Repetitive transcranial magnetic stimulation treats postpartum depression

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Background
Postpartum depression (PPD) is a prevalent illness, affecting 10-15% of new mothers. PPD is the most common complication of childbirth and is a significant public health concern. It is known to adversely impact maternal-infant bonding, childrearing practices, and can lead to suicide and infanticide. The current treatment approaches to PPD are suboptimal. Many mothers are reluctant to take medication because of concerns about side effects or exposure of their newborn infant through breastfeeding. The specific aims of this study were to (1) examine acute treatment effectiveness, (2) examine response durability, and (3) assess an effect of repetitive transcranial magnetic stimulation (rTMS) on maternal bonding.

Methods
Nine antidepressant-free women with PPD were given 20 rTMS treatments over 4 weeks (10 Hz, 120% motor threshold, left dorsolateral prefrontal cortex). Multiple characteristics were assessed at baseline and throughout treatment. Duration of effect was assessed at 30 days, 3 months and 6 months posttreatment.

Results
Friedman’s tests were conducted on Hamilton Rating Scale for Depression-24 item (HRSD-24), Edinburgh Postnatal Depression Scale (EPDS), Inventory of Depressive Symptomatology-Self-Report (IDS-SR) and Clinical Global Impressions-Severity (CGI-S) scores to compare performances at four time points (baseline, end of Week 2, end of Week 4, and 180-day follow-up). Overall, these results revealed a significant reduction in depressive symptoms by the end of Week 2 of treatment. Analyses yielded a medium effect size ($r = 0.68$) on the primary outcome variable (HRSD-24). Of note, all nine patients remained in treatment for the complete 4 weeks, did not miss any treatment sessions and eight participants achieved remission of symptoms, defined as a HRSD < 10 and a CGI-S = 1. Analysis of follow-up data indicated robustness of the rTMS treatment over time. At 6-month follow-up, of the eight women that remitted, seven remained in remission without further psychiatric intervention, including the addition of medication and one was lost to follow-up. Results also indicated a significant improvement in bonding.

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Conclusions
Our results demonstrate promising results for the use of rTMS in the treatment of PPD. Further randomized, sham-controlled studies need to be completed.
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Keywords repetitive transcranial magnetic stimulation; postpartum depression; transcranial magnetic stimulation

Postpartum depression (PPD) is reported to occur in 10-15% of delivering women.1,2 It is the most common complication of childbirth and is a significant public health concern.3,5 PPD disrupts maternal homeostasis and has an insidious impact on the lives of families by affecting maternal-infant bonding, breastfeeding, child-rearing practices, and overall child well-being.5,8 Furthermore, PPD has been shown to place children at significant risk of impaired cognitive and emotional development.7 Unfortunately, PPD is associated with both maternal suicide and infanticide.9,10 Treatment options for PPD are currently limited to psychotherapy, pharmacotherapy, and electroconvulsive therapy (ECT). Studies have found psychotherapeutic interventions to be an accepted intervention for PPD. Treatment in the form of individual therapy, peer support, and/or group therapy has been found to be helpful in alleviating the anxiety, irritability, and feelings of detachment experienced by women who have PPD.11-13 Specifically, interpersonal psychotherapy (IPT) is a proven, effective treatment for mild-to-moderate PPD and an alternative to pharmacotherapy, especially for women who are breastfeeding. However, IPT may not be the treatment of choice for women who have moderate-to-severe symptoms and/or have a history of severe depression in the past, or have had previous reproductive-related depressive disorders.14 In addition, only limited information regarding the durability of IPT exists and it has been shown that its beneficial effects may be time limited.15

Physicians generally prefer pharmacotherapy to treat women with PPD.16 However, patient acceptance of the use of psychotropic medication for the treatment of PPD is limited by maternal concerns regarding infant exposure through breastfeeding and the unknown future effects of such exposure.17,18 As a consequence of the perceived risk of breastfeeding while on medication, as well as other concerns, such as the potential impact of medication side effects on late night child care, a significant number of women report that they would not consider using psychotropic medication to treat their PPD.19 The end result is that many women choose to expose their infant to the adverse effects of PPD rather than receive treatment.

ECT has been the primary device-based therapy for treating unremitting major depression for over 6 decades, and is perhaps the most broadly effective treatment for major depression.20 Although there are no systematic trials of ECT in PPD, case literature supports its effectiveness in postpartum psychiatric states.21 ECT, however, has well-documented adverse effects, including headache, muscle pain, and memory deficits.22-24 In addition, recovery time from each ECT treatment may take several hours, which can limit the ability of a new mother to care for her infant.

Repetitive transcranial magnetic stimulation (rTMS) is a recently US Food and Drug Administration-approved depression therapy,25,26 which uses briefly pulsed, powerful magnetic fields to induce focused electrical currents in the brain, depolarizing neurons. Recent meta-analyses have shown that rTMS is superior to sham conditions in the treatment of patients with major depressive disorder (MDD).27-29 Unlike psychotherapeutic interventions, patients receiving rTMS respond rapidly, often within 2-4 weeks, and the response can be sustained.30 Repetitive TMS is unique compared with other somatic depression therapies because there are no systemic side effects that would interfere with child care and no risk of exposure to the infant through breastfeeding. Thus, the use of rTMS for the treatment of PPD would address many of the short comings of medication.

We have completed an open-label rTMS treatment trial (pilot) of unmedicated mothers with PPD in an attempt to estimate the utility of rTMS in this population. Outcome measures included investigator-administered, as well as self-reported, measures of depression, and response durability was monitored for 6 months. In addition, we examined the effects of rTMS on maternal bonding.

Methods
Human Research Protections protocol approval was obtained from the Washington University School of Medicine Human Research Protections Office before enrolling subjects. Informed consent was obtained during an appointment with the principal investigator before performing any protocol procedures.

Patients
Recruitment material was displayed in more than 50 obstetrics/gynecology offices and in local businesses frequented by women in a large metropolitan Midwestern community. Physicians in the community were encouraged to make referrals to the study through marketing methods, including presentations by the study nurse coordinator and principal investigator and mailings that informed them about inclusion requirements.
The entrance criteria included women with clinically diagnosed PPD, age 18-50 years old, who had experienced an uncomplicated pregnancy and delivery that resulted in a healthy, single infant. A score greater than nine points on the Edinburgh Postnatal Depression scale (EPDS), as well as documentation of meeting DSM-IV-TR criteria for a major depressive episode (completed by study psychiatrist/principal investigator, K.S.G.) was required for entry. Patients with a history of psychosis or bipolar disorder were excluded from participation.

A total of 39 women were screened by telephone. Of these, 27 women did not meet the inclusion criteria or were unable to participate because of other issues (two were calling for their daughters; two preferred medication; two had child care issues; two had a history of drug or ethyl alcohol dependence; one had transportation issues; three had a time commitment; one had a multiparous birth; one had an adopted infant; two had a history of drug or ethanol dependence; one had transportation issues; three had a time commitment; one had a multiparous birth; one stated medical reasons; three were bipolar and on medication; seven gave no reason [three of whom were scheduled for in-person informational appointments but did not show up]). Interviews were conducted for the remaining women and resulted in 12 signed informed consents. After the signing of the consent form, the principal investigator (K.S.G.) performed a protocol-specific interview that involved a discussion of the participant’s options for treatment, as stated in the consent form. Three participants consented and then withdrew their consent after the initial interview with the principal investigator. One woman was returning to work full time and was not sure her job would allow the time off for treatment. The other two women preferred the option of returning to their primary care physician for medication therapy. Nine women who completed the selection process were enrolled. Baseline characteristics for the participants are summarized in Table 1.

Participants were 30 days to 1-year postpartum. Fifty percent of our study’s subjects were breastfeeding, which reflected a section of the PPD population known to be unwilling to expose their infants to antidepressant medications. Before treatment, participants were queried as to their primary reason for choosing rTMS. The predominant response was “I was concerned about medication side effects.” Eight of the nine participants had a previous history of major depressive disorder, and two of the eight with a postpartum onset. Of these eight, four received successful pharmacologic intervention, two were intolerant of medication side effects, and two were not treated. Participants were antidepressant-free at study entry and other than one participant taking seven 2-mg doses of diazepam over the course of the 4 weeks of treatment for Meniere-related vertigo, no psychotropic or central nervous system medications were consumed.

### Study design

This study was an open-label, single-arm 4-week pilot of the use of high-frequency, high-intensity, left dorsolateral prefrontal cortex (DLPFC) rTMS for the treatment of PPD.

### Repetitive TMS treatment

Twenty rTMS treatments (10 Hz applied at 120% of the motor threshold for 4 seconds of stimulation and 26 seconds off for a total of 75 trains or 3000 pulses) (NeuroNetics Model 2100 CRS TMS System, Neuronetics, Inc., Malvern, PA) were delivered five times per week over the left DLPFC. Motor threshold testing was performed weekly by the principal investigator to modify dosing if required. Treatment was administered by an rTMS-experienced registered nurse or physician assistant.

### Assessment of depressive symptoms

Assessment of depressive symptoms included a clinical interview, Edinburgh Postnatal Depression Scale (EPDS), Hamilton Rating Scale of Depression-24 (HRSD-24), Inventory of Depressive Symptomatology-Self Report (IDS-SR), and Clinical Global Impressions-Severity (CGI-S) that occurred weekly throughout treatment and at 1-, 3- and 6-months posttreatment. In addition, a measure of bonding was administered before and immediately after the 4 weeks of treatment (Postpartum Bonding Questionnaire [PBQ]). The PBQ consists of 25 items.

### Table 1: Demographic characteristics of nine PPD patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>89% White, 11% Indian</td>
</tr>
<tr>
<td>Marital status</td>
<td>67% Married, 33% Single</td>
</tr>
<tr>
<td>Employment status</td>
<td>67% Employed</td>
</tr>
<tr>
<td>Breastfeeding status</td>
<td>50% Breastfeeding</td>
</tr>
<tr>
<td>Age (y)</td>
<td>34.11 (6.05)</td>
</tr>
<tr>
<td>Level of education</td>
<td>16.89 (2.47)</td>
</tr>
<tr>
<td>EPDS baseline score</td>
<td>18.22 (4.52)</td>
</tr>
<tr>
<td>HRSD-24 baseline score</td>
<td>22.67 (6.44)</td>
</tr>
<tr>
<td>IDS-SR baseline score</td>
<td>41.22 (11.69)</td>
</tr>
</tbody>
</table>

PPD = postpartum depression; EPDS = Edinburgh Postnatal Depression Scale; HRSD-24 = Hamilton Rating Scale of Depression-24; IDS-SR = Inventory of Depressive Symptomatology-Self Report; SD = standard deviation. Data are given as mean (SD).
rated on a scale of 0-5. The PBQ has 25 statements, each followed by six responses ranging from “always” to “never.” Positive responses, such as “I enjoy playing with my baby,” are scored from zero (always) to 5 (never). Negative responses, such as “I am afraid of my baby,” are scored from 5 (always) to zero (never). The sum of scores for all the 25 items is calculated, with a high score indicating pathology.

**Statistical analysis**

The primary outcome measure for the study was the HRSD-24. Secondary outcome variables included the EPDS, IDS-SR (self-report), and CGI-S. Treatment response was defined as a > 50% reduction in HRSD-24 scores from baseline. Remission was defined as a HRSD-24 < 10 and a CGI-S = 1.

Friedman’s tests were conducted on HRSD-24, EPDS, IDS-SR, and CGI-S scores to compare depressive symptomatology at four time points (baseline, end of treatment Week 2, end of treatment Week 4, and 180-day follow-up). Friedman’s test was chosen because the assumption of normality could not be verified and the sample size was small. In the presence of a significant overall test, post hoc comparisons were performed by using the Wilcoxon signed-ranks test. The critical alpha level was adjusted by using Bonferroni’s correction to take into account the potential for increased Type I error (critical alpha = .008). Effect size ($r$) was calculated by completing a Wilcoxon signed-ranks test comparing baseline with the end of week 4 HDRS-24 scores (a priori analysis point). The resulting Z score was then entered into the following formula: where $r = Z/\sqrt{N}$. Wilcoxon signed-ranks test was used to examine changes in mother-infant bonding from pretreatment to posttreatment as measured by the PBQ.

**Results**

The results of the Friedman’s tests indicated that there was a significant improvement in depressive symptomatology (Table 2). Post hoc analyses (i.e., Wilcoxon signed-ranks test) with adjustment of the two-tailed level to .008 to accommodate increased Type I error indicated that the significant decrease in symptoms occurred at the end of the second week of treatment (HRSD-24 baseline Md = 23.00, Week 2 Md = 10.00, $P = .008$; EPDS baseline Md = 19.00, Week 2 Md = 9.00, $P = .008$; IDS-SR baseline Md = 45.00, Week 2 Md = 21.00, $P = .008$). A Wilcoxon signed-ranks test comparing baseline with the end of week 4 HDRS-24 scores (a priori analysis point) yielded a medium effect size ($r = 0.68$). Of note, all nine patients remained in treatment for the complete 4 weeks and did not miss any treatment sessions. Eight participants achieved remission of symptoms, defined as a HRSD < 10 and a CGI-S = 1. Analysis of follow-up data indicated robustness of the rTMS treatment over time (Figures 1-3).

![Figure 1](image1.png)  
**Figure 1** Hamilton Rating Scale of Depression-24 items (HRSD-24) means across study duration.

![Figure 2](image2.png)  
**Figure 2** Inventory of Depressive Symptomatology-Self-Report (IDS-SR) means across study duration.
medication, and one was lost to follow-up. In addition, a Wilcoxon signed-ranks test was conducted to evaluate the impact of the intervention on women's bonding with their infants (as measured by the PBQ). There was a statistically significant improvement in bonding scores from pretreatment ($Md = 20.00$) to posttreatment ($Md = 7.00$, $P = .010$) assessment.

Repetitive TMS was safe and well tolerated. A patient satisfaction questionnaire given at the end of treatment indicated that eight of nine preferred rTMS to medication, but only six of nine believed it was convenient. Minor adverse events included headache, treatment site pain (both of which were relieved with pretreatment over-the-counter analgesics), and facial stimulation (which resolved with magnetic repositioning). There were no drop outs because of adverse events and there were no observed serious adverse events.

Discussion

This is the first open-label rTMS pilot group study of PPD to address the question of the use of rTMS as a treatment for PPD (three previous case studies existed). Treatment response was rapid, robust, and durable suggesting that rTMS could be used as a treatment bridge that would allow mothers with PPD to remain medication free until a time when they are no longer breastfeeding and the use of medication maintenance becomes more acceptable, if needed.

As with any small pilot, these results should be viewed as highly preliminary. Shortcomings of the study include small sample size and the lack of a sham control arm. In addition, although psychotherapy was not administered, daily contact with the professional psychiatric research staff administering rTMS treatments could have influenced the outcome. Depression was recurrent in eight of nine of our treatment population and, of these, four of six of our treatment population had been successfully treated with medication for previous episodes (two received no treatment). The patients in the study were not treatment refractory, but rather unwilling to pursue other systemic treatments such as medication during their postpartum period. Thus, rTMS appears to be ideally targeted toward mothers with PPD who are treatment responsive, but would otherwise forgo treatment because of concerns about the adverse impacts of medication.

Previous rTMS studies have not demonstrated the impressive remission rates and maintenance of remission observed in this small pilot study. This raises a concern that these results might be spurious. Several factors could account for this discrepancy. First, the study was open-label, thus our patients were aware they were receiving active treatment and may have experienced a placebo response. However, recent studies have shown that a placebo response is lower in rTMS trials in which it is not used as an add-on therapy. Second, our population was not treatment refractory and many had responded successfully to treatment in previous episodes. No current rTMS treatment literature exists describing nontreatment-resistant patients’ responses to rTMS. This is clearly an area that needs to be further explored. Third, our treatment protocol was more aggressive than most published protocols with higher dosing over longer treatment periods. Finally, PPD may be more responsive to rTMS than other forms of MDD because it may be a unique form of MDD or a form of MDD that may be more self-limiting. This area of interest could also benefit from further examination.

Conclusions

This small pilot study is encouraging. Future large-scale, sham-controlled studies are needed to confirm our observations. Feedback provided by participants highlighted the need for onsite child care to enhance treatment convenience and should be included in any future studies. The potential use of rTMS as a prophylactic treatment for depression occurring during pregnancy and during the postpartum period, when medication management is undesirable, represents an additional opportunity for the use of rTMS. There is an urgency to develop an alternative therapy for treating women who have PPD. We believe rTMS may become a preferred treatment for PPD.

We express our sincere thanks to the women participating in this unique pilot program. Our appreciation is also extended to Neuronetics, Inc., for supplying the Neuronetics Model 2100 CRS TMS System.

References


