9,10] and higher rates of infant admission to neonatal care units.[11] Importantly, depression during pregnancy usually continues into the postnatal period,[12] and maternal depression is known to have adverse effects on maternal-infant bonding as well as child development and behavior.[13–18]

Recently, expert consensus guidelines were published by the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) regarding the treatment of women with depression during pregnancy.[2] The guidelines recommend that psychotherapy be used for pregnant women with mild to moderate depression and antidepressants be prescribed for pregnant women with moderate to severe depression. Although most antidepressants are generally considered to be safe, there are risks associated with fetal exposure to these drugs, and as a result, some women elect to not take antidepressants during pregnancy. One potential option for such women is repetitive transcranial magnetic stimulation (TMS), a neuromodulation treatment that would not expose the fetus to medications.

TMS has been shown to be an efficacious treatment for MDD and is currently U.S. Food and Drug Administration (FDA) approved for adults with depression who have failed a single antidepressant trial in the current depressive episode.[19–21] TMS involves noninvasive delivery of focused magnetic pulses to targeted areas of the cerebral cortex. This causes local neuronal depolarization approximately 3 cm in depth from the coil surface, with an active area of

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depolarization on the cortex that is estimated to be 2 cm^2. The magnetic field, approximately 1.5 Tesla in intensity, can be pulsed at different frequencies to produce excitatory or inhibitory effects on cortical neurons. In depression, the target is the dorsolateral prefrontal cortex (DLPFC), which is thought to be abnormally hyperactive or hypoactive (depending on laterality).[22] Although the neuronal effects of TMS are not completely understood, TMS frequencies $\leq$1 Hz have mostly inhibitory neuronal effects by means of preferentially activating gamma-aminobutyric acid (GABA)ergic interneurons in the cortex, resulting in transsynaptic depression of pyramidal cell glutamatergic output.[23] TMS frequencies $\geq$1 Hz are believed to have mostly glutamatergic or excitatory neuronal effects. Both left high frequency (HFL) and right low frequency TMS (LFR) of the DLPFC have been shown to be more effective than a matched placebo (sham stimulation condition) in patients with depression.[24]

To date, there have been only 6 case reports of the use of TMS for MDD during pregnancy.[25–27] In all cases, there was improvement in maternal depressive symptoms and functioning. Although few details were provided, all neonates were reported to be in good general health. As there are as yet no systematic studies of TMS in depressed pregnant women, we conducted a standardized open label case series to further evaluate the feasibility, potential utility, and safety of this novel therapy for pregnant women with MDD.

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Subjects

Eligible participants were women 18–39 years old, 14–34 weeks gestational age, with a DSM-IV diagnosis of MDD and in a current major depressive episode (MDE), based on a semistructured assessment with the Mini International Neuropsychiatric Interview (MINI). Women were recruited from the Penn Perinatal Mood and Anxiety Program, with referrals through word of mouth and paid advertising. Subjects were included regardless of antidepressant treatment status but had to be on a stable dose for at least 2 weeks before study entry. Antidepressant doses were held constant during the TMS treatments. Women had to be experiencing at least moderate symptoms of depression, as evidenced by a Clinical Global Impression Severity (CGI-S) scale[28] $\geq$4 and a 17-item Hamilton Depression Rating Scale (HDRS)[29] score $\geq$14. Participants were not required to be in a treatment-resistant depressive episode. Participants with comorbid anxiety disorders were allowed as long as it was determined by clinical interview that the primary diagnosis was MDD.

Exclusionary criteria for study participation included a lifetime history of bipolar disorder, schizophrenia, or schizoaffective disorder; lack of response to an adequate trial of electroconvulsive therapy (ECT); prior treatment with TMS or a vagus nerve stimulator implant; a personal or close family history of a seizure disorder; presence of neurological disorder; current use of a known teratogenic medication; presence of ferromagnetic material in or in close proximity to the head; prior adverse pregnancy outcome; or current pregnancy complications. Routine laboratory studies (complete blood count [CBC], chemistry, thyroid-stimulating hormone [TSH]), urine toxicology screen, and electrocardiogram were performed at study screening, and subjects were required to be medically stable before entry. A Maternal-Fetal Medicine specialist screened and performed a physical examination for all subjects at study entry. In addition, fetal ultrasound and fetal heart rate monitoring were obtained before initiating the study.

Study overview

This single-site study was approved by the University of Pennsylvania. Institutional Review Board. The study was conducted under an Investigational Device Exemption from the FDA. All subjects signed an informed consent document before undergoing any study procedures.

The TMS sessions were delivered using the Neuronetics Model 2100 Therapy System (Neuronetics Inc., Malvern, Pennsylvania). There was no blinding procedure for patients, treaters, or raters, as treatment was open label. Psychiatric ratings were administered at baseline and after sessions 10 and 20.

Treatment Parameters

Treatment with 1-Hz LFR TMS was chosen over 10-Hz HFL TMS because of the anticonvulsant properties of the former.[30,31] The treatment protocol was 20 daily sessions of TMS (300 pulses/session, 60-second trains, 60-second intertrain intervals) at 100% motor threshold (MT) based on prior studies with LFR TMS.[32] A treatment session lasted for 10 minutes, for a total of 300 magnetic pulses delivered per session. The total study dose was 6000 pulses. MT was rechecked weekly. Stimulation was targeted to the right DLPFC based on a standardized surface anatomy approach. The figure-of-8 coil was advanced 5 cm anterior to the MT location along a right superior oblique plane with a rotation point about the tip of the patient's nose.[22] Spatial coordinates were recorded with a mechanical coil positioning system to ensure placement reproducibility. The MT estimation was repeated weekly by visual observation of thumb or other finger movement[33] using the MT Assist (Neuronetics Inc.). The latter is a standardized, software-based mathematical algorithm that provides an iterated estimate of the MT. Sessions were generally administered Monday–Friday but could be made up on the weekends if missed or cancelled.

Maternal vital signs were checked at each treatment. In addition, uterine tocodynamometry and fetal heart rate monitoring were performed, supervised by a Maternal-Fetal Medicine specialist during treatments 1, 10, and 20. All treatments were performed in a perinatal evaluation center with access to oxygen, obstetrical nurses, and physicians as well as anesthesiologists. An attending psychiatrist (D.R.K.) or fellow (P.C.) administered all treatments.

Feasibility and outcome assessments

The percentage attendance at scheduled sessions was assessed as the primary outcome of feasibility. The primary efficacy outcome was the difference between the baseline 17-item HDRS score and the HDRS score after session 20. Secondary outcome measures were the Beck Depression Inventory (BDI)[34] and Beck Anxiety Inventory (BAI)[35] after session 20. The CGI-S was also completed. Treatment response was defined as at least 50% reduction in the 17-item HDRS score from baseline to end of treatment. Remission was defined as an HDRS score $<$8 and a CGI-S $=$ 1.

Safety assessments

Safety was assessed at every treatment visit by recording spontaneous adverse events that were coded using the current version of the *Medical Dictionary for Regulatory Activities*. Posttreatment fetal growth ultrasound studies were obtained within 1 week of finishing treatment 20. Delivery records were obtained, and gestational age at delivery, infant weight and length, neonatal Apgar scores, neonatal intensive care unit (NICU) admissions, and congenital malformations were evaluated.

Statistical methods

Descriptive analyses were performed to characterize the study population and infant outcomes. This study comprised a single group with change in outcome assessed from baseline to study end point. For continuous variables (HDRS, CGI-I, CGI-S, BDI, BAI), Wilcoxon signed-rank test was used to compare within-woman change in outcome, with significance set at $p = 0.05$.

Results

Subject characteristics

A total of 13 women signed consent for study participation at the screening visit. Three women were excluded from starting treatment for the following reasons: 1 fetal ultrasound showed intrauterine growth retardation, 1 fetal ultrasound showed multiple congenital malformations, and 1 potential participant was determined to have adjustment disorder with depressed mood rather than MDD and was referred for psychotherapy. Seven Caucasian and 3 African American women were enrolled for treatment after giving written informed consent and concluding the screening process. Subject characteristics at study entry are shown in Table 1. Fifty percent (5 of 10) had a comorbid anxiety disorder. The majority, 9 of 10 (90%) had an entry HDRS-17 ≥ 20, indicating at least moderate depression severity. Also, 4 of 10 (40%) were on a concurrent antidepressant. No changes were made in antidepressant dosing for at least 2 weeks before study entry. Subjects 2, 3, 4, and 5 (Fig. 1) were on antidepressants as follows: subject 2, bupropion SR 300 mg, escitalopram 20 mg; subject 3, escitalopram 10 mg; subject 4, sertraline 100 mg; subject 5, fluoxetine 40 mg. The MT was determined weekly. The average percentage of device power output to obtain the MT was 77.8% (standard deviation [SD] 12.8) at session 1 and 81% (SD 14.9) for sessions 6, 11, and 16.

Table 1. Subject Characteristics

	Pre-TMS	*Post-TMS*	p *value*
Mean age (SD), in years	31.2 (5.6)	NA	
Mean gestational age (SD)	25.8 (5.16)	NA	
Race	7 white, 3 African American	NA	
Marital status	9 married, 1 single	NA	
Concurrent antidepressant	4 yes, 6 no	NA	
Mean HDRS-17 (SD)	24.4 (5.6)	9.7 (6.1)*	0.0050
Mean CGI-S (SD)	4.6 (0.5)	1.7 (0.7)*	0.0036
Mean BDI (SD)	33.2 (9.0)	18.7 (11)*	0.0050
Mean BAI (SD)	18.9 (12.5)	14.7 (16.3)	0.1022

*Significant.

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CGI-S, Clinical Global Impression Severity Scale; HDRS, Hamilton Depression Rating Scale; NA, not available; SD, standard deviation; TMS, transcranial magnetic stimulation.

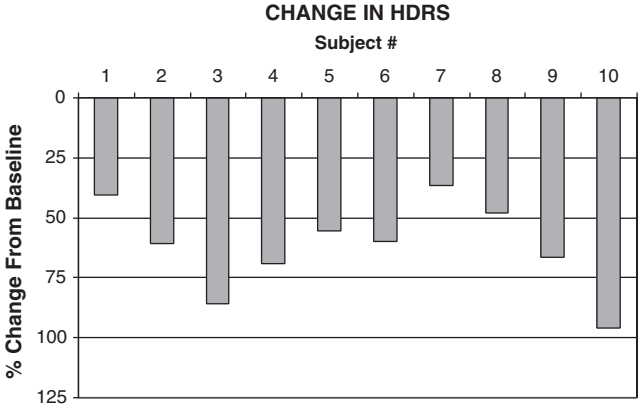

FIG. 1. Change in depression scores from baseline to treatment session 20. HDRS, Hamilton Depression Rating Scale.

Feasibility

All subjects completed all 20 planned sessions, although sessions were occasionally rescheduled because of illness or weather. No subjects dropped out of treatment due to intolerable side effects or symptom worsening.

Clinical response

Changes in HDRS-17 and CGI-S scores from baseline to week 4 were assessed (Fig. 1). Mean entry HDRS-17 was 24.4 (SD 5.2), and the mean posttreatment HDRS-17 was 9.7 (SD 6.1), showing a mean decrease of 60% ($p = 0.005$). Seven of 10 (70%) subjects had $\geq$50% improvement in HDRS-17 scores, indicating response. Significant improvements in other measures were also observed. Mean entry CGI-S was 4.6 (SD 0.5), and the mean posttreatment CGI-S was 2.4 (SD 0.9) ($p = 0.004$). Three participants (30%) had a post-TMS HDRS-17 score <8 and CGI-S of ≤ 1, indicating remission. The mean entry BDI and BAI were 33.2 (SD 9.2) and 18.8 (SD 12.5), respectively, and posttreatment they were 18.7 (SD 11.1) and 14.7 (SD 16.3), respectively. The BDI decreased by an average of 44%, which was significantly improved ($p = 0.005$), and there was little change in the BAI ($p = 0.10$). For all scales, there was no significant difference in response rates between the 4 participants on antidepressants and the 6 off antidepressants ($p > 0.05$). All subjects had 100% treatment compliance, attending every TMS session.

Maternal adverse events

No serious maternal adverse events were observed or reported. Mild headache was the only common adverse event and was reported by 4 of 10 (40%) subjects. Headaches

typically lasted 1–2 hours after the TMS session during the first week of treatment. Maternal vital signs were monitored before and after treatments, and no significant posttreatment changes in heart rate or blood pressure were noted. One participant had an episode of supine hypotension during her tenth treatment session. She felt light-headed, and her blood pressure was 66/30. The treatment was stopped, she was repositioned, and the hypotension and lightheadedness resolved quickly. It did not recur in this participant during the rest of the treatments despite no change in the protocol or positioning of the participant.

Pregnancy and neonatal outcomes

Antenatal monitoring was done with uterine tocodynamometry (to assess uterine contractions) and fetal heart rate monitoring for 20 minutes before, during, and 20 minutes after TMS treatments at sessions 1, 10, and 20. One participant had a uterine contraction followed by a fetal heart rate deceleration at 18 minutes after treatment 20. Uterine tocodynamometry and fetal heart rate monitoring were extended for another hour, with no further events. This was determined by the study obstetrician to not be a study-related event. No other abnormal uterine contraction patterns were observed.

Except as noted, fetal heart rate tracings were normal during all monitoring sessions. Ultrasound studies conducted at baseline and within 1 week of the end of treatment showed that all fetuses were appropriately grown for gestational age. All infants were healthy at delivery (Table 2). All were born >37 weeks gestational age, with mean/median 1-minute and 5-minute Apgar scores of 7.9/8 and 8.75/9, respectively. All infants were admitted to the well baby nursery and were discharged with the mother. No major congenital anomalies were detected on the initial pediatric assessment.

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This is the first case series to systematically describe TMS for treatment of MDD during pregnancy. In this cohort of 10 women, 70% responded to treatment, and 30% of the subjects met criteria for remission after the twentieth treatment session. LFR TMS has shown similar overall therapeutic benefit to HFL TMS, based on the results of five controlled studies.[32,36–39] LFR TMS was chosen because there is a small risk of seizure with HFL TMS. Seizures can be detrimental during pregnancy because of the risk of inducing preterm labor and fetal demise by reducing the blood supply to the fetus. Because the study was conducted in a non-treatment resistant depression (TRD) population, with TMS added adjunctively to existing antidepressant treatment in half of the subjects, the relevant comparative outcome data are with non-TRD populations treated with LFR TMS. In sham controlled trials with non-TRD populations, response rates with LFR TMS are between 48% and 63%.[38,39] Both of these studies used fewer sessions than ours, which is one possible explanation for the higher response rate observed in the current study. Of course, the open label nature of the study prohibits overly positive conclusions about these results. In addition, the TMS dose used in this study is relatively low, and higher doses, if safe, could improve efficacy results.

Table 2. Pregnancy and Fetal Outcomes

Offspring gender	4 male, 6 female
Mean gestational age at delivery (SD)	39 (0.32) weeks
Mean birth weight (gs) (SD)	3395.5 (458.98)
Mode of delivery	8 vaginal, 2 cesarean section
Mean Apgar 1 minute (SD)	7.9 (1.36)
Mean Apgar 5 minute (SD)	8.75 (0.48)
Major congenital malformations at birth	0/10
NICU admissions	0/10

NICU, neonatal intensive care unit.

An unexpected finding was that the MT differed from what we expected based on the literature[40] and our own experience delivering TMS. In particular, the device power output was significantly higher than expected (J.P. O'Reardon, M.D., personal communication). The unique neuroendocrine milieu of pregnancy may necessitate unique TMS device parameters. Data demonstrate that neurosteroids quickly affect neuronal excitability by binding to membrane-bound receptors for inhibitory or excitatory neurotransmitters.[41] Progesterone and its metabolite, allopregnanolone (ALLO), increase significantly during pregnancy,[42,43] and ALLO is known to have an inhibitory GABAergic effect on neuronal activity.[44–46] In pregnant mice, neuronal excitability increases and decreases in the absence and presence of ALLO, respectively.[47] Smith et al.[48] have shown that high progesterone states, such as during the luteal phase of the menstrual cycle, cause inhibition of the conditioned motor-evoked potential by paired pulse TMS, suggesting that TMS can be used to understand the effect of the neuroendocrine milieu on cortical excitability.

Treatment compliance was 100%, with all subjects attending all 20 treatment sessions. This was a highly motivated cohort, and they received a great deal of personal attention throughout the study period. However, TMS is a well-tolerated treatment with few side effects, and compliance tends to be high.[49] In the largest study to date, the discontinuation rate for active TMS because of adverse events was 4.5%.[21] Headache was the only study-related adverse event, and in all cases it was mild and resolved after the first week of treatment. All women reported wanting to avoid psychotropics or increases in psychotropics as their motivation for study participation.

Only 20%–30% of pregnant women report that antidepressants are an acceptable option during pregnancy.[50,51] The benefit of treating with antidepressants often outweighs the risk, but no antidepressant has been proven to be completely safe in pregnancy. In particular, the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has come under recent scrutiny regarding their potential to induce cardiac defects,[52] neonatal adjustment syndrome,[53] and persistent pulmonary hypertension of the newborn.[54,55] Given that expert consensus guidelines recommend initiating or continuing antidepressants for moderate to severe depression during pregnancy,[2] other options must be studied so that women can have a range of treatment choices. Education for women and their partners about the relative safety of antidepressants during pregnancy is imperative, but still, researchers should continue to pursue treatments that do not expose the fetus to psychotropics.

Other nonpharmacological alternatives for treatment of depression during pregnancy include psychotherapy and ECT.[2,56,57] Psychotherapy should be a first-line treatment recommendation for MDD during pregnancy. However, access to skilled practitioners remains a genuine clinical

concern, and as with many treatments, some patients will remain significantly symptomatic. ECT has been used safely in pregnant women but requires the use of anesthetic agents and neuromuscular blockers, again subjecting the fetus to the transplacental effects of pharmacological agents. There may also be risks, albeit small, of induction of premature labor and placental abruption.[58] It is, thus, necessarily reserved for treatment of the most severe or incapacitating depressive episodes during pregnancy.

Among the study participants, there were no major pregnancy or neonatal complications. One participant had an episode of supine hypotension that resolved with repositioning. In sum, however, this only happened once out of a total of 200 sessions performed in this study. Supine hypotension is more common during pregnancy as a result of uterine pressure on the inferior vena cava. It may be wise to consider using a wedge under the lower back of pregnant patients so they are tilted slightly to the side. We considered doing this, but as this was a single event that was not observed in prior participants, we were not convinced it was a study-related event. Therefore, we elected to proceed without requiring wedges, and there was no recurrence of supine hypotension. Our sample size is too small to make any conclusive statements about the safety of TMS during pregnancy, but the early data are encouraging. In all 6 previously reported cases in the literature regarding the use of TMS for MDD during pregnancy, all infants were reported to be healthy at delivery. In the first case reported in the literature, the patient received 14 sessions of HFL TMS beginning at week 22 of pregnancy.[25] Her depression remitted, and she delivered a healthy 7.5-lb term infant.

The next 2 cases were reported nearly a decade later, in 2008.[26] The first patient received 15 sessions of HFL TMS starting at 16 weeks of pregnancy. The second patient was treated with 15 sessions of LFR TMS starting at 31 weeks of pregnancy (300 pulses/session, 60-second trains, 60-second intertrain intervals) at 100% MT. This is the same design as our pilot study except we gave 20 sessions. Both patients had $\geq$50% reduction in depression scores. The second infant (who was also exposed to venlafaxine) was born slightly preterm at 36 weeks, but both infants were reported to be healthy. Most recently, in 2009, an additional 3 cases were reported.[27] No details about the frequency, duration, or number of pulses/session were included. The authors provided a general statement that the infants were born in good health.

With so few safe and effective options for the treatment of depression during pregnancy, it is crucial that novel techniques be studied. Ideally, treatments for depression during pregnancy would have a rapid onset of therapeutic action as well as no impact on fetal development. We propose that repetitive TMS is one such potential option. We have tested this hypothesis in an open label pilot trial of 10 women and have found that TMS has the potential to be a feasible and efficacious treatment for depression during pregnancy. In addition, these data indicate that dosing parameters of TMS may differ in pregnant women with respect to the MT. Given these promising results, a randomized, sham/placebo controlled trial is warranted.

D

D.R.K. received device and travel support from Neuronetics, Inc. M.E.T. has been a consultant to Neuronetics, Inc., and is a member of their Scientific Advisory Board; he has similar relationships with the manufacturers of antidepressants and second-generation antipsychotics. J.P.O'R. has received research support and has been a consultant to Neuronetics, Inc., has received research support from Cyberonics and Medtronics, and is on the Eli Lilly speaker's bureau. N.E. has stock options in Johnson & Johnson and receives research support from Eli Lilly. P.C. has received research support from Neuronetics, Inc., Cyberonics, and Medtronics. The other authors have no conflicts of interest to report.

R r s

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