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Efficacy of Non-Invasive and Non-Convulsive Brain Stimulation in Decreasing Depression Symptoms During the Peripartum Period: A systematic review

Dissertação no âmbito do Mestrado Integrado em Psicologia, Área de Psicologia Clínica e da Saúde, Subárea de Especialização em Intervenções Cognitivo-Comportamentais nas Perturbações Psicológicas e Saúde, orientada pela Doutora Ana Ganho-Ávila e Doutora Ana Fonseca e apresentada à Faculdade de Psicologia e Ciências da Educação da Universidade de Coimbra.

Julho de 2020

Faculdade de Psicologia e Ciências da Educação
da Universidade de Coimbra

EFFICACY OF NON-INVASIVE AND NON-CONVULSIVE BRAIN STIMULATION IN DECREASING DEPRESSION SYMPTOMS DURING THE PERIPARTUM PERIOD:

A Systematic Review

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Agradecimentos

À Professora Doutora Maria Cristina Canavarro pelo exemplo máximo de profissionalismo e que, ainda que em licença de sabática, garantiu que tudo decorria em plenitude através da sua orientação e exigência.

À Doutora Ana Fonseca e Doutora Helena Moreira pela orientação exigente e proximidade.

À Doutora Ana Ganho-Ávila, pela admirável capacidade de ensinar, permitindo autonomia e simultaneamente disponibilidade para acompanhar de forma próxima todo o processo, esclarecendo sempre todas as dúvidas. O meu muito obrigada pelos múltiplos desafios lançados, por toda a dedicação, preocupação e todo o interesse desde o início e ao longo de todo este ano.

A toda a equipa de Neurociência Translacional do CINEICC por toda a boa-disposição e toda a partilha de conhecimento. Em particular, um agradecimento muito especial à Raquel Guiomar por toda a disponibilidade e todo o carinho.

Aos amigos que são família e à família, que se traduzem na melhor companhia para partilhar todos os desafios e conquistas. Ao Carlos que de entre os mais especiais se destaca como a maior fonte de suporte emocional. À Rita que acompanha desde sempre o meu percurso pessoal e académico e a quem todos os agradecimentos não chegariam. À Inês por ter entrado na minha vida académica e se ter estendido a todas as outras áreas. A todos os outros que foram facilitando e tornando mais agradável este percurso.

A Eficácia das Técnicas de Estimulação Cerebral Não Invasivas e Não Convulsivas na Diminuição da Sintomatologia Depressiva no Período Periparto: Uma Revisão Sistemática

Resumo

Background: A Depressão Periparto é a perturbação mental mais comum no período perinatal, traduzindo-se em consequências para mães e bebés. As técnicas de estimulação cerebral não invasivas e não convulsivas têm sido sugeridas como um tratamento eficaz na redução dos sintomas depressivos, durante este período. **Objetivos:** No presente estudo pretende-se rever estudos que aplicaram estas mesmas técnicas com o objetivo de reduzir a sintomatologia depressiva no período periparto. **Métodos:** Por forma a analisar a eficácia, segurança, aceitabilidade e o impacto nas funções neurocognitivas, foi conduzida uma pesquisa de literatura em quatro bases de dados (PUBMED, psycINFO, Web of Science e Lilacs), desde que há publicações até maio de 2020. **Resultados**: Vinte e cinco estudos foram incluídos e os dados de interesse extraídos de acordo com o protocolo previamente registado. Para além da análise qualitativa e avaliação do risco de enviesamento, seguiu-se uma síntese quantitativa focada no resultado primário, a eficácia. A análise qualitativa mostrou resultados promissores em relação à eficácia da estimulação magnética e elétrica transcraniana na redução dos sintomas depressivos e confirmou seu perfil seguro para mães e bebés e aceitabilidade. Em relação à avaliação neurocognitiva, o seu impacto é inconclusivo. **Conclusões:** O número reduzido de estudos controlados e o risco de enviesamento limitam a robustez da síntese quantitativa. Estudos futuros são necessários para confirmar estes resultados. Não obstante, as técnicas de estimulação cerebral não invasivas e não convulsivas parecem contornar algumas das limitações de outros tratamentos, podendo, no futuro complementar o conjunto de tratamentos para a Depressão Periparto.

Palavras-chave: Técnicas de Estimulação Cerebral Não Invasivas, Estimulação Magnética Transcraniana, Estimulação Elétrica Transcraniana, Depressão no Periparto, Revisão Sistemática

Efficacy of Non-Invasive and Non-Convulsive Brain Stimulation in Decreasing Depression Symptoms During Peripartum Period: A Systematic Review

Abstract

Background: Peripartum depression disorder is the most common mental health disorder in the peripartum, leading to adverse consequences for mothers and babies. Non-invasive and non-convulsive brain stimulation has been suggested as an efficacy treatment for depressive symptoms in the peripartum. **Objectives:** Here we aim to review studies that applied non-convulsive and non-invasive stimulation techniques in women during the peripartum. **Methods:** To analyze the efficacy, security, acceptability, and the impact in the neurocognitive functions we conducted the search literature in four data bases (PUBMED, psycINFO, Web of Science and Lilacs) from inception to May 2020. **Results:** Twenty-five studies were included, and data of interest was systematically extracted according to a preregistered protocol. We conducted a qualitative synthesis, completed by a risk of bias assessment, and followed by a quantitative analysis focused on the primary outcome of efficacy in reducing depressive symptoms. The qualitative analysis shows promising results regarding the efficacy of repetitive transcranial magnetic stimulation and transcranial electric stimulation and confirmed its safe profile both for mothers and infants, and the acceptability by women in the peripartum period. Regarding the impact on neurocognitive functions, results are inconclusive. **Conclusions:** The reduced number of controlled studies and risk of bias limit the robustness of the quantitative synthesis in what concerns efficacy. Future studies are needed to ascertain these results, nonetheless non-invasive and non-convulsive brain stimulation techniques seem to address some of the concerns and limitations of other treatments and may in the future complement the treatment algorithm for peripartum depression.

***Keywords*:** Non-invasive Brain Stimulation, repetitive Transcranial Magnetic Stimulation, Transcranial Electric Stimulation, Peripartum Depression, Systematic Review

Content

1. Introduction

The World Health Organization estimates that depression affects more than 300 million people worldwide (2018). Due to peripartum vulnerability to mental illness (Valadares et al., 2020) and according to recent findings, overall pooled prevalence of peripartum depression (PPD) is 11.9%, indicating that a significant number of women are affected by this disorder. Hence, the prevalence of PPD is lower in high income countries (11.4%) and higher in low and middle income countries (13.1%; Woody et al., 2017).

According to the DSM-5, PPD is a Major Depressive Disorder (MDD) with a specifier that extends the diagnosis to clarify that PPD is present when the onset of the depressive symptoms occurs during pregnancy or within the four weeks following delivery (American Psychiatric Association, 2013). Nonetheless, some studies advise the extension of this period to 12 months postpartum (Wisner et al., 2013; Woody et al., 2017), clinicians should screen their patients across this period (Committee on Obstetric Practice, 2015).

Sharing most of the symptoms of major depressive disorder, the most common signs of PPD are persistent sadness, anhedonia, lethargy, guilt, irritability, psychomotor agitation, and sleep, weight, and appetite disturbances (Frieder et al., 2019). Considering the overlap between MDD symptoms and PPD it is essential to clarify the differences. A recent study suggests that postpartum depression and MDD may differ in the following characteristics: symptom severity, hormone contributions, heritability, epigenetic mechanisms, and response to standard and novel treatment interventions (Batt et al., 2020), although further research is needed on this topic. PPD during pregnancy and postpartum period also differ. Putnam and colleagues (2017) identified five subtypes of PPD based on symptom dimensions of depressed mood, anxiety, and anhedonia that can occur during different periods (across the trimesters and during early or later postpartum periods). According to the same study, anxious anhedonia was more present during first and second trimester of pregnancy, the subtype of anxious depression onset was in the first trimester and early postpartum period was associated with more severe depression.

PPD is a disorder that not only affects the mother but also the infant, leading to adverse outcomes. For example, depression during pregnancy increases the risk of premature birth, lower birth weight and delayed intrauterine growth (Grote et al., 2010). In the postpartum period, due to depressed symptoms, mothers are less communicative visually and verbally, leading to baby feeding (including breastfeeding) and sleep problems, compromising the baby wellbeing (Field, 2010; Slomian et al., 2019).

Despite the prevalence and negative consequences of PPD that place this clinical condition as a major public health issue (Meltzer-Brody et al., 2013), many women are either undertreated or untreated, due limited symptoms reporting and reluctance in seeking for care and/or concerns in taking antidepressants (Becker et al., 2016).

The decision about the most adequate treatment for PPD must be defined in a case-by-case basis, according to individual characteristics (e.g. severity of symptoms, willingness to breastfeed, first or recurrent depressive episode, previous antidepressant medication), the best clinical evidence (Charlton et al., 2014), the accessible treatments and respecting the women's preferences.

To guide health professionals in selecting the most effective but least harmful intervention, some countries have developed "Clinical Practice Guidelines". Molenaar and colleagues, (2018) reviewed the available literature in the field and summarized their results according to specific categories, such as the period of disease (pre pregnancy, pregnancy and postpartum), the onset of the first depressive episode, and the previous use of antidepressants. Whereas each document supports a national clinical consensus, it does not guarantee that national recommendations are followed. Furthermore, there are no cross-national guidelines and the authors claim the need for additional research to reach international perinatal-specific consensus (Molenaar et al., 2018).

For new depressive episodes, most guidelines consider psychotherapy as the preferred treatment for mild to moderate cases of peripartum depression and antidepressants for severe ones. However, 70% of cases are treated with antidepressants (Molenaar et al., 2018). In Charlton and colleagues (2014) study, across six European countries, Selective Serotonin Reuptake inhibitor (SSRI) was found to be the most frequent class of antidepressants prescribed. According to the authors, 2.3% of pregnant women and 7.0% postpartum women diagnosed with depression are prescribed with SSRIs. Additionally, even though overall authors and clinicians suggest that antidepressants are safe to use in the peripartum period, recent systematic reviews indicate that the safety of antidepressants is not confirmed (Bellantuono et al., 2015; Smit et al., 2016) making their use controversial.

However, according to the guidelines from Canada (BC) and the Netherlands (NVOG), pregnant women on medication before pregnancy should continue pharmacotherapy preventing relapse of depressive symptoms. Ideally, by the time of prescribing psychiatric medication, pregnancy should be discussed and planned considering the psychiatric history, the patient's past history of medication and its efficacy, the severity of current symptoms, and addressing the pros and cons of adherence to medication and alternative treatments (Payne, 2020).

The use of antidepressants in the peripartum period has been target of attention. Based on the available literature, a recent review (Mohammed Ali, 2019) stated that due to the threat that taking antidepressants during pregnancy represents to the growing fetus affecting motor and cognitive development, if possible, antidepressants should be avoided. Moreover, in the postpartum period, most guidelines encourage breastfeeding even when medication is used (Molenaar et al., 2018). In particular, the Nordic Federation of Societies of Obstetrics and Gynecology (NFGOG; Norway) advises switching medication, when women are breastfeeding, recommending sertraline as a favorable medication, mainly due to its low level in breast milk. Compared to the pregnancy period, there is a lack of literature exploring the effects of exposure of nursing infants to antidepressant contents of

breast milk (Mohammed Ali, 2019).

Recently, Food and Drug Administration (FDA) approved the first drug specifically for the treatment postpartum depression - Zulresso (brexanolone; Cristea & Naudet, 2019). Eldar-Lissai and colleagues compared this novel drug with SSRIs, concluding that this treatment is considered cost-effective in reducing depressive symptoms in the postpartum period (2020). Concerning brexanolone safety and acceptability, clinical trials showed that the drug is well tolerated, even though commonly associated with adverse effects such as headache, dizziness, and somnolence (Kanes et al., 2017; Meltzer-Brody et al., 2018).

Regarding psychotherapy, recent reviews recommended it when symptoms of depression are non-severe (Mohammed Ali, 2019). Hence, psychotherapy has been shown to be the women preferred treatment to address depressive symptoms both during pregnancy and after delivery (Hübner-Liebermann et al., 2012; Kim et al., 2011).

The most common psychotherapeutic models for PPD during pregnancy are Cognitive and Behavioural Therapy (CBT) and Interpersonal Psychotherapy (IPT) (Bledsoe & Grote, 2006; Misri et al., 2014).

Cognitive and Behavioural Therapy aims at modifying distorted patterns of negative thinking and alter behaviours, promoting coping strategies and reducing distress. CBT can be used as a stand-alone intervention or in combination with medication (Misri et al., 2014). In the recent years the search for e-mental health has been growing; in fact, international guidelines recommend online CBT for treatment integrating a stepped care intervention for women in the peripartum period experiencing anxiety and depressive symptoms (Kingston & Rocha, 2020). Focusing on reducing the depressive symptoms during pregnancy, Kim and colleagues (2014) analysed the efficacy of a computer-assisted CBT program, and found rates of 80% for treatment response and 60% for remission after only eight sessions. A more recent study (Milgrom et al., 2016) focused on the postpartum period, assessed the efficacy of an internet intervention. This intervention showed that depressive symptoms remitted in 79% of the women participating in the active group, compared to 18% of the women included in the control / treatment as usual.

Interpersonal Psychotherapy is a time-limited and problem focused therapy (Misri et al., 2014) particularly adapted for postpartum depression, focusing interpersonal relationships, and changes on women's roles and associated expectations (Hübner-Liebermann et al., 2012).

Both CBT (Huang et al., 2018; Sockol, 2015) and IPT (Miniati et al., 2014; Sockol, 2018) are considered efficacious for treating PPD , however psychological interventions have its own limitations such as its high cost per session, not effective in every case (van Ravesteyn et al., 2017), the needed time to reach treatment response and the low accessibility. Finally, the stigma psychotherapy involves is a particularly sensitive matter for mothers as woman fear that by disclosing depressive symptoms others, may perceived them as less competent mothers (Guille et al., 2013).

In conclusion, both pharmacotherapy and psychotherapy used as stand-alone or in combination are evidence-based interventions to reduce symptoms of peripartum depression (Bledsoe & Grote, 2006). Although medication combined with CBT was showed to be the most efficacious treatment followed by medication alone (Sockol et al., 2011), this evidence is outdated. Nonetheless considering the above-mentioned limitations, new alternatives need to be found to ensure universal high quality maternal mental health care particularly targeting women with depressive symptoms in the peripartum period.

Neuromodulation is one of the fastest-growing fields in medicine, and has been suggested for the treatment of several neuropsychiatric disorders (Borrione et al., 2020). Non-invasive brain stimulation (NIBS) is a set of techniques used to stimulate or modify brain activity from the surface of the head with non-implantable methods (Albizu et al., 2019). These techniques can be subdivided into convulsive and non-convulsive modalities. Non-convulsive techniques use electric current that can be induced by magnetic fields (e.g. repetitive transcranial magnetic stimulation [rTMS]) or injected (e.g. transcranial direct current stimulation [tDCS]). Besides, unlike convulsive techniques (e.g. Electroconvulsive therapy [ECT]), non-convulsive modalities do not require sedation or anaesthesia (Brunoni et al., 2019). In particular for the peripartum period, non-invasive and non-convulsive treatments seem to be promising due to its efficacy (Lefaucheur et al., 2017, 2020) and the absence of systemic effects in case of rTMS (Cole et al., 2019).

Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive technique that impacts synaptic transmission through patterned energy, changing neurons activity and connectivity (George & Aston-Jones, 2010). The magnetic field produced by TMS creates immediately local effects under the coil and remotely activating the axons to or from the site of stimulation (Terranova et al., 2019). The most studied condition for the therapeutic application of rTMS is depression. Actually, the extensive review by the European Chapter of the Neurophysiology Society confirmed the efficacy of rTMS in the treatment of unipolar depression with a Level A recommendation for both high frequency (HF) rTMS delivered in the left dorsolateral prefrontal cortex (DLPFC) and low frequency (LF) rTMS delivered in the right DLPFC (Lefaucheur et al., 2020). Further, two recent systematic reviews concluded for rTMS efficacy in reducing depressive symptoms in the peripartum period and its acceptability and tolerability by women (Cole et al., 2019; Ganho-Ávila et al., 2019). Although effective, the adoption of rTMS has been slow especially due to its high cost and intensiveness, requiring daily sessions of 19-37.5 min each with 10Hz, according to the standard protocol approved by the FDA (Trevizol et al., 2019).

Theta burst stimulation (TBS) is a pattern form of transcranial magnetic stimulation that can be administered through a continuous or an intermittent protocol (cTBS or iTBS, respectivelly; Di Lazzaro et al., 2008). To address the time consuming issue associated with rTMS, iTBS has been recently suggested due to its shorter protocols with sessions duration of only three minutes

(Blumberger et al., 2018). Accordingly, a recent case report of iTBS to treat depression in pregnancy (Trevizol et al., 2019), showed that remission of symptoms was achieved after 20 sessions, demonstrating that this technique is promising and can be an alternative to pregnant women who are reluctant to taking antidepressants.

Transcranial direct current stimulation (tDCS) is a technique that involves the application of a low intensity electric current between two electrodes placed over the scalp, inducing neuronal activity (Merzagora et al., 2010; Miranda et al., 2006). Through changing the polarity of the current it is possible to modulate cortical excitability. Anodal tDCS depolarizes neurons creating cortical excitability and cathodal tDCS reduces excitability, hyperpolarizing neurons (Antal et al., 2004). Contrary to rTMS, tDCS does not generate action potentials per se, instead facilitates or inhibits synaptic transmission through increasing or decreasing the frequency of action potentials during endogenous neuronal firing (Brunoni et al., 2012)

This technique seems to be a promising treatment for depression due to its effectiveness in MDD, safety profile, and thanks to its nonpharmacological nature and low costs (Vigod et al., 2014). The majority of tDCS protocols for MDD use a constant direct current of low intensity (0.5-2 mA; Bennabi & Haffen, 2018) and level B recommendation was proposed for tDCS in MDD patients, with a minimum of ten sessions of 20-30 minutes each (Lefaucheur et al., 2017). Similarly, to what happens with rTMS, such features lead researchers and clinicians to consider tDCS as a promising alternative treatment for depressed women in the peripartum period. Hence, due to tDCS portability and low cost, at-home protocols have been proposed (Alonzo et al., 2019; Alonzo & Charvet, 2016). Home use of tDCS refers to self-administered tDCS upon the clinician establishing the frequency and number of sessions. However, treatment success depends on patient's compliance, the use of preprogramed and secured devices and the guarantee of virtual care/supervision, being more appropriate for patients that previously showed adherence to the treatment (Ulrich Palm et al., 2018). To our knowledge there is no review regarding tDCS effectiveness in the peripartum period.

Similar to tDCS, transcranial alternating current stimulation (tACS), delivers an oscillating sinusoidal current at a chosen frequency (Antal et al., 2008). Results from a recent RCT, suggested that targeting alpha oscillations with tACS is a potential approach to treat MDD (Alexander et al., 2019). The first report using gamma-tACS for depression during pregnancy showed symptoms' improvement after nine sessions and remission was achieved at three months follow-up (Wilkening et al., 2019).

In sum, evidence concerning NIBS to reduce depressive symptoms in the peripartum period are promising although scattered. Therefore, aiming at fostering an improved understanding of the efficacy of NIBS during the peripartum period, and and given the lack of synthesized knowledge about the use of different techniques and across the whole peripartum period (from pregnancy to the postpartum), we conducted the herein systematic review. The current thesis is part of a broader

comprehensive review, which includes all non-implantable brain stimulation techniques (tDCS, rTMS, tACS and ECT). By limiting the focus on non-invasive and non-convulsive techniques, this thesis aims to answer the following question: What is the efficacy of non-invasive and non-convulsive brain stimulation treatments in decreasing peripartum depression symptoms (either as a stand-alone, add-on therapy or augmentation intervention to antidepressants) when compared to pharmacotherapy, psychological interventions, other brain stimulation techniques or no treatment?

2. Methods

2.1. Protocol and registration

The protocol of this systematic review was registered in PROSPERO, submitted the first time in October 2019, currently under review, and resubmitted after review in May 2020 (ID 153132). This document is available in Appendix A. This review is conducted under COST Action RISEUP-PPD (CA18138) activities, supported by COST Association.

2.2. Literature review and search methods

The data search was conducted from inception to October 2019, for available publications and reports in the following languages: English, French, Spanish or Portuguese. The search was conducted in the following databases: Pubmed/Medline, PsycINFO, Web of Science and Lillacs for peer-reviewed studies and for unpublished studies in Network Digital Thesis and Dissertations. The complete search strategy can be consulted in Appendix B. Since the present study is only part of a broader review concerning all methods of non-invasive brain stimulation, in agreement with remaining authors, the current review will only focus on non-invasive and non-convulsive techniques. Additionally, a manual verification of the list of references for each eligible study was performed to find potential new reports.

Aiming at updating the search and including new reports, according to the Methodological Expectations of Cochrane Intervention Reviews (MECIR), an update of the search was conducted in May 2020.

2.3. Eligibility criteria

Randomized clinical trials and non-randomized studies which enrolled women diagnosed with MDD in the peripartum period according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) or the International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organization, 2018) were included.

The studies' participants should have at least 18 years old, and have received rTMS, iTBS, tDCS or tACS as a stand-alone, add-on or augmentation treatment, during pregnancy and/or the

postpartum period. Eligible comparators were other types of brain stimulation, psychotherapy, pharmacotherapy, or no treatment.

2.4. Data extraction and outcome measures

Titles and abstracts of retrieved studies were screened by two independent researchers using Ryyaan (Ouzzani et al., 2016), a web application for systematic reviews, to identify studies that meet the inclusion criteria. The inter-rater reliability was substantial (k= .80; Landis & Koch, 1977). Disagreements were solved through in-depth discussions until consensus was reached. Extraction of data from the full-text reports was conducted by one researcher and reviewed by other three. Data was extracted for: study design, study population, demographic and baseline characteristics, type of intervention and type of comparator and outcomes. We defined reduction of depressive symptoms as the primary outcome, as assessed by one of the following instruments: all versions of the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), the Edinburgh Postnatal Depression Scale (EPDS; Cox & Holden, 2003), the Inventory of Depressive Symptomatology-Self-Report (IDS-SR; Rush et al., 1986), the Clinical Global Impressions scales (CGI; Busner & Targum, 2007; Guy, 1976), the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), and the Beck Depression Inventory (BDI; Beck, 1961). Safety neonatal outcomes were defined as co-primary outcomes.

Additionally, the secondary outcomes defined were the response rate; remission status; time to response; safety for mothers; acceptability measures; neurocognitive assessment measures. In case of missing or unclear data, two attempts were made to contact the authors of the uncomplete reports by email, with a two-week interval between each attempt.

2.5. Qualitative and quantitative data synthesis

The qualitative analysis was conducted for the included studies considering efficacy, acceptability according to the dropout rates, adverse effects, and neonatal safety outcomes.

Concerning the quantitative analysis, a meta-analysis was performed using R (R Core Team, 2016) to estimate the effectiveness of non-invasive brain stimulation techniques. Unfortunately, due the nature of the study designs (most of which were case reports), and the lack of homogenous information (e.g. heterogeneity of measures and endpoints) the meta-analysis was limited to seven rTMS studies. Of these, two separated meta-analysis were estimated: one where we estimated the effect size of rTMS treatment during pregnancy (combining three studies) and a second one estimating the effect size of rTMS treatment in the postpartum period (combining four studies). No meta-analysis was possible regarding transcranial electric stimulation (TES) studies.

2.6. Risk of bias assessment

Risk of bias (RoB) was assessed by selecting the adequate tool according to the study design. Therefore, for the RCTs we used the Cochrane Collaboration's tool (Higgins et al., 2011). For open label studies, we used the Risk of Bias in Non-Randomized Studies of Interventions – Robins-I seven domains (Sterne et al., 2016). Additionally, after data obtained from Robins-I, to visualize RoB assessment we used the Risk-of-bias Visualization (robvis; McGuinness & Higgins, 2020). To assess RoB in case reports, we adapted the 20-criterion quality appraisal checklist from the Institute of Health Economics (IHE's; Guo et al., 2016) and used 12 of the available criteria. According to each study design, the RoB assessment was performed by one rater and checked by two other raters. Discrepancies on ratings were fully discussed and a final judgment of overall risk of bias was agreed.

3. Results

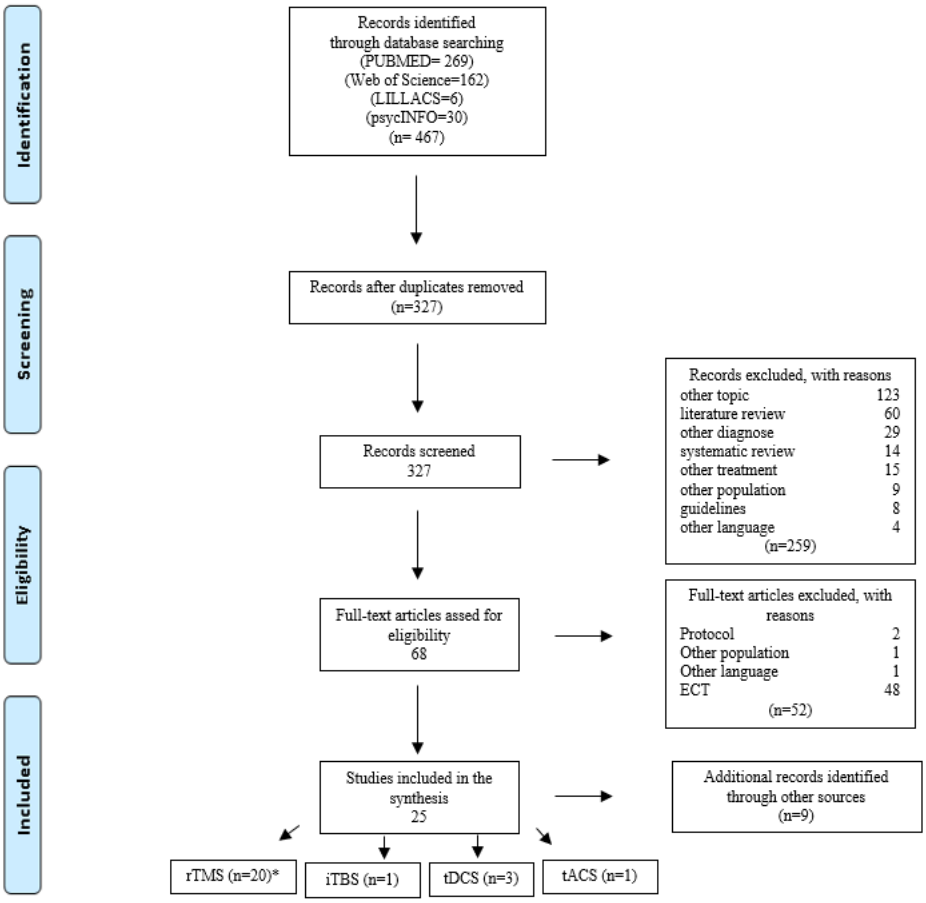
3.1. Search results

A summary of search results is presented in Figure 1. Although the search of grey literature was conducted, the only report found was a Master's thesis (Myczkowski, 2009) describing the same data that was later published as a peer reviewed (Myczkowski et al., 2012); considering this, we only assumed one report. According to the original protocol's primary objective of reviewing all categories of neurostimulation (non-invasive brain stimulation, convulsive and non-convulsive techniques), after eliminating duplicates (140), 327 articles were identified. In agreement with the remaining authors, the aim of the current study was adjusted, and the inclusion criteria was restricted to include only non-invasive and non-convulsive techniques. Therefore, reports on ECT were excluded (n=48) during the full-text eligibility. For the purpose of the current thesis, the final assessment concerned 20 full text articles. Of these, four were excluded (two were protocols, one referred to other population and the other was written in Danish), and 16 were retained. During the full-text eligibility, nine new reports were found and included in the present study.

Although a search update was planned to occur in May 2020, due to the update of PUBMED search engine, the previous search strategy was not reproducible. As such, a manual search was conducted instead in the previous databases, and two new articles were found. During the screening of the title and abstracts, one report was excluded because it concerned a different diagnose (Damar et al., 2020) and the other was included (Cox et al., 2020).

Figure 1

Flow diagram of the study selection procedure according to PRISMA, 2009



*****A new rTMS study was included after the search update in May, 2020

3.2. Qualitative synthesis

3.2.1. Description of the included studies

Twenty-five studies were included, corresponding to 27 reports. Of these, 20 used rTMS stimulation, one used iTBS, three used tDCS and one used tACS. The following tables (table 1-2) present a summary of the characteristics of the included studies, separated by type of simulation (rTMS and TES) and peripartum period (pregnancy or postpartum).

Repetitive transcranial direct stimulation. Considering rTMS and iTBS studies, 15 started treatments during pregnancy, between the first to the third trimester. Of these, two continued treatments during the postpartum period (Burton et al., 2014; Tan et al., 2008). Five studies started treatment in the postpartum period.

From the studies that included pregnant women, the most common diagnose was MDD or women experiencing a Major Depressive Episode (MDE). Nonetheless, studies including participants

with primary diagnose of Bipolar Depression were also included corresponding to two participants (Xiong et al., 2018). One study also included one participant with anxious depression.

Considering the studies conducted in the postpartum period, four included women diagnosed with MDD, and one participant in one report was diagnosed with bipolar disorder (Cohen et a., 2008). Besides the MDE, in the RCT (Myczkowski et al.,2012) three patients in the active rTMS group and two patients in the sham rTMS group were found to be experiencing their first bipolar depressive episode.

Regarding the stimulation protocol, in the RCT (Kim et al., 2018) rTMS was applied over the right dorsolateral prefrontal cortex (DLPFC), at 1 Hz frequency, during 20 sessions in the active group at 100% motor threshold (MT). In the sham group, an e-sham system was used to replicate some of the rTMS characteristics (e.g. facial twitching and the noise generated by TMS), narrowing the differences between active and sham group.

Two of the three open label studies applied the same stimulation parameters (Sayar et al., 2014; Tarhan et al., 2012), with stimulation over the left DLPFC, at 25 Hz frequency, for 18 sessions at 100% MT. The third open-label study (Kim et al., 2011) applied low frequency (1 Hz) rTMS, over the right DLPFC, during 20 sessions at 100% MT.

Four case reports (Gahr et al., 2012; Nahas et al., 1999; Özten et al., 2013; Tan et al., 2008) applied stimulation over the left DLPFC, the number of sessions ranged between nine and 77 sessions and frequency was applied between 5 Hz and 25 Hz, at 110% MT (Gahr et al., 2012; Tan et al., 2008;) and 100% MT (Nahas et al., 1999). Özten and colleagues (2013) did not report this information. Two case reports applied stimulation over the right and the left DLPFC. Xiong and colleagues (2018) applied 10 Hz over the left DLPFC followed by 1 Hz over the right DLPFC during 41 sessions at 129% MT. Burton and colleagues (2014) applied sequential bilateral rTMS, intermittent high-frequency (10 Hz) to left DLPFC followed by continuous low-frequency (1 Hz) at 110% MT. Ferrão and Silva (2018) used different parameters across participants, with three participants receiving 10 Hz rTMS in the left DLPFC over 38 to 50 sessions. The fourth participant received 1 Hz rTMS over the right DLPFC during 20 sessions always at 120% MT. Similarly, one case series (Klirova et al., 2008) during 15 sessions, report the application of 20 Hz over left DLPFC in one case and 1 Hz over right DLPFC in another, both at 100% MT. Zhang and colleagues (2010), administered low frequency rTMS (1 Hz) in three different courses at 90% MT. During the first course, at approximately 14 weeks of pregnancy, stimulation was applied over left DLPFC during 20 sessions after two months due a relapse low frequency rTMS was applied on both right DLPFC and the left DLPFC during 14 sessions, during the third course, two and a half months later same parameters of the second course were applied, lasting eight sessions. Cohen and colleagues (2008) targeted only the right DLPFC applying 1Hz in only one session. Particular caution to one study (Zhang & Hu, 2009) that does not offer information about the stimulation parameters. The single iTBS study available so far (Trevizol,

2019) applied triplet 50 Hz bursts, repeated at 5 Hz, 2s on and 8s off, with a total of 600 pulses (3 min, 9 seconds) per session during 20 sessions, using 120% of the motor threshold.

Concomitant treatment, including medication was allowed if stable during the study. Only two rTMS studies report no use of medication (Cohen et al., 2008; Nahas et al., 1999). Regarding psychotherapy, three participants from two studies (Ferrão & da Silva, 2018; Özten et al., 2013) were in psychotherapy.

During the postpartum period, all studies targeted the left DLPFC. The RCT applied 5 Hz over 20 sessions. Considering the three open-labels, two of them used protocols of 20 sessions using 10 Hz (Cox et al., 2020; Garcia et al., 2010). The third open label study (Brock et al., 2016) reported that that applied 10 Hz over left DLPFC during 11 sessions. The only case report in the postpartum that was included refers to the first publication ever regarding the application of rTMS in the peripartum period, which applied 20 Hz over 13 sessions (Odgen et al., 1999). Concomitant medication was administered in two studies, in the RCT (Myczkowski et al., 2012) 37.5% of the active group was taking clonazepam (1 mg/day), during the first case report in this period (Odgen et al, 1999), the female was taking risperidone (0.5 mg/day).

Transcranial electrical stimulation studies. Concerning the TES studies, all reports started stimulation during pregnancy but varied across trimesters. The primary diagnose was the same across studies: MDD during pregnancy.

From the four TES studies identified, one was an RCT (Vigod et al., 2019),one was an open label (Palm et al., 2017) and two were case reports (Sreeraj et al., 2016; Wilkening, et al., 2019).

Concerning stimulation parameters of tDCS studies, all applied stimulation over the same location, targeting the DLPFC, the anode was placed over the F3 and the cathode over the F4 (10-20 international system for EEG placement), using the same current intensity (2 mA). Even though the site of stimulation and dosage were homogenous, the number of sessions were not. Two studies applied stimulation once a day during 10 and 15 sessions, respectively (Sreeraj et al., 2016; Vigod et al., 2019). Palm and colleagues (2017), presented a different protocol, applying stimulation twice daily over the first 10 days followed by another 10 days with one daily session, corresponding to 30 sessions in total.

One study used tACS (Wilkening et al., 2019) over nine sessions applying Gamma-tACS for 20 min at 40 Hz of frequency completing 48 000 cycles, 2 mA range, offset at 1 mA without ramp-in/ramp-out. The electrodes were placed over the dorsolateral prefrontal cortices (F3 and the F4 positions). None of the TES studies administered concomitant medication.

Table 1

Characteristics of the included rTMS studies.

Study	Study design	# participants	Trimester at start of stimulation	Stimulation site	Frequency (Hz)	# pulses/session	Inter event interval (s)	Intensity (% MT)	# sessions
rTMS-pregnancy									
Burton et al., 2014*	Case report	1	First	Bilateral DLPFC	10 (left) 1 (right)	N.I.	N.I.	110	21
Cohen et al., 2008	Case report	1	First	Right DLPFC	1	1600	N.I.	100	1
Ferrão and Silva, 2018	Case series	3	First	Left DLPFC	10	3000	N.I.	120	50, 38,40
		1	First	Right DLPFC	1	1800	N.I.	120	20
Gahr et al., 2012	Case report	1	Second	Left DLPFC	15	2970	2s on, 8s off	110	24
Kim et al., 2018	RCT	22 (11 active + 11 sham)	Second and third	Right DLPFC	1	900	60s on, 60s off	100	20
Kim et al., 2011	Open label	10	Second to third	Right DLPFC	1	300	60s on, 60s off	100	20
Klirova, et al., 2008	Case report	2	Second	Left DLPFC	20	2000	2.5s on, 30s off	100	15
			Third	Right DLPFC	1	300	60s on, 60 off	100	15
Nahas et al., 1999	Case report	1	Second	Left Prefrontal	5	N.I.	5s on, 25s off	100	9
Özten et al., 2013	Case report	1	Second	Left DLPFC	25	1000	2s on, 30s off	N.I.	76

Study	Study design	# participants	Trimester at start of stimulation	Stimulation site	Frequency (Hz)	# pulses/session	Inter event interval (s)	Intensity (% MT)	# sessions
Sayar et al., 2014	Open label	30	First and third	Left DLPFC	25	1000	2s on, 30 off	100	18
Tan et al., 2008*	Case report	1	First	Left DLPFC	25	50	2s on, 28s off	110	77
Tarhan et al.,2012	Open label	7	-	Left DLPFC	25	1000	2s on, 30s off	100	18
Trevizol et al., 2019 **	Case report	1	Third	Left DLPFC	triplet 50 Hz bursts, repeated at 5 Hz	600	2s on; 8 off	120	20
Xiong et al., 2018	Case report	1	Second	Bilateral DLPFC	10 (left)	4000	4s on,16s off	120	41
					1 (right)	900	300s on, 60s off		
Zhang et al., 2010	Case report	1	14 weeks of gestation	Left DLPFC	1	1200	20s off	90	20
				Bilateral DLPFC	1	1200	20s off	90	14
				Bilateral DLPFC	1	1200	20s off	90	8
Zhang and Hu, 2009	Case series	3	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
rTMS-postpartum									
Brock et al., 2016	Open label	19	N.I.	Left DLPFC	10	3000	75s on, 26 off	120	11
Cox et al., 2020	Open label	6	2 weeks to 9 months postpartum	Left DLPFC	10	3000	4s on, 26 off	120	20

Study	Study design	# participants	Trimester at start of stimulation	Stimulation site	Frequency (Hz)	# pulses/session	Inter event interval (s)	Intensity (% MT)	# sessions
Garcia et al., 2010	Open label	9	1 month to 12 months postpartum	Left DLPFC	10	3000	75s on, 26 off	120	20
Myczkowski et al., 2012	RCT	14 (7 active + 7 sham)	1 to 2 months postpartum	Left DLPFC	5	1250	25s on, 20s off	120	20
Odgen et al., 1999	Case report	1	N.I.	Left DLPFC	20	1200	30s on, 28 off	100	13

Note. *Studies that applied stimulation during pregnancy and throughout the postpartum period. **Study that used (iTBS). iTBS = intermittent theta burst stimulation. rTMS = repetitive Transcranial Magnetic Stimulation. DLPFC = dorsolateral prefrontal cortex. MT = motor threshold. N.I.= No information.

Table 2

Characteristics of the included TES studies.

Study	Study design	# participants	Trimester at start of stimulation	Anode	Cathode	Current intensity (mA)	# sessions
Palm et al., 2017	Open label	3	All	F3	F4	2	30
Sreeraj et al., 2016	Case report	1	First	F3	F4	2	10
Vigod et al., 2019	RCT	20 (10 active + 10 sham)	Second to third	F3	F4	2	15
Wilkening et al., 2019*	Case report	1	First	F3	F4	2	9

Note. * Study that used tDCS. ** Study that used tACS. TES = Transcranial electric current stimulation. tDCS = transcranial Direct Current Stimulation. tACS = transcranial alternating current stimulation.

3.2.2. Efficacy

Regarding our primary outcome, reduction in depressive symptoms, in Table 6 we present a synthesis of the scores between baseline and end of treatment for the included studies. In order to assess the efficacy of rTMS and TES we also present the number of participants that achieved remission and/ or responded to the treatment. Since not all studies use the same definition of treatment response, we will adopt definitions hierarchically: at least 50% reduction of the baseline score, followed by at least 30% reduction of the baseline score. If none of these definitions is available, we will use the original authors' primary definition.

Concerning rTMS studies during pregnancy, and considering only study completers, in the RCT (Kim et al.,2018), from the 11 participants in the active group, nine were considered treatment responders (81.8%) and three achieved clinical remission (27.7%), versus five responders (45.5%) and two that remitted in the sham group (18.8%).

In Kim and colleagues open label study (Kim et al., 2011), seven (70%) women responded and three (30%) reached clinical remission. Sayar's open label (Sayar et al., 2014), showed slightly lower rates, reporting that 12 women responded (38.8%) and six remitted (61.11%). Although Tarhen and colleagues (2012) did not provide the mean scores, the authors reported that five participants were treatment responders and two remitted.

Regarding case reports, some studies did not present information regarding the remission of symptoms (Ferrão & Silva, 2018; Garh et al., 2012; Özten et al., 2013; Zhang and Hu, 2009) 11 from the 18 women responded to the treatment (64,7%) and eleven remitted (41,4%). Although two case reports (Garh et al., 2012; Zhang and Hu, 2009) did not report the scores or estimations of baseline and end of treatment, in one of these studies no response was observed after 24 sessions (Garh et al., 2012), while the other reported that after the treatment symptoms relieved significantly (Zhang and Hu, 2009).

In the postpartum period the single available RCT (Myczkowski et al., 2012) did not report the number of participants that responded and/or remitted, although the mean difference between baseline and posttreatment HDRS-21 score was greater in the active group (29.1 to 18.38) than in the sham group (26.7 to 21.8).

Brock and colleagues (2016) in their open label study, reported that 14 out of 19 participants (73.7%) achieved clinical remission. With a smaller sample (n = 6), Cox and colleagues (2020) reported that two women responded to the treatment (33.3%) and four achieved remission (66.6%). In the other open label eight of nine women achieved clinical remission (Garcia et al., 2010).

In the only case report in this period (Odgen et al., 1999) the subject achieved remission.

Concerning the studies using TES, the RCT (Vigod et al., 2019) demonstrated the antidepressant effect of tDCS, as the mean MADRS score although non-significantly different between groups, was lower for the active group than for the sham group across endpoints. Moreover,

immediately post-treatment assessments indicated remission in three out of the eight participants in the active group (37.5%) versus two out of nine in the sham condition (22.2%), revealed remission in six out of eight mothers in the active group (75%) and the same results were found at follow up at 12 weeks postpartum. In the sham group, follow up assessments at 4 weeks postpartum showed remission in one out eight participants (21.8%) and at 12 weeks postpartum, two out of eight participants achieved remission (25%).

In Palm and colleagues (Palm et al., 2017), from the three reported participants in the open label, two completed the treatment and one achieved remission.

In the only case report using tDCS (Sreejaj et al., 2016) the participant achieved remission. Concerning the case report (Wilkening et al., 2019), the woman treated with tACS, also achieved remission.

Table 3

Reports of efficacy for the included studies

Study	# participants	Primary Psychiatric Diagnosis	Endpoint	Baseline (mean)	Final (mean)	Remission (# participants)	Response (# participants)
rTMS-pregnancy							
Burton et al., 2014*	1	PPD (pregnancy)	HDRS-21	13	10	1	1
Cohen, et al., 2008	1	BDII during pregnancy	HDRS-17	18	6	1	1
Ferrão & Silva, 2018	3	PPD (pregnancy)	HDRS-21	24.3	7.3	N.I.	3
	1	PPD (pregnancy)	HDRS-22	12	6	N.I.	1
Gahr et al., 2012	1	PPD (pregnancy)	N.I.	N.I.	N.I.	N.I.	N.I.
Klirova, et al., 2008	1	PPD (pregnancy)	MADRS	33	2	1	1
	1	PPD (pregnancy)	BDI	29	12	0	1
Kim et al., 2018	11 active	PPD (pregnancy)	HDRS-17	23.2	9.3	3	9
	11 sham	PPD (pregnancy)	HDRS-17	22.3	13.2	2	5
Kim et al., 2011	10	PPD (pregnancy)	HDRS-17	24.4	9.7	3	7
Nahas et al., 1999	1	PPD (pregnancy)	HDRS	32	15	1	N.A.
Özten et al., 2013	1	PPD (pregnancy)	HDRS-17	29	8	-	-
Sayar et al., 2014	30	PPD (pregnancy)	HDRS-17	26.8	13	6	12
Tan et al., 2008*	1	PPD (pregnancy)	HDRS-17	38	4	1	1
Tarhan et al., 2012	7	PPD (pregnancy)	HDRS-17	N.I.	N.I.	2	5
Trevizol et al., 2019 **	1	PPD (pregnancy)	QIDS-SR	10	3	1	N.A.
Xiong et al., 2018	1	BDII during pregnancy	EPDS	23	4	1	1
Zhang et al., 2010	1	PPD (pregnancy)	HDRS-24	35	8	0	1
Zhang and Hu, 2009	3	PPD (pregnancy)	HDRS-17	N.I.	N.I.	N.I.	N.I.
rTMS-pospartum							
Brock et al., 2016	19	PPD (postpartum)	EPDS	20.6	8.2	14	N.I.
Cox et al., 2020	6	PPD (postpartum)	EPDS	16.33	9.33	4	2
Garcia et al., 2010	9	PPD (postpartum)	HDRS-24	23.4	2.1	8	N.I.
Myczkowski, 2012	8 active	PPD (postpartum)	HDRS-17	29.1	18.38	N.I.	N.I.
	6 sham	PPD (postpartum)	HDRS-17	26.7	21.8	N.I.	N.I.
Odgen et al., 1999	1	PPD (postpartum)	HDRS-17	29	3	N.I.	N.I.

Study	# participants	Primary Psychiatric Diagnosis	Endpoint	Baseline (mean)	Final (mean)	Remission (# participants)	Response (# participants)
TES-pregnancy							
Palm et al., 2017	3	PPD (pregnancy)	HDRS-21	24.7	7.0	1	N.I.
Sreeraj et al., 2016	1	PPD (pregnancy)	HDRS-17	18	6 (at 1-month FU)	1	N.A.
Vigod, 2019	10	PPD (pregnancy)	MADRS	23.5	11.8	6	N.I.
	10	PPD (pregnancy)	MADRS	26.8	15.4	2	N.I.
Wilkening et al., 2019***	1	PPD (pregnancy)	HDRS-21	19	11	1	1

Note. *Studies that applied stimulation during pregnancy and throughout the postpartum period. **Study that used iTBS; iTBS = intermittent theta burst. *** Study that used tDCS. tDCS= transcranial direct current stimulation. **** Study that used tACS. tACS = transcranial alternating current stimulation. rTMS = repetitive Transcranial Magnetic Stimulation. TES= transcranial Electric Stimulation. MDD= Major Depressive Disorder. BD= Bipolar Depression. HDRS=Hamilton Depression Rating Scale. MADRS= Montgomery-Asberg Depression Rating Scale. EPDS= Edinburgh Postnatal Depression Scale. QIDS-SR = Quick Inventory of Depressive Symptomatology Self-Report. TES= tDCS = transcranial Direct Current Stimulation. N.I.= No information. N.A.= Non applicable; PPD= peripartum depression; FU= Follow up.

3.2.3. Safety

Additionally, we conducted a qualitative analysis concerning safety both for mothers and infants.

Regarding rTMS studies in pregnancy, RCT by Kim and colleagues reported the occurrence of three pre-term births in the active group versus none in the sham group; however, a larger sample was needed to interpret this rate statistically. Concerning safety for mothers, the most common side effect found in this study was headache. Prior session 10, headache was reported by 36.4% of mothers in the active group versus 9.1% in the sham group (Fisher's Exact, p = .311). After treatment 10, headache was reported by 9.1 % of active the group versus 0 % in the sham group (Fisher's Exact, p = 1.00). Other side effects such as dizziness, nausea, site pain, supine hypotension, jaw pain and eye twitch were also reported but there were no significant differences between groups (Kim et al., 2018).

None of the open label studies reported information about neonatal safety. Adverse effects reported for mothers included mild headache and supine hypotension (Kim et al., 2011), and contraction in facial muscles (Sayar et al., 2014). Tarhan and colleagues (Tarhan et al., 2012) reported that no participants reported side effects and the treatment was considered well tolerated.

From the case reports, only three did not report information concerning neonatal safety (Cohen et al., 2008; Gahr et al., 2012; Nahas et al., 1999). From the remaining, out for 16 births, three (18.35 %) were pre-term (Ferrão & Silva, 2018; Klirova et al., 2018; Tan et al., 2008) and one baby had an APGAR score lower that seven (Ferrão & Silva, 2018). The only adverse effects for mothers were pain/discomfort at the application site, transient difficulty in concentration and sore throat (Ferrão & Silva, 2018), and tension in the abdominal muscles at the pelvic line (attributed to anxiety) (Nahas et al., 1999).

During the postpartum period, the single RCT by Myczkowski and colleagues (Myczkowski et al., 2012) reported no significant side effects during the study. However, two participants complained of minor scalp discomfort during the application and/or mild headache immediately after stimulation. Brock and colleagues (2016) reported that no serious adverse events occurred. In the remaining two open label studies headache and scalp discomfort (Cox et al., 2020) and treatment site pain and facial stimulation (Garcia et al., 2010) were also reported.

Regarding TES studies, only the RCT by Vigod and colleagues (2019) reported information about neo-natal safety. In this study, one pre-term birth occurred in the tDCS group. During treatment sessions, women in the active group reported minor transient side effects in 22 out of 124 (17.7%) versus in five out of 122 (4.7%) in sham-control sessions (p = .001). The most common side effect, reported more than three times was “buzzing” or “tingling” at the electrode site, reported in nine (7.3%) tDCS sessions and no sham-control sessions (p = .003).

In the open label study by Palm and colleagues (2017) tDCS was considered well tolerated and no adverse effects occurred. Two case reports (Sreejaj et al, 2016; Wilkening et al., 2019) reported phosphenes and one reported transient mild burning sensations at the site of stimulation. One case report did not provide information concerning this outcome (Odgen et al., 1999).

APGAR scores were only reported when seven and bellow seven, to be considered intermediate (American Academy of Pediatrics et al., 2006). In Table 4 we present a summary of the available data.

Considering the breastfeeding status, although it was not a pre-defined outcome, it is noteworthy that, from a total of 25 women ([Brock et al. 2016] did not report this information), 17 (68%) were breastfeeding.

Table 4

Safety of the included studies

Study	Adverse effects (mothers)	Neonatal safety
rTMS – pregnancy		
Burton et al., 2014*	N.A.	N.A.
Cohen, et al., 2008	N.I.	N.I.
Ferrão & Silva, 2018	Pain/discomfort at application site, transient difficulty in concentration, sore throat	1 pre-term birth, 1 baby APGAR score= 6
Gahr et al., 2012	N.I.	N.I.
Kim et al., 2018	Headache, dizziness, nausea, Pain/discomfort at application site, supine hypotension, jaw pain and eye twitch	3 pre-term births
Kim et al., 2011	Mild headache, supine hypotension	N.I.
Klirova, et al., 2008	N.A.	1 pre-term birth
Nahas et al., 1999	Tension in the abdominal muscles at the pelvic line (probably due to anxiety)	N.I.
Özten, 2013	N.I.	N.A.
Sayar et al., 2014	Contraction of facial muscles	N.I.
Tan et al., 2008*	N.I.	1 pre-term birth
Tarhan et al., 2012	N.A.	N.I.
Trevizol et al., 2019 **	N.I.	N.A.
Xiong et al., 2018	N.I.	N.A.
Zhang et al., 2010	N.A.	N.A.
Zhang and Hu, 2009	N.I.	N.A.
rTMS – postpartum		
Brock et al., 2016	N.A.	N.A.
Cox et al., 2020	Headache and scalp discomfort	N.A.
Garcia et al., 2010	Headache, pain at application site and facial stimulation	N.A.
Myczkowski et al., 2012	Minor scalp discomfort and/or mild	N.A.

	headache	
Odgen et al., 1999	N.I.	N.A.
Study	**Adverse effects (mothers)**	**Neonatal safety**
	TES – pregnancy	
Palm et al., 2017	N.A.	N.I.
Sreeraj et al., 2016	Transient, mild burning sensations at application site and fleeting experience of phosphenes	N.I.
Vigod et al., 2019	"buzzing" or "tingling" application site	1 pre-term birth
Wilkening et al., 2019*	Mild phosphenes during stimulation	N.I.

Note. *Studies that applied stimulation during pregnancy and throughout the postpartum period. **Studies that used iTBS. iTBS= intermittent theta burst stimulation. ***Studies that used tDCS. tDCS= transcranial direct current stimulation. ****Studies that used tACS. tACS= transcranial alternating current stimulation. rTMS = repetitive Transcranial Magnetic Stimulation. TES= transcranial electric stimulation. N.I.= No information. N.A.= Not applicable.

3.2.4. Acceptability

The acceptability was calculated from the number of dropouts. Considering the rTMS studies that enrolled pregnant women, in the RCT only 22 participants completed the intervention although 26 women were recruited and allocated for the active and the sham group (Kim et al., 2018). For the open label studies all but one participant (Sayar et al., 2014) completed the treatment (Trevizol et al., 2019; Xiong et al., 2018). Across case reports, all women completed treatment.

In the rTMS studies conducted in the postpartum period all women recruited for the RCT completed treatment (Myczkowski et al., 2012). Similarly, in one open label, all participants completed the treatment as well (Cox et al, 2020). From the total of 25 women recruited in Brock et al. (2016) study, only 19 completed treatment. In Garcia et al. (2010), a total of nine participants were enrolled and of these only one was lost to follow up. In the case report by Odgen et al. (1999) the only participant recruited completed the treatment.

Considering the studies that used TES, the RCT (Vigod et al., 2019) lost four participants, two in the active group and two in the sham group, two of these women, one of each group prior to the start of the protocol. From the sample of ten participants in the open label study (Palm et al., 2017), results were reported for only three participants.

Table 5 summarizes reports information concerning acceptability.

Table 5

Acceptability for the included studies

Study	Number of participants	
	Recruited	**Completed**
rTMS-pregnancy		
Burton et al., 2014*	1	1
Cohen, et al., 2008	1	1
Ferrão & Silva, 2018	4	4
Gahr et al., 2012	1	1
Kim et al., 2018	14 active	11 active
	12 sham	11 sham
Kim et al., 2011	10	10
Klirova, et al., 2008	2	2
Nahas et al., 1999	1	1
Özten, 2013	1	1
Sayar et al., 2014	30	29
Tan et al., 2008*	1	1
Tarhan et al., 2012	7	7
Trevizol et al., 2019 **	1	1
Xiong et al., 2018	1	1
Zhang et al., 2010	1	1
Zhang and Hu, 2009	3	3
rTMS – postpartum		
Brock et al., 2016	25	19
Cox et al., 2020	6	6
Garcia et al., 2010	9	8
Myczkowski et al., 2012	14	14
Odgen et al., 1999	1	1
TES – pregnancy		
Palm et al., 2017	3	3
Sreeraj et al., 2016	1	1
Vigod et al., 2019	10 active	8 active
	10 sham	8 sham
Wilkening et al., 2019*	1	1

Note. *Studies that applied stimulation during pregnancy and throughout the postpartum period. **Studies that used iTBS. iTBS= intermittent theta burst stimulation. ***Studies that used tDCS. tDCS= transcranial direct current stimulation. ****Studies that used tACS. tACS= transcranial alternating current stimulation. rTMS = repetitive Transcranial Magnetic Stimulation. TES= transcranial electric stimulation. N.I.= No information. N.A.= Not applicable.

3.2.5. Neurocognitive assessment

Although neurocognitive assessment was also defined as a secondary outcome, only a few studies had assessed this outcome.

Regarding rTMS during pregnancy, the RCT (Kim et al., 2018) collected data on Mini Mental State Examination, Trail Making Test A&B, Stroop Interference Test, Wechsler Memory Scale 3rd Edition, Letter-Number Sequencing (LNS), Wechsler Memory Scale 3rd

Edition and Digit Span. However, the authors reported that the only significant differences were found in LNS for which the active group performed worse in the posttreatment when compared to pre-treatment. No other results were made available.

During the postpartum period, Myczkowski and colleagues (2012) applied a neuropsychological battery and performed a between-group comparison. Concerning the different tests applied, statistically significant differences were found in Trail Making Test- B (TMT-B; 31.4% versus 12.9%) and in the Victoria Stroop Test-Interference (31.7% versus 10.0%). Analysis performed using false discovery rate correction did not revealed significant differences in Vitoria Stroop Test-Interference neither in TMT-B. However, without false discovery rate correction, statistical differences were found in both tests TMT-B (baseline versus week 4, P = .039) and Victoria Stroop Test-Interference (baseline versus week 6, P = .034). Still regarding the postpartum period, Cox and colleagues (2020) did not found statistically significant differences between baseline and end of treatment for data collected using the Mini Mental State Examination, the TMT-B and the List Generation.

An open label (Palm et al., 2017), reporting the results of tDCS, measured the scores of TMT at baseline, at week 2 of treatment and at follow up. At baseline, TMT-A mean score was 25.0 ± 6.4 and reduced to 23.3 ± 9.7 in week 2 (p = 1.00), and to 18.5 ± 4.9 in week 4 (p = 0.20). TMT-B mean baseline was 81.0 ± 56.9, reduced to 69.3 ± 42.4 in week 2 (p = 0.38), and to 40.5 ± 12.0 in week 4 (p = 0.53).

The case report in tACS (Wilkening et al., 2019), presented the scores of the Trail Making Test (TMT-A and TMT-B) at baseline and at the end of treatment. Both tests showed improvement (TMT-A was completed within 25s at baseline versus 19s at the end of treatment, and TMT-B was completed within 82s at baseline versus 50s at the end of treatment. At two weeks after treatment follow up, performance was still improving with the TMT-A was being completed within 15s and TMT-B within 35s.

3.2.6. Risk of bias

The quality of the data extracted from the distinctive reports is different concerning the bias in each one; considering that bias affects the conclusions of each study and consequently the conclusions of the present study, risk of bias of each study was accessed.

To access the RoB of the three randomized control trials, we used The Cochrane Collaboration's tool. According to this tool, within a trial, the judgment can be considered low (low risk of bias for all key domains), unclear (low or unclear risk of bias for all key domains) or high (at least one of the key domains is considered high). Considering this, the RoB across reports was considered high since two out of the three studies were assessed as high. Further detailed information is available in Table 6.

Table 6

Risk of Bias Assessment for RCTs using the Cochrane Collaboration's Tool.

Study	Random sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition Bias	Reporting bias	Overall risk of bias
rTMS							
Kim et al., 2018	Unclear	Unclear	Low	Low	High	Low	Unclear
Myczkowski etal., 2012	Low	Unclear	Low	Low	High	High	High
TES							
Vigod et al., 2019	Low	Low	Low	Low	High	Low	High

Note. rTMS = repetitive Transcranial Magnetic Stimulation. TES= transcranial electric stimulation.

Concerning the five non-randomized studies included, a RoB assessment was conducted according to the Non-randomized Studies of Interventions tool (ROBINS-I). According to the ROBINS-I, the overall RoB is judged as critical when at least one domain is judged as critical. In Brock et al. (2016), although none of the domains are judged as critical, the overall RoB was assessed as critical regarding the absence of an article. Similarly, even though in the case of Palm et al study (2016), one domain was assessed as critical, the major concern regarded the fact that data extracted was limited to one available abstract. The overall RoB was considered critical mainly due to incomplete information. Table 7 depicts RoB assessed by domain.

Table 7

Risk of Bias Assessment for non-randomized studies using ROBINS-I

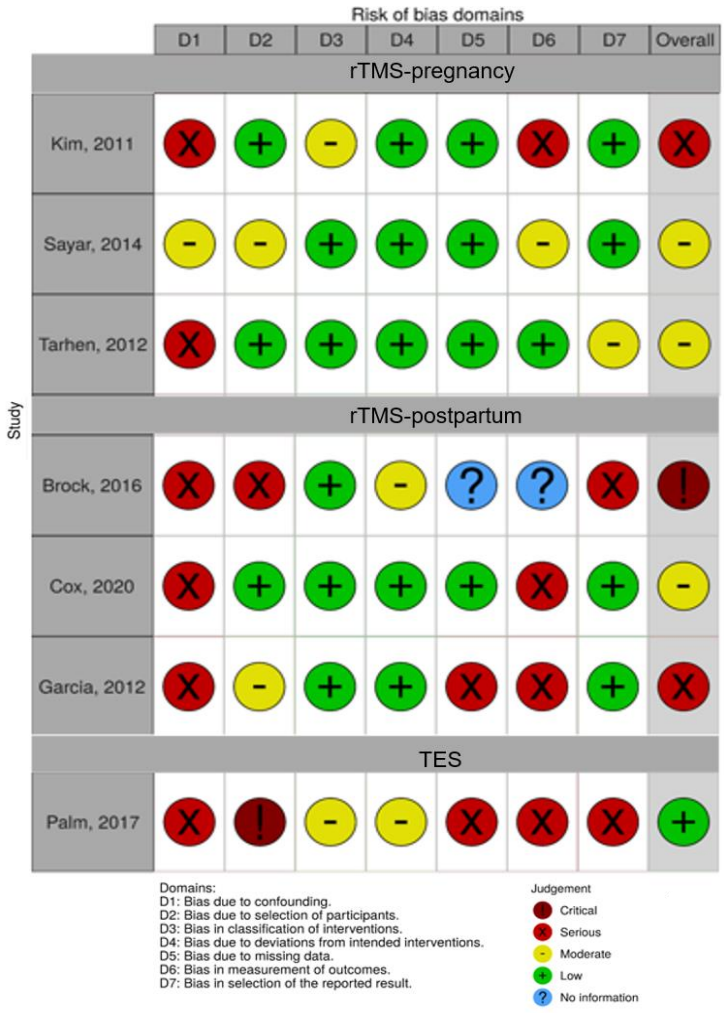
Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
rTMS – pregnancy								
Kim et al., 2011	Serious	Low	Moderate	Low	Low	Serious	Low	Serious
Saya et al., 2014	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Tarhen et al., 2012	Serious	Low	Low	Low	Low	Low	Moderate	Moderate
rTMS – postpartum								
Brock et al., 2016	Serious	Serious	Low	Moderate	NI	NI	Serious	Critical
Cox et al., 2020	Serious	Low	Low	Low	Low	Serious	Low	Moderate
Garcia et al., 2012	Serious	Moderate	Low	Low	Serious	Serious	Low	Serious
TES								
Palm et al., 2017	Serious	Critical	Moderate	Moderate	Serious	Serious	Low	Critical

Note. rTMS = repetitive Transcranial Magnetic Stimulation. TES= transcranial electric stimulation.

Using the robvis (McGuinness & Higgins, 2020) visualization tool, we prepared a graphical table to support the visualization of the RoB assessment. Even though this tool only considers open labels, considering the sample size different weights were given to the studies, in order to guarantee a more reliable judgement. Figure 2 shows a "traffic light" plot of the domain-level judgements for each individual result, presented in Table 7. In Figure 3, it is possible to analyze the distribution of risk of bias judgements within each bias domain. Analyzing this graphic is possible to conclude that the domain assessed poorly was *Bias due to confounding.*

Figure 2

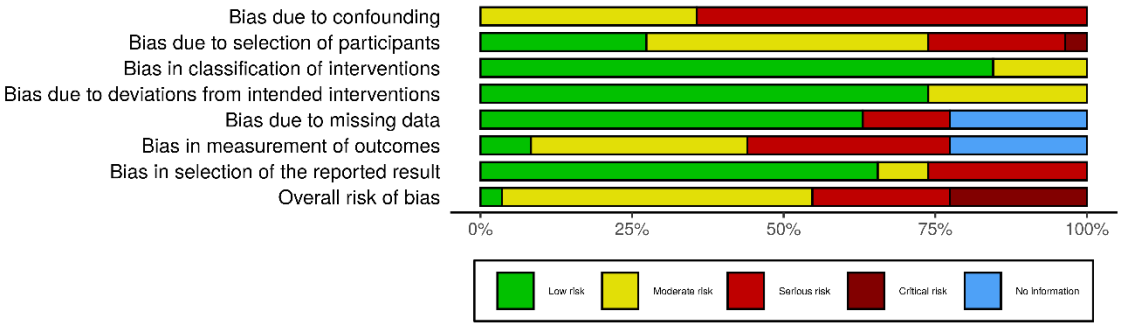
Traffic light plot



Note. *Studies that applied rTMS during pregnancy. **Studies that applied rTMS during postpartum period. *** Study that applied tDCS during pregnancy.

Figure 3

Weighted summary plot



The adapted version of the Institute of Health Economics (IHE's) quality appraisal checklist (Guo et al., 2016) was used for assessing case-series studies. Most studies did not establish the outcome measures a priori neither blinded the assessment of outcome measures. In order to guarantee a homogeneous assessment, a criterion concerning the minimum follow-up length of 6 months was established by us, based in our clinical and experimental judgment and expertise. The criteria regarding the description of co-interventions was not applied to those studies where there was no co-intervention. In Table 8, detailed scores are available for each included case report.

Table 8

Risk of bias assessment case-series and case reports studies using the IHE's quality appraisal checklist.

Author	Study objective	Patient's characteristics described	Intervention of interest clearly described	Cointervention's reported	Outcome measures established a priori	Outcome measures blinded	Outcome measures appropriately	Outcome measured before-after	Sufficient length of follow-up	Adverse events reported	Conclusions supported by results	Competing interest and source of support	Scores (maximum of 12)
rTMS – pregnancy													
Burton et al., 2014	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Partial/Unclear	Yes	Yes	No	8
Cohen et al., 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	6
Ferrão & Silva, 2018	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Partial/Unclear	8
Trevizol et al.,2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Partial/Unclear	8

Author	Study objective	Patient's characteristics described	Intervention of interest clearly described	Cointervention's reported	Outcome measures established a priori	Outcome measures blinded	Outcome measures appropriately	Outcome measured before-after	Sufficient length of follow-up	Adverse events reported	Conclusions supported by results	Competing interest and source of support	Scores (maximum of 12)
Gahr et al.,2018	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	4
Klirova et al.,2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Partial/Unclear	8
Nahas et al., 1999	Yes	Yes	Yes	Yes	No	Partial/Unclear	Yes	Yes	Partial/Unclear	Yes	Yes	No	8
rTMS – postpartum													
Öztenet al., 2013	Yes	Yes	Yes	Yes	Partial/Unclear	Yes	Yes	Partial/Unclear	No	Partial/Unclear	Yes	No	7
Tan, 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Partial/Unclear	Partial/Unclear	7
Xiog et al., 2018	Yes	Yes	Yes	Yes	Partial/Unclear	No	Yes	Yes	No	Yes	Yes	Yes	9

Author	Study objective	Patient's characteristics described	Intervention of interest clearly described	Cointervention's reported	Outcome measures established a priori	Outcome measures blinded	Outcome measures appropriately	Outcome measured before-after	Sufficient length of follow-up	Adverse events reported	Conclusions supported by results	Competing interest and source of support	Scores (maximum of 12)
Zhang et al., 2010	Yes	Yes	Yes	Yes	Partial/Unclear	Partial/Unclear	Yes	Partial/Unclear	No	Yes	Yes	No	7
Zhang & Hu, 2009	Yes	No	No	No	Partial/Unclear	No	No	Partial/Unclear	No	Partial/Unclear	Yes	No	2
Odgen et al.,, 1999	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	8
TES													
Sreejaj et al., 2016	Yes	Yes	Yes	Yes	No	No	Yes	Partial/Unclear	No	Yes	Yes	Yes	8
Wilkening et al., 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	9

Note. rTMS = repetitive Transcranial Magnetic Stimulation. TES= transcranial electric stimulation.

3.3. Quantitative synthesis – meta-analysis of the data extracted

To access the efficacy of interventions, we aimed at comparing different scores for different endpoints at different intervention phases and follow-up periods. However, due to lack of information across studies we were only able to compare scores between baseline and the end of treatment. Considering the differences between these scores, two meta-analysis were conducted, analyzing the efficacy of rTMS in reducing the depressive symptoms: one was focused on pregnancy and the other on the peripartum period. Although the authors were contacted to clarify and obtain more information, in the case of the other open-label that could be included in the meta-analysis of rTMS during pregnancy, the absence of scores in the baseline and post-treatment considering only the pregnant women did not allow its inclusion.

Effectiveness of rTMS for PPD in pregnancy

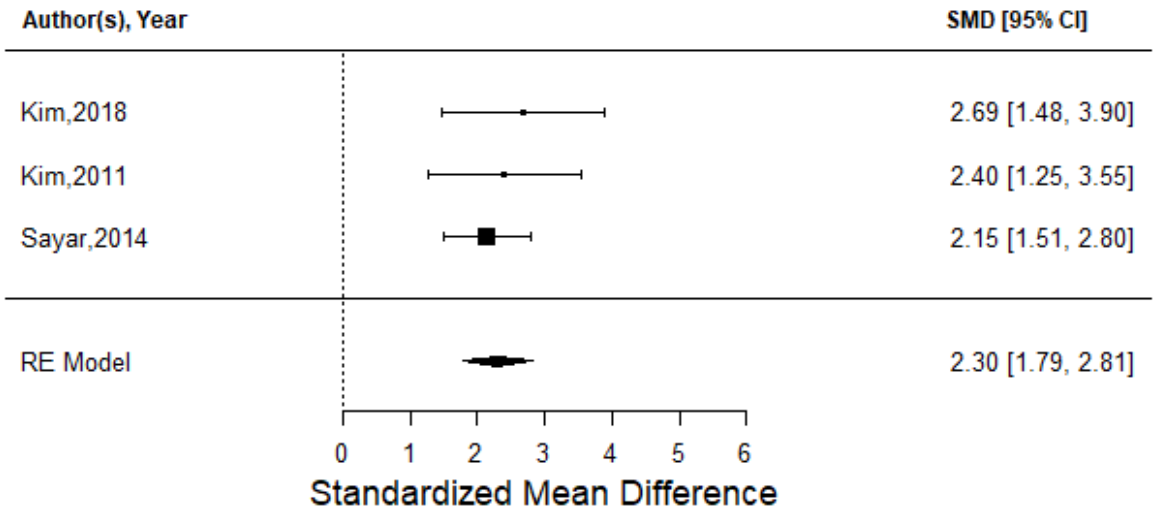
Three studies were included (Kim et al., 2018; Kim et al., 2011; Tarhan et al., 2012). Considering the study design, one was an RCT (Kim et al., 2018) and the other two were open-label studies. The three studies included 50 women, receiving treatment.

The comparison was made between the results collected at baseline and by the end of treatment, considering HDRS-17 scores.

Even though heterogeneity was not greater than 25% (I^2 = 0.00%), we choose to use the random effects model, assuming the methodological differences between studies (REM; Ried, 2006). As shown in Figure 4, all studies included are significant, demonstrating the effectiveness of rTMS (SMD=2.30 IC 95% = [1.79, 2.81]; p <.*0001*). All studies shown an SMD of at least 1.25, confirming its significance.

Figure 4

Meta-analysis of the effectiveness of rTMS in PPD during pregnancy



Effectiveness of rTMS for PPD in the postpartum

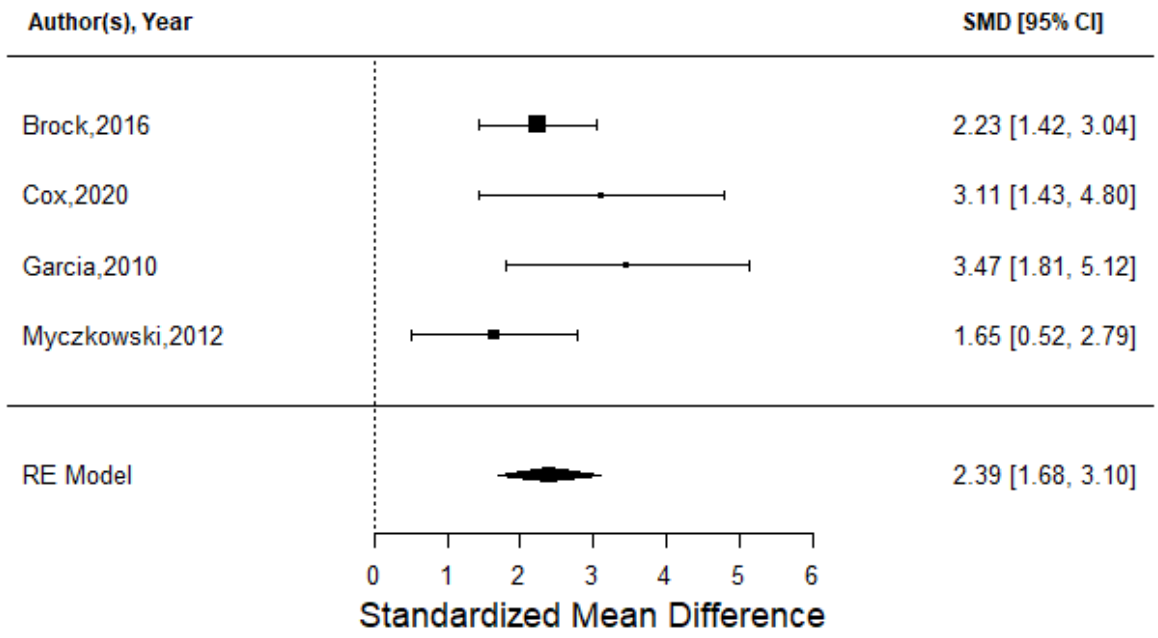
Four rTMS studies were included (Cox, 2020; Brock et al., 2016; Garcia et al., 2010; Myczkowski et al, 2012). Except for one RCT (Myczkowski et al, 2012) the other three were open-label studies. Gathered, including 47 women.

Again, we considered the mean differences between the scores at baseline and by the end of treatment, using EPDS values.

Since the heterogeneity was greater than 25% (I^2 = 26.12%) we choose to use the random effect model (REM; Ried, 2006). The results across studies were statistically significant, showing rTMS efficacy in decreasing depressive symptoms in PPD (SMD= 2.39 IC 95%= [1.68, 3.10]; p <.*0001*). It is noteworthy that the RCT shown an SMD lower than the other open-label studies.

Figure 5

Meta-analysis of the effectiveness of rTMS in PPD in the postpartum period



Since the number of the included studies was limited, we chose to not present the funnel plots. This statistic has low power when the number of studies is lower than ten, increasing the likelihood of resulting in false positives in the presence of substantial heterogeneity between studies (Egger et al., 1997).

4. Discussion

This study aimed to analyze the efficacy of NIBS techniques in reducing depressive symptoms in the peripartum period, updating previous reviews (Kim et al., 2015; Konstantinou et al., 2020) by including reports across all peripartum period. In this review, we collect data from 25 reports, gathering the information from 170 women. Overall qualitative results show that NIBS are promising for depressive symptoms in the peripartum period, being overall effective, safe (both for mothers and babies), as well as an acceptable alternative. Our study seems to be in line with previous qualitative literature, confirming the efficacy of rTMS during the peripartum period (Cole et al., 2019). Moreover, in our review we were able to confirm the efficacy of rTMS, through a meta-analysis that combined of 16 studies in pregnancy and five studies in the postpartum. Concerning TES studies, there were no previous systematic review about its use in PPD. Considering the studies included in the present study despite the reduced number of studies, the limited sample size, and the risk of bias observed, overall efficacy is coherent between studies but caution is warranted for further interpretations.

Overall, it is important to note that the use of concomitant medication was allowed in rTMS studies in PPD during pregnancy more than in the postpartum period. On the contrary, no concomitant medication was allowed in studies that used TES.

rTMS and peripartum depression

As shown in the meta-analysis, rTMS seems to be efficacious in reducing depressive symptoms both during pregnancy and postpartum period. Regarding, the quantitative synthesis we used random effects models since they are considered more reliable because of the larger confidence interval, nonetheless this type of studies is criticized because they give greater weight to minor studies (Moayyedi, 2004).

Considering the included studies, different protocols were tested: bilateral (left-HF and right-LF), left-HF, right-LF and left-LF. Although the more common was left-HF followed by right-LF, no study defined yet the most beneficial protocol. Both stimulation parameters showed reduction in depressive symptoms, the decision regarding one is difficult, warning for the need of comparative studies to define the most advantageous protocol.

rTMS studies during the postpartum period, concerning the stimulation parameters follow the principles of its use in MDD, with wider use of high frequency to the left DLPFC (Ganho-Ávila et al., 2019). All studies in the present review applied stimulation over left DLPFC, and only one used low frequency rTMS (Myczkowski et al., 2012).

Thereby, rTMS seems to reduce depressive symptoms both in pregnancy and in the postpartum period, as all studies reported a decrease between baseline and end of treatment

scores, with one exception (Garh et al., 2013). This case report describes a woman diagnosed with PPD that towards no amelioration with rTMS add-on treatment considered ECT.

From the studies that reported information about neonatal safety, the most common consequence was pre-term birth, highlighting a potential association of rTMS with preterm birth. The difference between active and sham stimulation (three pre-term births in the active group versus none in the sham group) reported by Kim and colleagues (2018) should be further examined (Kim et al., 2019). Unlike exposure in utero to antidepressants, none of the included studies reported cardiac malformation or persistent pulmonary hypertension (Huybrechts et al., 2014, 2015). The most common reported adverse effect for mothers was headache, in the most of cases transient.

Of note, although it was not a defined outcome, during the postpartum period, most of the mothers were breastfeeding their babies (Brock et al. [2016] study did not report breastfeeding status). This information addresses one of the major concerns of women regarding medication in the perinatal period, as depressed women tend to not breastfeed their babies while on medication (Hamdan & Tamim, 2012).

rTMS was overall acceptable, considering the dropout rates. The extracted data showed that from a total of 124 women receiving stimulation, only 10 discontinued treatment (8,04%). Besides efficacy and safety, acceptability is an important feature. The low percentage of women dropping the studies suggests that this treatment is acceptable for women in this period, showing once more that this treatment is an option and additionally that future investigation is possible.

Only one study in pregnancy and one study in the postpartum found significant differences in neurocognitive measures before and after treatment. While during pregnancy, the performance in an attentional test, LNS, was worse in posttreatment (Kim et al., 2018), during the postpartum period, and also targeting attention assessment, Myczkowski et al. (2012), reported better results in TMT-B and in Vitoria Stroop Test post-treatment compared to after treatment. The available information is controversial and the reduced number of studies reporting neurocognitive assessments does not allow for conclusions to be made, suggesting instead the need for more information.

Contemplating the information gathered and considering the pressing need for controlled studies with larger samples, rTMS seems to be a legitimate option for women during the peripartum period. As besides its efficacy, rTMS showed to represent a safe and acceptable treatment, particularly in postpartum. Although during pregnancy this treatment showed not to be harmful for the baby, more information is needed to explore the association between rTMS and premature birth. In this sense women should be informed about this alternative treatment. Furthermore, the greatest advantage of rTMS is allowing women to breastfeed in safe way.

TES and peripartum depression

Concerning tDCS studies, all applied the stimulation over the same location: the anode over F3 and the cathode over F4, using the same current density (2 mA) but distinctive number of sessions, ranging between 10-30. The study that used tACS (Wilkening et al., 2019) placed the electrodes over F3 and F4 and lasted 9 sessions. The studies included were conducted in pregnancy and showed promising effects for any of the TES techniques with reduced scores at end of treatment comparing to baseline. Due its novelty, tDCS and tACS are not yet FDA approved treatments, however considering the articles included in the preset study it seems to provide the basis to proceed with future larger studies confirming the efficacy of the suggested protocol, preferable with 15 sessions since it was the number of sessions conducted in the RCT (Vigod et al., 2019).

Only one study reported information concerning neonatal safety, indicating 1 pre-term birth (Vigod et al., 2019). The lack of information concerning the association between tDCS and pre-term births highlights the urge for more investigation. However, considering the information gathered in the present review no positive association can be confirmed.

Concerning the acceptability, only the RCT (Vigod et al., 2019) reported withdraws, two women from each group. From a total of 15 women receiving electrical stimulation only two were lost. Considering this low rate, TES can be considered acceptable for pregnant women.

The only TES study (Vigod et al., 2019) that reported neurocognitive measures showed an improvement at end of treatment both in TMT-A and TMT-B, suggesting a positive association between tDCS and attentional functions. Nonetheless there is a need of future studies exploring this association.

From the available information synthesized in the present study, having in consideration the limited number of studies, the small samples and their bias, TES seems to represent an efficacious, safe and acceptable treatment. Additionally, it also seems to have a positive impact in attentional functions. To ascertain these positive findings, future studies with larger samples are needed.

Although our review advances the field in the sense that it explores the efficacy of non-invasive and non-convulsive techniques in reducing PPD, it has also had a few limitations worth of discussion. First the meta-analysis was conducted with a small number of reports (three studies in the pregnancy and four during peripartum) representing a statistical risk. Additionally, the available reports referred to studies with small sample sizes, mostly of which open labels hampering the possibility to compare active treatments with active comparators or placebo. Instead we compared baseline scores versus end of treatment scores. The scope of the

present study was meant to include ECT, allowing all types of stimulation to be explored and possibly compared. Due to time restriction, it was not possible to complete the ECT synthesis, narrowing the conclusions. The lack of registered protocol also constitutes a limitation, even though it was submitted in October it is not yet approved.

In conclusion, non-invasive and non-convulsive neurostimulation seems to be effective, safe, and acceptable in the peripartum period. Moreover, these treatments seem to hold an alternative to medication and psychotherapy or also be integrated in combined treatments, both for pregnancy and postpartum period. Nonetheless trials with larger samples are needed to compare the active versus sham effect, and to allow more reliable quantitative synthesis.

Contributors

The present review is a part of a major study conducted as an output for a COST action (CA18138). Authors AGA and FPP wrote the protocol. FPP conducted all phases of the systematic review and meta-analysis. RG was the second author to screen the articles and to calculate inter-rater reliability. Qualitative analysis was discussed with MM. AGA and AF supervised and contributed throughout the conduction of these tasks. All authors approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Funding

This article/publication is based upon work from COST Action Riseup-PPD (CA18138), supported by COST (European Cooperation in Science and Technology). COST (European Cooperation in Science and Technology) is a funding agency for research and innovation networks. Our Actions help connect research initiatives across Europe and enable scientists to grow their ideas by sharing them with their peers. This boosts their research, career and innovation.

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6. Appendices

Appendix A

PROSPERO

International prospective register of systematic reviews

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Efficacy of brain stimulation in decreasing depression symptoms during the peripartum period: a systematic review

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

English

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

20/09/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

30/03/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review
The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).
protocol finalised
6. * Named contact.
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Ana Ganho Ávila

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Dr Ana Ganho Ávila

7. * Named contact email.
Give the electronic mail address of the named contact.
ganhoavila@fpce.uc.pt

8. Named contact address
Give the full postal address for the named contact.
Rua do Colégio Novo, 3000-115 Coimbra, Portugal

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+351968106007

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Center for Research in Neuropsychology and Cognitive and Behavioral Intervention (CINEICC), Faculty of Psychology and Educational Sciences, University of Coimbra

Organisation web address:

http://www.uc.pt/fpce/

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team.

Affiliation refers to groups or organisations to which review team members belong.

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12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

This review is part of the COST Action Riseup-PPD CA18138 and is supported by COST under COST Action Riseup-PPD CA18138.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What is the efficacy of brain stimulation treatments in decreasing peripartum depressive symptoms (either as a stand-alone, add-on therapy or augmentation intervention to antidepressants) when compared to pharmacotherapy, psychological interventions, other brain stimulation or no treatment?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

1) Publication period: from inception to 1 October 2019 (updated in 19th May 2020)

2) Studies available in English, French, Spanish, Portuguese

3) Types of studies included: Randomized and non-randomized clinical trials and case reports

4) Search terms:

Depression, postpartum, peripartum, perinatal, antenatal, ante-natal, pregnancy, natal, post-partum, "post partum", peri-natal, pre-natal ,"pre natal", neuromodulation, neurostimulation, electric current stimulation, Deep Brain Stimulation , ECT, electroconvulsive therapy, tDCS , transcranial direct current stimulation, tACS, alternate current, tNRS, random noise, pulse direct current stimulation, tDCS, magnetic current stimulation, rTMS, repetitive Transcranial magnetic stimulation, single pulse transcranial magnetic stimulation, theta burst stimulation)

5) Search in the following databases: PubMed/MEDLINE, PsycINFO, LILACS, Scopus, Web of Science

6) Grey literature search: Search for thesis and dissertations in the following databases: Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, OpenAIRE, RCCAP b) Other unpublished datasets available from clinical trials registered (all clinical trials registry platforms accepted by the ICMJE)

7) Manual verification of the references from the title/abstract selected publications

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Example of Search strategy for Pubmed

Depression AND (postpartum OR peripartum OR perinatal OR antenatal OR ante-natal OR pregnancy OR natal OR post-partum OR "post partum" OR peri-natal OR pre-natal OR "pre natal") AND (neuromodulation OR neurostimulation OR electric current stimulation OR Deep Brain Stimulation OR ECT OR electroconvulsive therapy OR tDCS OR transcranial direct current stimulation OR tACS OR alternate current OR tNRS OR random noise OR pulse direct current stimulation OR pDCS OR magnetic current stimulation OR rTMS OR repetitive Transcranial magnetic stimulation OR single pulse transcranial magnetic stimulation OR theta burst stimulation).

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Peripartum depression disorder

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Women diagnosed with depression (F32 in the peripartum period (0.90.6) for ICD-10; peripartum depression disorder according to DSM-IV (Major Depressive Disorder with postpartum onset), DSM-5 (Major Depressive Disorder with peripartum onset), aged 18 or older, treated before and after delivery.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Non implantable brain stimulation (as a stand-alone or an add-on therapy, or augmentation strategy).

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Non implantable brain stimulation, pharmacotherapy, psychological interventions or no treatment.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Randomized and non-randomized clinical trials, uncontrolled studies and case studies

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Experimental, translational and clinical settings (inpatient or outpatient clinics)

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Primary Outcome: Reduction in depressive symptoms (mean change of score from baseline to time of effect)

Endpoint measures: As not all studies use the same instrument, we will apply the following hierarchy (starting with the gold standard to assess depressive symptoms: Hamilton Rating Scale for Depression- 24 item[HRSD-24], Hamilton Rating Scale for Depression-17 item [HRSD-17], Edinburgh Postnatal Depression Scale [EPDS], Inventory of Depressive Symptomatology-Self-Report [IDS-SR]; Clinical Global Impression [CGI], Montgomery–Asberg Depression Rating Scale [MADRS]; Beck Depression Inventory [BDI].

Measures of effect: Standard mean difference will be used to estimate group differences in what concerns the primary outcome.

Co-primary outcomes: neo-natal safety**.**

Endpoint measures: self-report questionnaires of safety/tolerability and clinical reports (ex. Preterm birth)

Measures of effect: Odds ratio will be used to estimate the probability of occurrence of adverse effects.

Timing and effect measures

2,4,6, weeks of treatment; 3 months, 6 months, and 1-year follow-up

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review

1) **Response rate, remission status**

Endpoint measures: as not all studies use the same definition of treatment response, we will adopt definitions hierarchically: at least 50% reduction of the baseline score, followed by at least 30% reduction of the of the baseline score. If none of these definitions is available, we will use the original authors' primary definition.

Again, as not all studies use the same instrument, we will apply the following hierarchy (starting with the gold standard to assess depressive symptoms): Hamilton Rating Scale for Depression-24 item[HRSD-24], Hamilton Rating Scale for Depression-17 item [HRSD-17]; Montgomery–Asberg Depression Rating Scale [MADRS]; Edinburgh Postnatal Depression Scale [EPDS], Inventory of Depressive Symptomatology-Self-Report [IDS-SR]; Clinical Global Impression [CGI], Beck Depression Inventory [BDI].

Measures of effect: The odds ratio (OR) and 95% confidence interval (CI) will be used to estimate group differences in what concerns the rate of response and remission (as more robust effects of estimation are found with OR when definition of outcomes is variable between studies).

2) **Time to response**

Endpoint measures: Hamilton Rating Scale for Depression- 24 item[HRSD-24], Hamilton Rating Scale for Depression-17 item [HRSD-17], Edinburgh Postnatal Depression Scale [EPDS], Inventory of Depressive Symptomatology-Self-Report [IDS-SR]; Clinical Global Impression [CGI], Montgomery–Asberg Depression Rating Scale [MADRS]; Beck Depression Inventory [BDI].

Measures of effect: Survival functions between the intervention and the comparator will be estimated (e.g. using for example Kaplan–Meier estimator) for the length of time women take to respond to treatment.

3) **Safety for mothers (e.g. headaches) and acceptability (e.g. dropout rate)**

Endpoint measures: Self-report questionnaires of adverse effects and tolerability; trial reports on dropout rates

Measures of effect: The odds ratio (OR) and 95% confidence interval (CI) will be used to estimate group differences in what concerns the rate of adverse effects, tolerability and dropouts.

4) **Secondary outcomes of Neurocognitive functioning**

Endpoint measures: Neurocognitive assessment measures of executive functioning (e.g. working memory, selective attention, sustained attention)

Measures of effect: The absolute risk difference will be used to estimate group differences in what concerns neurocognitive functioning.

Timing and effect measures

2,4,6, weeks of treatment; 3 months, 6 months, and 1-year follow-up

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

An individual standardized form for data search and extraction will be conducted by two independent researchers according to an apriori checklist. Titles and abstracts of studies and other information obtained from grey literature sources will be listed for potential eligibility according to the checklist. Full text/information will be retrieved and assessed independently by two researchers. Between researchers' discrepancies will be fully discussed and in case of no consensus a third researcher will decide according to the established criteria. Study evidence will be extracted as follows: study population; demographic and baseline characteristics; type of intervention and type of comparator; study design; completion/dropout rates; outcomes (primary and secondary) and times of measurement; acceptability.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two researchers per intervention method will independently assess the risk of bias. Considering the study design different tolls will be used: Cochrane's (ROB 2.0) for randomized controlled studies, ROBINS-1.0 for non-randomized Studies and Interventions and to assess risk of bias in case reports we will use an adapted version of the quality appraisal checklist (Guo et al., 2016). Discrepancies will be fully discussed and in case of no consensus a third researcher will decide according to the established criteria.

Whether needed publication/study authors will be contacted for further information.

Risk of bias assessment will contribute to weight reports' according to low, unclear and high risk of bias within meta-analysis, and observe how bias affects meta-analysis estimations.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

We aim to conduct a qualitative and quantitative synthesis. In the qualitative synthesis the efficacy, dropouts and safety for mother and infant will be conducted for the included studies. Concerning the quantitative synthesis, a meta-analysis will be performed for the studies where the information is available. Random effects models will be used as the heterogeneity between studies is assumed due to distinctive sampling, interventions, etc., regardless heterogeneity estimations.

For continuous outcomes the effect size measure will be the standardized mean difference (SMD), using Hedges's g, adopted considering studies distinctive instruments to assess depression. SMDs will be calculated for both: within group (the change from baseline to endpoint; including placebo to access placebo effect) and between groups (differences between intervention and comparator).

We will use standard deviations (SD) or standard errors (SE) converted to standard deviations. To manage missing data, we will estimate SDs from confidence intervals or p-values.

For dichotomous outcomes, the effect size will be estimated using odds ratio (OR) and its 95% CI. We will conduct intention to treat analysis (ITT) where all participants identified and

allocated to the study groups will be considered regardless completion status. Whether the original authors present only the results for completers we will adopt the conservative approach and assume that participants lost to follow-up are non-responders.

Regarding publication bias, we will use contour-enhanced funnel-plots to overcome the limitations of standard visualization of funnel-plots and Egger's regression tests and differentiate asymmetry due to publication bias and asymmetry due to other factors (e.g. heterogeneity or lower quality of small trials). With contour enhanced funnel-plots we will be able to observe significance studies levels overlapping on the standard funnel plot.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or comorbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

If the necessary data are available, subgroup analyses will be conducted. Currently, we anticipate a small number of studies with high variability, and possibly we will not have margin for sub-group analysis. Be the number of studies in the field higher than expected and the following potential moderator effects should be explored (by hierarchical order):

- Intervention/treatment – ECT, rTMS, tDCS, tACS – distinctive brain stimulation interventions are expected to have distinctive effect sizes.
- Time of intervention – Pregnancy vs. postpartum – the neurobiological profile of women during pregnancy and postpartum is distinctive and thus may influence differently the effect of the interventions.
- Study design – randomized vs non-randomized – studies' design follows distinctive parameters for clinical research standards thus contributing differently to the estimation of effect sizes.
- Nature of comparator – grouping studies by intervention and comparator will increase homogeneity and contribute differently to the estimation of effect sizes.
- First episode patients – resistant vs first episode patients seem to respond differently to distinctive neuromodulation strategies.
- Severity of illness at baseline – less severe samples may show floor effects that limit size effects.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

Yes

Intervention

Yes

Meta-analysis

Yes

Methodology

No

Network meta-analysis

Yes

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Qualitative synthesis

Yes

Review of reviews

Yes

Service delivery

No

Systematic review

Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system

No

Cancer

No

Cardiovascular

No

Care of the elderly

No

Child health

No

Complementary therapies

No

Crime and justice

No

Dental

No

Digestive system

No

Ear, nose and throat

No

Education

No

Endocrine and metabolic disorders

No

Eye disorders

No

General interest

No

Genetics

No

Health inequalities/health equity

No

Infections and infestations

No

International development

No

Mental health and behavioural conditions

Yes

Musculoskeletal

No

Neurological

No

Nursing

No

Obstetrics and gynaecology

No

Oral health

No

Palliative care

No

Perioperative care

No

Physiotherapy

No

Pregnancy and childbirth

Yes

Public health (including social determinants of health)

No

Rehabilitation

No

Respiratory disorders

No

Service delivery

No

Skin disorders

No

Social care

No

Surgery

No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English; French, Portuguese, Spanish

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Brazil

Germany

Portugal

Spain

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

I do not wish to make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

This review is a task defined within a COST Action (CA18138) and the results will be disseminated in National and International conferences. Also, findings will be submitted to a peer-reviewed journal.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Peripartum depression, Brain Stimulation, Neuromodulation, Transcranial Direct Current Stimulation, Random noise tDCS, Alternate current tDCS,Transcranial Magnetic Stimulation, Theta Burst stimulation, Electroconvulsive therapy, Systematic Review, Meta-analysis

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Please provide anticipated publication date

Ongoing. Anticipated publication date: April 2020

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix B

Search Strategy

1. Language restrictions

Search strategy was limited to English, French, Spanish or Portuguese reports.

2. Online databases:

a) Published reports (from inception to September 2019)

PubMed/MEDLINE, PSycINFO, LILACS and Web of Sience

b) Unpublished reports (from inception to September 2019)

Thesis and dissertations: Networked Digital Library of Thesis and Dissertations

3. Search expressions and variations

#1 neuromodulation OR neurostimulation OR electric current stimulation OR Deep Brain Stimulation OR ECT OR electroconvulsive therapy OR tDCS OR transcranial direct current stimulation OR tACS OR alternate current OR tNRS OR random noise OR pulse direct current stimulation OR pDCS OR magnetic current stimulation OR rTMS OR repetitive Transcranial magnetic stimulation OR single pulse transcranial magnetic stimulation OR theta burst stimulation)

#2 ("depress*")

#3 postpartum OR peripartum OR perinatal OR antenatal OR ante-natal OR pregnancy OR natal OR post-partum OR "post partum" OR peri-natal OR pre-natal OR "pre natal"

#4 (1# AND #2 AND #3)

Examples of Search strategy for the different databases:

- **PUBMED through September 28th, 2019**

  (neuromodulation OR neurostimulation OR electric current stimulation OR Deep Brain Stimulation OR ECT OR electroconvulsive therapy OR tDCS OR transcranial direct current stimulation OR tACS OR alternate current OR tNRS OR random noise OR pulse direct current stimulation OR magnetic current stimulation OR rTMS OR repetitive Transcranial magnetic stimulation OR single pulse transcranial magnetic stimulation OR theta burst stimulation)

AND ("depress*")

AND (postpartum OR peripartum OR perinatal OR antenatal OR ante-natal OR pregnancy OR natal OR post-partum OR "post partum" OR peri-natal OR pre-natal OR "pre natal")

- **Web of Science through September 28th, 2019**

  (neuromodulation OR neurostimulation OR electric current stimulation OR Deep Brain Stimulation OR ECT OR electroconvulsive therapy OR tDCS OR transcranial direct

current stimulation OR tACS OR alternate current OR tNRS OR random noise OR pulse direct current stimulation OR magnetic current stimulation OR rTMS OR repetitive Transcranial magnetic stimulation OR single pulse transcranial magnetic stimulation OR theta burst stimulation)

AND (depress$)

AND (postpartum OR peripartum OR perinatal OR antenatal OR ante-natal OR pregnancy OR natal OR post-partum OR post partum OR peri-natal OR pre-natal OR pre natal)

- **Lillacs through September 29th, 2019**

  (neuromodulation OR neurostimulation OR electric current stimulation OR Deep Brain Stimulation OR ECT OR electroconvulsive therapy OR tDCS OR transcranial direct current stimulation OR tACS OR alternate current OR tNRS OR random noise OR pulse direct current stimulation OR magnetic current stimulation OR rTMS OR repetitive Transcranial magnetic stimulation OR single pulse transcranial magnetic stimulation OR theta burst stimulation)

AND (depress$)

AND (postpartum OR peripartum OR perinatal OR antenatal OR ante-natal OR pregnancy OR natal OR post-partum OR post partum OR peri-natal OR pre-natal OR pre natal)

- **psycINFO through October 2nd, 2019**

  (neuromodulation OR neurostimulation OR electric current stimulation OR Deep Brain Stimulation OR ECT OR electroconvulsive therapy OR tDCS OR transcranial direct current stimulation OR tACS OR alternate current OR tNRS OR random noise OR pulse direct current stimulation OR magnetic current stimulation OR rTMS OR repetitive Transcranial magnetic stimulation OR single pulse transcranial magnetic stimulation OR theta burst stimulation)

AND (depress*)

AND (postpartum OR peripartum OR perinatal OR antenatal OR ante-natal OR pregnancy OR natal OR post-partum OR post partum OR peri-natal OR pre-natal OR pre natal)

- **Networked Digital Library of Theses and Dissertations through September 22 nd, 2019**

(neuromodulation OR neurostimulation OR electric current stimulation OR Deep Brain Stimulation OR ECT OR electroconvulsive therapy OR tDCS OR transcranial direct current stimulation OR tACS OR alternate current OR tNRS OR random noise OR pulse direct current

stimulation OR magnetic current stimulation OR rTMS OR repetitive Transcranial magnetic stimulation OR single pulse transcranial magnetic stimulation OR theta burst stimulation)
AND (“depress$”)
AND (postpartum OR peripartum OR perinatal OR antenatal OR ante-natal OR pregnancy OR natal OR post-partum OR “post partum” OR peri-natal OR pre-natal OR “pre natal”)