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# A systematic review of the safety and effectiveness of repetitive transcranial magnetic stimulation in the treatment of peripartum depression

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ABSTRACT

*Background:* Repetitive Transcranial Magnetic Stimulation (rTMS) is an efficacious treatment for major depressive disorder (MDD), however there is limited safety and efficacy data in the peripartum period. The purpose of this review is to systematically examine the safety, acceptability and effectiveness of rTMS administered during the peripartum period as an intervention for MDD.

*Methods:* We searched MEDLINE, EMBASE and PsychINFO from 2008 to January 2019 to identify peer reviewed publications evaluating rTMS during the peripartum period as an intervention for peripartum MDD. We systematically extracted reported adverse events, side effects, rates of discontinuation, as well as clinical response and remission.

*Results:* Data was synthesized from 1 randomized control trial, 3 uncontrolled trials, 3 case series and 5 case studies, representing a total of 87 patients. No serious adverse events were reported. Side effects occurred at rates comparable to those observed in the non-peripartum population, and obstetric and neonatal complications are infrequent and do not separate from sham-rTMS. Randomized controlled data suggests antidepressant efficacy with an effect size of 0.87. Uncontrolled studies report rates of clinical response between 41.4% and 71.4%, and rates of clinical remission between 20.7 and 30.0%. The treatment appears acceptable, with few patients opting to discontinue treatment.

*Limitations:* Due to the paucity of research in this population, majority of data comes from sources with inherently higher risk of bias.

Conclusions: rTMS in the peripartum period appears to be efficacious, acceptable and well tolerated. Additional research is required, however rTMS's risk benefit profile may be attractive to women in the peripartum period.

## 1. Background

Peripartum Depression (PPD) is a common condition accompanied by severe health risks to mother and offspring. PPD is defined as a major depressive episode occurring during gestation and within the four weeks following delivery (Diagnostic and Statistical Manual of Mental Disorders (5th ed.), 2013), although some data calls into question this temporally restrictive definition (Forty et al., 2006). Onset of PPD occurs in an estimated 10–15% of women (Hall, 2012) and has been associated with disturbances in infant behavior and developmental delays, with effects extending into childhood and adolescence (Hoffman et al., 2017; Wisner et al., 2006). Antenatal depression is associated with poorer gestational outcomes including higher rates of inadequate maternal weight gain (Bodnar et al., 2010), prenatal hypertension (Mautner et al., 2009), gestational diabetes (Hinkle et al., 2016), and increased substance use (Flynn and Chermack, 2008; Orr et al., 2012). Furthermore, postpartum depression is associated with disturbed maternal-fetal bonding, reduced parenting quality and long term developmental delays of the infant (Hall, 2012; Hoffman et al., 2017; Ising et al., 2007). Tragically, severe cases postnatal depression have been associated with infanticide and suicide is a leading cause of maternal death in the first year following delivery (Grigoriadis et al., 2017; Pearlstein, 2008).

Though psychotherapy is first line in this population (MacQueen et al., 2016), it is not effective in every case (Ravesteyn et al., 2017) and is generally not indicated for severe depressive symptoms (MacQueen et al., 2016). A significant portion of women with PPD are reluctant to take medications during pregnancy or while breastfeeding (Brummelte

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and Galea, 2016; Pearlstein, 2013). Exposure to antidepressants during foetal development has been associated with cardiac malformation (Huybrechts et al., 2014), persistent pulmonary hypertension (Huybrechts et al., 2015), and admission to neonatal intensive care (Norby et al., 2016). While other risks, such as an increased risk of autism or attention deficit hyperactivity disorder, can be accounted for by other factors (Man et al., 2017; Morales et al., 2018; Rai et al., 2017; Viktorin et al., 2017; Zhou et al., 2018), expecting mothers remain concerned of the adverse effects that may result from pharmacological antidepressants. Accordingly, taking antidepressants during pregnancy and lactation remains controversial, and many women face the difficult decision of exposing their baby to the potential risks of pharmaceuticals or the risks of untreated depressive symptoms (Pearlstein, 2008; Suri et al., 2014). Novel treatment methods for this population are needed.

Neuromodulation treatments for depression involve selective targeting of brain areas implicated in depression. These are promising treatment options during the peripartum period due to the absence of systemic effects. Repetitive Transcranial magnetic stimulation (rTMS) is an investigational and therapeutic modality that impacts synaptic transmission by delivering patterned energy safely and noninvasively. In response to this patterned energy, neurons adapt by changing their connection strengths (George and Aston-Jones, 2010) and large scale networks are impacted (Liston et al., 2014). The antidepressant efficacy and safety of this treatment approach is supported by many meta-analyses of double-blind placebo controlled trials (Berlim et al., 2013a; 2013b, 2014; Brunoni et al., 2017).

Here, we systematically review the literature using rTMS to treat depression during the peripartum period. We focused on studies published since rTMS was approved by the United States of America Food and Drug Administration in order to capture a more homogeneous set of treatment parameters, and defined the peripartum period as pregnancy and until 6 weeks after parturition to include both ICD10 (World Health Organization, 1993) and DSMV (Diagnostic and Statistical Manual of Mental Disorders (5th ed.), 2013) definitions.

## 2. Objectives

To systematically examine the safety, acceptability and effectiveness of rTMS administered during the peripartum period as an intervention for depression.

## 3. Methods

This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42018114209).

*Search methods for identification of studies:* An electronic search was done to identify literature on rTMS administered during the peripartum period as an intervention for depression. EMBASE, MEDLINE and PsycINFO databases were used to identify peer reviewed reports written in English until January 16th, 2019. Prior to FDA approval of rTMS in 2008, stimulation protocols varied widely. As such, we selected studies, case reports and articles since 2008 to optimize the homogeneity of interventions.

Search procedures are described in further detail in the supplementary material (Supplementary Fig. 1). Briefly, search terms “depress*”, “pregnan*“, “*partum”, “*natal”, “transcranial magnetic stimulation” “repetitive transcranial magnetic stimulation” “rTMS” and “TMS” were used. Titles and abstracts of studies retrieved using the search strategy were screened to identify studies that explicitly met exclusion criteria. Full texts were then retrieved and reviewed by two independent reviewers (JC and AM). Bibliographies of review papers and retained studies were reviewed to identify additional literature.

Risk of bias for included studies was assessed independently by two investigators. The Cochrane Collaboration's Tool for Assessing Risk of Bias was used to evaluate the quality of included controlled trials (Higgins et al., 2011), while the risk of bias for registries and cohort studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016).

## 4. Data collection and analysis

We systematically extracted the following:

*Study characteristics*-number of participants, study design, treatment allocation, recruitment and study completion rates, information for assessment of the risk of bias.

*Sample characteristics*-primary psychiatric diagnosis, depression severity, number of weeks gestation or weeks post-delivery, previously identified obstetrical complications.

*Stimulation parameters*-site of stimulation, frequency, number of pulses, inter-event interval, intensity as a percentage of resting motor threshold, number of sessions.

*Primary safety outcome measures*-any side effects/adverse events recorded.

*Primary efficacy outcomes measures*–rates of clinical response ($\geq$50% improvement in clinician rated depressive symptoms) and clinical remission (MADRS $\leq$10, HDRS17 $\leq$ 7, HDRS21 $\leq$ 7, HDRS24 $\leq$ 4, BDI $\leq$13, EPDS$\leq$9) at treatment end.

*Secondary outcome measures*-acceptability as measured by rates of discontinuation, self-reported changes in depression severity.

In cases of missing data, 2 attempts were made to contact the corresponding author(s) by email at 2-week intervals.

## 5. Results

### 5.1. Search results

A summary of the search results is presented in Fig. 1. After eliminating duplicates, 87 studies were identified and screened, and the full publications of 22 articles were assessed for eligibility. Of these, 10 were excluded for the following reasons: preliminary report of a completed study that was included ($n$ = 1) (Lamprou et al., 2013), a published trial protocol that did not contain data ($n$ = 1) (Andriotti et al., 2017), the use of TMS as a maintenance treatment during pregnancy ($n$ = 1) (Burton et al., 2014) or were not peer reviewed ($n$ = 5) (Brock et al., 2016; Ozmut et al., 2015; Rosenberg and Richardville, 2013; Stultz et al., 2018; Yilan et al., 2014). One randomized controlled trial (Myczkowski et al., 2012) and one open label study (Garcia et al., 2010) had administered TMS treatment to some women outside of the peripartum window and attempts to retrieve eligible participant data by correspondence with study authors were unsuccessful. Twelve original studies therefore met inclusion criteria.

## 6. Description of studies

The 12 records identified as suitable for our systematic review consisted of 1 randomized controlled trial (Kim et al., 2018), 3 uncontrolled studies (Hizli Sayar et al., 2014; Kim et al., 2011a; Tarhan et al., 2012), 3 case series (Ferrão and Felipe da Silva, 2018; Klirova et al., 2008 . Zhang and Hu, 2009), and 5 case studies (Cohen et al., 2008; Gahr et al., 2012; Tan et al., 2008; Xiong et al., 2018;Zhang et al., 2010), representing data on 87 participants, of which 75 were assigned to active-rTMS. Characteristics of included studies are presented in Tables 1–3.

All participants included in the review began rTMS during pregnancy, ranging from the first to third trimester. One case study continued treatment postpartum (Tan et al., 2008). Most patients were in an episode of acute unipolar depression of at least moderate severity, though cases of bipolar depression ($n$ = 2) were also included (Cohen et al., 2008; Xiong et al., 2018). Stimulation protocol and parameters were not reported for 3 patients (Zhang and Hu, 2009), however all other protocols target the left or right dorsolateral prefrontal cortex (DLPFC). Most stimulation parameters varied between high intensity

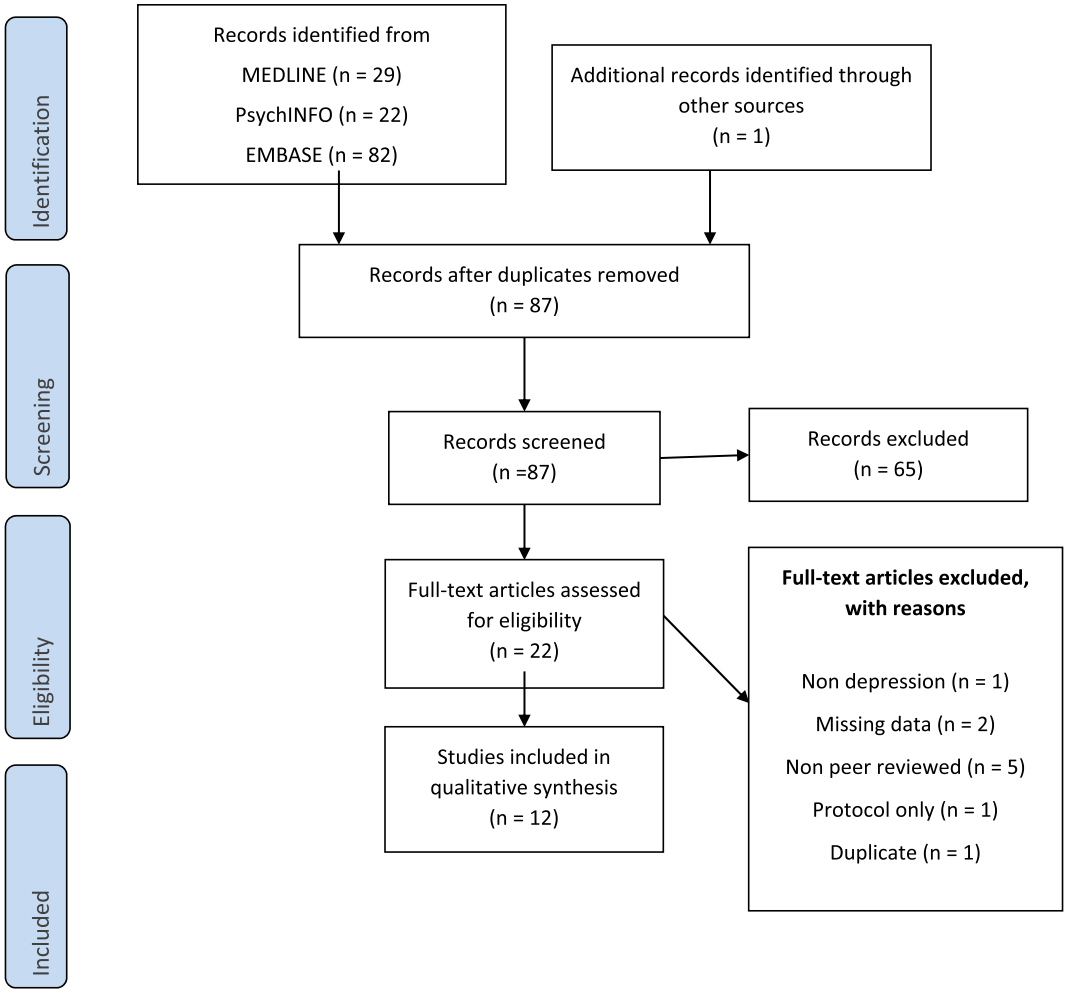


**Fig. 1.** Study Selection PRISMA flow diagram.

stimulation (≥10 Hz) on the left DLPFC (Ferrão and Felipe da Silva, 2018; Gahr et al., 2012; Hizli Sayar et al., 2014; Klirova et al., 2008; Tan et al., 2008; Tarhan et al., 2012), low intensity (1 Hz) on the right DLPFC (Cohen et al., 2008; Ferrão and Felipe da Silva, 2018; Kim et al., 2011a, 2018; Klirova et al., 2008), or a combination, bilaterally stimulating the DLPFC with high frequency stimulation on the left and low frequency stimulation on the right (Xiong et al., 2018).

One case report stimulated the left DLPFC using low frequency (1 Hz) (Zhang et al., 2010).

### 6.1. Risk of bias in included studies

Using the Cochrane Collaboration's Tool for Assessing Risk of Bias, risk of bias in the randomized control trial was moderate (Supplementary Table 2). The overall risk of bias was moderate for all non-randomized studies (n = 3) based on the ROBINS-I tool (Supplementary Table 3).

### 6.2. Safety

#### 6.2.1. Randomized controlled trials (n = 1)

In the randomized control trial, three preterm births (35–36 weeks gestation) occurred in the active group (27%) and none occurred in the sham group, however 2 of these women had previous medical conditions that were risk factors for preterm births. One incidence of fetal brachial plexus weakness was reported in the active group due to shoulder dystocia. Mean APGAR scores at 1 and 5 min were 7.14 and 8.55 respectively, with no significant differences between active-rTMS and sham-rTMS groups.

Women in the active group performed significantly worse on a working memory test (letter number sequencing) after rTMS than women in the sham group ($p = 0.013$), one of four neurocognitive domains that were assessed.

Side effects reported were headache, treatment site pain, eye twitch/jaw pain, supine hypotension, dizziness and nausea, without significant differences between active and sham groups (Kim et al., 2018).

#### 6.2.2. Uncontrolled studies (n = 3)

The three uncontrolled trials represent 46 participants who received open-label rTMS during pregnancy. Within this sample, there were no adverse events reported and pregnancies progressed normally, resulting in healthy babies with no abnormalities. Specific side effects were reported in two trials of $n = 30$ (Hizli Sayar et al., 2014) and $n = 10$ (Kim et al., 2011a), though lack of consistency among how and which side effects are reported makes synthesis of data unfeasible. The side effects reported were headache, contraction of facial muscles and supine hypotension. Side effects were not reported in the third trial ($n = 7$) (Tarhan et al., 2012), but instead offered a general statement of patient wellbeing, reporting the stimulus was well tolerated, with no significant side effects.

#### 6.2.3. Case reports and case series (n = 8)

Case studies provided information on 14 peripartum depressed

**Table 1**
Characteristics of included studies.

Panel A- Randomized Controlled Trials

| Study | Number of Participants | Began rTMS | Site of Stimulation | Frequency (Hz) | Number of pulses/ session | Inter-event interval | Intensity (% RMT) | Number of Sessions |
|---|---|---|---|---|---|---|---|---|
| Kim et al., 2018 | 14 Active | 22.2 weeks gestation | Right DLPFC | 1 | 900 | 60s on, 60s off | 100 | 20 |
| | 12 Sham | 25.6 weeks gestation | Right DLPFC | 1 | 900 | 60s on, 60s off | 100 | 20 |

Panel B- Uncontrolled Trials

| Study | Number of Participants | Began rTMS | Site of Stim | Frequency (Hz) | Number of pulses/ session | Inter-event interval | Intensity (% RMT) | Number of Sessions |
|---|---|---|---|---|---|---|---|---|
| Hizli Sayar et al., 2014 | 30 | 14.26 weeks gestation | Left DLPFC | 25 | 1000 | 2s on, 30 s off | 100 | 16.46 |
| Kim et al., 2011a | 10 | 25.8 weeks gestation | Right DLPFC | 1 | 300 | 60s on, 60s off | 100 | 20 |
| Tarhan et al., 2012 | 7 | . | Left DLPFC | 25 | 1000 | 2 s on, 30 s off | 100 | 18 |

Characteristics of included studies (Continued)

Panel C- Case Reports

| Study | Number of Participants | Began rTMS | Site of Stim | Frequency (Hz) | Number of pulses/ session | Inter-event interval | Intensity (%RMT) | Number of Sessions |
|---|---|---|---|---|---|---|---|---|
| Cohen et al., 2008 | 1 | ~20 weeks gestation | Right DLPFC | 1 | 1600 | . | 100 | 1 |
| Ferrão and Felipe da Silva, 2018 | 3 | 6 weeks gestation | Left DLPFC | 10 | 3000 | . | 120 | 42.67 |
| | 1 | 10 weeks gestation | Right DLPFC | 1 | 1800 | . | 120 | 20 |
| Gahr et al., 2012 | 1 | First Trimester | Left DLPFC | 15 | 2970 | 2s on, 8s off | 110 | 24 |
| Klirova et al., 2008 | 1 | 16 weeks gestation | Left DLPFC | 20 | 2000 | 2.5s on, 30s off | 100 | 15 |
| | 1 | 31 weeks gestation | Right DLPFC | 1 | 300 | 60s on, 60s off | 100 | 15 |
| Tan et al., 2008 | 1 | Throughout pregnancy and postpartum period | Left DLPFC | 25 | 1000 | 2s on, 28s off | 110 | 77 |
| Xiong et al., 2018 | 1 | 20 weeks gestation | Bilateral DLPFC | 10 Left, 1 Right | 4000 Left, 900 Right | Left 4s on, 16s off. Right 300s on, 60s off | 120 | 41 |
| Zhang and Hu, 2009 | 3 | . | . | . | . | . | . | . |
| Zhang et al., 2010 | 1 | 14 weeks gestation | Left DLPFC | 1 | 1200 | 20s off | 90 | 42 |

MDD = major depressive disorder. rTMS = repetitive Transcranial Magnetic Stimulation. DLPFC = dorsolateral prefrontal cortex. RMT = resting motor threshold.

patients treated with rTMS. Two instances of preterm birth were reported. One of these infants was described as irritable but healthy upon follow up (Klirova et al., 2008), and the other was a case of twins, with APGAR scores of 6 and 9 (Ferrão and Felipe da Silva, 2018). Most cases provided a general statement of participant wellbeing with no significant side effects reported, and pregnancies resulting in healthy babies (Tan et al., 2008; Xiong et al., 2018; Zhang and Hu, 2009; Zhang et al., 2010). Of these cases, three offered follow up data reporting healthy mothers and infants at 6 weeks (Xiong et al., 2018), 6 months (Zhang and Hu, 2009) and 22 months (Tan et al., 2008). Specific side effects were recorded in one case series (Ferrão and Felipe da Silva, 2018) ($n = 4$), reporting pain/discomfort at application site ($n = 3$), transient difficulty in concentration ($n = 1$) and sore throat ($n = 1$). One offered no statements relating specifically to rTMS, but had subsequent ECT therapy that resulted in remission of symptoms and no adverse events for mother or foetus (Gahr et al., 2012).

One participant with bipolar disorder achieved clinical remission with a single treatment without an increase in manic symptoms (Cohen et al., 2008). This participant went on to have a manic episode approximately 4 months later, which was successfully managed with rTMS.

### 6.3. Acceptability

#### 6.3.1. Randomized controlled trials ($n = 1$)

In the randomized controlled trial, three participants dropped out of the active-rTMS group compared to one participant in the sham-rTMS group (Kim et al., 2018). This was not statistically significant, however this must be interpreted in light of the small sample ($n = 26$). Two participants (one from each active ($n = 14$) and sham ($n = 12$) groups) dropped out due to issues with time commitment, and two additional participants allocated to the active group dropped out for unreported reasons.

#### 6.3.2. Uncontrolled trials ($n = 3$)

Out of the 47 participants enrolled in uncontrolled studies, 1 discontinued rTMS treatment (2.1%) (Hizli Sayar et al., 2014). No other discontinuations or dropouts were reported.

#### 6.3.3. Case reports ($n = 8$)

None of the patients reported in the case studies discontinued rTMS treatment.

**Table 2**
Safety and acceptability of included studies.

Panel A- Randomized Controlled Trials

| Study | Number of Participants | | Side effects/adverse events recorded | Previously identified obstetrical complications | Adverse Events |
|---|---|---|---|---|---|
| | Recruited | Completed | | | |
| Kim et al., 2018 | 14 Active | 11 Active | Headache, treatment site pain, eye twitch/jaw pain, supine hypotension, dizziness, nausea | 1 Pre-eclampsia, 1 LEEP | 3 pre-term births, 1 shoulder dystocia |
| | 12 Sham | 11 Sham | Headache, treatment site pain, eye twitch/jaw pain, supine hypotension, dizziness, nausea | . | . |

Panel B- Uncontrolled Trials

| Study | Number of Participants | | Side effects/adverse events recorded | Previously identified obstetrical complications | Adverse Events |
|---|---|---|---|---|---|
| | Recruited | Completed | | | |
| Hizli Sayar et al., 2014 | 30 | 29 | Contraction of facial muscles | . | . |
| Kim et al., 2011a | 10 | 10 | Headache, Supine hypotension | . | . |
| Tarhan et al., 2012 | 7 | 7 | Not Reported | . | . |

Panel C- Case Reports

| Study | Number of Participants | | Side effects/adverse events recorded | Previously identified obstetrical complications | Adverse Events |
|---|---|---|---|---|---|
| | Recruited | Completed | | | |
| Cohen et al., 2008 | 1 | 1 | Not Reported | . | . |
| Ferrão and Felipe da Silva, 2018 | 4 | 4 | Pain/discomfort at application site, transient difficulty in concentration, sore throat | . | 1 preterm birth; twins- APGAR scores of 6 and 8 |
| Gahr et al., 2012 | 1 | 1 | Not Reported | . | . |
| Klirova et al., 2008 | 2 | 2 | Not Reported | . | 1 preterm birth |
| Tan et al., 2008 | 1 | 1 | Not Reported | . | . |
| Xiong et al., 2018 | 1 | 1 | Not Reported | . | . |
| Zhang and Hu, 2009 | 3 | 3 | Not Reported | . | . |
| Zhang et al., 2010 | 1 | 1 | Not Reported | . | . |

LEEP = Loop electrosurgical excision procedure.

**Table 3**
Effectiveness of Included studies.

Panel A- Randomized Controlled Trials

| Study | Number of Participants | Primary Psychiatric Diagnosis | Instrument | Baseline | Final | Initial Depression Severity | Remission | Response | < 50% |
|---|---|---|---|---|---|---|---|---|---|
| Kim et al., 2018 | 14 Active | MDD | HDRS-17 | 23.2 | 9.3 | Severe | 3 | 9 | 2 |
| | 12 Sham | MDD | HDRS-17 | 22.3 | 13.2 | Severe | 2 | 5 | 6 |

Panel B- Uncontrolled Trials

| Study | Number of Participants | Primary Psychiatric Diagnosis | Instrument | Baseline | Final | Initial Depression Severity | Remission | Response | < 50% |
|---|---|---|---|---|---|---|---|---|---|
| Hizli Sayar et al., 2014 | 30 | MDD | HDRS-17 | 26.8 | 13 | Severe | 6 | 12 | 17 |
| Kim et al., 2011a | 10 | MDD | HDRS-17 | 24.4 | 9.7 | Moderate-Severe | 3 | 7 | 3 |
| Tarhan et al., 2012 | 7 | MDD | HDRS-17 | . | . | . | 2 | 5 | 2 |

Panel C- Case Reports

| Study | Number of Participants | Primary Psychiatric Diagnosis | Instrument | Baseline | Final | Initial Depression Severity | Remission | Response | < 50% |
|---|---|---|---|---|---|---|---|---|---|
| Cohen et al., 2008 | 1 | BD (type unspecified) | HDRS-17 | 18 | 6 | Moderate | 1 | 1 | |
| Ferrão and Felipe da | 3 | MDD | HDRS-21 | 24.3 | 7.3 | Moderate-Severe | 2 | 3 | 0 |
| Silva, 2018 | 1 | MDD | HDRS-22 | 12 | 6 | Mild | 1 | 1 | 0 |
| Gahr et al., 2012 | 1 | MDD | . | . | . | Severe | 0 | 0 | 1 |
| Klirova et al., 2008 | 1 | MDD | MADRS | 33 | 2 | Moderate | 1 | 1 | 0 |
| | 1 | MDD | BDI | 29 | 12 | Severe | 0 | 1 | 0 |
| Tan et al., 2008 | 1 | MDD | HDRS-17 | 38 | 4 | Severe | 1 | 1 | 0 |
| Xiong et al., 2018 | 1 | BDII | EPDS | 23 | 4 | | 1 | 1 | 0 |
| Zhang and Hu, 2009 | 3 | MDD | . | . | . | | . | . | . |
| Zhang et al., 2010 | 1 | MDD | HDRS24 | 35 | 8 | Severe | 0 | 1 | 0 |

MDD = Major Depressive Disorder. RMT = Resting motor threshold. BP = Bipolar Disorder. BDII = Bipolar Disorder, type II. HDRS = Hamilton Depression Rating Scale. MADRS = Montgomery-Asberg Depression Rating Scale. BDI = Beck Depression Inventory. EPDS = Edinburgh Postnatal Depression Scale.

### 6.4. Efficacy and effectiveness

#### 6.4.1. Randomized controlled trials (n = 1)

Reporting only results from study completers, the randomized controlled trial demonstrated antidepressant efficacy, with linear mixed models revealing significant reductions in Hamilton Depression Rating Scale-17 by study end in the active-rTMS group compared to sham-rTMS group. Conservatively assuming a pre-post correlation of 0.7, this corresponds to a standardized mean difference of 0.87. At study end, 81.8% of participants treated in the active-rTMS group were classified as clinical responders compared to 45.5% of sham-treated participants. Clinical remission was achieved in 27.3% of active-rTMS treated participants compared to 18.2% of sham-treated participants (Kim et al., 2018).

#### 6.4.2. Uncontrolled studies (n = 3)

In an open label trial by Kim et al., 70% of the sample ($n = 7$) achieved clinical response, of which 30% ($n = 3$) went on to achieve clinical remission of depressive symptoms (Kim et al., 2011a). This is similar to results from an open label trial by Tarhan et al. (2012) reporting clinical response in 71.4% ($n = 5$) participants, with 28.6% ($n = 2$) of those achieving clinical remission (Tarhan et al., 2012).

Slightly lower rates of response and remission were reported in a larger open label trial ($n = 30$) (Hizli Sayar et al., 2014). 41.4% ($n = 12$) were classified as clinical responders, with 20.7% ($n = 6$) achieving clinical remission.

#### 6.4.3. Case reports (n = 8)

Ten of the eleven participants from case reports (90.9%) were classified as clinical responders, and seven (63.6%) individuals achieved clinical remission.

## 7. Discussion

We performed a systematic review of the literature employing rTMS to treat PPD focusing on studies published since regulatory approval of rTMS and using a strict definition of the peripartum period. Our search identified one randomized controlled trial, 3 uncontrolled studies, and 8 case reports or case series, for a total of 87 patients. rTMS appears to be effective in reducing the symptoms of PPD, and the efficacy, effectiveness, and acceptability of the intervention appear on par with rTMS in the treatment of non-peripartum major depressive disorder (Berlim et al., 2013a; 2013b, 2014).

Though the current literature does not permit a quantitative synthesis, the available evidence suggests that rTMS may be viable option for the treatment of depression during the peripartum period. This conclusion is supported by previous reviews and policies evaluating the safety and effectiveness of rTMS as a therapeutic intervention for depression during the peripartum period (Felipe and Ferrão, 2016; Kim et al., 2015; Robakis and Williams, 2013).

### 7.1. Efficacy and effectiveness

The randomized controlled trial included in our study suggested antidepressant efficacy, with a medium-large effect size of 0.87 and high rates of clinical response and remission (Kim et al., 2018). An additional randomized sham-controlled trial was not retained in our review as it included mothers outside of our strict peripartum definition (Myczkowski et al., 2012). This randomized controlled trial similarly reported statistical separation of active-rTMS compared to sham-rTMS after 4 weeks of daily active-rTMS ($n = 8$) or sham-rTMS ($n = 6$) 5 Hz stimulation at 120% RMT. Conservatively assuming a pre-post correlation of 0.7, this study reported a standardized mean difference of 0.94 in favor of active-rTMS.

The uncontrolled studies supported clinical effectiveness, with rates of clinical response between 41 and 70% and clinical remission between 20 and 30% in three open-label studies (Hizli Sayar et al., 2014; Kim et al., 2011a; Tarhan et al., 2012). Other excluded studies similarly suggest effectiveness. In an open label trial of patients treated for postpartum depression, 8 of 9 participants reached clinical response and remission of symptoms (Garcia et al., 2010). Another study that was not included presented the successful continuation of regular maintenance rTMS throughout pregnancy and postpartum to prevent relapse of chronic depression (Burton et al., 2014). Five grey literature sources that were not retained in our systemic review also suggest effectiveness. These include an open-label trial of 19 cases of PPD, 14 of which (73.7%) achieved response and subsequent remission of symptoms after rTMS treatment (Brock et al., 2016), a case series in which 4/15 (26%) patients achieved clinical response (Ozmut et al., 2015), a case series in which 3 patients improved with rTMS (Yilan et al., 2014), and two positive case reports (Rosenberg and Richardville, 2013; Stultz et al., 2018). Succinctly, rTMS appears to be clinically effective with clinical improvements using multiple stimulation protocols.

Although the studies included in this review focus on change in depressive symptoms, perinatal anxiety often accompanies PPD with symptoms that can be quite problematic (Fairbrother et al., 2016; Leach et al., 2017). A recent systematic review of non-invasive brain stimulation on the effects of anxiety in the general population provides support for rTMS as a therapeutic approach for the treatment of anxiety disorders (Vicario et al., 2019). Though outside the scope of this review, the anti-anxiety effects of rTMS may provide additional benefit to the peripartum population and highlight the need for additional research.

### 7.2. Safety

A recent study using computational modelling to estimate electric field exposure induced by TMS on the foetus, showed fetal exposure is less than or equal to 100 mV/m during all trimesters, well below the recommended safe limit of 800 mV/m for both pregnant patients and pregnant TMS operators (Yanamadala et al., 2017). As such, adverse events to the foetus induced by the electric field of rTMS would be unexpected.

Accordingly, there were no serious obstetrical adverse events reported in the reviewed studies. In the randomized controlled trial, six babies were admitted to the neonatal intensive care unit, a circumstance which is linked to antidepressant exposure in utero (Norby et al., 2016). However, this occurred equally in both active-rTMS (n = 3) and sham-rTMS (n = 3) groups (Kim et al., 2018). No cases of cardiac malformation or persistent pulmonary hypertension were reported; both of which are adverse events associated with antidepressant exposure in utero (Huybrechts et al., 2015, 2014). Yet, despite the small number of antenatal patients included in our review, five preterm births were reported (Ferrão and Felipe da Silva, 2018; Kim et al., 2018; Klirova et al., 2008). While this is at the lower range for pre-term births worldwide (Blencowe et al., 2012), uncontrolled studies reported few cases while pre-term births were greater in the active-group of the randomized sham controlled trial (Kim et al., 2018). This did not vary statistically from the sham-rTMS group and two of the three women had previous medical conditions unrelated to rTMS that are risk factors for preterm birth (Table 2). However, this difference between active and sham-treatment highlights the need for adequately powered sham-controlled trials to definitively prove safety. This is particularly important given that preterm birth rates in the depressed population are estimated to be higher than the general population (Grote et al., 2010), and therefore uncontrolled studies are ill suited to determine safety.

A follow-up study to one of our included open label trials (Hizli Sayar et al., 2014) assessed the long term safety of rTMS on children 1–5 years later (Eryılmaz et al., 2015) compared with children born to healthy mothers and to depressed but untreated expectant mothers. Treatment with rTMS was not associated with decreased cognitive or motor development, however a perceived delay in language development was reported by mothers among children exposed to rTMS in-

utero compared to those in healthy pregnancies. It is unlikely that this is rTMS related, however, as the reported delays were comparable to a sample of children whose mothers had untreated depression during pregnancy.

With respect to psychiatric safety, there were no serious adverse psychiatric events reported in the peer-reviewed publications we included. One case report described using rTMS initially to treat an episode of antenatal bipolar depression without a concomitant mood stabilizer or antipsychotic, which is recommended for other antidepressant interventions in bipolar disorder (McGirr et al., 2016; Picchiarotti et al., 2013). This patient went on to have a manic episode after delivering, approximately four months later (Cohen et al., 2008). The risk of postpartum mania is extremely high compared with another period in a woman's life and, thus, this is unlikely related to rTMS (Heron et al., 2005). It is unclear whether rTMS should be considered in peripartum bipolar depression.

Side effects of rTMS in the peripartum population are similar to those reported in the non-peripartum population (Loo et al., 2008), however this conclusion is limited by inconsistent reporting between studies. Reported side effects included mild headache, treatment site pain, and facial stimulation (Ferrão and Felipe da Silva, 2018; Hizli Sayar et al., 2014; Kim et al., 2011a, 2018). Supine hypotension was also reported (Kim et al., 2011a, 2018) though the authors addressed this in a subsequent paper, managing the issue through postural adjustments (Kim and Wang, 2014). Side effects from the excluded studies were headache and/or pain at treatment application site (Garcia et al., 2010; Myczkowski et al., 2012; Ozmut et al., 2015) facial stimulation (Garcia et al., 2010), or were unreported (Brock et al., 2016; Rosenberg and Richardville, 2013; Stultz et al., 2018; Yilan et al., 2014).

While the risk-benefit ratio for antidepressant medications supports their use in some women, pregnant and lactating women are understandably reluctant to initiate pharmacotherapy due to transplacental passage and/or passage into breast milk (Battle et al., 2013; Patel and Wisner, 2011). rTMS offers an alternative antidepressant technique that limits chemical exposure to the foetus while offering a side-effect profile that appears tolerable.

### 7.3. Acceptability

In the randomized controlled trial, 4 of an original 26 (15.4%) participants withdrew from the study (Kim et al., 2018). Two (7.7%) women withdrew prior to stimulation, due to difficulties with the time commitment of the study. The other two (7.7%) individuals withdrew from the active group after rTMS stimulation for unreported reasons. One participant (3.3%) in an open label trial discontinued rTMS due to a reconsideration of the risks and benefits (Hizli Sayar et al., 2014). There was no report of patient discontinuation in the case series and case studies. By comparison, the mean dropout rate of placebo controlled antidepressant clinical trials is estimated to be around 30% (Rutherford et al., 2013), and therefore one possible interpretation is that rTMS, despite its considerable time commitments, is acceptable in the peripartum population.

A survey evaluating patient acceptability to rTMS found that women were more likely to consider rTMS during pregnancy after an informational video, indicating a lack of awareness and stigma may be an obstacle in implementing rTMS as a treatment during the peripartum period (Kim et al., 2011b).

### 7.4. Limitations

This review consists of a single randomized controlled trial, and the majority of data qualitatively synthesized comes from uncontrolled trials, case series and case studies. These intrinsically have a higher risk of bias, and therefore more sham-controlled trials are required to determine both efficacy and safety. We attempted to maximize the relevance of our review by focusing the search to the publication period following FDA approval to minimize variability in protocols. Nevertheless, protocol variability was substantial and this limited our ability to determine superiority of individual stimulation protocols.

Moreover, despite our aims to reduce variability, two of the included studies use stimulation parameters that are outside of the current FDA approved parameters (Klirova et al., 2008; Tan et al., 2008). Other potential confounds include concomitant interventions, though most studies specify that pharmacotherapy or psychotherapy was held stable before and during rTMS treatment. Our review was limited to the peer reviewed English literature, which may have restricted our search results.

Should additional research solidify the efficacy, acceptability and safety of rTMS in the treatment of PPD, the role for rTMS in PPD management and the optimal treatment parameters remain to be determined. At the same time, other neurostimulation modalities such as ECT are well established in the peripartum population and have been demonstrated to be more effective than rTMS in non-peripartum MDD (Milev et al., 2016). Other neurostimulation treatments, such as transcranial direct current stimulation (Vigod et al., 2014), are under investigation in PPD and may also be attractive options with fewer side effects.

Meanwhile, novel agents are being investigated that may expand the pharmacological options for peripartum patients, such as brexanolone (Meltzer-Brody et al., 2018).

## 8. Conclusions

The use of rTMS in the peripartum period appears to be efficacious, acceptable and well tolerated. Additional research is required to demonstrate safety; however, there have been no serious adverse events in the peripartum population to date and its risk benefit profile may be attractive to women in the peripartum period. Additional prospective data is needed.

## Conflicts of interests

All authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.05.015.

## References

Andriotti, T., Stavale, R., Nafee, T., Fakhry, S., Mohamed, M.M.A., Sofiyeva, N., Ganho-Ávila, A., Bogner, A., Barbosa, S.P., Piton, L.S., Hirayama, A.L.S., Gaccia, G., Smith-Howard Junior, T.P., Miranda, P.C., Reyes, K.J.C., Gragera, A., Nishiwaki, H., Boechat-Barros, R., 2017. ASSERT trial – how to assess the safety and efficacy of a high frequency rTMS in postpartum depression ? A multicenter, double blinded, randomized, placebo-controlled clinical trial. Contemp. Clin. Trials Commun. 5, 86–91. https://doi.org/10.1016/j.conctc.2017.01.004.

Battle, C.L., Salisbury, A.L., Schofield, C.A., Oritz-Hernandez, S., 2013. Perinatal antidepressant use: understanding women's preferences and concerns. J. Psychiatr. Pract. 19, 443–453. https://doi.org/10.1097/01.pra.0000438183.74359.46.Perinatal.

Berlim, M.T., Van Den Eynde, F., Daskalakis, J.Z., 2013a. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol. Med. 43, 2245–2254. https://doi.org/10.1017/S0033291712002802.

Berlim, M.T., Van Den Eynde, F., Jeff Daskalakis, Z., 2013b. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 38, 543–551. https://doi.org/10.1038/npp.2012.237.

Berlim, M.T., Van Den Eynde, F., Tovar-Perdomo, S., Daskalakis, Z.J., 2014. Response , remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation ( rTMS ) for treating major depression : a systematic review and meta-analysis of randomized , double-blind and sham-controlled trials. Psychol. Med. 44, 225–239. https://doi.org/10.1017/S0033291713000512.

Blencowe, H., Cousens, S., Oestergaard, M.Z., Chou, D., Moller, A.B., Narwal, R., Adler, A., Vera Garcia, C., Rohde, S., Say, L., Lawn, J.E., 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since

1990 for selected countries: a systematic analysis and implications. Lancet 379, 2162–2172. https://doi.org/10.1016/S0140-6736(12)60820-4.
Bodnar, L.M., Wisner, K.L., Moses-kolko, E., Sit, D.K.Y., Hanusa, B.H., 2010. Prepregnancy body mass index, gestational weight gain and the likelihood of major depression during pregnancy. J. Clin. Psychiatry 70, 1290–1296. https://doi.org/10.4088/JCP.08m04651.Prepregnancy.
Brock, D.G., Demitrack, M.A., Groom, P., Holbert, R., Rado, J.T., Gross, P.K., Goethe, J.W., Schrodt, R.G., Weeks, H.R., 2016. Effectiveness of neurostar transcranial magnetic stimulation (TMS) in patients with major depressive disorder with postpartum onset. Brain Stimul. 79, 399S. https://doi.org/10.1016/j.biopsych.2016.03.1410.
Brummelte, S., Galea, L.A.M., 2016. Postpartum depression: etiology, treatment and consequences for maternal care. Horm. Behav. 77, 153–166. https://doi.org/10.1016/j.yhbeh.2015.08.008.
Brunoni, A.R., Chaimani, A., Moffa, A.H., Razza, L.B., Gattaz, W.F., Daskalakis, Z.J., Carvalho, A.F., 2017. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA Psychiatr. 74, 143–153. https://doi.org/10.1001/jamapsychiatry.2016.3644.
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. https://doi.org/10.1007/s00737-014-0418-7.
Cohen, R.B., Ferreira, M.S., Ferreira, M.J.L., Fregni, F., 2008. Use of repetitive transcranial magnetic stimulation for the management of bipolar disorder during the postpartum period. Brain Stimul. 1, 224–226. https://doi.org/10.1016/j.brs.2008.05.002.
Diagnostic and Statistical Manual of Mental Disorders (5th ed), 2013. Americain Psychiatric Association. https://doi.org/10.1016/S0031-9422(00)86656-X.
Eryılmaz, G., Hızlı Sayar, G., Özten, E., Göğcegöz Gül, I., Yorbik, Ö., Işiten, N., Bağcı, E., 2015. Follow-up study of children whose mothers were treated with transcranial magnetic stimulation during pregnancy: preliminary results. Neuromodulation Technol. Neural Interface. https://doi.org/10.1111/ner.12231.
Fairbrother, N., Janssen, P., Antony, M.M., Tucker, E., Young, A.H., 2016. Perinatal anxiety disorder prevalence and incidence. J. Affect. Disord. 200, 148–155. https://doi.org/10.1016/j.jad.2015.12.082.
Felipe, R. de M., Ferrão, Y.A., 2016. Transcranial magnetic stimulation for treatment of major depression during pregnancy: a review. Trends Psychiatr. Psychother. 38, 190–197. https://doi.org/10.1590/2237-6089-2015-0076.
Ferrão, Y.A., Felipe da Silva, R. de M., 2018. Repetitive transcranial magnetic stimulation for the treatment of major depression during pregnancy. Rev. Bras. Psiquiatr. 40, 227–228.
Flynn, H.A., Chermack, S.T., 2008. Prenatal alcohol use: the role of lifetime problems with alcohol, drugs, depression, and violence. J. Stud. Alcohol Drugs 69, 500–509. https://doi.org/10.15288/jsad.2008.69.500.
Forty, L., Jones, L., Macgregor, S., Caesar, S., Cooper, C., Hough, A., Dean, L., Dave, S., Farmer, A., McGuffin, P., Brewster, S., Craddock, N., Jones, I., 2006. Familiality of postpartum depression in unipolar disorder: results of a family study. Am. J. Psychiatry 163, 1549–1553. https://doi.org/10.1176/ajp.2006.163.9.1549.
Gahr, M., Blacha, C., Connemann, B.J., Freudenmann, R.W., Schönfeldt-Lecuona, C., 2012. Successful electroconvulsive therapy of major depression during pregnancy after previous non-response to prefrontal rtms. Eur. Psychiatry 27, 1. https://doi.org/10.1016/S0924-9338(12)74648-5.
Garcia, K.S., Flynn, P., Pierce, K.J., Caudle, M., 2010. Repetitive transcranial magnetic stimulation treats postpartum depression. Brain Stimul. 3, 36–41. https://doi.org/10.1016/j.brs.2009.06.001.
George, M.S., Aston-Jones, G., 2010. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology 35, 301–316. https://doi.org/10.1038/npp.2009.87.
Grigoriadis, S., Wilton, A.S., Kurdyak, P.A., Rhodes, A.E., Mph, E.H.V., Mbbs, A.L., Cheung, A., Vigod, S.N., 2017. Perinatal suicide in Ontario, Canada: a 15-year population-based study. Can. Med. Assoc. J. 189, 1085–1092. https://doi.org/10.1503/cmaj.
Grote, N.K., Bridge, J.A., Gavin, A.R., Melville, J.L., Iyengar, S., Katon, W.J., 2010. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch. Gen. Psychiatr. 67, 1012–1024. https://doi.org/10.1001/archgenpsychiatry.2010.111.A.
Hall, P., 2012. Current considerations of the effects of untreated maternal perinatal depression and the National Perinatal Depression Initiative. J. Dev. Orig. Health Dis. 3, 293–295. https://doi.org/10.1017/S2040174412000013.
Heron, J., Craddok, N., Jones, I., 2005. Postnatal euphoria : are ‘ the highs ’ an indicator of bipolarity ? Bipolar Disord. 7, 103–110.
Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343. https://doi.org/10.1136/bmj.d5928.
Hinkle, S.N., Buck Louise, G.M., Rawal, S., Zhu, Y., Alberta, P.S., Zhang, C., 2016. A longitudinal study of depression and gestational diabetes in pregnancy and the postpartum period. Diabetologia 59, 2594–2602. https://doi.org/10.1016/B0-72-160797-7/50116-6.
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. https://doi.org/10.1007/s00737-013-0397-0.
Hoffman, C., Dunn, D.M., Njoroge, W.F.M., 2017. Impact of postpartum mental illness upon infant development. Curr. Psychiatr. Rep. 19, 1–6. https://doi.org/10.1007/s11920-017-0857-8.
Huybrechts, K.F., Bateman, B.T., Palmsten, K., Desai, R.J., Patorno, E., Gopalakrishnan, C., Levin, R., Mogun, H., Hernandez-diaz, S., 2015. Antidepressent use in late pregnancy and risk of pulmonary hypertension of the newborn. J. Am. Med. Assoc. 313, 2142–2151. https://doi.org/10.1001/jama.2015.5605.
Huybrechts, K.F., Palmsten, K., Avorn, J., Cohen, L.S., Holmes, L.B., Franklin, J.M., Mogun, H., Levin, R., Kowal, M., Setoguchi, S., Hernández-Díaz, S., 2014. Antidepressant use in pregnancy and the risk of cardiac defects. N. Engl. J. Med. 370, 2397–2407. https://doi.org/10.1056/NEJMoa1312828.
Ising, M., Horstmann, S., Kloiber, S., Lucae, S., Binder, E.B., Kern, N., Künzel, H.E., Pfennig, A., Uhr, M., Holsboer, F., 2007. Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression-A potential biomarker? Biol. Psychiatry 62, 47–54. https://doi.org/10.1016/j.biopsych.2006.07.039.
Kim, D.R., Epperson, N., Paré, E., Gonzalez, J.M., Parry, S., Thase, M.E., Cristancho, P., Sammel, M.D., O'Reardon, J.P., 2011a. An open label pilot study of transcranial magnetic stimulation for pregnant women with major depressive disorder. J. Women’s Heal. 20, 255–261. https://doi.org/10.1089/jwh.2010.2353.
Kim, D.R., Snell, J.L., Ewing, G.C., Reardon, J.O., 2015. Neuromodulation and Antenatal Depression : a Review 975–982.
Kim, D.R., Sockol, L., Barber, J.P., Moseley, M., Lamprou, L., Rickels, K., Reardon, J.P.O., Epperson, C.N., 2011b. A survey of patient acceptability of repetitive transcranial magnetic stimulation ( TMS ) during pregnancy. J. Affect. Disord. 129, 385–390. https://doi.org/10.1016/j.jad.2010.08.027.
Kim, D.R., Wang, E., 2014. Prevention of supine hypotensive syndrome in pregnant women treated with transcranial magnetic stimulation. Psychiatr. Res. 218, 247–248. https://doi.org/10.1016/j.psychres.2014.04.001.
Kim, D.R., Wang, E., McGeehan, B., Snell, J., Ewing, G., Iannelli, C., O'Reardon, J.P., Sammel, M.D., Epperson, C.N., 2018. Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. Brain Stimul. https://doi.org/10.1016/j.brs.2018.09.005.
Klirova, M., Novak, T., Kopecek, M., Mohr, P., Strunzova, V., 2008. Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode during pregnancy. Neuroendocrinol. Lett. 29, 69–70.
Lamprou, L.C., Epperson, C.N., Wang, E.Y., Parry, S.I., Reardon, J.P.O., Sammel, M.D., Kim, D.R., Kellner, C.H., Knapp, R.G., Mueller, M., Vaughn, W., Petrides, G., Husain, M.M., Young, R.C., Greenberg, M., Mcclintock, S.M., Prudic, J., Weiner, R.D., 2013. Randomized Controlled Trial Assessing the Efficacy of Transcranial Magnetic Stimulation for the Treatment of Major Depressive Disorder in Pregnancy, vol. 29. pp. 150–152.
Leach, L.S., Poyser, C., Fairweather-schmidt, K., 2017. Maternal perinatal anxiety : a review of prevalence and correlates. Clin. Psychol. 21. https://doi.org/10.1111/cp.12058.
Liston, C., Chen, A.C., Zebley, B.D., Drysdale, A.T., Gordon, R., Leuchter, B., Voss, H.U., Casey, B.J., Etkin, A., Dubin, M.J., 2014. Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol. Psychiatry 76, 517–526. https://doi.org/10.1016/j.biopsych.2014.01.023.
Loo, C.K., McFarquhar, T.F., Mitchell, P.B., 2008. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int. J. Neuropsychopharmacol. https://doi.org/10.1017/S1461145707007717.
MacQueen, G.M., Frey, B.N., Ismail, Z., Jaworska, N., Steiner, M., Van Lieshout, R.J., Kennedy, S.H., Lam, R.W., Milev, R.V., Parikh, S.V., Ravindran, A.V., 2016. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 6. Special populations: youth, women, and the elderly. Can. J. Psychiatr. 61, 588–603. https://doi.org/10.1177/0706743716659276.
Man, K.K.C., Chan, E.W., Ip, P., Coghill, D., Simonoff, E., Chan, P.K.L., Lau, W.C.Y., Schuemie, M.J., Sturkenboom, M.C.J.M., Wong, I.C.K., 2017. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. BMJ 357. https://doi.org/10.1136/bmj.j2350.
Mautner, E., Greimel, E., Trutnovsky, G., Daghofer, F., Egger, J.W., Lang, U., 2009. Quality of life outcomes in pregnancy and postpartum complicated by hypertensive disorders, gestational diabetes, and preterm birth. J. Psychosom. Obstet. Gynecol. 30, 231–237. https://doi.org/10.3109/01674820903254757.
McGirr, A., Vöhringer, P.A., Ghaemi, S.N., Lam, R.W., Yatham, L.N., 2016. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression : a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatr. 3, 1138–1146. https://doi.org/10.1016/S2215-0366(16)30264-4.
Meltzer-Brody, S., Colquhoun, H., Riesenberg, R., Epperson, C.N., Deligiannidis, K.M., Rubinow, D.R., Li, H., Sankoh, A.J., Clemson, C., Schacterle, A., Jonas, J., Kanes, S., 2018. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet 392, 1058–1070. https://doi.org/10.1016/S0140-6736(18)31551-4.
Milev, R.V., Giacobbe, P., Kennedy, S.H., Blumberger, D.M., Daskalakis, Z.J., Downar, J., Modirrousta, M., Patry, S., Vila-rodriguez, F., Lam, R.W., Macqueen, G.M., Parikh, S.V., 2016. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive Disorder : section 4 . Neurostimulation treatments. Can. J. Psychiatr. 61, 561–575. https://doi.org/10.1177/0706743716660033.
Morales, D.R., Slattery, J., Evans, S., Kurz, X., 2018. Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder : systematic review of observational studies and methodological considerations. BMC Med. 16, 1–14. https://doi.org/10.1186/s12916-017-0993-3.
Myczkowski, M.L., Dias, A.M., Luvisotto, T., Arnaut, D., Bellini, B.B., Mansur, C.G., Rennó, J., Tortella, G., Ribeiro, P.L., Marcolin, M.A., 2012. Effects of repetitive transcranial magnetic stimulation on clinical, social, and cognitive performance in

postpartum depression. Neuropsychiatric Dis. Treat. 8, 491–500. https://doi.org/10.2147/NDT.S33851.
Norby, U., Forsberg, L., Wide, K., Sjors, G., Winbladh, B., Kallen, K., 2016. Neonatal morbidity after maternal use of antidepressant drugs during pregnancy. Pediatrics 138 e20160181–e20160181. https://doi.org/10.1542/peds.2016-0181.
Orr, S.T., Blazer, D.G., Orr, C.A., 2012. Maternal prenatal depressive symptoms, nicotine addiction, and smoking-related knowledge, attitudes, beliefs, and behaviors. Matern. Child Health J. 16, 973–978. https://doi.org/10.1007/s10995-011-0822-9.
Ozmut, O., Balibey, H., Yilan, Y., Algul, A., Ebrinc, S., Cetin, M., Tutuncu, R., Ates, A., 2015. Repetitive transcranial magnetic stimulation for the treatment of depression during pregnancy and postpartum period. Klin. Psikofarmakol. Bul. 25, S203. https://doi.org/10.1590/1516-4446-2017-2522.
Patel, S.R., Wisner, K.L., 2011. Decision making for depression treatment during pregnancy and the postpartum period. Depress. Anxiety. Depress. Anxiety 28, 589–595. https://doi.org/10.1002/da.20844.
Pearlstein, T., 2013. Use of psychotropic medication during pregnancy and the postpartum period. Wom. Health 9, 605–615. https://doi.org/10.2217/whe.13.54.
Pearlstein, T., 2008. Perinatal depression: treatment options and dilemmas. J. Psychiatry Neurosci. 33, 302–318.
Picchiarotti, I., Bond, D.J., Ph, D., Baldessarini, R.J., Nolen, W.A., Ph, D., Grunze, H., Berk, M., Ph, D., Goodwin, G.M., Sci, F.M., Sachs, G.S., Tondo, L., Findling, R.L., Youngstrom, E.A., Psy, D., Ph, D., Tohen, M., Undurraga, J., González-pinto, A., Ph, D., Goldberg, J.F., Calabrese, J.R., Malhi, G.S., Ketter, T.A., Cassidy, F., Akiskal, H., Lafer, B., Martínez-aran, A., Psy, D., Bauer, M., Ph, D., Amsterdam, J.D., 2013. The international society for bipolar disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am. J. Psychiatry 170, 1249–1262.
Rai, D., Lee, B.K., Dalman, C., Newschaffer, C., Lewis, G., Magnusson, C., 2017. Antidepressants during pregnancy and autism in offspring: population based cohort study. Obstet. Gynecol. Surv. 72, 689–692. https://doi.org/10.1097/01.ogx.0000527930.12186.9d.
Ravesteyn, L.M.V., Berg, M.P.L., Van Den, Hoogendijk, W.J.G., Kamperman, A.M., 2017. Interventions to treat mental disorders during pregnancy: a systematic review and multiple treatment meta-Analysis. PLoS One 12, 1–17. https://doi.org/10.1371/journal.pone.0173397.
Robakis, T.K., Williams, K.E., 2013. Biologically based treatment approaches to the patient with resistant perinatal depression. Arch. Womens. Ment. Health 16, 343–351. https://doi.org/10.1007/s00737-013-0366-7.
Rosenberg, R.W., Richardville, D., 2013. Case Report. pp. 367. https://doi.org/10.1017/S1092852913000837.
Rutherford, B.R., Cooper, T.M., Persaud, A., Brown, P.J., Sneed, J.R., Roose, S.P., 2013. Less is more in antidepressant clinical trials. J. Clin. Psychiatry 74, 703–715. https://doi.org/10.4088/JCP.12r08267.
Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., Ramsay, C.R., Regidor, D., Rothstein, H.R., Sandhu, L., Santaguida, P.L., Schünemann, H.J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J.C., Waddington, H., Waters, E., Wells, G.A., Whiting, P.F., Higgins, J.P., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, 4–10. https://doi.org/10.1136/bmj.i4919.
Stultz, D.J., Thistlethwaite, D., Voltin, R., Osburn, S., Walton, R., Burns, T., 2018. Bipolar, depressed, and pregnant – transcranial magnetic stimulation as a treatment alternative. Brain Stimul. 11, e15. https://doi.org/10.1016/j.brs.2018.07.025.
Suri, R., Lin, A.S., Cohen, L.S., Altshuler, L.L., 2014. Acute and long-term behavioral outcome of infants and children exposed in utero to either maternal depression or antidepressants: a review of the literature. J. Clin. Psychiatry 75, 1142–1152. https://doi.org/10.4088/JCP.13r08926.
Tan, O., Tarhan, N., Coban, A., Baripoglu, S.K., Guducu, F., Izgi, H.B., Hizli, G., Ates, O., Bulut, H., 2008. Antidepressant effect of 58 sessions of rTMS in a pregnant woman with recurrent major depressive disorder: a case report. J. Clin. Psychiatry 10, 69–71. https://doi.org/10.4088/PCC.v10n0113a.
Tarhan, N., Sayar, G.H., Tam, O., Kag, G., 2012. Efficacy of high-frequency repetitive transcranial magnetic stimulation in treatment-resistant depression. Clin. EEG Neurosci. 43, 279–284. https://doi.org/10.1177/1550059412449752.
Vicario, C.M., Ali, M., Felmingham, K., Martino, G., Nitsche, M.A., 2019. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. Neurosci. Biobehav. Rev. 96, 219–231. https://doi.org/10.1016/j.neubiorev.2018.12.012.
Vigod, S., Dennis, C., Daskalakis, Z., Murphy, K., Ray, J., Oberlander, T., Somerton, S., Hussain-shamsy, N., Blumberger, D., 2014. Transcranial direct current stimulation ( tDCS ) for treatment of major depression during pregnancy : study protocol for a pilot randomized controlled trial. Trials 15, 366–377.
Viktorin, A., Uher, R., Reichenberg, A., Levine, S.Z., Sandin, S., 2017. Autism risk following antidepressant medication during pregnancy. Psychol. Med. 47, 2787–2796. https://doi.org/10.1017/S0033291717001301.
Wisner, K.L., Hanusa, B.H., Perel, J.M., Peindl, K.S., Piontek, C.M., Sit, D.K.Y., Findling, R.L., Moses-Kolko, E.L., 2006. Postpartum depression: a major public health problem. J. Clin. Psychopharmacol. 26, 353–360. https://doi.org/10.1097/01.jcp.0000227706.56870.dd.
World Health Organization, 1993. The ICD-10 classification of mental and behavioural disorders. World heal. Organ 1–267. https://doi.org/10.4103/0019.
Xiong, W., Lopez, R., Cristancho, P., 2018. Transcranial magnetic stimulation in the treatment of peripartum bipolar depression : a case report. Brazilian J. Psychiatry 40, 344–345. https://doi.org/10.1590/1516-4446-2018-0037.
Yanamadala, J., Noetscher, G.M., Makarov, S.N., Member, S., 2017. Estimates of peak electric fields induced by transcranial magnetic stimulation in pregnant women as patients using an FEM full - body model. 2017 39th. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. 1441–1444. https://doi.org/10.1109/EMBC.2017.8037105.
Yilan, Y., Balibey, H., Tutuncu, R., Basoglu, C., Cetin, M., 2014. Transmagnetic Stimulation in Treatment of Peripartum Depression-Three Case Series. 0–1.
Zhang, D., Hu, Z., 2009. RTMS may be a good choice for pregnant women with depression. Arch. Womens. Ment. Health 12, 189–190. https://doi.org/10.1007/s00737-009-0058-5.
Zhang, X., Liu, K., Sun, J., 2010. Safety and feasibility of repetitive transcranial magnetic stimulation ( rTMS ) as a treatment for major depression during pregnancy. pp. 369–370. https://doi.org/10.1007/s00737-010-0163-5.
Zhou, X., Li, Y., Ou, J., Li, Y., 2018. Association between maternal antidepressant use during pregnancy and autism spectrum disorder : an updated meta-analysis. Mol. Autism. 3, 1–7.