Published in final edited form as:

Brain Stimul. 2019 ; 12(1): 96–102. doi:10.1016/j.brs.2018.09.005.

Randomized Controlled Trial of Transcranial Magnetic Stimulation in Pregnant Women with Major Depressive Disorder

Deborah R. Kim, M.D.^a, Eileen Wang, M.D.^b, Brendan McGeehan, M.S.^a, Jessica Snell, M.S.^{a,*}, Grace Ewing, B.A.^a, Claudia Iannelli, M.S.^a, John P. O'Reardon, M.D.^{a,**}, Mary D. Sammel, Sc.D.^c, and C. Neill Epperson, M.D.^a

^aDepartment of Psychiatry, Perelman School of Medicine at the University of Pennsylvania

^bDepartment of Obstetrics and Gynecology, Perelman School of Medicine at the University of Pennsylvania

^cDepartment of Biostatistics, Epidemiology & Informatics, Perelman School of Medicine at the University of Pennsylvania

Introduction:

Repetitive transcranial magnetic stimulation (TMS) was developed for the treatment of depressed patients who suffer treatment resistance. Because TMS is a non-medication option, patients who do not tolerate or prefer to avoid antidepressants are good candidates for TMS even in the absence of treatment resistance. Ample data suggests that pregnant women experience high decisional conflict regarding psychiatric treatment options during pregnancy and prefer non-medication alternatives when possible (Kim et al., 2011b, Patel and Wisner, 2011, Walton et al., 2014). Therefore, pregnant women with depression may be good candidates for TMS.

Approximately 10% of women experience major depressive disorder (MDD) during pregnancy. Both untreated depression and antidepressant use during pregnancy have been associated with adverse maternal and child outcome (Bennett et al., 2004, Chatillon and Even, 2010, Ibanez et al., 2012), such as preterm birth (PTB; birth prior to 37 weeks gestational age) (Kim et al., 2013). This makes treatment decisions complex for both doctor and patient, sometimes leading to the avoidance of treatment in pregnant women with MDD

Corresponding author – Deborah R. Kim, M.D.; Associate Clinical Professor of Psychiatry; 385 Lancaster Ave, Haverford, PA 19041 (present address); drkim@pennmedicine.upenn.edu.

Permanent address: Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, 3rd Floor, Philadelphia, PA 19014

*Present Address – Scranton, PA

**Present address - 2301 E Evesham Rd #304, Voorhees Township, NJ 08043

Conflict of Interest: Neuronetics, Inc (Malvern, PA) provided the TMS device to Dr. Deborah Kim. The other authors of no conflict of interest to declare.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

which can result in profound consequences for the pregnancy and on child development (Betts et al., 2014, Grigoriadis et al., 2013, O'Donnell et al., 2014, Pearson et al., 2013).

Following up on our open label, pilot study (Kim et al., 2011a), we conducted a randomized controlled trial (RCT) of TMS in pregnant women with MDD with a main hypothesis that active TMS would significantly improve depression. The pilot study did not evaluate if TMS had any effect on hormone levels during pregnancy that may affect pregnancy outcomes. Therefore, measurements of estradiol and progesterone were collected pre-and post-TMS. Although no previous studies have looked at the effect of TMS on estradiol and progesterone, given data on the effect of TMS on prolactin and thyroid stimulating hormone levels (Szuba et al., 2000, Szuba et al., 2001), we hypothesized that estradiol and progesterone levels would be unaffected by TMS.

Materials and Methods:

Subjects

Eligible women were required to be 18–39 years old, 14–34 weeks gestational age (GA) by last menstrual period and first trimester ultrasound, with a DSM-IV diagnosis of MDD based on the Structured Clinical Interview for DSM-IV (SCID-I) (First MB, Spitzer RL, Gibbon M, Williams JB, 1995). Subjects taking psychotropics were included if the dose was stable for two weeks prior to randomization. A Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1967) score ≥ 18 and a Clinical Global Impression Scale-Severity (CGI-S) (Guy W, 1976) ≥ 3 were required for study admission. Participants with comorbid anxiety disorders were allowed if it was determined clinically that the primary diagnosis was MDD. Exclusion criteria included a history of PTB; a seizure disorder in self or first degree relative; any metallic object implanted in the skull; significant cardiac disease; presence of a known abnormality in the fetus; known obstetrical complications including; gestational hypertension or diabetes or abnormal prenatal testing; drug or alcohol abuse history within the previous six months; life-time diagnosis of a psychiatric disorder other than MDD or an anxiety disorder; previous failure to respond to electroconvulsive therapy; and active suicidal ideation. Advertising and referrals were used for subject recruitment.

Study Overview

This single-site, RCT was approved by the University of Pennsylvania Institutional Review Board (NCT01492309). Informed consent was obtained prior to initiation of study procedures. Recruitment lasted for 36 months. Subjects were screened for any TMS administration risk factors with the TMS Adult Safety Screen (TASS) (Keel et al., 2001). Subjects received 20 daily sessions of TMS. Clinician ratings were completed by a trained, blinded research staff member at study admission, before session 1 and after sessions 10 and 20. Subjects were contacted to assess depression status at 6 weeks postpartum.

Sham

The eSham system (Borckardt et al., 2008) was used to replicate both the facial twitching and the noise generated by TMS. The expected electrical stimulation with the eSham is very

low (2mA to 7mA) and does not produce cortical effects or confer any risk to the mother or the pregnancy or fetus beyond minor maternal facial discomfort.

To determine the integrity of the sham, 10 TMS-naïve, healthy volunteers (recruited by word of mouth) received alternating sessions of active or sham TMS. Four 60 second trains (continuous pulses of TMS) of active or sham 1 Hz TMS at 100% MT over the right dorsolateral prefrontal cortex (DLPFC) were administered with 60 seconds breaks between trains. After each train, volunteers rated the sensations and overall tolerability on visual analogue scales (VAS) ranging from 0–100. Upon completion, participants were asked to guess whether they had received active or sham TMS.

Laboratory and physical exam screening

A medical history and physical exam were performed by a high-risk obstetrics specialist. Prior to session 1 and within a week after session 20, a growth ultrasound was completed. Routine blood work including a urine drug screen, complete blood count, electrolytes, blood urea nitrogen, creatinine, liver function tests, thyroid stimulating hormone as well as a urinalysis were collected prior to randomization. Laboratory values were required to be within normal range or without clinical significance. To measure serum estradiol and progesterone samples were collected before session 1 and after session 20.

Study Treatment

Participants received 20 sessions (15 minutes each, 5 days per week) of active or sham TMS to the right DLPFC administered using a Neuronetics 2100 CRS TMS System (Neuronetocs, Inc; Malvern, Pa). Active TMS was administered at 1 Hz as a single train of 900 pulses per session at 100% motor threshold (MT). This is 3 times the amount of stimulation in the open-label study, but 50% of what is acceptable according to TMS safety guidelines (Rossi et al., 2009). Over 4 weeks the total dose was 18,000 pulses. The dosing parameters were chosen based on our pilot data and our collective TMS experience. Patients over 24 weeks gestational age were tilted thirty degrees to the left to reduce risk of postural hypotension (Kim and Wang, 2014). This positioning should be done prior to obtaining the MT. Stimulation was targeted to the right DLPFC based on a standardized surface anatomy approach. The MT was determined weekly and defined as the minimal amount of energy output necessary to evoke a visible twitch of the left thumb or other fingers when laying at rest (Pridmore et al., 1998) using the MT Assist (Neuronetics Inc.) for at least 3 out of 5 stimulations. MT Assist is a standardized, software-based mathematical algorithm that provides an iterated estimate of the MT. A single magnetic pulse at 0.2 Hz frequency was delivered every 5 seconds after placing the coil over the scalp area overlying the right motor cortex (starting one-inch lateral and inferior to the vertex). 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 (George et al., 1995). Spatial coordinates were recorded with a mechanical coil positioning system to ensure placement reproducibility.

Blinding of Treatment

There were 3 figure-eight coils used in this study. Coil A was marked “active” and used in obtaining the MT. Coils B and C (active or sham) were only marked B or C. All were driven by the console power system and had identical physical appearances. The sham coil contained a shielding mechanism, diverting the magnetic field away from the patient. The eSham system was added to the traditional sham coil. The subject, TMS administrator, and rater were blinded to the randomization assignment. After treatments 1 and 5, subjects completed the best guess questionnaire to determine their prediction of their treatment assignment. Blinding was broken if one of the stopping rules was met. If unblinded, there were 3 options for rescue care: 1) For an active group subject, a free consultation was performed to discuss treatment options; 2) For a sham group subject, they were offered open label treatment with TMS (same parameters as for the active treatment); 3) If the subject was in the sham group and did not opt for active TMS, the subject was given a free consultation regarding treatment options.

Behavioral Assessments

Subjects underwent a standardized psychiatric evaluation to determine diagnosis and symptom severity. The SCID was used to confirm a primary diagnosis of MDD. The clinician rated HDRS-17 and CGI-S were the primary outcome measures. Clinician based assessments were conducted by a member of the research team blinded to the group assignment (Table 1). The subjects rated their symptoms using the Beck Depression Inventory (BDI)(BECK et al., 1961) and Beck Anxiety Inventory (BAI) (Beck et al., 1988). Response was defined as at least a 50% decrease from baseline HDRS-17 score and remission was defined as an HDRS-17 score < 8 and a CGI-S score = 1. Cognitive assessments were performed pre- and post-treatment, mainly focusing on working memory tasks. The Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1996) was done during a phone call at 6 weeks postpartum to assess depression status.

Safety Assessments

Safety was assessed at every visit by recording adverse events coded using the Medical Dictionary for Regulatory Activities. Yearly reviews of adverse events were done by an independent psychiatrist and obstetrician. Vital signs were checked before and after each treatment. Posttreatment fetal growth ultrasound studies were obtained within 1 week of finishing session 20 and infant outcomes were evaluated by obtaining delivery records.

Pre-Study Power and Sample Size Considerations

Assumptions for calculations included equal numbers of women assigned to active and control treatments, type I error, alpha, of 5%, and 80% statistical power. For the outcome of response, a 50% or greater decrease in the HDRS-17, we anticipated that less than 15% of the control group would achieve this goal. If 50% of participants who received the active therapy met this criterion for response, we would have required 33 women per study arm to complete the trial.

Statistical Analysis

Descriptive analyses were performed to characterize the study population and infant outcomes. Histograms and box plots were used to assess modeling assumptions for the integrity of the sham coil analysis and continuous outcome variables. The treatments were compared using t-Tests and Wilcoxon signed-rank tests as appropriate with statistical significance set at $p=0.05$. Primary outcome scores were modeled using linear mixed models for two timepoints, session 10 and session 20, with baseline HDRS-17 scores as a covariate to adjust for the potential that the observed decline in scores with treatment may depend on baseline scores. Primary interest was in the time (T10 vs T20) by treatment (sham vs active) interaction. The outcomes of response and remission were modeled using logistic regression. We did observe 4 patients with an anxiety disorder, all randomized to the Sham treatment. We therefore repeated our analyses including anxiety diagnosis as an additional covariate. Results from these adjusted analyses were no different than the results which did not adjust for anxiety, data not shown.

Results

The Blind

Testing of the blind was done prior to beginning the RCT. The integrity of the blind was tested in ten participants naïve to TMS exposure (Supplementary Table 1). There was no evidence of differences between any of the 8 VAS measures (Supplementary Table 2). The average pain rating for active treatment was 1.44 (SD=1.42) and for sham treatment was 2.11 (SD=1.54), which were statistically similar, $p=0.246$ (Wilcoxon Rank Sum). Therefore, we concluded that the sham system was an effective blind. RCT subjects overwhelmingly guessed they were receiving the active coil and there were no significant differences in their responses by coil (Fisher's Exact, $p=0.411$) suggesting participants were well-blinded.

Population and sample

Of 139 women screened, 26 were randomized to the active or control group (Consort chart). Fourteen and twelve women were randomized to the active or sham group, respectively, and 11 women in each group completed the protocol. Two women (one from each group) withdrew due to study time commitment. Of these 22 women, 20 completed all sessions, 1 completed 19 sessions, and 1 completed 17 sessions (both in sham group) and no subjects were withdrawn by investigators. For the participant who completed 19 sessions, data from session 10 were carried forward. For the subject that completed 17 sessions, end study data were collected the following day. All results are intent to treat. Baseline subject demographics and psychiatric ratings are presented in Table 2. Five subjects were on psychiatric medication at stable doses at least 2 weeks prior to study entry (sham group - 1 taking citalopram, 1 taking bupropion and 1 taking bupropion, duloxetine, clonazepam, and low dose quetiapine; active subjects - 1 taking sertraline and 1 taking lamotrigine and sertraline). Four participants had generalized anxiety disorder or panic disorder, all in the control group (Fisher's Exact, $p\text{-value} = .090$).

Clinical Response

The baseline MT was not significantly different in women based on screening gestational age ($p = 0.355$). Changes in psychiatric ratings were assessed at baseline and after sessions 10 and 20. At baseline HDRS-17 scores were similar between groups (Mean $\pm$ SD, Active vs. Sham: 23.18 ± 3.54 vs. 22.27 ± 2.65 ; Welch T-test: $t_{18.15} = -0.68$, $p = 0.504$). Controlling for baseline measures, there was a statistically significant interaction between follow-up time and treatment (Mixed Model: $B = -6.82$, $SE = 1.99$, $t_{20} = -3.41$, $p = 0.003$) with the active group having significantly decreased HDRS-17 scores at session 20 compared to the sham group (Table 3). At the end of the study (T20) the average HDRS-17 scores in the active TMS group was $9.27 (\pm 6.05)$ and $13.18 (\pm 8.00)$ in the sham TMS group (Linear model controlling for Baseline: $B = -4.73$, $SE = 2.88$, $t_{19} = -1.64$, $p = .117$) (Figure 1). Linear mixed models of the severity of depression using the CGI-S showed a larger decline in scores in the active compared to the sham group from session 10 to 20, controlling for baseline scores (Active vs Sham: $B = -1.00$, $SE = .44$, $t_{20} = -2.26$, $p = 0.035$).

Response was defined as at least a 50% decrease from baseline HDRS-17 score and remission was defined as an HDRS-17 score < 8 and a CGI-S score ≤ 1 . HDRS-17 response rates after session 20 were 81.82% for the active coil and 45.45% for the sham coil (Logistic Regression: $B = 1.67$, $SE = .99$, $z_{20} = 1.71$, $p = 0.088$). This corresponds to NNT (number needed to treat) = 2.8. For every 3 women treated with active TMS we would expect to see 1 achieve a decline in score of 50% or greater. Interestingly, subjects receiving the sham coil showed response much earlier than the subjects receiving the active coil, 27.3% versus 0% respectively at session 10. The remission rate for the active coil was 27.27% and for the sham coil was 18.18% (Logistic Regression: $B = 0.52$, $SE = 1.03$, $z_{20} = 0.51$, $p = 0.613$).

EPDS scores decreased over time significantly more in subjects receiving active TMS compared to sham TMS (Linear Mixed Model, $B = -4.36$, $SE = 1.48$, $t_{20} = -2.944$, $p = 0.008$). There were no significant differences between groups in BDI (Mixed Model: $B = -3.91$, $SE = 2.65$, $t_{20} = -1.47$, $p = .156$) and BAI (Mixed Model: $B = 0.26$, $SE = 2.65$, $t_{20} = -1.47$, $p = .156$) scores over treatment session. Out of the 13 participants with 6-week postpartum EPDS scores (7 sham, 6 active), there was no significant difference between groups (Welch T-test: $t_{10.85} = -0.26$, $p = 0.801$). Medication status did not affect the results (data not shown).

Delivery and Infant Outcomes

There were no significant differences in infant outcomes among groups (Table 4, Welch T-tests and Fisher Exact Tests). In the 18 women with pre-and post-treatment ultrasound data, all fetuses had similar growth across the study (Mixed Model, $t_{20} = -1.197$, $p = 0.245$). There was no significant difference between groups for GA at delivery (Wilcoxon Rank Sum, $p = 0.158$). However, there were 3 PTBs (35.3, 36.3 and 35.2 weeks) all within the active group. Rate of PTB was not significantly different between groups (Fisher Exact Test, p -value = 0.214). However, a post-hoc power calculation showed that 33 subjects per group would be needed to show statistical significance in the rate of PTB by coil assignment. One infant from the active group had an abnormal initial pediatric assessment due to a possible

brachial plexus injury. This was determined to be a result of shoulder dystocia, in which fetal shoulders are large compared to maternal pelvic size and unrelated to TMS.

Hormone Measurements and Cognitive Measures

No significant differences were found for pre- and post-intervention estradiol (Linear Model controlling for baseline: $B < .01$, $SE = .09$, $t(19) = 0.02$, $p = 0.98$) or progesterone (Linear Model controlling for baseline: $B = .04$, $SE = .14$, $t_{19} = 0.31$, $p = 0.757$) levels between groups. There were no significant differences in cognitive tests post-treatment by coil (controlling for HDRS-17 and baseline cognitive score) except for letter number sequencing (LNS), 1 of 4 working memory tests given, in those receiving the active treatment (Linear Model: $B = .25$, $SE = .92$, $t_{17} = .27$, $p = 0.013$). The active group performed worse post-treatment on the LNS compared to pre-treatment.

Maternal adverse events

Before and after a session, there were no significant differences in vital signs between groups. Headache was the most common side effect. Since all but 1 occurrence of headache was observed prior to session 10, the percentage of participants with headache reported before session 10 and after session 10 were compared. Before session 10, headache was reported by 36.4% of active group subjects versus 9.1% in the sham group (Fisher's Exact, $p = 0.311$). After treatment 10, headache was reported by 9.1% of active group subjects versus 0% in the sham group (Fisher's Exact, $p = 1.00$). Other side effects reported were dizziness, nausea, site pain, supine hypotension, jaw pain and eye twitch without significance between groups. These were mostly reported by single subjects.

Conclusions:

In this RCT of active versus sham TMS in 2nd and 3rd trimester pregnant women with MDD, active TMS resulted in a significant decrease in HDRS-17 scores compared to sham TMS. The reduction in depression severity was also significant as measured by the CGI-S and the EPDS. Response rates were not significantly different for the active coil were (81.8%) versus the sham coil (45.5%). Remission rates for the active coil were 27.3% and for the sham coil were 18.8% and this was also not a significant difference. And while the depression symptoms decreased significantly more in the active group, when looked at as response or remission rates we did not find significance. This is most likely related to the small sample size such that continuous measures were significant but categorical ones were not. For the outcome of remission, increasing the sample size to 31 participants per treatment arm would have provided 80% statistical power to detect the magnitude of the difference which was observed. However, many more than 31 participants per group would be required to establish differences in remission. Another potential is that we used an active placebo, however, this is unlikely given the very low cortical stimulation used with the placebo coil.

The average GA at delivery was non-significant between groups. However, there were 3 late PTBs in the active group (27%) and none of these women were on psychotropics. Because the study was underpowered to detect a significant difference between groups, we cannot

conclude whether active TMS is a risk for late PTB. Of note, 2 of the women with PTBs had medical conditions or histories that are PTB risk factors, unrelated to TMS. One of the women had a medically induced birth due to severe pre-eclampsia, while the other had a history of loop electrosurgical excision procedure (LEEP). Beyond the findings from this study, there is only one case report in the literature of PTB with TMS in pregnancy in a woman on venlafaxine who received 15 sessions of left-sided TMS starting at 31 weeks of pregnancy at 100% MT who delivered at 36 weeks (Klirova et al., 2008). Both psychiatric medications and depression have been associated with PTB (Wisner et al., 2009) so more data is required to investigate the association with TMS.

Maternal side effects were minimal aside from expected headaches during early sessions. Fetal and delivery outcomes were not significant between groups and TMS did not change estradiol or progesterone levels. Cognitive changes were minimal with 1 out of 4 working memory tests showing that active TMS adversely affected working memory. Working memory has been shown to improve with TMS in both depressed and healthy subjects although most of that data used left-sided, high frequency TMS (Bagherzadeh et al., 2016, Levkovitz et al., 2009) (Bagherzadeh et al., 2016, Levkovitz et al., 2009).

This study contributes to the literature on the safety of TMS during pregnancy. Our initial work was started before the risk of seizure was known to be minimal with left-sided TMS and as seizures in pregnancy are dangerous, we chose right-sided TMS for both the pilot and RCT. A recent open label study in pregnancy (N=29) using left-sided, 25 HZ TMS at 100% MT (a total of 1000 pulses per session) was given for 18 days (Hizli Sayar et al., 2014). In this study 41.4% showed at least a 50% decrease in HDRS-17 and 20.7% had a HDRS-17 < 8. At the time of publication 25 healthy babies had been born > 36 weeks GA. A follow-up publication reported that there was no evidence of cognitive or motor development abnormalities in exposed children at ages 16–62 months (Eryilmaz et al., 2014). There is no reason to believe that left sided TMS would be dangerous during pregnancy, but more studies would validate this hypothesis. Lastly, since publication of our pilot study, one other case report was published examining the effect of maintenance TMS on a woman with bipolar 2 disorder who became pregnant during her 4 years of maintenance treatments (Burton et al., 2014). She received sequential bilateral treatments of 15 min of left-sided 10 Hz TMS followed by 15 min of rightsided 1 Hz TMS (110% MT) every 2 weeks and delivered a healthy male infant and remained in remission.

Treatment compliance was extremely high in the active and sham groups (< 1% of sessions missed). Only 20–30% of pregnant women are amenable to medication during pregnancy (Kim et al., 2011b, Goodman, 2009, Wisner et al., 2000). Therefore, other modalities must be studied and offered to this population. Lastly, this first RCT of a biological treatment in pregnancy shows such a study is feasible.

Limitations:

The main limitations of this study are dosing and choice of using right-sided low frequency TMS. Left-sided, high frequency TMS with taper and maintenance is becoming standard of care. However, data suggests that the two modalities may be comparable in efficacy (Chen et al., 2013). Increasing the motor threshold or increasing the number of pulses per session

may have also increased efficacy. In our pilot study, we used 300 pulses per session and in this RCT we used 900 pulses per session. The 900 pulses per session used in this study is only 50% of what is considered safe for low frequency TMS at 100% MT (Rossi et al., 2009). Importantly, a larger sample to confirm our results would be helpful as would follow up infant data. Based on our pilot data, the power calculation estimated that 33 women per study arm would be needed to complete the trial. This study only achieved 1/3 of that goal in each study arm and therefore, this study was underpowered based on the time allotted for recruitment. The recruitment time was shorter than originally planned and to complete a study like this would take more resources than we planned. There were multiple studies recruiting pregnant women being carried out during our recruitment period which limited our ability to have access to as many pregnant women as we would have liked. In our opinion, the best way to proceed would be to do a multi-center trial which would include women during all three trimesters of pregnancy. Additionally, given that many subjects could not be enrolled due to a past diagnosis of bipolar disorder, it would be wise to consider including this diagnosis in a larger trial. If these results are replicated, investigating the mechanism of action would enhance the ability to target which pregnant women with MDD would best be candidates for TMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: NIMH K Award 5-K23-MH-092399-05

References:

- Bagherzadeh Y, Khorrami A, Zarrindast MR, Shariat SV, Pantazis D, 2016 Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex enhances working memory. *Exp. Brain Res.* 234, 1807–1818. [PubMed: 26884132]
- Beck AT, Epstein N, Brown G, Steer RA, 1988 An inventory for measuring clinical anxiety: psychometric properties. *J. Consult. Clin. Psychol.* 56, 893–897. [PubMed: 3204199]
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J, 1961 An inventory for measuring depression. *Arch. Gen. Psychiatry* 4, 561–571. [PubMed: 13688369]
- Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR, 2004 Prevalence of depression during pregnancy: systematic review. *Obstet. Gynecol.* 103, 698–709. [PubMed: 15051562]
- Betts KS, Williams GM, Najman JM, Alati R, 2014 The Relationship between Maternal Depressive, Anxious, and Stress Symptoms during Pregnancy and Adult Offspring Behavioral and Emotional Problems. *Depress. Anxiety*.
- Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H, Reeves ST, Madan A, Sackeim H, George MS, 2008 Development and evaluation of a portable sham transcranial magnetic stimulation system. *Brain Stimul* 1, 52–59. [PubMed: 19424444]
- Burton C, Gill S, Clarke P, Galletly C, 2014 Maintaining remission of depression with repetitive transcranial magnetic stimulation during pregnancy: a case report. *Arch. Womens Ment. Health.* 17, 247–250. [PubMed: 24638141]
- Chatillon O, Even C, 2010 Antepartum depression: prevalence, diagnosis and treatment. *Encephale* 36, 443–451.

- Chen J, Zhou C, Wu B, Wang Y, Li Q, Wei Y, Yang D, Mu J, Zhu D, Zou D, Xie P, 2013 Left versus right repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomised controlled trials. *Psychiatry Res.* 210, 1260–1264. [PubMed: 24113125]
- Cox JL, Chapman G, Murray D, Jones P, 1996 Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. *J. Affect. Disord.* 39, 185–189. [PubMed: 8856422]
- Eryilmaz G, Hizli Sayar G, Ozten E, Gogcegoz Gul I, Yorbik O, Isiten N, Bagci E, 2014 Follow-Up Study of Children Whose Mothers Were Treated With Transcranial Magnetic Stimulation During Pregnancy: Preliminary Results. *Neuromodulation.*
- First MB, Spitzer RL, Gibbon M, Williams JB, 1995 Structured Clinical Interview for DSM-IV Axis I Disorders- Patient Edition SCID-I/P.
- George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, Hallett M, Post RM, 1995 Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 6, 1853–1856. [PubMed: 8547583]
- Goodman JH, 2009 Women's attitudes, preferences, and perceived barriers to treatment for perinatal depression. *Birth* 36, 60–69. [PubMed: 19278385]
- Grigoriadis S, VonderPorten EH, Mamisashvili L, Tomlinson G, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Radford K, Martinovic J, Ross LE, 2013 The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. *J. Clin. Psychiatry* 74, e32141.
- Guy W, 1976 Clinical Global Impression Scale.
- Hamilton M, 1967 Development of a rating scale for primary depressive illness. *Br. J. Soc. Clin. Psychol.* 6, 278–296. [PubMed: 6080235]
- Hizli Sayar G, Ozten E, Tufan E, Cerit C, Kagan G, Dilbaz N, Tarhan N, 2014 Transcranial magnetic stimulation during pregnancy. *Arch. Womens Ment. Health.* 17, 311–315. [PubMed: 24248413]
- Ibanez G, Charles MA, Forhan A, Magnin G, Thiebaugeorges O, Kaminski M, Saurel-Cubizolles MJ, EDEN Mother-Child Cohort Study Group, 2012 Depression and anxiety in women during pregnancy and neonatal outcome: data from the EDEN mother-child cohort. *Early Hum. Dev.* 88, 643–649. [PubMed: 22361259]
- Keel JC, Smith MJ, Wassermann EM, 2001 A safety screening questionnaire for transcranial magnetic stimulation. *Clin. Neurophysiol.* 112, 720. [PubMed: 11332408]
- Kim DR, Epperson N, Pare E, Gonzalez JM, Parry S, Thase ME, Cristancho P, Sammel MD, O'Reardon JP, 2011a An open label pilot study of transcranial magnetic stimulation for pregnant women with major depressive disorder. *J. Womens Health. (Larchmt)* 20, 255–261. [PubMed: 21314450]
- Kim DR, Sockol L, Barber JP, Moseley M, Lamprou L, Rickels K, O'Reardon JP, Epperson CN, 2011b A survey of patient acceptability of repetitive transcranial magnetic stimulation (TMS) during pregnancy. *J. Affect. Disord.* 129, 385–390. [PubMed: 20864179]
- Kim DR, Sockol LE, Sammel MD, Kelly C, Moseley M, Epperson CN, 2013 Elevated risk of adverse obstetric outcomes in pregnant women with depression. *Arch. Womens Ment. Health.* 16, 475–482. [PubMed: 23934018]
- Kim DR, Wang E, 2014 Prevention of supine hypotensive syndrome in pregnant women treated with transcranial magnetic stimulation. *Psychiatry Res.* 218, 247–248. [PubMed: 24768354]
- Klirova M, Novak T, Kopecek M, Mohr P, Strunzova V, 2008 Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode during pregnancy. *Neuro Endocrinol. Lett.* 29, 69–70. [PubMed: 18283246]
- Levkovitz Y, Harel EV, Roth Y, Braw Y, Most D, Katz LN, Sheer A, Gersner R, Zangen A, 2009 Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimul* 2, 188–200. [PubMed: 20633419]
- O'Donnell KJ, Glover V, Barker ED, O'Connor TG, 2014 The persisting effect of maternal mood in pregnancy on childhood psychopathology. *Dev. Psychopathol.* 26, 393–403. [PubMed: 24621564]
- Patel SR, Wisner KL, 2011 Decision making for depression treatment during pregnancy and the postpartum period. *Depress. Anxiety* 28, 589–595. [PubMed: 21681871]

- Pearson RM, Evans J, Kounali D, Lewis G, Heron J, Ramchandani PG, O'Connor TG, Stein A, 2013 Maternal depression during pregnancy and the postnatal period: risks and possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry*. 70, 1312–1319. [PubMed: 24108418]
- Pridmore S, Fernandes Filho JA, Nahas Z, Liberatos C, George MS, 1998 Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *J. ECT* 14, 25–27. [PubMed: 9661090]
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group, 2009 Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin. Neurophysiol.* 120, 2008–2039. [PubMed: 19833552]
- Szuba MP, O'Reardon JP, Evans DL, 2000 Physiological effects of electroconvulsive therapy and transcranial magnetic stimulation in major depression. *Depress. Anxiety* 12, 170–177. [PubMed: 11126192]
- Szuba MP, O'Reardon JP, Rai AS, Snyder-Kastenberg J, Amsterdam JD, Gettes DR, Wassermann E, Evans DL, 2001 Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biol. Psychiatry* 50, 22–27. [PubMed: 11457420]
- Walton GD, Ross LE, Stewart DE, Grigoriadis S, Dennis CL, Vigod S, 2014 Decisional conflict among women considering antidepressant medication use in pregnancy. *Arch. Womens Ment. Health*..
- Wisner KL, Sit DK, Hanusa BH, Moses-Kolko EL, Bogen DL, Hunker DF, Perel JM, Jones-Ivy S, Bodnar LM, Singer LT, 2009 Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *Am. J. Psychiatry* 166, 557–566. [PubMed: 19289451]
- Wisner KL, Zarin DA, Holmboe ES, Appelbaum PS, Gelenberg AJ, Leonard HL, Frank E, 2000 Risk-benefit decision making for treatment of depression during pregnancy. *Am. J. Psychiatry* 157, 1933–1940. [PubMed: 11097953]

Highlights:

- Major depressive disorder during pregnancy is common but women experience high decisional conflict regarding treatment.
- Transcranial magnetic stimulation is a non-pharmacologic biologic treatment option for pregnant women with depression.
- In a randomized controlled trial of low frequency TMS over the right DLPFC, women in the active TMS group showed a larger decrease in depressive symptoms compared to the sham TMS group.
- TMS was generally safe although there were 3 late pre-term births in the active group which was statistically non-significant.
- There was no change difference in estradiol or progesterone levels between the active and sham groups.

Figure 1:
Total HDRS-17 Score by Coil and Treatment Sessions.

Study Procedures

Table 1.

	Screening/Entry Visit	Treatment Visit 1	Treatment Visits 2-9	Treatment Visit 10	Treatment Visits 11-19	Treatment Visit 20
Psychiatric History	X					
Obstetric History & Physical ^{*/ **/ ***}	X					
Structured Clinical Interview (SCID -II)	X					
Cognitive Testing ^{****}	X					X
Hamilton Depression Rating Scale (HDRS-17)	X	X		X		X
Adverse Childhood Experiences Questionnaire (ACE)	X					
Beck Depression Inventory (BDI)	X	X		X		X
Beck Anxiety Inventory (BAI)	X	X		X		X
Clinical Global Impressions Scale (CGI - S/I)	X	X		X		X
Edinburgh Postpartum Depression Scale (EPDS)	X	X		X		X
Repetitive Transcranial Magnetic Stimulation (rTMS)		X	X	X	X	X
Growth Fetal Ultrasound	X					X

* Subjects were followed by their obstetrician as frequently as their obstetrician deemed necessary

** Laboratory screening prior to study entrance included CBC with platelets, chemistry panel, and liver function tests (AST, ALT)

*** Blood was drawn for allopregnanalone, BDNF, estradiol, progesterone, oxytocin, and corticotropin releasing hormone.

**** Cognitive tests included: Mini Mental Status Examination (MMSE; administered only at screening/entry visit), Trails A&B, Stroop, Interference Test, Wechsler Memory Scale 3rd Edition (WMS-3) Letter-Number Sequencing & WMS-3 Digit Span

Table 2.

Participant Baseline Characteristics

	Total	Active	Sham
Mean age (SD), in years	28.27 (5.65)	30.13 (5.78)	26.41 (5.11)
Mean gestational age (SD), in weeks	23.91 (7.40)	22.19 (7.11)	25.62 (7.61)
Race			
Caucasian	7 (31.82%)	4 (36.36%)	3 (27.27%)
African American/Black	11(50.00%)	4 (36.36%)	7 (63.64%)
Asian	3 (13.64%)	2 (18.18%)	1 (9.09%)
Other	1 (4.55%)	1 (9.09%)	0 (0.00%)
Ethnicity (N = 18)			
Non-Hispanic	17 (94.44%)	10 (100%)	7 (87.50%)
Hispanic	1 (5.56%)	0 (0.00%)	1 (12.50%)
Marriage status			
Single (Never Married)	13 (59.09%)	6 (54.55%)	7 (63.64%)
Married	8 (36.36%)	5 (45.45%)	3 (37.27%)
Domestic Partnership	1 (4.55%)	0 (0.00%)	1 (9.09%)
Household Income			
\$50,000	16 (72.73%)	8 (72.73%)	8 (72.73%)
>\$50,000	6 (27.27%)	3 (27.27%)	3 (27.27%)
Education			
High School Graduate	4 (18.18%)	2 (18.18%)	2 (18.18%)
Some College or College Graduate	11 (50.00%)	5 (45.45%)	6 (54.55%)
Above College Graduate	7 (31.82%)	4(36.36%)	3 (27.27%)
Mean Baseline HDRS-17 (SD)	22.73 (3.09)	23.18 (3.54)	22.27 (2.65)
Mean Baseline CGI-S (SD)	4.64 (0.79)	4.45 (0.82)	4.82 (0.75)
Mean Baseline BDI (SD)	28.77 (8.28)	28.09 (6.47)	29.45 (10.05)
Mean Baseline EPDS (SD)	18.73 (3.24)	18.36 (2.84)	19.09 (3.70)
Mean Baseline BAI (SD)	21.64 (11.52)	22.45 (9.36)	20.82 (13.78)

Table 3.

Outcomes by Treatment Session and Treatment Group

Psychiatric Outcomes	Active			Sham		P-value [*]
	Baseline	Treatment 10	Post Intervention	Baseline	Treatment 10	
Mean HDRS-17 (SD)	23.18 (3.54)	17.00 (4.45)	9.27 (6.05)	22.27 (2.65)	14.09 (7.57)	0.003
Mean CGI-S (SD)	4.45 (0.82)	3.82 (1.08)	2.36 (1.12)	4.82 (0.75)	3.67 (1.21)	0.035
Mean BDI (SD)	28.09 (6.47)	17.82 (10.04)	2.09 (7.23)	29.45 (10.05)	17.91 (11.55)	0.156
Mean EPDS (SD)	18.36 (2.84)	14.00 (5.46)	9.55 (5.047)	19.09 (3.70)	13.09 (6.20)	0.008
Mean BAI (SD)	22.45 (9.36)	14.55 (8.17)	12.27 (7.44)	20.82 (13.78)	15.18 (14.30)	0.890

* p-value corresponding to a treatment (active vs sham) by Time (T10 vs T20) interaction from linear mixed models, which included baseline level as a covariate. This p-value compares the change in scores between T10 and 20 for Active versus Sham treatment.

Table 4.

Infant outcomes

	Total (n=22)	Active (n=11)	Sham (n=11)	p-value
APGAR 1	7.14 (1.96)	7.00 (2.28)	7.27 (1.68)	0.753
APGAR 5	8.55 (1.22)	8.36 (1.50)	8.73 (0.90)	0.501
Baby Sex				0.183
Male	14 (63.63%)	9 (81.82%)	5 (45.45%)	
Female	8 (36.36%)	2 (18.18%)	6 (54.55%)	
Delivery Comps.	4 (18.18 %)	2 (18.18%)	2 (18.18%)	1.000
Mode of Delivery				0.183
Vaginal	14 (63.63%)	9 (81.82%)	5 (45.45%)	
C-Section	8 (36.36%)	2 (18.18%)	6 (54.55%)	
NICU Admission	6 (27.27%)	3 (13.64%)	3 (13.64%)	1.000
Normal Assessment by Pediatrician	21 (95.45%)	11 (100%)	10 (90.91%)	1.000
Gestational Age at delivery	39.16 (1.64)	38.47 (2.01)	39.86 (0.74)	0.158
Birth Length (Inches) (N = 17)	51.28 (1.95)	50.90 (2.17)	51.62 (1.79)	0.472
Birth Weight (lbs)	7.23 (1.34)	6.77 (1.48)	7.69 (1.05)	0.109
Major Congenital Malformations	0 (0.00%)	0 (0.00%)	0 (0.00%)	1.000
Preterm Birth	3 (13.64 %)	3 (27.27%)	0 (0.00%)	0.214

* Differences between sham and active groups