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Review article

Efficacy of non-invasive brain stimulation in decreasing depression symptoms during the peripartum period: A systematic review

Francisca Pacheco [a], Raquel Guiomar [b], Andre R. Brunoni [c], Rachel Buhagiar [d], Olympia Evagorou [e], Alba Roca-Lecumberri [f], Anna Poleszczyk [g], Mijke Lambregtse-van den Berg [h], Rafael A. Caparros-Gonzalez [i], Ana Fonseca [a,b], Ana Osório [j], Mahmoud Soliman [k], Ana Ganho-Ávila [b,*]

[a] University of Coimbra, Faculty of Psychology and Educational Sciences, Coimbra, Portugal
[b] Center for Research in Neuropsychology and Cognitive-Behavior Interventions, Faculty of Psychology and Educational Sciences, University of Coimbra, Coimbra, Portugal
[c] Department of Internal Medicine and Psychiatry, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[d] Mental Health Services, Malta
[e] University General Hospital of Alexandroupolis, Department of Psychiatry, Greece
[f] Perinatal Mental Health Unit, Psychiatry and Clinical Psychology Service, Hospital Clinic de Barcelona, Barcelona, Spain
[g] Centre Hospitalier Sainte Marie, Pôle Est, Nice, France
[h] Departments of Psychiatry and Child & Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands
[i] University of Granada, Faculty of Health Sciences, Department of Nursing, Granada, Spain
[j] Graduate Program on Developmental Disorders, Center for Biological and Health Sciences, Mackenzie Presbyterian University, São Paulo, Brazil
[k] Department of Radiology, Charité - Universitätsmedizin Berlin, Berlin, Germany

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ABSTRACT

Background: Non-invasive brain stimulation (NIBS) techniques have been suggested as alternative treatments to decrease depression symptoms during the perinatal period. These include brain stimulation techniques that do not require surgery and that are nonpharmacological and non-psychotherapeutic. NIBS with evidence of antidepressant effects include repetitive transcranial magnetic stimulation (rTMS), transcranial electric stimulation (TES) and electroconvulsive therapy (ECT).

Objectives: This systematic review aims to summarize evidence on NIBS efficacy, safety and acceptability in treating peripartum depression (PPD).

Methods: We included randomized, non-randomized and case reports, that used NIBS during pregnancy and the postpartum. The reduction of depressive symptoms and neonatal safety were the primary and co-primary outcomes, respectively.

Results: rTMS shows promising results for the treatment of PPD, with clinically significant decreases in depressive symptoms between baseline and end of treatment and overall good acceptability. Although the safety profile for rTMS is adequate in the postpartum, caution is warranted during pregnancy. In TES, evidence on efficacy derives mostly from single-arm studies, compromising the encouraging findings. Further investigation is necessary concerning ECT, as clinical practice relies on clinical experience and is only described in low-quality case-reports.

Limitations: The reduced number of controlled studies, the lack of complete datasets and the serious/high risk of bias of the reports warrant cautious interpretations.

Conclusions and implications: Existing evidence is limited across NIBS techniques; comparative studies are lacking, and standard stimulation parameters are yet to be established. Although rTMS benefits from the most robust research, future multicenter randomized clinical trials are needed to determine the position of each NIBS strategy within the pathways of care.

* Corresponding author. Center for Research in Neuropsychology and Cognitive-Behavior Interventions, Faculty of Psychology and Educational Sciences of the University of Coimbra, Rua do Colégio Novo, 3001-802, Coimbra, Portugal.
E-mail address: ganhoavila@fpce.uc.pt (A. Ganho-Ávila).

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1. Introduction[1]

Peripartum Depressive Disorder (PPD) is a Major Depressive Disorder (MDD) with the onset of the depressive symptoms occurring during pregnancy or within 12 months postpartum (Wisner et al., 2013; Woody et al., 2017). The pooled prevalence of PPD is 11.9%, representing a major public health issue (Woody et al., 2017; Meltzer-Brody et al., 2013). PPD affects mothers and infants, leading to adverse outcomes in pregnancy (Grote et al., 2010) and in the postpartum (Field, 2010; Slomian et al., 2019).

Decision-making about PPD treatment must be defined on a case-by-case basis, according to individual characteristics (e.g., severity of symptoms, willingness to use medication, and previous antidepressant response), the best clinical evidence, the available treatments, and respecting women's preferences (Charlton et al., 2014; Fonseca et al., 2020). Pharmacotherapy and psychotherapy are first- and second-line treatments in PPD (Bledsoe and Grote, 2006) and both present limitations. Whereas antidepressants lack investigation (Howard et al., 2020) and pose risks for fetal development (Molenaar et al., 2018), psychotherapy is not always effective and is a costly treatment (van Ravesteyn et al., 2017). New alternatives are thus needed to ensure universal high-quality perinatal mental health.

Non-invasive brain stimulation (NIBS) is one of the fastest-growing fields in medicine (Borrione et al., 2020) and refers to a set of techniques used to modulate brain activity using non-implantable methods (Albizu et al., 2019).

rTMS impacts synaptic transmission through patterned energy that changes neuron's activity and connectivity (George and Aston-Jones, 2010) with an immediate local and remote effect (Terranova et al., 2019). The most studied condition for its therapeutic application is unipolar depression (Lefaucheur et al., 2020) with two systematic reviews concluding for rTMS efficacy, acceptability and tolerability in PPD (Cole et al., 2019; Ganho-Ávila et al., 2019).

Theta burst stimulation (TBS) is a shorter form of rTMS that can be administered through continuous or intermittent protocols (cTBS and iTBS, respectively; Di Lazzaro et al., 2008), addressing the time-consuming issue associated with rTMS (Blumberger et al., 2018).

Transcranial Electrical Stimulation (TES) techniques involve the application of a low-intensity electrical current. Transcranial direct current stimulation (tDCS) applies an electric current between two electrodes placed over the scalp, inducing cortical excitability (Merzagora et al., 2010), facilitating or inhibiting the synaptic transmission and the frequency of action potentials during endogenous neuronal firing (Brunoni et al., 2012). tDCS is a low-cost treatment that uses a constant direct current (Bennabi and Haffen, 2018), shows favorable results in MDD and has a good safety profile (Lefaucheur et al., 2017). To our knowledge, there is no review on the effectiveness of tDCS in PPD, despite its promising features for the peripartum, in particular, at-home protocols (Alonzo et al., 2019; Alonzo and Charvet, 2016). Other TES techniques of interest are transcranial alternating current stimulation (tACS), that in MDD uses an oscillating sinusoidal current to target alpha oscillations (Antal et al., 2008; Alexander et al., 2019); and trigeminal nerve stimulation (TNS) that applies electric current over a branch of the trigeminal nerve, allowing for the propagation of the stimuli to brain areas involved in mood regulation (Chiluwal et al., 2017; Shiozawa et al., 2015).

Electroconvulsive therapy (ECT) is recommended for severe psychiatric symptoms, including depression with psychosis, suicidal ideation, and mania, when patients have had previous positive response to ECT or/and are non-responsive to medication (American Psychiatric Association Committee on Electroconvulsive Therapy, 2001). Used as a tertiary treatment for severe MDD, ECT involves a generalized controlled seizure, produced by a series of short electric current bursts delivered through electrodes to the brain (Mutz et al., 2019). ECT seems to be more efficacious and safer than medication for severely ill pregnant women and in minimizing fetal exposure to psychotropics (American Psychiatric Association Committee on Electroconvulsive Therapy, 2001). To address the adverse effects that have been reported, additional obstetric care and close maternal and fetal monitoring is added during ECT treatments in pregnancy (Coshal et al., 2019). Although women in the postpartum period seem to be those who most benefit from ECT treatments (Rundgren et al., 2018), recent literature suggests the association between ECT and memory impairments, lower rates of treatment response and remission, and longer treatment courses in young, educated women with no history of suicidal self-injury (Li et al., 2020).

Evidence concerning NIBS in PPD is promising but scattered. Therefore, this study aimed to synthesize knowledge about its use from pregnancy to postpartum. We aimed to clarify the efficacy of NIBS in decreasing peripartum depressive symptoms (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

This systematic review aimed at gathering evidence about the efficacy, safety, and acceptability of NIBS in PPD, by addressing the following critical questions:

i) What is the evidence of efficacy in reducing depressive symptoms during the peripartum period, across NIBS?
ii) What is the safety profile of each NIBS technique regarding women, fetuses and neonatal outcomes?
iii) What is the level of acceptability of NIBS for women, as measured by dropout rates?
iv) What is the impact of NIBS in the neuropsychological functioning of women?

2.1. Protocol and registration

This systematic review was registered in PROSPERO (CRD42020153132) and was conducted under COST Action RISEUP-PPD (CA18138).

2.2. Literature review and search methods

Data search was conducted independently by two authors (FP e RG) from inception to October 2019 in Pubmed/Medline, PsycINFO, Web of Science, and Lilacs for peer-reviewed studies and for unpublished studies in the Networked Digital Thesis and Dissertations, for the available publications and reports in English, French, Spanish, or Portuguese. Manual verification of the list of references was also conducted by the same authors and disagreements were resolved with a third author in agreement to their specific expertise (AGA, AP, MLvdB). According to the Methodological Expectations of Cochrane Intervention Reviews (MECIR), a search update was performed in May 2020. The complete search strategy can be consulted in Supplementary Materials.

2.3. Eligibility criteria

Randomized clinical trials (RCT) and non-randomized studies (NRS) were included, enrolling women diagnosed with PPD at the start of

[1] Abbreviations: MDD: major depressive disorder; PPD: peripartum depression disorder; NIBS: noninvasive brain stimulation; rTMS: repetitive transcranial magnetic stimulation; TES: transcranial electrical stimulation; tDCS: transcranial direct current stimulation; TBS: theta burst stimulation; ECT: electroconvulsive therapy; tACS: transcranial alternating current stimulation; TNS: trigeminal nerve stimulation; RCT: randomized clinical trials; NRS: non-randomized studies.

treatment, 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, 2004).

The studies' participants should be at least 18 years old and have received rTMS, iTBS, tDCS, tACS, TNS or ECT as a stand-alone, add-on or augmentation treatment, across the peripartum period. Eligible comparators were other types of brain stimulation, psychotherapy, pharmacotherapy, or no treatment.

2.4. Data extraction and outcome measures

Titles and abstracts were screened by two independent researchers using Ryyaan (Ouzzani et al., 2016) to identify studies that met the inclusion criteria, with substantial inter-rater reliability (k = 0.80) (Landis and Koch, 1977). Disagreements were solved through in-depth discussions until consensus was reached. Data for study design, study population, demographic and baseline characteristics, type of intervention and comparator, and outcomes, were extracted from the full-text reports by one researcher and reviewed by other three. Reduction of depressive symptoms was the primary outcome, as assessed by all versions of the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), the Edinburgh Postnatal Depression Scale (EPDS) (Cox and Holden, 2003), the Inventory of Depressive Symptomatology-Self-Report (IDS-SR) (Rush et al., 1986), the Clinical Global Impressions scales (CGI) (Busner and Targum, 2007; Guy, 1976), the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), and the Beck Depression Inventory (BDI) (Beck et al., 1961). Neonatal safety indicators were primary co-outcomes.

The response rate, remission status, time to response, safety for mothers, acceptability measures and neurocognitive assessment measures were secondary outcomes. In case of missing or unclear data, two attempts were made to contact the original authors by email, in a two-week interval.

2.5. Qualitative and quantitative data synthesis

The synthesis of results was conducted considering efficacy, acceptability (according to the dropout rates), adverse effects, and neonatal safety outcomes.

2.6. Risk of bias assessment

To assess the risk of bias (RoB) in RCTs, we used the Cochrane

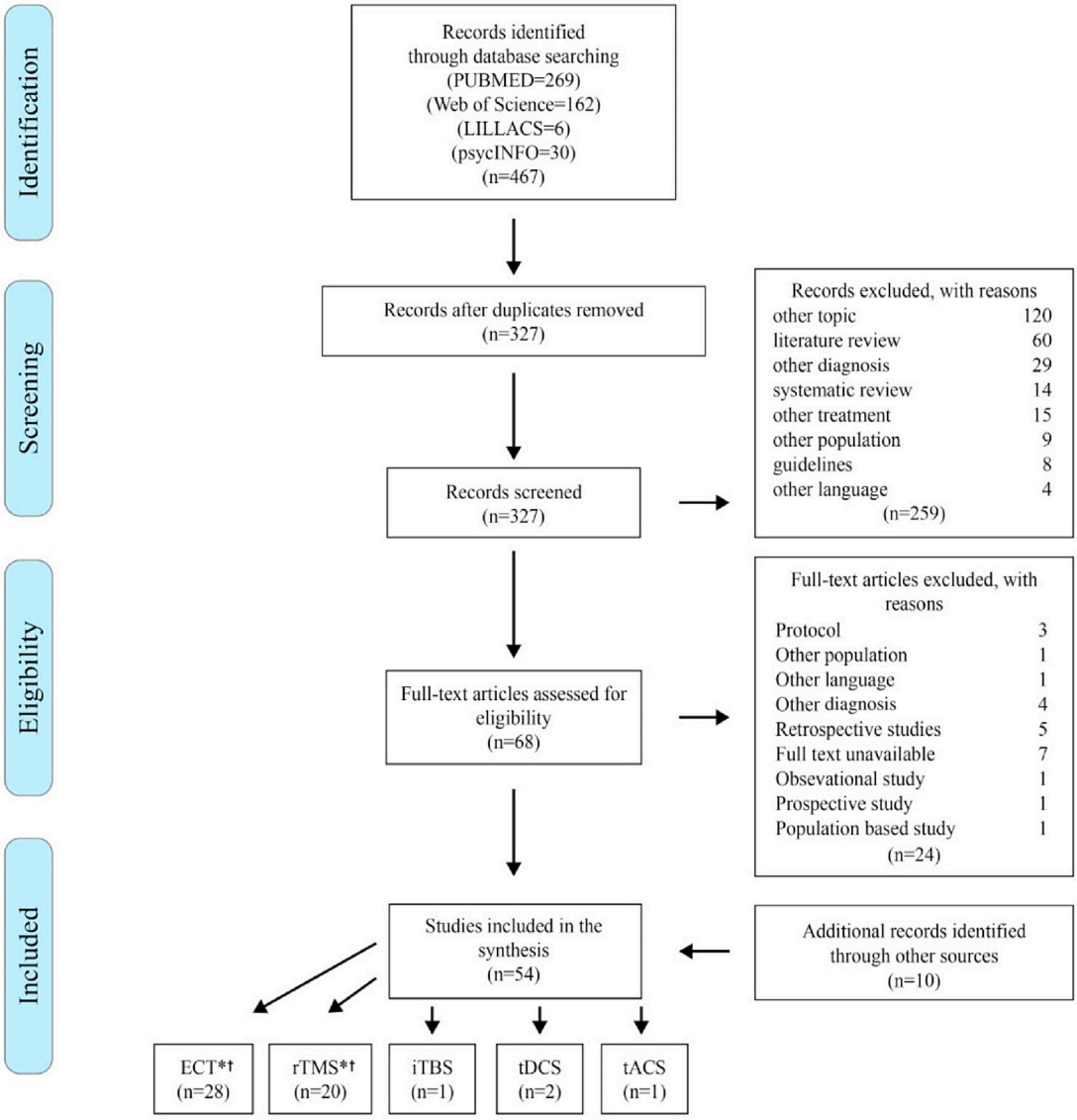

Fig. 1. Flow diagram of the study selection procedure according to PRISMA, 2009

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) and robvis for visualization (McGuinness and 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. The RoB assessment was performed by one rater and checked by two others. Discrepancies were fully discussed and a final judgment of overall RoB was agreed.

3. Results

3.1. Search results

We identified 327 articles, as summarized in Fig. 1. The single grey literature report found was a master's thesis (Myczkowski, 2009) describing the same data later published as a peer-reviewed manuscript (Myczkowski et al., 2012) therefore, we assumed one report. Despite the planned search update to occur in May 2020, due to the update of the PUBMED search engine, the previous search strategy was not reproducible. Therefore, a manual search was conducted, and three new articles were found. During the screening of the title and abstracts of these new articles, one of the reports was excluded and two were included.

3.2. Synthesis of the extracted data

3.2.1. Description of the included studies

Fifty-three studies were included, corresponding to 54 reports (20 rTMS one of which using rTMS followed by ECT [Gahr et al., 2012], 28 ECT, one iTBS, three tDCS, one tACS and one TNS.

3.2.1.1. Repetitive transcranial magnetic stimulation. Sixteen rTMS/iTBS studies started treatment between the first and the third trimesters of pregnancy of which, two continued the treatment after delivery (Burton et al., 2014; Tan et al., 2008). Five studies started treatment only in the postpartum period (Brock et al., 2016; Cox et al., 2020; Garcia et al., 2010; Myczkowski et al., 2012; Odgen et al., 1999).

MDD or Major Depressive Episode (MDE) were the most common diagnosis in studies conducted during pregnancy and only two case studies described Bipolar Depression and Anxious Depression. rTMS studies in the postpartum period included only women initially diagnosed with MDD or MDE in the postpartum. In the RCT (Myczkowski et al., 2012), besides MDE, three patients in the active group and two patients in the sham group were found to be experiencing their first bipolar depressive episode.

In pregnancy, the first rTMS studies used a single-arm design, applied stimulation over the right or left dorsolateral prefrontal cortex (DLPFC) and used frequencies between 1Hz or 25Hz across 18–20 sessions at 100% motor threshold (MT; Kim et al., 2011; Sayar et al., 2014; Tarhan et al., 2012). The RCT by Kim et al. (2018) replicated Kim et al. (2011) single-arm parameters.

Individual case studies and case series applied stimulation over left, right or left and right DLPFC, frequencies varied between 1Hz and 25Hz at 90–120% MT and the number of sessions was also variable, ranging between 8 and 50. Zhang and Hu (2009) and Özten et al. (2013) did not offer information about the stimulation parameters. The single iTBS study available (Trevizol et al., 2019) applied triplet 50Hz bursts, repeated at 5Hz (2s on and 8s off), with a total of 600 pulses (3min, 9s) per session during 20 sessions, using 120% of the motor threshold. Across studies, concomitant medication, was allowed if stable, except in two studies reporting no use of medication (Cohen et al., 2008; Nahas et al., 1999). Three participants from two studies completed their rTMS treatment while in psychotherapy (Ferrão et al., 2018; Özten et al., 2013).

During the postpartum period, all studies targeted the left DLPFC. The RCT applied 5Hz over 20 sessions (Myczkowski et al., 2012), single-arm studies applied 10Hz over 20 sessions (Cox et al., 2020; Garcia et al., 2010) or 11 sessions (Brock et al., 2016). The only case report included applied 20Hz over 13 sessions (Ogden et al., 1999). Concomitant medication was administered in the RCT (clonazepam; Myczkowski et al., 2012) and in the case report (risperidone; Ogden et al., 1999 (see Table 1).

3.2.1.2. Transcranial electrical stimulation. The primary diagnosis across the four TES studies was MDD with all patients starting stimulation during pregnancy, varying across trimesters. We identified one pilot RCT (Vigod et al., 2019), one single-arm study (Palm et al., 2017) and one case report using tDCS (Sreeraj et al., 2016). tDCS studies applied stimulation to the DLPFC, with the anode placed over the F3 and the cathode over the F4 (10–20 international system for EEG placement; Jasper, 1958), using the same current intensity (2 mA). Stimulation was applied once or twice daily during 10–30 sessions. TNS and tACS were described in two case studies (Trevizol et al., 2015; Wilkening et al., 2019, respectively). Wilkening et al. (2019) applied Gamma-tACS over nine sessions for 20min at 40Hz, completing 48000 cycles, at 2 mA range, and offset at 1 mA without ramp-in/ramp-out. The electrodes were placed over the F3 and the F4 positions. The case study by Trevizol (2015), applied TNS for 10 sessions of bilateral stimulation at 120Hz, over the supraorbital trigeminal branches (V1). None of the TES studies administered concomitant medication (see Table 2).

3.2.1.3. Electroconvulsive therapy. The 28 ECT reports were case studies, for a total of 25 pregnant and 13 postpartum women. Two reports described ECT treatments during the first trimester, 19 during the second and third trimesters, and five during the first 12 months postpartum. Six reports do not detail when treatment was delivered. The first report using ECT in PPD during pregnancy dates from 1984 and refers to a woman in her second trimester that received ECT unilaterally to the non-dominant hemisphere for eight sessions (Wise et al., 1984). No further information regarding stimulation parameters was available. In the following years, several published reports described ECT treatments in pregnant women diagnosed with PPD with psychotic features, peripartum depressive symptoms, severe depression and bipolar depression.

In the second trimester of pregnancy, ECT studies used bilateral stimulation (with seizure duration between 17s and 186s, across 9–10 in the first trimester), or unilateral right and bifrontal montages (with seizure durations between 20s and 201s), across 7–15 sessions. ECT treatments delivered in the third trimester, placed the electrodes bilaterally over the temporal, frontal or frontotemporal regions, or unilaterally at the right hemisphere. One report did not detail the placement of the electrodes (Rineh et al., 2020). The number of sessions per treatment ranged from 5 to 9 and the seizure duration was established between 37s and 90s.

Whereas in some ECT reports there was a lack of information concerning medication, for the majority ECT was applied in the context of severe psychiatric disorder not responding to previous pharmacotherapy, or to pharmacotherapy with one course of rTMS. Frequently it was not clear if ineffective pharmacologic treatment was maintained during ECT. The medication used during ECT included fluoxetine and duloxetine. Across ECT reports during pregnancy, treatment was sometimes offered as first-line treatment (DeBattista et al., 2002; Maletzky et al., 2004; Salzbrenner et al., 2011; Rineh et al., 2020; Wise et al., 1984; De Asis et al., 2013).

In the postpartum period, seven reports were published, describing 13 case studies where ECT was used to treat severe PPD, with and without psychotic features. Frequently reports are not clear whether the ineffective pharmacologic treatment was maintained (for exceptions see Forray and Ostroff (2007) and Levy et al. (2015)). Lorazepam was stopped before ECT in Strain et al. (2012), and fluvoxamine and alprazolam were stopped before ECT in Kisa et al. (2005). Often, the exact

Table 1
Characteristics of the included rTMS studies.

Study	Study design	# participants	Concomitant medication	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	Yes	First	Bilateral DLPFC	10 (left) 1 (right)	N.R.	N.R.	110	21
Cohen et al. (2008)	Case report	1	No	First	Right DLPFC	1	1600	N.R.	100	1
Ferrão and Silva (2018)	Case series	3	Yes	First	Left DLPFC	10	3000	N.R.	120	50, 38,40
		1		First	Right DLPFC	1	1800	N.R.	120	20
Gahr et al. (2012)	Case report	1	Yes	Second	Left DLPFC	15	2970	2s on, 8s off	110	24
Kim et al. (2018)	RCT	22 (11 active + 11 sham)	Yes	Second and third	Right DLPFC	1	900	60s on, 60s off	100	20
Kim et al. (2011)	Single-arm	10	Yes	Second to third	Right DLPFC	1	300	60s on, 60s off	100	20
Klirova et al. (2008)	Case report	2	Yes	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	No	Second	Left Prefrontal	5	N.R.	5s on, 25s off	100	9
Özten et al. (2013)	Case report	1	No	Second	Left DLPFC	25	1000	2s on, 30s off	N.R.	76
Sayar et al. (2014)	Single-arm	30	Yes	First and third	Left DLPFC	25	1000	2s on, 30 off	100	18
Tan et al., 2008*	Case report	1	No	First	Left DLPFC	25	50	2s on, 28s off	110	77
Tarhan et al. (2012)	Single-arm	7	Yes	N.R.	Left DLPFC	25	1000	2s on, 30s off	100	18
Trevizol et al. (2019) **	Case report	1	No	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	Yes	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	No	14 weeks of gestation	Left DLPFC	1	1200	20s off	90	14
					Bilateral DLPFC	1	1200	20s off	90	14
					Bilateral DLPFC	1	1200	20s off	90	8
Zhang and Hu (2009)	Case series	3	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
rTMS-postpartum										
Brock et al. (2016)	Single-arm	19	No	N.R.	Left DLPFC	10	3000	75s on, 26 off	120	11
Cox et al. (2020)	Single-arm	6	No	2 weeks to 9 months postpartum	Left DLPFC	10	3000	4s on, 26 off	120	20
Garcia et al. (2010)	Single-arm	9	No	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)	Yes	1–2 months postpartum	Left DLPFC	5	1250	25s on, 20s off	120	20
Odgen et al. (1999)	Case report	1	Yes	N.R.	Left DLPFC	20	1200	30s on, 28 off	100	13

Note. *Applied stimulation during pregnancy and continued in the postpartum period. **Used iTBS). iTBS = intermittent theta burst stimulation. rTMS = repetitive transcranial magnetic stimulation. DLPFC = dorsolateral prefrontal cortex. MT = motor threshold. N.R. = Not reported.

time when ECT treatment was started, within the postpartum period, was not mentioned. However, for the reports that offer this information, the treatment started between week six and month five postpartum (Robinson and Stewart, 1986; Kisa et al., 2005; Forray and Ostroff, 2007; Strain et al., 2012). The use of ECT in the postpartum was consistently preceded by failure of pharmacologic treatment and worsening of the patient's clinical status.

ECT in the postpartum, was delivered for 6 to 29 sessions, and a continuation phase was performed in Forray and Ostroff (2007). To be effective, the duration of seizures was indicated in two studies to be greater than or equal to 15s (Levy et al., 2015), or at least 20s (Forray and Ostroff, 2007; Kisa et al., 2005) with postictal suppression. From the few detailed studies, the montage used was either bilateral, bifrontal, or right unilateral. The width of the stimulus used was either the standard brief pulse of 1.0 ms or the ultra-brief pulse of 0.3 ms (see Table 3).

3.2.2. *Efficacy*

The available data regarding the reduction of depressive symptoms was extracted from the scores according to the endpoints. However, the per-protocol defined time-points for data extraction was not accomplished due to lack of available information. Therefore, to assess the efficacy of rTMS, TES, and ECT, we limited data extraction to baseline and end of treatment (Table 4).

Because the definition for treatment response was distinctive across

Table 2
Characteristics of the included TES studies.

Study	Study design	# participants	Concomitant treatment	Trimester at start of stimulation	Anode	Cathode	Current intensity	# sessions
Palm et al., 2017*	Single-arm	3	No	First, second and third	F3	F4	2 mA	30
Sreeraj et al., 2016*	Case report	1	No	First	F3	F4	2 mA	10
Vigod et al., 2019*	RCT	20 (10 active + 10 sham)	No	Second to third	F3	F4	2 mA	15
Wilkening et al., 2019**	Case report	1	No	First	F3	F4	40Hz at 2 mA range	9
Trevizol et al., 2015***	Case report	1	No	Second to third	supraorbital trigeminal branches (V1) bilaterally		120 Hz	10

Note. *Used tDCS. **Used TNS.*** Study that used tACS. TES = transcranial electric current stimulation. tDCS = transcranial direct current stimulation. tACS = transcranial alternating current stimulation. TNS = trigeminal nerve stimulation.

studies, we adopted definitions hierarchically: at least 50% reduction of the baseline score, followed by at least a 30% reduction of the baseline score. Whenever none of these definitions was available, we used the original authors' primary definition.

Concerning rTMS studies during pregnancy, and considering only study completers, in the RCT, 81.8% of the participants in the active group showed response to treatment, of whom 27.7% achieved clinical remission. In the sham group, 45.5% showed response to treatment and 18.8% remitted (Kim et al., 2018). In Kim's single-arm study (2011), 70% of the patients responded and 30% reached clinical remission. Sayar's single arm (2014), showed slightly lower rates, with 38.8% responders and 61.1% remitted. Although Tarhen et al. (2012) did not provide the mean scores, the authors reported 71.4% responders 71.4% and 28.6% remitted. Regarding case reports, 100% of the patients were responders and 64.3% remitted. Garh et al. (2012) and Zhang and Hu (2009) did not report the scores at baseline and at the end of treatment but reported treatment response or significant symptoms relief after treatment.

In the postpartum period, 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 (MD = 10.72) than in the sham group (MD = 4.9). Brock et al. (2016) single-arm study, reported that 73.7% of the participants achieved clinical remission and Cox et al. (2020) reported that 33.3% responded to treatment 66.6% achieved remission (66.6%). In Garcia et al. (2010), 88,90% women achieved clinical remission. The single case report available in the postpartum period reported clinical remission (Odgen et al., 1999).

In TES studies, the RCT showed the antidepressant effect of tDCS (Vigod et al., 2019). In fact, although the group difference was not statistically significant, the differences from baseline to the end of treatment in the mean MADRS score was higher for the active group (MD = 11.7; mean scores: baseline 23.5 [SD = 5.15]; post-treatment 11.4 [SD = 7.11]) than for the sham group (MD = 11.4; mean scores: baseline 26.8 [SD = 7.48]; post-treatment: 15.8 [SD = 7.65]). Moreover, post-treatment assessments indicated remission in 37.5% of the participants in the active group versus 22.2% in the sham condition. In Palm et al. (2017), two out of three women completed the treatment, and one achieved remission. Finally, all TES case studies reported clinical remission.

Out of 28 ECT studies in pregnancy, only seven offered the exact individual data before and after treatment with six patients responding to treatment and six achieving remission. Similarly, in the postpartum, only three studies out of seven offered individual data and all reported treatment response and symptoms remission.

3.2.3. Safety

Safety for mothers and infants is summarized in Table 5. *"Apgar scores (a measure of the newborn physical condition immediately after birth) were reported* when intermediate (seven or below seven; American Academy of Pediatrics et al., 2006).

Regarding rTMS safety in pregnancy, the RCT by Kim et al. (2018) reported three preterm births in the active group versus none in the sham group. Across studies, the most common side effect reported by mothers was headache, particularly during the first 10 sessions of treatment (36.4%) for women in the active group versus 9.1% for women in the sham group (Fisher's Exact, $p = .311$). From session 10 onwards, headache was reported by 9.1% of women in the active group versus 0% in the sham group (Fisher's Exact, $p = 1.00$). Dizziness, nausea, site pain, supine hypotension, jaw pain, and eye twitch were also reported but no significant group differences were found (Kim et al., 2018).

None of the rTMS single-arm studies reported information about neonatal safety. The adverse effects for mothers included mild headache and supine hypotension (Kim et al., 2011), and facial muscles contraction (Sayar et al., 2014). In Tarhan et al. (2012) no side effects were reported by participants, and the treatment was considered well-tolerated.

As for the case studies in rTMS, three did not offer information concerning neonatal safety (Cohen et al., 2008; Gahr et al., 2012; Nahas et al., 1999). Of the remaining, 18.35% of the births were preterm Ferrão and Silva, 2018; Klirova et al., 2018; Tan et al., 2008) and one baby registered an Apgar score below seven (Ferrão and Silva, 2018). Pain/discomfort at the application site, transient difficulty in concentration and sore throat (Ferrão and Silva, 2018), and tension in the abdominal muscles at the pelvic line (attributed to anxiety) (Nahas et al., 1999) were the adverse effects of rTMS reported during pregnancy.

During the postpartum period, the RCT (Myczkowski et al., 2012) reported no significant side effects. However, two participants complained of minor scalp discomfort during the session and/or mild headache immediately after stimulation. Brock et al. (2016) reported no serious adverse events. In the remaining single-arm studies, headache and scalp discomfort (Cox et al., 2020), and treatment site pain and facial stimulation (Garcia et al., 2010) were also reported. Ogden et al. (1999) did not provide information concerning safety.

In TES studies, the RCT by Vigod et al. (2019) was the single study reporting information about neonatal safety with one preterm birth occurring in the tDCS group. Minor transient side effects were reported by women in 17.7% of the sessions in the active group versus 4.7% in the sham-control ($p = .001$). The most common side effect was "buzzing" or "tingling" at the electrode site, reported in 7.3% of the active tDCS sessions versus 0% in the sham-control ($p = .003$). In the single-arm study, tDCS was considered well-tolerated and no adverse effects occurred (Palm et al., 2017). Two case reports described phosphenes (Sreejaj et al., 2016; Wilkening et al., 2019), and one described transient mild burning sensations at the site (Sreejaj et al., 2016). Trevizol et al. (2015) did not report adverse effects in mothers but stated no side effects to the newborn.

After ECT sessions, several adverse effects potentially associated with the treatment were reported in pregnant women, such as pelvic

Table 3
Characteristics of the included ECT studies.

Study	Study design	#participants	Concomitant treatment	Trimester at start of stimulation	Electrode placement:	Stimulus parameters	Anesthetic used	Seizure duration	#sessions
ECT-pregnancy									
Bhatia et al. (1999)	Case report	2	Yes	Third	Bilateral	N.R.	thiamylal, succinylcholine and curare	37–39 s	6
			No	Third	Bilateral	N.R.	Methohexital and succinlylcholine	67 s	5
Bozkurt et al. (2007)	Case report	1	No	Second	Bilateral	N.R.	Thiopental	N.R.	13
Brown et al. (2003)	Case report	1	No	Second	N.R.	N.R.	tiopental succinylocholine	N.R.	8
Ceccaldi et al. (2008)	Case report	1	N.R.	Second	N.R.	N.R.	etomidate, propofol, succamethonium	N.R.	9
De Asis et al. (2013)	Case report	1	No	Second	Unilateral (Right)	N.R.	methohexital + succinylcholine, methohexital replaced with propofol because of fetal bradycardia	62–201 s	14
DeBattista et al. (2003)	Case report	1	No	Second	Bilateral	45% maximum setting for each treatment	first two: thiopental succinylcholine for the remaining: thiopental was replaced with etomidate (to increase seizure duration)	1st session:22s,2nd:18s,3rd −36s, the rest not described	5
Erturk et al. (2020)	Case report	1	Yes	Second -	Frontal placements	N.R.	thiopental (300 mg) and rocuronium (30 mg)	N.R.	10
Gahr et al. (2013)	Case report	1	Yes	Second	Unilateral (Right)	stimulus intensity between 30 and 65% of max. stimulator output	alfentanil +propofol + succinylcholine	21–32	15
Gonzales et al. (2014)*	Case report	1	Yes	Second	Unilateral (right)	N.R.	N.R.	N.R.	10
			Yes	Postpartum	Unilateral (right)	N.R.	N.R.	N.R.	12
Kasar et al. (2007)	Case report	1	No	Third	Bilateral frontotemporal	suprathreshold stimulus dose of 126 mC(first); 108 mC 4th	Propofol and succinylcholine	N.R.	4
Livingston et al., 1994*	Case report	1	Yes	Third	Bilateral	N.R.	N.R.	Target duration 60–90s	8 during pregnancy, continued during postpartum
Maletzky (2004)	Case report	4	No	N.R.	Bilateral frontotemporal	N.R.	methohexital, glycopyrrolate, succinylocholin	N.R.	5–8
Moreno, 1998	Case report	1	No	First	Bilateral	2.5s duration at an intensity of 0.7A	0.01 mg/kg atropine, thiopental and succinylcholine	17s-first seizure,24s, 22s/total duration 186s	9
Ozgul et al. (2014)	Case report	1	N.R.	First	Bilateral frontotem poral	N.R.	H2antagonist+1 mL/kg Propofol +1 ml = L/kg succinylcholine (muscle relexant)	mean = 20s (EMG),25s (EEG)	10
Pesiridou et al. (2010)	Case report	1	Yes	Third	Unilateral (right)- > bilateral-bifrontal	2.5-s stimulus duration, and 800-mA	Metholexial (170 mg) – after decreased, etomidate, and succinylocholine (100 mg)	35.5s (EEG)	6
		1	N.R.		Bifrontal	N.R.	N.R.	N.R.	7

(*continued on next page*)

Table 3 (*continued*)

Study	Study design	#participants	Concomitant treatment	Trimester at start of stimulation	Electrode placement:	Stimulus parameters	Anesthetic used	Seizure duration	#sessions
Pinette et al. (2007)	Case report			Second and third					
Rineh et al. (2020)	Case report	1	No	Third	N.R.	N.R.	Ranitidine, metoclopramide, propofol 120 mg and succinylcholine 60 mg	N.R.	6
Salzbrenner et al., 2011	Case report	1	N.R.	Third	Bilateral Temporal	Dose titration schedule, stimulus intensity was increased progressively to 75% of maximum on subsequent sessions	Glycopyrrolate, ondasetron, bicitrate, esmolol, labetalol- > remifentanil, methohexital 100–150 mg and succinylcholine 100–120 mg	N.R.	9
Sherer (1991)	Case report	1	Yes	Third	Bilateral Temporal	30% energy (pulsed bidirectional square-wave stimulus with a fixed pulse width of I msec and a frequency of 70 Hz)	thiopental sodium 125 mg, and succinylcholine 50 mg	50 s (first session)	7
Watanabe et al. (2019)	Case report	1	Yes	Third	Bilateral -brief pulse	electrical stimulus of 10%–25%	N.R.	N.R.	6
Wise et al. (1984)	Case report	1	N.R.	Second	UL non-dominant hemisphere	N.I.	general anesthesia, the pharmacological agent not mentioned	N.R.	12
ECT- postpartum									
Forray & Ostroff (2007)	Case report	5	Yes	First 12 months	Bilateral	Mean energy (J):17.5	ketamine	Mean EEG seizure duration:97.1	10
			Yes	postpartum	Bilateral	16.1	Propofol replaced to ketamine	57.5	18
			Yes		Bilateral	41.5	Propofol replaced to ketamine	29.8	12
			Yes		Bilateral	18.9	Thiopental replaced to propofol and then to ketamine	60.8	18
			Yes		Bilateral	32.1	Methohexital	74.5	6
Gressier et al. (2015)	Case report	1	Yes	N.R.	N.R.	N.R.	N.R.	N.R.	28
Kisa et al. (2005)	Case report	1	No	Two moths postpartum	Bifrontal	dynamic energy 23.6 J, pulse width 1.0 ms, frequency 90 Hz, duration 1.2 s, current 800 mA)	40 mg propofol and 40 mg succinylcholine	1st-30s, 2-150s-interrupted with 3 mg midazolam i.v. (on ciprofloxacine), 3rd - after ciprofloxacin's discontinuation - 70s, 4th - 35s, after no seizure longer than 70s	8
Robinson and Stewart (1986)	Case report	1	Yes	Six weeks postpartum	N.R.	N.R.	N.R.	N.R.	8
Levy et al. (2012)	Case report	3	Yes	N.R.	Unilateral (right)ultra-brief pulse-	Total dose (mc) = 2833	Propofol Remifentanil Suxamethonium	20	10
			Yes	N.R.	pulse width 0.3 ms;	3594	Propofol Suxamethonium	34	20
			Yes	N.R.		1129	Propofol Suxamethonium	33	9
Strain et al. (2012)	Case report	1	Yes	5 months	N.R.	N.R.	N.R.	N.R.	6
Takubo et al. (2019)	Case report	1	Yes	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.

Note. *Applied stimulation during pregnancy and throughout the postpartum period. ECT = electroconvulsive therapy; N.R. = not reported; N.A. = Non applicable; EEG = electroencephalogram.

pain (Bozkurt et al., 2007), contractions (Pesiridou et al., 2010; Rineh, 2020; Watanabe et al., 2019), increased blood pressure and increased heart rate (DeBattista et al., 2003; Livingston et al., 1994; Salzbrenner et al., 2011; Wise et al., 1984). Additionally, prolonged seizures were reported in one patient on ciprofloxacin (Kisa et al., 2005) and memory loss was mentioned in two other reports (Livingston et al., 1994; Pesiridou et al., 2010).

As for neonatal safety of ECT, pregnancy complications were reported by several studies, such as vaginal bleeding and a miscarriage (Moreno et al., 1998), threatened premature labor (Ceccaldi et al., 2008; Pesiridou et al., 2010), preterm labor (Kasar et al., 2007; Livingston et al., 1994), abruptio placentae in association with transient hypertension (Sherer, 1991), vaginal bleeding (Livingston et al., 1994), and miscarriage post ECT session (Livingston et al., 1994). Also, four studies reported the newborn Apgar below seven at the first minute (Pinette et al., 2007; Livingston et al., 1994; Sherer, 1991), and three reported the Apgar below seven at the fifth minute (Livingston et al., 1994; Pinette et al., 2007). These scores are considered to be eventually unrelated to ECT. Tonic extension posturing of upper extremities with small left cerebellar, bihemispheric deep white matter, and cortical infarcts were detected by tomography and magnetic resonance image were reported by Pinette et al. (2007) but the relation to ECT is purely speculative. Moreover, in utero complications such as fetal tachycardia induced by maternal hypoxia, uterine contractions (Bhatia et al., 1999; Watanabe et al., 2019), and transient deceleration of fetal heart rate (Bhatia et al., 1999; Bozkurt et al., 2007; DeBattista et al., 2003; De Asis et al., 2013; Livingston et al., 1994; Rineh et al., 2020) were as well reported. In De Asis et al. (2013), fetal heart rate decelerations were attributed to methohexital for anesthesia and in Sherer et al. (1991) a reduced fetal heart rate variability was attributed to intravenous thiopental sodium. Interestingly, for ECT in the postpartum, only one study reported transient memory loss (Forray and Ostroff; 2007), whereas the remaining six did not mention ECT adverse effects.

3.2.4. Acceptability

Acceptability was calculated from the number of dropouts. The RCT in rTMS during pregnancy showed that 84.6% women completed the intervention (Kim et al., 2018). In the single-arm studies, all but one participant completed the treatment (93.75%) and across case reports all women completed treatment (100%).

As for the rTMS studies conducted in the postpartum period, all women recruited for the RCT (Myczkowski et al., 2012) and for the single-arm study (Cox et al., 2020) completed the treatment protocol. In Brock et al. (2016), 76% completed the treatment, and in Garcia et al. (2010), 89% completed the treatment with a mean acceptability rate across single-arm studies of 88,3%. Finally, in the case report by Odgen et al. (1999) the patient completed the treatment.

Considering TES in pregnancy, the RCT by Vigod et al. (2019) lost four participants (two from the active group and two from the sham group), two of which withdrew prior to starting, meaning an estimated dropout rate of 80%. From the participants anticipated for the single-arm study by Palm et al. (2017), results reported three completers and it is not clear if the remaining seven were not enrolled or lost. The patients described in TES case studies in pregnancy completed the treatments. No studies have been published in the postpartum.

Studies of ECT in PPD are limited to case reports, describing 36 case studies. Although the assessment of treatment acceptability according to dropout rates is biased by nature, treatment stoppage or discontinuation was reported in pregnant women, due to the incidence of adverse effects such as contractions and risk of preterm labor (Ceccaldi et al., 2008; Watanabe et al., 2019; Kasar et al., 2007), the observation of cognitive decline (Salzbrenner et al., 2011), transportation difficulties (Bozkurt et al., 2007) or other unknown reasons (Maletzky et al., 2004). Summing an estimated ECT acceptability in pregnancy of 83.2%. In the postpartum, all patients described completed the treatment suggesting an acceptability of 100% (see Table 6).

3.2.5. Neurocognitive assessment

Only a few studies reported neurocognitive outcomes across treatment. Regarding rTMS during pregnancy, the RCT by Kim et al. (2018) collected data using the Mini-Mental State Examination (MMSE), the Trail Making Test A&B (TMT-A; TMT-B), the Stroop Interference Test, the Wechsler Memory Scale 3rd Edition, the Letter-Number Sequencing (LNS), and the Wechsler Memory Scale 3rd Edition and Digit Span. The authors found significant differences in LNS with the active group performing worse in post-treatment when compared to pre-treatment. No other results were made available.

In the postpartum period, Myczkowski and colleagues' (2012), used a neuropsychological battery that included the MMSE, the TMT-B, and the Stroop Test-Interference. A statistically significant difference was found between the active and the sham groups in the TMT-B (31.4% versus 12.9%; $p = .039$) and in the Stroop Test-Interference (31.7% versus 10.0%; $p = .034$) with the active group outperforming. However, these differences did not survive false discovery rate for multiple comparisons. Similarly, in the postpartum period, Cox et al. (2020) did not find statistically significant differences between baseline scores and end of treatment in the MMSE, the TMT-B, and the List Generation. The tDCS study by Palm et al. (2017), measured the scores of TMT A&B at baseline, at week 2 of treatment and at follow-up in three patients with data suggesting neuropsychological improvement. The case report by Wilkening et al. (2019) using tACS, presented TMT-A&B scores at baseline, at the end of treatment and at follow-up and both tests showing improvement. Trevizol et al. (2015) observed the impact of TNS in cognitive functions using the Montreal Cognitive Assessment (MOCA) and found stable cognitive performance and improved memory. In ECT, only Salzbrenner et al. (2011) assessed neurocognitive performance using the MMSE and suggest nine as the maximum number of sessions before cognitive decline.

3.2.6. Risk of bias

Two out of the three RCT were assessed with high RoB (see Table S1 in supplementary materials). RoB across NRS studies was considered critical due to incomplete information and confounding (see Fig. 2 and Fig. 3, as well as Table S2 in supplementary materials to support the interpretation of results). For case-series and case-studies, to guarantee the homogeneous assessment, the criterion of a minimum follow-up length of 6 months was established, based on our clinical and experimental judgment. Across interventions, RoB was found to be high as the majority did not establish the outcome measures *a priori*, did not blind the assessment of outcome measures, and did not complete the follow-up length of 6 months. The case studies using rTMS and TES during pregnancy, scored the highest (meaning the lowest RoB). These were followed by rTMS studies in the postpartum mainly threatened by the lack of *a priori* establishment of outcome measures, or these were not appropriate, or because the authors did not apply procedures for blinding assessments. The most threatened reports were the ECTs conducted through the peripartum period with a generalized absence of critical information across all parameters (see Table S3 in supplementary materials).

4. Discussion

This study aimed to gather the available literature on the efficacy of NIBS techniques in PPD, combining and updating previous reviews (Kim et al., 2015; Konstantinou et al., 2020). We collected data from 54 reports, gathering the information about 173 women under treatment.

Table 4
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	4	Successful maintenance treatment		
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	2	3
	1	PPD (pregnancy)	HDRS-22	12	6	1	1
Gahr et al. (2012)	1	PPD (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
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	0	1
Özten et al. (2013)	1	PPD (pregnancy)	HDRS-17	29	8	0	1
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.R.	N.R.	2	5
Trevizol et al. (2019)**	1	PPD (pregnancy)	QIDS-SR	10	3	1	1
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.R.	N.R.	N.R.	N.R.
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.R.
Myczkowski (2012)	8 active	PPD (postpartum)	HDRS-17	29.1	18.38	N.R.	N.R.
	6 sham	PPD (postpartum)	HDRS-17	26.7	21.8	N.R.	N.R.
Odgen et al. (1999)	1	PPD (postpartum)	HDRS-17	29	3	1	1
TES-pregnancy							
Palm et al., 2017***	3	PPD (pregnancy)	HDRS-21	24.7	7.0	1	N.R.
Sreeraj et al., 2016***	1	PPD (pregnancy)	HDRS-17	18	6 (at 1-month FU)	1	1
Trevizol et al., 2015*****	1	PPD (pregnancy)	HDRS-17	26	5	1	1
Vigod et al., 2019***	10 active	PPD (pregnancy)	MADRS	23.5	11.8	6	N.I.
	10 sham	PPD (pregnancy)	MADRS	26.8	15.4	2	N.I.
Wilkening et al., 2019****	1	PPD (pregnancy)	HDRS-21	19	11	0	1+
ECT – pregnancy							
Bhatia et al. (1999)	2	PPD (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
Bozkurt et al. (2007)	1	Psychotic depression	HDRS	33	3	1	1
Brown et al. (2003)	1	Psychotic depression	N.R.	N.R.	N.R.	N.R.	N.R.
Ceccaldi et al. (2008)	1	PPD (pregnancy)	HDRS	N.R.	N.R.	N.R.	N.R.
De Asis et al. (2013)	1	PPD (pregnancy)	N.R.	N.R.	N.R.	1	N.R.
DeBattista et al. (2003)	1	PPD (pregnancy)	HDRS	31	7	1	1
Erturk et al. (2020)	1	MD (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
Gahr et al. (2013)	1	PPD (pregnancy)	BDI	56	4	1	1
Gonzales et al. (2014)		PPD with psychotic features (pregnancy) and catatonia	N.R.	N.R.	N.R.	N.R.	N.R.
Kasar et al. (2007)	1	PPD with psychotic features (pregnancy)	HDRS	47	15	1	1
Livingston et al., 1994*	1	Severe PPD (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
Maletzky (2004)	4	PPD (pregnancy)	CGI	N.R.	3.9	N.R.	N.R.
				N.R.	3.2	N.R.	N.R.

(continued on next page)

Table 4 (*continued*)

Study	# participants	Primary Psychiatric Diagnosis	Endpoint	Baseline (mean)	Final (mean)	Remission (# participants)	Response (# participants)
		PPD with psychotic features (pregnancy)					
		PPD (pregnancy)		N.R.	3.5	N.R.	N.R.
		PPD with psychotic features (pregnancy)		N.R.	4.0	N.R.	N.R.
Moreno et al. (1998)	1	Severe PPD with psychotic symptoms (pregnancy)	N.R.	N.R.	N.R.	1	N.R.
Ozgul et al. (2014)	1	PPD (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
Pesiridou et al. (2010)	1	Depressive symptoms during pregnancy	BDI	33	15	0	1
Pinette et al. (2007)	1	PPD (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
Rineh et al. (2020)	1	PPD (pregnancy)	N.R.	N.R.	N.R.	1	N.R.
Salzbrenner et al. (2011)	1	Bipolar depression (pregnancy)	MADRS	32	12	0	1
Sherer (1991)	1	PDD with psychotic features (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
Watanabe et al. (2019)	1	PPD (pregnancy)	HDRS-24	36	26	0	0
Wise et al., 1984	1	Psychotic PPD (pregnancy)	N.R.	N.R.	N.R.	N.R.	N.R.
ECT – postpartum							
Forray & Ostroff (2007)	5	Mood disorder not otherwise specified Postpartum psychosis, bipolar I MDD, psychotic features Bipolar I, mixed episode MDD, psychotic features	N.R.	N.R.	N.R.	Women were treated until remission was achieved	
Gressier et al. (2015)	1	PPD (postpartum)	HDRS-17	32	3	1	1
Kisa et al. (2005)	1	PPD (postpartum)	N.R.	N.R.	N.R.	N.R.	N.R.
Levy et al. (2012)	3	PPD (postpartum)	EPDS	22	2	1	1
			EPDS	21	4	1	1
			N.I.	N.I.	N.I.	N.I.	N.I.
Robinson and Stewart (1986)	1	PPD (postpartum) with psychotic symptoms	N.R.	N.R.	N.R.	N.R.	N.R.
Strain et al. (2012)	1	Postpartum depression with Psychomotor retardation Postpartum psychosis	N.R.	N.R.	N.R.	1	1
Takubo et al. (2019)	1	PPD (postpartum)	HDRS	35	7	1	1

Note. *Applied stimulation during pregnancy and throughout the postpartum period. **Used iTBS; iTBS = intermittent theta burst. ***Used tDCS. tDCS = transcranial direct current stimulation. ****Used tACS. tACS = transcranial alternating current stimulation. *****Used TNS; TNS = trigeminal nerve stimulation. rTMS = repetitive transcranial magnetic stimulation. TES = transcranial electric etimulation. 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. DASS: Depression Anxiety Stress Scales. D = depression. A = Anxiety. TES = tDCS = transcranial Direct Current Stimulation. ECT = electroconvulsive therapy. N.R. = not reported; N.A. = Not applicable. $^{+}$Response at 30% from baseline.

Overall, NIBS are promising for treating PPD, being effective, potentially safe, and benefiting from significant acceptability by women. Particular attention to the specificities of each intervention will be discussed in the following paragraphs.

rTMS seems to be efficacious in PPD both during pregnancy and the postpartum period. Bilateral, left-HF, right-LF and left-LF protocols were so far tested. Studies in the postpartum period followed the principles of rTMS use in MDD, with the left-HF in the DLPFC being the single protocol under study. Overall, a decrease in depressive symptoms occurred between baseline and the end of treatment, except for Gahr et al. (2013) which described a woman who experienced no benefit with rTMS as an add-on treatment to ECT. In pregnancy, left-HF was the most common protocol across reports, followed by right-LF, with both alternatives showing encouraging results. No comparative reports establishing the advantage of one protocol over the other are available. Despite the literature suggesting that the severity of PPD decreases over time, potentially resolving within three to 12 months after delivery (Stein et al., 1991; Torres et al., 2019), PPD frequently becomes chronic (Vliegen et al., 2014), suggesting high heterogeneity among peripartum women.

The most common neonatal event after rTMS was preterm birth, highlighting its potential association with the treatment. Hence, Kim et al. (2018) reports of three preterm births need to be further examined. However, unlike what is reported as potentially associated with exposure in utero to antidepressants and ECT, none of the included rTMS studies described cardiac malformation, persistent pulmonary hypertension, or other in utero complications. The most frequent adverse effect for mothers was a transient benevolent headache when compared to the common antidepressants' side effects such as nausea and diarrhea/loose stool, or the potential cognitive decline in ECT. Together, these data suggest that regarding the risk-benefit ratio, rTMS research is worth pursuing.

Of note, although breastfeeding was not defined as a study outcome, we found that during the postpartum period, most mothers were breastfeeding. As this may be a factor of treatment acceptability in postpartum women, rTMS may resonate with those reluctant to use medication in the perinatal period that seek alternative medication-free treatments (Hamdan and Tamim, 2012; Walton et al., 2014). In fact, rTMS was overall acceptable, with only 8,04% of women discontinuing treatment.

The benefits or drawbacks of rTMS in neurocognitive performance in the peripartum have been barely reported and the limited data available is controversial. The modest evidence for a specific impact of rTMS in cognition in the peripartum period is in line with similar reports for MDD, generally (Martin et al., 2017). Furthermore, considering that brain plasticity in the peripartum interferes with cognitive performance (Bannbers et al., 2013; Glynn, 2010) acting as a confounder, no particular assumption is currently possible.

In sum, the available data suggests caution regarding rTMS as a legitimate option for women diagnosed with PPD, both concerning its

Table 5
Safety of the included studies.

Study	Adverse effects (mothers)	Neonatal safety
	rTMS – pregnancy	
Burton et al., 2014*	N.O.	N.O.
Cohen et al. (2008)	N.R.	N.R.
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.R.	N.R.
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.R.
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.R.
Özten et al., 2013	N.R.	N.O.
Sayar et al. (2014)	Contraction of facial muscles	N.R.
Tan et al., 2008*	N.R.	1 pre-term birth
Tarhan et al. (2012)	N.O.	N.R.
Trevizol et al. (2019) **	N.R.	N.O.
Xiong et al. (2018)	N.R.	N.O.
Zhang et al. (2010)	N.O.	N.O.
Zhang and Hu (2009)	N.R.	N.O.
	rTMS – postpartum	
Brock et al. (2016)	N.O.	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 headache	N.A.
Odgen et al. (1999)	N.R.	N.A.
TES – pregnancy		
Palm et al. (2017)	N.O.	N.R.
Sreeraj et al. (2016)	Transient, mild burning sensations at application site and fleeting experience of phosphenes	N.R.
Trevizol et al. (2015)	N.R.	N.O.
Vigod et al. (2019)	"buzzing" or "tingling" application site	1 pre-term birth
Wilkening et al., 2019*	Mild phosphenes during stimulation	N.R.
ECT-pregnancy		
Bhatia et al. (1999)	Case 1: Uterine contractions Case 2: N.O.	Case 1: Cardiac decelerations Case 2: preterm labor[+]
Bozkurt et al. (2007)	Pelvic pain after the 8th and 9th ECT	Fetal decelerations after 13th and 16th ECT
Brown, 2003	N.R.	N.R.
Ceccaldi et al. (2008)	N.R.	preterm birth
De Asis et al. (2013)	N.R.	Fetal decelerations caused by anesthetic use
DeBattista et al. (2003)	Maternal HR and blood pressure increase	Decelerations during the seizure and immediately post ictally
Erturk et al. (2020)	N.O.	N.O.
Gahr et al. (2013)	N.O.	N.O.
Gonzales et al. (2014)	N.O.	N.O.
Kasar et al. (2007)	N.R.	After 4th ECT session-contractions - preterm labor – cesarean section
Livingston et al., 1994*	blood pressure and pulse rate were slightly higher after ECT than pretreatment	Fetal HR deceleration during third ECT Preterm birth: Twins with congenital malformations – the patient received chemotherapy even during early pregnancy -A: Apgar 6 (1′) and 7 (5′) Twin-B: Apgar 6 (1′) and 8 (5′)
Maletzky (2004)	N.R.	N.R.
Moreno et al. (1998)	Vaginal bleeding after 2nd session. Miscarried post 3rd ECT session	N.O.
Ozgul et al. (2014)	N.R.	N.O.
Pesiridou et al. (2010)	At the 3rd session -disorientation, confusion, short-term memory difficulties, painful contractions	N.O.
Pinette et al. (2007)	labor induction at 36.1 weeks of gestation[+]	APGAR - 1 min - 4, 5 min–7, small left cerebellar, bihemispheric deep white matter and cortical infarcts – upper extremities were tonic with extension posturing – expected long term motor control issues
Rineh (2020)	intermittent contraction	Transient episode of fetal heart rate reduction was observed at the second session
Salzbrenner et al., 2011	cesarean delivery at 38 + 6 because of preeclampsia and breech presentation because of preeclampsia and breech presentation[+]	N.R.
Sherer (1991)	abruptio placentae in association with transient hypertension	Apgar 3 (1′)
Watanabe et al. (2019)	Uterine contractions, retarded oxygenation during the procedure resulting in maternal hypoxia	fetal tachycardia, threatened preterm labor
Wise (1984)	N.O.	N.O.
ECT-postpartum		
Forray & Ostroff (2007)	transient memory loss during the initial ECT treatments	N.A.
Gressier, 2015	N.R.	N.A.
Kisa et al. (2005)	Prolonged seizures due to co-administered medication	N.A.
Levy (2012)	N.O.	N.A.
Robinson and Stewart (1986)	N.R.	N.A.
Strain et al. (2012)	N.R.	N.A.
Takubo et al. (2019)	N.R.	N.R.

Note. *Applied stimulation during pregnancy and throughout the postpartum period. **Used iTBS. iTBS = intermittent theta burst stimulation. ***Used tDCS. tDCS = transcranial direct current stimulation. ****Used tACS. tACS = transcranial alternating current stimulation. *****Used TNS; TNS = trigeminal nerve stimulation. rTMS = repetitive transcranial magnetic stimulation. TES = transcranial electric stimulation. ECT = electroconvulsive therapy. N.R. = Not

reported. N.A. = Not applicable. N.O. = Not observed [+]apparently unrelated to ECT.

efficacy and safety. Although the single RCT conducted during pregnancy showed the highest benefit, further research is needed to explore the possible association between rTMS and premature birth. In future research, this link needs to be addressed in the context of the well-known relationship between prenatal depression and preterm birth (Jarde et al., 2016) and the impact of each variable needs to be disentangled. Complementary vectors of research aimed at fine-tunning treatment parameters are also welcome for head-to-head studies comparing left-HF and right-LF montages, as the latter is experienced with much less discomfort by mothers. Despite some resistance about the use of rTMS in pregnancy, its use in the postpartum period seems to be particularly beneficial with no adverse effects to the newborn expected through breastfeeding and only minor and transient side effects to mothers. Additionally, because studies observing the antidepressant effect of rTMS in the peripartum used concomitant medication, future research must control for this confounder. Lastly, to ascertain rTMS position in the pathway of perinatal mental health care, large sample controlled clinical trials should be prioritized.

All TES reports included were conducted in pregnancy and showed clinical benefits across techniques. Despite the limited evidence about its antidepressant efficacy, TES is certainly a field worth pursuing. In particular, the F3–F4 tDCS montage within a protocol of 15 daily sessions, as defined by Vigod's RCT (2019), seems to be the best research approach, the safest clinical option available benefiting of good acceptability. Also, the potential association between TES and preterm birth (Vigod et al., 2019) highlights the need for more investigation. The impact of TES in neurocognitive measures in the peripartum is still barely explored but so far showed to be beneficial. Because the available TES studies were conducted during pregnancy, information regarding the willingness to maintain breastfeeding while in treatment is not available. The use of concomitant medication was not allowed in TES studies, clearing medication as a potential confounder of its efficacy. However, despite its promising features, the limited number of studies, the small sample sizes, and the high risk of bias compromise strong positioning regarding TES and future controlled studies with larger samples are needed.

Although the present study showed good rates of acceptability both for rTMS and TES, more can be done regarding acceptability. In fact, the peripartum period is very challenging, highlighting the need to have alternatives that are not only effective but also that overcome demanding clinic-based NIBS treatments. Home-based versions of NIBS treatments are very attractive as they optimize individual resources while enabling patients to actively contribute to managing their mental health. In particular, home-based tDCS has been tested successfully in several neuropsychiatric disorders including depression (e.g. Alonzo et al., 2019) and may well be the next step in PPD, freeing patients from the clinic-setting. However, to guarantee tDCS safe and effective application, three conditions must be satisfied: 1) The tDCS device has to include electronic remote supervision (such as single session code-locks and other dose control mechanisms) and has to collect post-stimulation information to assess compliance and quality of stimulation (e.g. time of start and completion, interruption and restart of the session), sending alert signals to health care professionals; 2) the tDCS treatment should be accompanied by the appropriate assessment and training provided to patients regarding the minimum skills required to comply with the treatment; 3) tDCS should be complemented by eHealth solutions, for supervision and collection of real-time data to improve adherence and inform clinical decision.

Although our review is suggestive of the clinical benefits of ECT in severely depressed women, currently available data is restricted to case studies and case-series with high RoB. When balancing the risk-benefits ratio of ECT in PPD, safety issues must be carefully weighted particularly for pregnant women and for the fetus. Seizures and the impact of

Table 6
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 et al., 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
Trevizol et al. (2015)	1	1
Vigod et al. (2019)	10 active	8 active
	10 sham	8 sham
Wilkening et al., 2019*	1	1
ECT-pregnancy		
Bhatia et al. (1999)	2	2
Bozkurt et al. (2007)	1	1
Brown et al. (2003)	1	1
Ceccaldi (2008)	1	1
De Asis et al. (2013)	1	1
DeBattista (2003)	1	1
Erturk et al. (2020)	1	1
Gahr et al. (2013)	1	1
Gonzales 2014	1	1
Kasar et al. (2007)	1	1
Livingston et al. (1994)	1	1
Maletzky (2004)	4	4
Moreno et al. (1998)	1	1
Ozgul et al. (2014)	1	1
Pesiridou et al. (2010)	1	1
Pinette et al. (2007)	1	1
Rineh (2020)	1	1
Salzbrenner et al. (2011)	1	1
Sherer et al. (1991)	1	1
Watanabe et al. (2019)	1	1
Wise (1984)	1	1
ECT-postpartum		
Forray & Ostroff (2007)	5	5
Gressier et al. (2015)	1	1
Kisa et al. (2005)	1	1
Levy et al. (2012)	1	1
Robinson and Stewart, 1986	1	1
Strain et al. (2012)	1	1
Takubo et al. (2019)	1	1

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

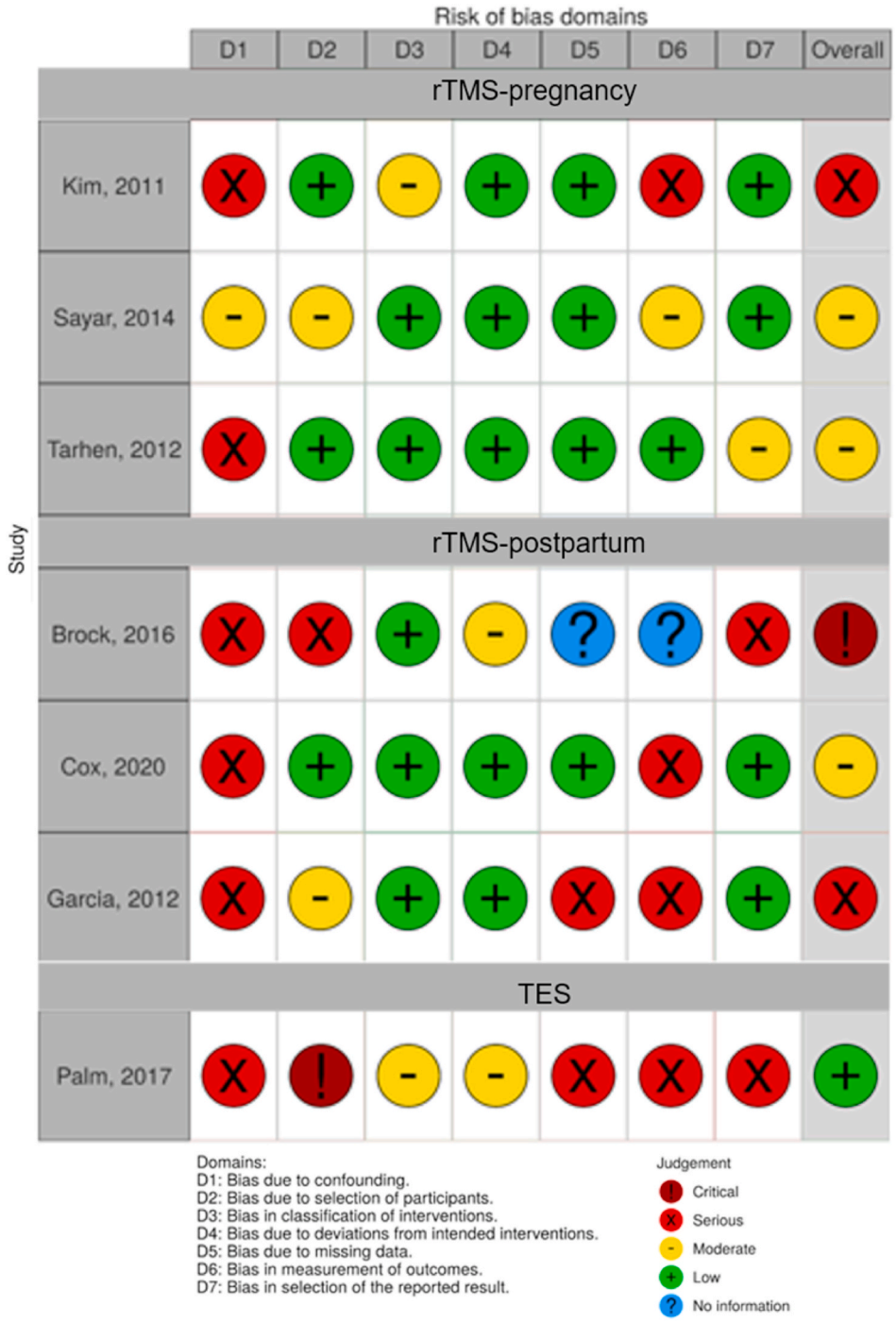

Fig. 2. Traffic light plot for Risk of Bias of individual studies.

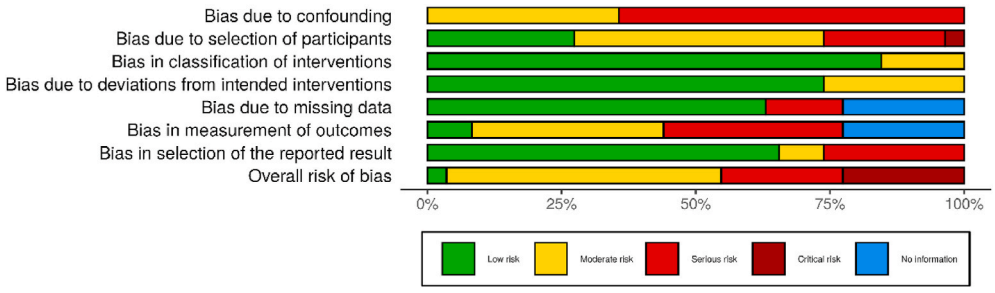

Fig. 3. Weighted summary plot for Risk of Bias of individual studies.

concurrent medication and anesthesia seem to be associated to pregnancy and/or delivery complications and to severe in utero complications. Whilst only anecdotal evidence is available on the impact of ECT in neurocognitive performance of peripartum women, the information available suggests a potential cognitive decline associated with ECT, leading to similar concerns as those described in the literature for MDD. Breastfeeding is frequently compromised in ECT, as acute treatments are completed during in-patient regimen where infants are not allowed to stay, and mother-infants units are still an infrequent reality. However, despite the decisional conflict concerning the compatibility of the anesthetic drugs used during ECT with breastfeeding, there is some evidence showing no adverse effects of these drugs to breastfed infants (Babu et al., 2013). Our review observed this practice with most studies reporting that patients were not breastfeeding during treatment and only one reporting that the patient did not stop breastfeeding. Of note, the available data in ECT is limited to the course of the acute treatment, with only scarce information about treatment maintenance and follow-up.

5. Conclusions

Although our review advances the field by exploring the efficacy of NIBS in reducing PPD, it has also some limitations. Firstly, the available reports regard studies with small sample sizes, mainly single-arm or case report studies, with moderate to high/critical RoB. To better understand the current situation, we did not exclude low-quality reports, but this warrants cautious conclusions. The quality of the data extracted from ECT reports is fragile as it fully relies on case reports. Further, the design of the studies hampers conclusions regarding comparative treatments (e.g., treatment vs active comparators or placebo). Thus, any analysis aiming at understanding the impact of NIBS in PPD is currently limited to the comparison between baseline and the end of treatment. Also, issues of clinical significance can be raised as we estimated differences between baseline and end of treatment scores that are expected to spontaneously decrease along the course of the disease. Although we aimed for meta-analyses, these limitations would raise issues on its robustness.

In the field of NIBS, rTMS is the technique that benefits from the most robust research, with promising results regarding efficacy but some pending questions when it comes to safety during pregnancy. In the postpartum period, the positive perspective towards NIBS efficacy suggests that whenever available, women diagnosed with mild to moderate PPD, and particularly those who do not wish to start medication, should be offered rTMS/TES as an alternative treatment. However, in pregnancy caution is needed until new findings allow for the clarification about the contribution of these treatments to preterm birth. Although the overall efficacy and safety profile of TES was found to be good across reports, only anecdotal RCTs and single-arm studies were available, limiting this treatment as a current clinical option. As for ECT, until further investigation, the nature and low quality of the available data suggest it should be considered only for severe cases and when no other alternative is available. Furthermore, in every clinical situation for which ECT is suggested, the risk-benefit balance must be assessed, and the patient and the fetus need to be closely monitored for the impact of the seizures and the anesthesia (with particular attention to fetal heart rate variability during the first trimester, and to obstetric complications).

Of interest, although NIBS seems to be acceptable to women, no data is available regarding its acceptability by health practitioners, who have a core role in the process of referring and implementing novel health interventions. This vector of research should be explored aiming for the uptake of safe and efficacious treatments by the perinatal mental health systems. Hence, NIBS seems to constitute an alternative to medication and psychotherapy and can be added into combined treatments as well. Larger RCTs are needed for comparative studies strengthening the field and clarifying the position of each technique within the algorithms of perinatal mental health care.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.06.005.

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