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Review article

Efficacy of rTMS in decreasing postnatal depression symptoms: A systematic review

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A B S T R A C T

Background: Repetitive Transcranial Magnetic Stimulation (rTMS) has been suggested as an alternative treatment to postnatal depression (PPD).
Objectives: This systematic review aims to examine and summarise evidence on rTMS efficacy in treating depression during the postnatal period.
Methods: We included randomized and non-randomized, single arm, and case report studies, with active rTMS and theta-burst stimulation, sham rTMS, pharmacotherapy or no treatment as comparators. Participants included women with PPD, who were administered rTMS after delivery and up to 12 months postpartum. The observed outcomes were response rate and acceptability.
Results: rTMS shows promising results, with clinically significant decreases in Edinburgh Postnatal Depression Scale (EPDS) scores at week 4 and an overall low risk of dropout.
Limitations: The reduced number of reports, the lack of complete datasets and the serious/high risk of bias of the studies warrant cautious interpretations.
Conclusions and implications: Despite the promising results, existing evidence on rTMS efficacy is limited, and questions remain on what the most beneficial stimulation parameters should be. Future multicentre randomized clinical trials are needed to better ascertain the clinical efficacy of rTMS in the treatment of depression in the postpartum period.

1. Introduction

Postnatal depression disorder (PPD) is one of the most prevalent mental health problems occurring during the childbearing years, with a negative impact on maternal and infant health and well-being. Currently, non-pharmacological and non-invasive brain stimulation techniques such as repetitive Transcranial Magnetic Stimulation (rTMS) have been presented as an option to manage PPD as it can address certain disadvantages seen in more traditional treatments. Here we aim to update previous qualitative reviews (Kim et al., 2015) and to suggest directions for future studies.

The Diagnostic and Statistical Manual of Mental Disorders-5 (5th ed.; DSM-5, American Psychiatric Association, 2013) defines PPD as a Major Depressive Disorder (MDD) with the onset of its most recent episode occurring during pregnancy (prenatal) or within the four weeks following delivery (postnatal). However, existing research, clinical practice, and epidemiological studies recommend the extension of the postpartum period to 12 months after delivery (Wisner et al., 2013; Woody et al., 2017).

Postpartum depression has a period prevalence of 21.9% (Wisner et al., 2013), manifesting a negative impact on women's physical and mental health (e.g. Pereira et al., 2014), maternal caregiving abilities (e.g. Easterbrooks et al., 2013), the quality of mother-infant interaction (Tsivos et al., 2015), a new-born's cognitive and emotional neurodevelopment (Kingston et al., 2012; Stein et al., 2014), and couple/family functioning (Malus et al., 2016), factors which lead to a heavy social burden (Bauer et al., 2014).

Evidence-based treatments for moderate to severe postnatal PPD are electroconvulsive therapy (ECT), psychotherapy, pharmacotherapy, or a combination of these. Whereas ECT is established as an effective treatment (Greenberg and Kellner, 2005), it requires anaesthesia and causes muscle pain, transient disorientation and temporary memory impairment (Semkovska and McLoughlin, 2010; Semkovska et al., 2012). Psychotherapeutic approaches are broadly accepted and show

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relative efficacy (Guille et al., 2013; Parsons et al., 2012) with medium to large effect sizes (Sockol et al., 2011). However, psychotherapy is not always available, neither is it effective for all individuals, and some reluctance exists due to stigma (Guille et al., 2013).

Although meta-analyses on the use of pharmacotherapy in PPD are inconclusive (e.g. De Crescenzo et al., 2014; Sharma et al., 2013), the clinical consensus points to Selective Serotonin Reuptake Inhibitors (SSRIs) as the first line of treatment. Some studies suggest that SSRIs show satisfactory efficacy rates (50% - 67%) and response to treatment between the 6th and the 8th week (Kim et al., 2014). Additionally, the two latest expert opinions suggest the relative low risk of using Sertraline during breastfeeding (Thomson and Sharma, 2017). Notwithstanding SSRIs' apparent efficacy, acceptability studies indicate that physicians resist prescribing them when women are breastfeeding, or if they do, they prescribe at doses below effective levels (Kim et al., 2014). Likewise, breastfeeding women suffering from depression are less likely to take medication (Munk-Olsen et al., 2012; Pearlstein et al., 2006).

Alternatively, rTMS is an evidence-based, non-invasive and non-pharmacological treatment for MDD, with a very good safety profile (Lefaucheur et al., 2014). Its principal mechanism of action is consistent with Faraday's law establishing that a time-varying current creates a magnetic field and hence a secondary perpendicular current within a nearby conducting medium. TMS devices store electrical charge in capacitors and their periodic discharge (through a conducting coil) produces a time-varying electrical field. Then a magnetic field is produced which leads current to flow in secondary conducting material, such as neurons. In rTMS repeated trains of magnetic pulses are applied to the cerebral cortex. By convention, stimulation at frequencies greater than 1 Hz is referred to as high-frequency rTMS (HF), whereas stimulation at 1 Hz or lower is referred to as low-frequency rTMS (LF). Following studies on motor cortex excitability in healthy subjects, HF-rTMS is generally considered "excitatory" and LF-rTMS "inhibitory" (Siebner and Rothwell, 2003). Although this approach demands caution with respect to non-motor cortical regions, especially under pathological conditions, it has become the main principle of rTMS application in depression.

Depression is the most studied condition for the therapeutic application of rTMS (Lefaucheur et al., 2014). The use of rTMS is aimed to modulate disturbed structural and functional connectivity both within and between large scale fronto-limbic networks. Additionally, rTMS is thought to result in readjustment of several neurobiological processes associated with depressive symptoms (e.g. dysfunctional neurotransmission, disturbed hypothalamic-pituitary-adrenal axis [HPA], and altered neurotrophic factors concentrations; Anderson et al., 2016).

Functionally, a particular fronto-limbic network is targeted by rTMS protocols in depression – the default mode network (DMN) that includes the medial and ventral prefrontal cortices (mPFC and vPFC, respectively), the posterior cingulate cortex (PCC), the inferior parietal lobe (IPL) and the hippocampus. An increased activity of the DMN characterizes depressive patients and is associated with the dysfunction of several emotion regulation mechanisms. For example, DMN hyperactivation in depressed patients is strongly related with hypoactivation of the fronto-parietal network (FPN) that encompasses the central executive network (CEN) and the salience network (SN). The hypoactivation of the CEN structures (the DLPFC and the lateral posterior parietal cortex) has been linked to rumination, inattention and impaired working memory (Philip et al., 2018b). The hypoactivation of the SN structures (the dorso-anterior cingulate cortex, the fronto-insular cortex, the amygdala and the ventral tegmental area) has been linked to preoccupation and negative bias (Hamilton et al., 2011).

Structurally, evidence shows that reduced integrity of the white matter tracts connecting the FPN with the limbic system structures is involved in the aetiology of depression (for studies on diffusion tensor imaging see Zhu et al., 2011; Diego-Adeliño et al., 2014; for studies in post-mortem evidence see Regenold et al., 2007).

Moreover, studies show a significant reversibility of local and network functional and structural abnormalities leading to persistent clinical changes after repeated rTMS sessions, supporting the therapeutic effect of rTMS (e.g. Ridding and Rothwell, 2007; Liston et al., 2014; Salomons et al., 2014).

Lastly, rTMS has been associated to mechanisms involved in cellular level synaptic plasticity processes, such as increased brain-derived neurotrophic factor (BDNF) and glutamatergic transmission, leading to synaptic strength, axons and dendrites growth and consequent post-treatment improvement of depressive symptoms (Gresner et al., 2011; Peng et al., 2018).

In depressed patients, the functional asymmetry of the frontal brain regions, namely the hypometabolic state in the left hemisphere with concomitant hypermetabolic state in the right, was shown in early functional neuroimaging studies (Kennedy et al., 1997; Bench et al., 1995). Consequently, two main rTMS protocols have been suggested to manage depressive symptoms: i) HF-rTMS delivered to the left anterior cortex (hypoactive) and ii) LF-rTMS delivered to the right anterior cortex (hyperactive). The stimulation is typically applied to the DLPFC (a main structure of the CEN network) due to its accessibility and connection to the limbic system involved in mood regulation (Petrides and Pandaya, 1999; Philip et al., 2018a).

Overall, the use of rTMS in MDD shows moderate effect sizes and the protocol that benefits from the larger number of studies, showing the strongest evidence of efficacy as a stand-alone or augmentative therapy is HF-rTMS to the lDLPFC, followed by LF-rTMS to the rDLPFC and bilateral rTMS (Mutz et al., 2018). Moreover, rTMS has been posited as an add-on or augmentation strategy to antidepressants (Tendler et al., 2018) but still little is known about the interactions between both therapeutic approaches.

The negative impact of postnatal PPD, the need for non-pharmacological alternatives and the seemingly promising results of rTMS in alleviating depression led to the present systematic review. We aim to assess the effect of rTMS in PPD, from delivery and up to the 12th month, as observed in randomized and non-randomized studies and case reports.

2. Methods

This systematic review complies with the PRISMA statement (Moher et al., 2009) for reporting standards, and its protocol was registered in PROSPERO (CRD42018105435).

2.1. Literature review and search methods

Two researchers (AGA and AP) conducted the data search independently, from inception to July 2018, for available publications and reports in the following languages: English, French, Spanish, Polish or Portuguese. For published peer-reviewed studies we used PubMed/MEDLINE, PSycINFO and LILACS. For unpublished reports, we used the Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, OpenAIRE and RCCAP. For other unpublished datasets, we searched the platforbib13ms accepted by the ICMJE (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/). The complete search strategy can be consulted in Appendix 1. Eligibility was assessed by examining title and abstract. Furthermore, we performed a manual verification of the reference lists from eligible studies, in search of potential new additions.

2.2. Eligibility criteria

We included randomized clinical trials (RCTs), and non-randomized studies (NRSIs) which enrolled women diagnosed with PPD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, DSM-IV-TR, DSM-5; American Psychiatric Association, 1994, 2000, 2013) or the International Statistical Classification of Diseases and

Related Health Problems (ICD-10; World Health Organization, 1990), aged 18 or older, and for whom intervention was delivered postpartum. We selected studies describing active rTMS, delivered as a stand-alone, an add-on or as an augmentation strategy. Eligible comparators were theta-burst stimulation (TBS), sham rTMS, SSRIs or no treatment.

2.3. Data extraction and outcome measures

AGA and AP independently completed data search and extraction for the full-text reports. Discrepancies were fully discussed and if no agreement was reached a third author would intervene to decide. Study evidence was extracted for: study population, demographic and baseline characteristics, type of intervention and type of comparator, study design, primary and secondary outcomes. We defined the response rate and the time to response as primary outcomes, as assessed by 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; Triverdi et al., 2004) and the Clinical Global Impression (CGI; Rush et al., 1986; Triverdi et al., 2004). We defined the remission status, acceptability, and the neurocognitive assessment measures as secondary outcomes. We contacted all authors to access the full data sets or for further clarification on unclear information in the available reports. In the absence of a reply, data extraction was collected by study, based on the assessment scores and individual studies' definition.

2.4. Risk of bias assessment

The two raters independently extracted information for assessing the quality of the data and the risk of bias. For the RCT studies, we used *The Cochrane Collaboration's tool for assessing risk of bias for RCTs* six domains (Higgins et al., 2011). For the NRSIs we used *Risk of Bias in Non-Randomised Studies of Interventions – ROBINS-I* seven domains (Sterne et al., 2016). For case reports we adapted the 20-criterion quality appraisal checklist and used 12 of the available criteria (Guo et al., 2016). Discrepancies on ratings were fully discussed with no need for intervention from a third researcher. A final judgement of overall risk of bias was agreed between raters (Table S3, Appendix 2).

2.5. Data synthesis

We completed a qualitative analysis on the primary and secondary outcomes for all available reports. The lack of access to complete data sets limited us to two outcomes: the response change, using the EPDS scores between the baseline and week four of treatment (the common tool and assessment moment across studies), and the acceptability rate according to the dropout rates.

3. Results

After we applied the aforementioned search procedure, a total of 64 entries were found, 60 of which were excluded, with four included in the qualitative synthesis: one RCT (Myczkowski et al., 2012), two open label studies (Brock et al., 2016; Garcia et al., 2010), and one case report (Ogden et al., 1999; Fig. 1). In Table 1, we present the characteristics of the selected studies.

3.1. Qualitative synthesis

The first report on the use of rTMS to treat PPD was a case study published by Ogden et al. (1999) on a 40-year-old woman diagnosed with MDD with Psychotic Features with Postpartum Onset. Following a previous episode, the patient remained moderately depressed for two years, after which time symptoms spontaneously remitted. Following the birth of her second child, and upon the reappearance of depressive symptoms, this woman was included in an in-patient rTMS trial protocol. rTMS was applied to the lPFC with 20 Hz and at 100% motor threshold (MT), in trains of 2 s, inter-train-intervals (ITI) of 28 s, 30 trains per session, 1200 pulses per day. The patient completed 13 daily rTMS sessions, 5 days/week. Simultaneously, she received a daily dose of 0.5 mg antipsychotic (Resperidone) for the first six days and a daily dose of 20 mg antidepressant (Citalopram) for the last four days (maintenance treatment). A blind assessment found significant improvement from baseline to the end of treatment (3 weeks) using the HDRS-17 (29 and 3, respectively), the Beck Depression Inventory (BDI; 48 and 13, respectively), and a visual analogue scale (VAS; 8.2 and 3.4, respectively), with no side effects. The authors then concluded that rTMS led to rapid clinical improvement, with remission observed within 2 weeks.

Later, Garcia et al. (2010) published the first open-label single arm study observing the effect of rTMS in nine antidepressant-free women (mean age = 34.11 [± 6.05]) diagnosed with PPD in an outpatient regimen. Inclusion criteria were diagnosis of MDD according to DSM-IV (4th ed., American Psychiatric Association, 1994) and an EPDS score above 9. The exclusion criteria were previous history of psychosis or bipolar disorder. Participants were enrolled between month one to 12 post-delivery, and half were breastfeeding during the trial. One participant was taking a daily dose of 2 mg Diazepam to control for Meniere-related vertigo. The trial followed a 4-week treatment protocol, with a total of 20 rTMS sessions (once daily). rTMS was applied to the lDLPFC, with a frequency of 10 Hz and an intensity of 120% MT, in 75 trains of 4 s, with 26 s ITI, for a total of 3000 pulses per session. Unblinded assessments occurred weekly and at follow-up (1, 3- and 6-months post-treatment). Symptom improvement was achieved at week 2, for EPDS (18-9), HDRS-24 (23-9), IDS-SR (42-21), and CGI-S (4-2.57). Response to treatment was defined as at least 50% reduction in HDRS-24 scores from baseline. The Postpartum Bonding Questionnaire (PBQ; Brockington et al., 2006) was used to assess mother-infant bonding at baseline and at the end of treatment with significant improvement (20-7). Self-reported questionnaires showed reasonable acceptability despite minor side effects (e.g., easily resolved headache, site pain and facial stimulation). Eight out of nine patients remitted (<10 in HDRS-24; CGI-S = 1) by the end of the treatment phase, of which six persisted in remission at 6 months (one patient was lost at follow-up). Response rate was not reported. Depressive symptoms and bonding improved significantly by the end of week 2. All nine participants complied with the protocol (100% acceptability). The authors suggest rTMS as a potential "treatment bridge" to avoid medication during the breastfeeding period.

Myczkowski et al. (2012), published the first randomized sham-controlled trial comparing the effect of active 5 Hz rTMS with sham stimulation in PPD clinical, cognitive and social measures. This study enrolled 14 women with PPD between the 1st and 6th month post-delivery who were attending an outpatient clinic (mean age = 28.15 [± 6.05]). Inclusion criteria were MDD diagnosis according to DSM-IV-TR (4th ed. rev; American Psychiatric Association, 2000). Simultaneous controlled pharmacological treatment for insomnia or physical symptoms was acceptable (three patients were using a maximum daily dose of 1 mg Clonazepam). Exclusion criteria included previous psychiatric disorder, apart from anxiety or depression. The trial followed a 4-week treatment protocol, with five daily rTMS sessions (total of 20 sessions). rTMS was applied in the lDLPFC, at 5 Hz and 120% MT intensity, in 25 trains, lasting 10 s, with 20 s ITI, leading to 1250 pulses per session. For the sham stimulation, the same protocol was used with a placebo coil. Patients and raters were blind to treatment and assessments, respectively, but no mention was made of the blinding of intervention delivery staff. Participants were assessed at baseline, end of treatment, and follow-up (week 6). The authors found promising results for the clinical measures, with statistically significant differences between the active rTMS group and the sham group, when comparing baseline and week 6 scores for the HDRS-17 (p = .001) and EPDS (p = .007). The authors defined response to treatment as 30% reduction in HDRS-17

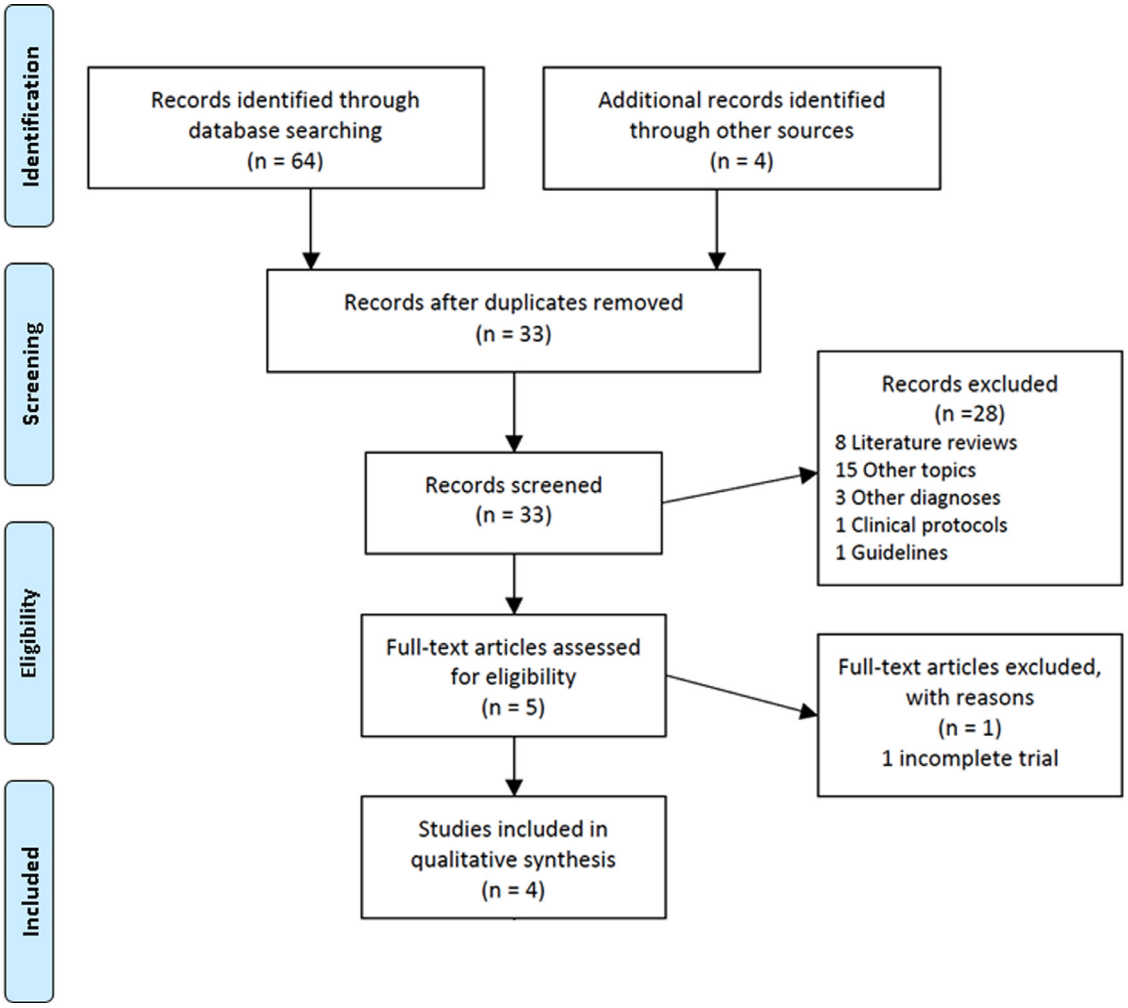

Fig. 1. Flow diagram of the study selection procedure according to PRISMA 2009.

and EPDS scores from baseline; however, they did not present the response rate. Similarly, the authors did not define remission or present the remission rates. All participants completed the study (acceptability rate of 100%) and two patients reported minor to mild adverse effects (scalp discomfort and headache). The authors suggest the future use of rTMS in PPD, as it overcomes potential risks associated with infant exposure to antidepressants during breastfeeding, showing clinical benefits equivalent to those found for pharmacotherapy.

The most recent study on the impact of rTMS in PPD was an open label, single arm trial conducted in an outpatient setting by Brock et al. (2016). This study enrolled 25 medication-free women (mean age = 29.9; SD = unknown) within the first 9 months postpartum and no history of psychiatric disorders, as diagnosed according to the DSM-IV-TR (4th ed. rev; American Psychiatric Association, 2000). The trial used 5 daily rTMS sessions at 10 Hz and intensity of 120% MT [4-second trains, 26 s ITI, 75 trains, 3000 pulses/session], delivered to the lPFC. The treatment was administered five times a week, for up to eight weeks during the acute phase, and included a three-week taper phase (week 1 with three rTMS sessions, week 2 with two rTMS sessions, and week 3 with one rTMS session). During the taper phase patients could potentially be under some type of medication, if this was the physicians' instruction. The available data was extracted from a conference presentation record and concerns the results of 19 patients for the acute phase (no data was available for the taper phase). There was a significant reduction of EPDS scores from baseline (20.6 - 8.2; response to treatment was not defined), with 14 participants achieving remission (EPDS < 10; 73.7%). Despite the promising results suggesting rTMS as an effective alternative to antidepressants, six patients discontinued treatment due to its demanding schedule, leading to an acceptability rate of 76%. There were no significant adverse effects reported.

The overall risk of bias of the included studies was assessed as serious (for the two open labels studies) and high (for the single RCT). The main factors contributing to the serious/high risk of bias were the blinding strategies, the selection of data reported, and the incomplete information. The detailed rationale for the overall risk of bias assessment is presented in Appendix 2.

4. Discussion

In this review, we gathered information on the efficacy of rTMS in treating postnatal PPD. We qualitatively discussed the findings of four reports for a total sample of 43 women.

The analysis suggests promising effects of rTMS treatment protocols ranging from 13 to 20 sessions (once daily), using stimulation frequencies between 5 and 20 Hz, intensities between 100 and 120% of the MT, and 1200 and 3000 pulses per session to the left anterior prefrontal region of the brain (potentially the DLPFC although two reports were imprecise concerning stimulation site). The reported side effects were transient and non-significant, confirming a profile for rTMS as a well-tolerated and safe treatment.

Notwithstanding the low degree of statistical heterogeneity between studies at baseline, there were clear differences that need to be addressed. Mirroring what happens in clinical practice, the clinical

Table 1
Characteristics of the included studies.

Author	Study Design	Random.	Participants N	Age [mean and SD or ranges]	Intervention # weeks/sessions	Tx.	Com.	Stim site	Hz	MT%	# Pulses # Trains ITI	Outcomes Prim. outcomes	Time-points	Secon. outcomes	Time-points
Ogden et al. (1999)	Case report	n.a	1	40	2 weeks/13 sessions (rTMS is to be continued until remission or change of treatment)	rTMS	n.a.	lPFC	20 Hz	100	1200	HDRS 17	baseline, 3 weeks	Adverse effects	presumably from the first session
						Risperidon 0.5 mg/day up to day 7					30	&			
						Citalopram 20 mg/day from day 7 to day 11					28s	BDI & VAS			
Garcia et al. (2010)	Open label	n.a	9	34.11 ± 6.05	4 weeks/20 sessions	rTMS	n.a.	lDLPFC	10 Hz	120	3000 75	HDRS 24 &	baseline, weekly during treatment	IDS-SR CGI-1	baseline, weekly during treatment; FU - 1-, 3-, 6- months
											26s	EPDS	FU: 1-,3-,6-months	PBQ	baseline, 4 weeks of treatment
														Adverse effects	presumably from the first session
	Study		Participants		Intervention							Outcomes			
Myczkowski et al., 2012	RCT	computerized random-number generator	14	28.5 (range 18–36)	4 weeks/20 sessions	rTMS and Clonazepam 1 mg/day	sham	lDLPFC	5Hz	120	1250 25	HDRS 17 &	baseline, 4 weeks, 6 weeks (2 weeks follow-up)	HARS 14 CGI-1, −2, −3 GA	baseline, 4 weeks of treatment
											20s	EPDS		SF-36 SAS NAB	& FU: week 6
														Adverse effects	presumably from the first session
Brock et al. (2016)	Open label	n.a	19 (medication free during acute phase)	unavailable	4–8 weeks Acute phase: 20–40 sessions	rTMS	n.a.	lPFC	10 Hz	120	3000	EPDS	baseline and end of acute phase (between 4 and 8 weeks)	Adverse effects	from the first session to the end of Taper Phase
					3 weeks Taper phase: 6 sessions	In taper phase patients could be medicated					75 26s				

Abbreviations: Random, randomization procedure; Tx, Treatment; Com = Comparator; n.*a* , not applicable; lPFC , left Prefrontal cortex; lDLPFC = left dorsolateral prefrontal cortex; HDRS-D 17 , 17 item Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; VAS , Visual Analog Scale; HDRS-D 24, 24 item Hamilton Rating Scale for Depression; EPDS , Edimburg Postnatal Depression Scale; IDS-SR , Inventory of Depressive Scale; HARS 14, 14 item Hamilton Anxiety Scale; CGI-1 , Clinical Global Impression of Severity; CGI-2, Clinical Global Impression of Change; CGI-3, Quality of Life; SF-36, 36-item Short-Form Health Survey; SAS, Social Adjustment Scale-Self Report; NAB , Neurocognitive Assessment Battery comprised by the Trail Making Test (A&B)Wisconsin Card Sorting Test, Controller Oral Word Association Test, Victoria Stroop Test, Rey Auditory Verbal Learning Test, WAIS-III subtests (similarities, picture completion, digit span forward, backward, total and coding).

conditions of the recruited patients were heterogeneous. Of the 35 women submitted to active rTMS stimulation, 19 were unipolar non-psychotic depressive patients with postpartum onset (54%) and one patient was diagnosed with recurrent MDD with postnatal psychotic features (2.86%) which is suggestive of bipolarity (Chaudron and Pies, 2003; Di Florio et al., 2014; Nager et al., 2013). Ten patients were diagnosed with recurrent MDD with no psychotic features (28.57%); two were first bipolar depressive (5.71%); and only four were first episode MDD patients (11.43%). In fact, postpartum depression disorder frequently refers to both unipolar (70%) and bipolar depression (30%) as those diagnoses present similar clinical symptoms within the first episode (Munk-Olsen et al., 2012; Wisner et al., 2013). Nonetheless, to define the proper treatment, a clear distinction between uni and bipolar PPD should be established early on. This distinction is important as antidepressants (and eventually rTMS) may lead to undesirable treatment effects in bipolar depression (e.g., enhanced hypomanic symptoms and increased suicidal risk; Thomson and Sharma, 2017).

Also, the selected studies presented different criteria with respect to medication. Whereas participants in Brock et al. (2016) and Garcia et al. (2010) were medication free, those in Myczkowski et al., 2012 could be taking 1 mg Clonazepam. Similarly, the patient reported by Ogden et al. (1999) was taking antipsychotics during the first six days of the trial and an antidepressant in the last four. Because the management of a severe depressive episode with psychotic features is different from moderate to severe PPD (Bergink et al., 2016) caution should be exercised when considering this case report.

The instruments and cut-off scores used to establish the diagnosis were clinically equivalent across studies. However, participants were enrolled between the 1st and the 12th month after delivery, which may include different PPD profiles (early and late) with distinct response phenotypes (Putnam et al., 2017). The distinction between treatment responsive phenotypes has been previously suggested in the literature, where women with earlier PPD onset symptoms associated with the rapid decreasing levels of neurosteroids showed a distinctive response to medication treatment (Kim et al., 2014). Despite the equivalent length of treatment observed across studies (4 weeks), some MDD patients may need longer treatments to achieve clinical response or longer follow-ups to confirm response (George and Post, 2011). As such, in the future, the time for data collection must be consistent to understand patients' profiles and the improvement rates of early and late responders.

Finally, only one trial offered information about breastfeeding status of participants (Garcia et al., 2010) and this is an aspect to be addressed, as it may contribute to the relief of PPD symptoms in the first 3 months postpartum (Figueiredo et al., 2014).

Despite qualitative variability between studies, this systematic review confirmed the therapeutic potential of rTMS for PPD, with the open label studies showing the expected larger effect sizes than the RCT. However, the stimulation parameters should also be accounted for in this difference because the open label studies followed a more intensive protocol than the RCT (10 Hz vs 5 Hz, at 120% MT, with 3000 pulses for 75 trains, 26 s ITI). The use of lower intensity is argued to reduce patients' discomfort, but it may also have led to less pronounced results in the RCT.

Importantly, every study employed stimulation to the left hemisphere, previously established as the most promising site for MDD (Brunoni et al., 2017), addressing the assumption of an inter-hemispheric imbalance in depressive patients, with a hypo-activation to the left and a hyper-activation to the right (Lefaucheur et al., 2014; Perera et al., 2016). Recently, the Brunoni et al. (2017) meta-analysis even suggested bilateral stimulation (right LF and left HF) to be the most beneficial protocol in MDD, which may be also true for postnatal PPD.

The data extracted concerning the treatment response was collected by study, with definitions taken from individual studies. Whereas in Brock et al. (2016) the treatment response definition was unclear, Garcia et al. (2010) defined remission as a 50% reduction from baseline in HRSD-24, and Myczkowski et al., 2012 as a 30% reduction from baseline in HRSD-17. However, a 30% reduction from baseline in HRSD-17 is usually assumed to be a partial response to treatment and not an effective remission, leading to inflated perception.

Unexpectedly, acceptability (dropout rate) was found to be encouraging, despite the time-consuming protocols that rTMS entails. This finding suggests that patients' acceptability should not be an obstacle to the future uptake of rTMS to health-care practice.

Studies in PPD follow the rationale for the use of rTMS in MDD with respect to stimulation parameters, with a broad use of HF-rTMS to the left DPLPF. Importantly, every study in our review employed HF-rTMS to the left hemisphere, putatively to address the inter-hemispheric imbalance in depression (Lefaucheur et al., 2014; Perera et al., 2016). Despite the meta-analysis by Mutz et al., 2018 on MDD patients showing superior clinical efficacy when using left-HF rTMS, there is still a reduced number of studies on either LF-rTMS or bilateral stimulation, precluding a definite consensus on the best parameter option.

Few studies in depression during pregnancy have tested the clinical efficacy of LF-rTMS (Kim et al., 2011, 2019), and concluded LF-rTMS to reduce depressive symptoms in this subpopulation. Hence, the meta-analysis by Brunoni et al. (2017) suggests bilateral stimulation to be the most beneficial protocol in MDD, which may be also true for postnatal PPD. Importantly, studies in MDD have noted that HF- and LF-rTMS do not seem to have opposing effects in distal network connectivity, converging to similar clinical improvement (Philip et al., 2018a). Furthermore, LF-rTMS is better tolerated than HF-rTMS, producing fewer side effects (e.g., headaches) and being less likely to induce seizures (Shutter, 2010). Hence, the latest reviews on rTMS efficacy show that higher stimulation intensities (MT > 100%) and increased number of sessions (>20) produce more robust clinical improvement (Philip et al., 2018a). Accordingly, LF-rTMS protocols delivered to the right DLPFC, at >100% MT and for more than 20 daily sessions, are of increased interest in MDD and PPD in particular, claiming for future RCT studies.

Recently, alternative and faster stimulation strategies have been tested in MDD. In particular, a case study describing the use of iTBS (intermittent theta burst stimulation; Trevizol et al., 2019) in a depressed pregnant woman reports full remission, with no side effects, no pregnancy/delivery complications nor negative impact on the foetus/neonate. iTBS has the advantage of decreasing the treatment burden by reducing session duration from 10–40 min to 3 min. However, further studies are needed to set its clinical significance as a shorter treatment. Accelerated rTMS (multiple sessions a day) has been under study in MDD with promising results as well (Baeken, 2018). However, to our knowledge, there is no report concerning PPD.

Finally, according to the International Federation of Clinical Neurophysiology (Lefaucheur et al., 2014), HF-rTMS to the lDLPFC has definite efficacy in non-resistant unipolar depressive episodes (with level A of recommendation), LF-rTMS to the rDLPFC has a probable antidepressant effect (with level B of recommendation), and as of the year 2014 there was no recommendation for bilateral stimulation.

In this study, we present a qualitative synthesis on the efficacy and acceptability of rTMS in postnatal PPD, complemented by a risk of bias assessment. Time to response was defined as one of the primary outcomes of this review given the expected advantage of rTMS over pharmacotherapy: to achieve faster symptom alleviation, thus boosting mother-infant interaction and new-borns' development. However, data to analyze time to response was not available.

Although the evidence reviewed here supports rTMS efficacy in PPD, careful consideration is warranted due to the small number of studies included, the uncontrolled nature of two of them, and the serious/high risk of bias owing to potential selection of data reported, and incomplete information obtained. Finally, insufficient clinical information for half the sample and the diversity of clinical trajectories generate uncertainty as to which patient profiles would most benefit from rTMS.

Future multicentre RCT studies with increased sample sizes are

needed to support the existing evidence and establish rTMS efficacy in PPD. Further studies should control for symptom onset profiles and concomitant medication intake. Moreover, future studies should address the question of whether rTMS effectively leads to an accelerated response to treatment when compared with SSRI's (Wang et al., 2017), thus positioning rTMS within the PPD clinical management algorithm.

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.05.042.

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