

# Treatment Repetitive Transcranial Magnetic Stimulation to Peripartum Depression: Systematic Review

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## Research

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# Abstract

## Background

Peripartum depression is a common disorder; it has very high potential hazards for both patients and their babies. Although peripartum depression therapy have typical options, antidepressant and electroconvulsive, these are not ensured concerning safe of fetus. Recently, repetitive Transcranial Magnetic Stimulation (rTMS) have been emerging as promising treatment for neuropathies including type of depression. Using magnetic field is expected to minimize effect on fetuses when used to treat peripartum depression. In this study, we are considering that whether the rTMS treatment is safe and effective for the mother and fetus in the treatment of peripartum depression.

## Purpose

Performing systematical review, we confirm whether repetitive Transcranial Magnetic Stimulation is suitable treatment option for peripartum depression.

## Methods

A systematic review followed the PRISMA guidelines and meta-analysis was performed by CMA3 software. We investigated literature prior to July 2020 using databases including MEDLINE, PsycINFO, EMBASE and Cochrane libraries, and conducted bias evaluation for suitable literature.

## Results

rTMS have an effect on mitigating depression with SMD = 1.394, 95% CI: 0.944 – 1.843 and. 37% of participants showed remission of the depression and 66% showed responded to repetitive Transcranial Magnetic Stimulation. A few side effect was reported and case of unusual side effect was two. However, we confirmed these are not related to TMS. There were no life-threatening side effects.

## Conclusions

rTMS might be an attractive alternative treatment for pregnant women who are afraid of chemical effect to their child and life threatening side effect of ECT. Furthermore, rTMS could reduce socioeconomic costs of peripartum depression. However, much research is needed to determine standardized protocol and evaluate effectiveness.

## Systematic review registration

This systematic review was not registered.

## Background

Peripartum depression (PPD) is commonly classified as occurrence of major depressive disorder (MDD) during pregnancy period and within 4 weeks after childbirth [1]. Even though PPD is common disorder that 10 ~ 20% of pregnant women can experience [2], you will spend expensive life time cost of 75,728 pounds

(US\$95.656) [3] if you have disease. PPD also threatens the health of pregnant women by causing an imbalance in hormones in the mother [4], potentially exposing her to alcohol and substance abuse [5], increasing risk of complications; maternal suicide [6] and PPD also lead serious hazard to the fetus by setting premature [7] and low weight [8]. Furthermore, it interferes with the formation of a stable attachment relationship with childhood, thus causing child self-control and cognitive function behavior [9].

Methods for treating PPD are mainly electroconvulsive therapy (ECT) and antidepressant [10]. Although both of them have proven their treatment effectiveness for PPD [11–14], those are being raised many problems about the safety of pregnant women and fetuses.

Antidepressants are a method to relieve depression by regulating the amount of neurotransmitters that related to emotion [15]. Neurotransmitters released from pre-synaptic neurons are transferred to the neurons after synapses; some of which are reabsorbed or decomposed by monoamine oxidase (MAO). Antidepressants interrupt reabsorption and MAO enzymes, making neurotransmitters less decomposed and finally reducing the degree of depression [16]. However, antidepressant could have a chemical effect on the fetus because components of antidepressant can pass through the placenta [17]. When the mother takes antidepressants during PPD, it causes 7-fold increase in the risk of spontaneously induced abortion [18, 19], premature birth and underweight of children [20], increase risk of fetal infections more than 3-fold [21], autism spectrum disorder of baby [22], increase risk of motor, speech and scholastic disorder [23], cardiac defects [24] and persistent pulmonary hypertension [25]. In addition, antidepressant components can be exposed to the fetus during the breastfeeding [26], which can increase monoamine levels and affect the functional maturity of the brain [27]. Side effects such as decreased feeding [28], colic, and irritability [29] have been reported.

Another treatment, ECT, is a method stimulating electrical shock in the brain to relieve depression. Electric shocks affecting neurons and chemicals in the brain lead to short and controlled seizures which have excellent effects in various neurological disorders [30]. However, treating ECT with pregnant women shows various adverse effects including vaginal bleeding and miscarriage [31], uterine contraction [32], abdominal pain [33], and Preeclampsia [34].

Since the risk of PPD is smaller than that of ECT and antidepressant [35, 36], those are used as a treatment for PPD, but considering the impact of each treatment on the fetus and baby, a study of safer treatments is needed.

Recently, with the recent development of brain stimulation research, many researchers are increasingly trying to use brain stimulation for various neurological treatment [37]. One of brain stimulation named repetitive Transcranial Magnetic Stimulation (rTMS) stimulates the brain's dorsolateral prefrontal Cortex (DLPFC) with magnetic fields to induce degeneration of neurons and activate neural system of brain to control nerve control materials to relieve depression [38]. Although studies have shown that rTMS is safe because of using magnetic fields that are harmless to the human [39] and is effective in a number of neurological diseases including depression [40–42], treatment using rTMS for PPD is reluctant due to the specificity of pregnancy [43–45].

In this regard, there were four systematic literature studies on how to treat TMS related PPD [46–49]. However, Gersimos N study was a comprehensive study of non-drug treatment available to pregnant patients and did

not address the therapeutic effect or safety of rTMS [46]. A Ganho-Ávila study conducted a systematic literature review on patients with only postpartum depression [47]. Felipe's research was unreliable because the systematic review protocol was unclear and the number of study was only 3 [48]. J cole study did not quantitatively synthesize therapeutic effect size or safety [49].

In this study, we will evaluate the effect size and safety of rTMS on the mother's depression and whether it is a suitable method for the mother through systematic literature review and meta-analysis and reviewed the literature that received rTMS treatment from pregnancy to one year after childbirth, considering that the process of breastfeeding, etc. is affecting the growth of newborn babies [50–52].

## Data Source And Search Strategy

We performed the search by using the literature published before June 2020 as keyword, using the EMBASE, MEDLINE, PsycINFO, and Cochrane Library database. Indication search term is not only peripartum depression but also antepartum depression, postpartum depression and pregnancy depression and the terms of treatment search were repeated transcranial magnetic stimulation, rTMS, transcranial magnetic stimulation and TMS. The detailed searching term and strategy are presented in Appendix 1. Generally, the literature used in meta-analysis is a randomized controlled trial(RCT) study, but non-randomized studies (NRS) which properly set up patients, intervention, comparison, outcome also can include in meta-analysis [53]. So in this study, NRS which were suitable through Cochrane algorithm were included. To minimize the omission of data and increase the reliability, two researchers independently reviewed the literature. But if the opinions of the researchers are different, the literature were reviewed together and reached an agreement. Following studies have been reported the major depressive disorder occurred months after childbirth, though DSM-5 states that the criteria for the peripartum depression is from gestation period to 1 month after delivery [50–52]. Therefore, we collected literature that treated rTMS within a year of birth, not 4 weeks, to consider not only the therapeutic effect of rTMS on the treatment of the peripartum depression, but also the effect on fetuses and newborns.

The criteria for exclusion are as follows: (1) experimental studies with animals, (2) when the depression rating scale was not Hamilton Depression Rating Scale, (3) studies were not published in English, (4) studies were not original or were grey literature, (5) when symptoms were baby blues and postpartum psychosis and (6) major depressive disorder did not occur from pregnancy to 1 year after childbirth.

The literature was selected according to the criteria set for all literature searched. After the screening process, the selected literature was extracted. The extracted data include basic information about literature, study characteristics to ensure that rTMS well designed for peripartum depression treatment and side effects, demographic and sociological characteristics to see whether proper patients screening has been performed, rTMS parameters known to affect the therapeutic effect [54] and the condition of a mother and newborn. The detailed are presented in Fig. 1.

Two evaluators independently reviewed the quality of the data and the risk of bias. RCT studies were examined using the Risk of bias 2 (ROB2) [55] and NRS were examined using the Risk of Bias Assessment tool for Nonrandomized Studies (ROBINS-I) [56]. Case reports and series were not ignored as a medical

literature [57]. Therefore, we evaluating using Methodological quality tool [58]. The final judgment on the overall risk of bias was agreed between the two evaluators.

Data analysis was conducted using CMA3 statistical software. For therapeutic effects, two group pre-post data in RCT and one group pre-post data for NRS were analyzed and for safety, Event rates both RCT and NRS were analyzed. Effect size was confirmed by Standardized Mean Deviation (SMD) 95% CI. The final calculation results are shown in the Forest plot.

## Results

### Search results

The literature search was conducted in accordance with PRISMA FLOW, and a summary of the search results is presented in Fig. 2. The total number of studies found in each database was 215. After excluding 101 studies due to duplication, 114 studies were left. Afterwards, 83 studies were excluded due to animal studies, non-original grey literature, non-English literature, and literature with unsuitable indications and treatments according to the inclusion and exclusion criteria. 31 documents were judged by the full text review whether they were suitable for our research purposes and finally, 11 literatures were suitable for identifying the effects and safety of rTMS on peripartum depression and detailed Excluded literature and the reasons are presented in Appendix 2. The original text was requested through the author's e-mail if only abstract was present. Finally, there were 11 studies suitable for qualitative synthesis and 5 studies suitable for quantitative synthesis.

### Characteristics of Selected Studies

There were a total of 11 selected literature related to the efficacy and safety of rTMS for PPD, of which 2 RCT studies [59, 60], 4 NRS [61–64], and 5 case studies [64–68]. The total number of participants are 100, 83 of whom received active rTMS treatment. During pregnancy, 65 patients were treated with rTMS and most of them consisted of the second and third trimester of pregnancy. 17 patients were treated for postpartum depression and 2 patients were treated during pregnancy and after childbirth. The people included in the study were suffering from severe depression with HDRS scores of 17 or more point, two of which showed bipolar disorder. 20 participants were treated antidepressants [61, 63, 66, 69] along with rTMS, 6 participants were treated on psychotropic [59, 64] and 1 participant was treated on clonazepam for insomnia [62].

Table 1  
 Characteristics of subjects included studies

Study	Study design	Subjects	Age	Gestational age	Psychiatric diagnosis	Simultaneous treatment
D. R. Kim et al., 2019 [59]	Randomized controlled trial	Active 11	30.13 ± 5.78	22.19 ± 7.11 (Weeks)	MDD	Free
		Sham 11	26.41 ± 5.11	25.62 ± 7.61 (Weeks)		
Myczkowski et al., 2012 [60]	Double-blind Randomized controlled trial	Active 8	29.63 ± 6.37	4.13 ± 2.85 (Month)	MDD	Free
		Sham 6	26.67 ± 7.15	3.50 ± 2.74 (Month)		
D. R. Kim et al., 2011 [61]	Non Randomized controlled trial	10	31.2 ± 5.6	25.8 ± 5.16 (weeks)	MDD	4 patients treated on antidepressant
Hizli Sayar et al., 2014 [63]	Non-Randomized controlled trial	29	32.69 ± 3.69	14.26 ± 8.25 (weeks)	MDD	12 patients treated on antidepressant
Garcia et al., 2010 [62]	Non-Randomized controlled trial	7	34.11 ± 6.05	After birth 30 days to 1 year	MDD	Free
Tarhan et al., 2012 [70]	Non-Randomized controlled trial	7	*	*	MDD	*
Zhang et al., 2010 [65]	Case report	1	28	14 (weeks)	MDD	Free
Tan et al., 2008 [64]	Case report	1	30	From 0 to postpartum period	MDD	Free
Ferraõ et al., 2018 [66]	Case report	3 (Left)	35.7 ± 2.05	6.67 ± 3.06 (weeks)	MDD	2 patients treated on antidepressant

Study	Study design	Subjects	Age	Gestational age	Psychiatric diagnosis	Simultaneous treatment
		1 (Right)	36	8 (weeks)		1 patients treated on antidepressant
Cohen et al., 2008 [67]	Case report	1	30	20 (weeks)	MDD	Free
Monika Klírová et al [68]	Case report	1 (Left)	30	16 (weeks)	MDD	Treated on antidepressant
		1 (Right)	30	31 (weeks)	MDD	Treated on antidepressant

Because protocols for rTMS treatment for peripartum depression have not yet been established, protocols for each study have all been different. 22 patients were stimulated the right DLPFC [59, 61, 66, 67], 79 patients were stimulated the left DLPFC [60, 62–66, 70], and Burton et al [69] attempted to treat using combination of right and left DLPFC stimulation, and Ferrão et al [66] assigned different protocol and stimulation sites depending on the symptom of patients. The right DLPFC was stimulated using 1 Hz and the left DLPFC was treated with relatively high frequencies of 1 to 25 Hz. In the process of treatment, some rTMS parameters such as number of pulses, and number of session were different in all studies, but researcher consider interval time and stimulus duration to minimize adverse event like a seizure.

Table 2  
Characteristics of Treatment included studies

Study	Motor threshold	Site of Stimulation	Frequency	Number of pulses	Inter-event interval	Number of Session
D. R. Kim et al., 2019 [59]	100%	Right DLPFC*	1-Hz	900	60 s on 60 s off	20
Myczkowski et al., 2012 [60]	120%	Left DLPFC	5-Hz	1250	10 s on 20 s off	25
D. R. Kim et al., 2011 [61]	100%	Right DLPFC	1-Hz	300	60 s on 60 s off	20
Hizli Sayar et al., 2014 [63]	100%	Left DLPFC	25-Hz	1000	2 s on 30 s off	18
Garcia et al., 2010 [62]	120%	Left DLPFC	10-Hz	150	4 s on 26 s off	20
Tarhan et al., 2012 [70]	100%	Left DLPFC	25-Hz	1000	2 s on 30 s off	18
Zhang et al., 2010 [65]	90%	Left DLPFC	1-Hz	1200	20 s off	42
Tan et al., 2008 [64]	110%	Left DLPFC	25-Hz	1000	2 s on 28 s off	77
Ferraõ et al., 2018 [66]	120%	Left DLPFC	10-Hz	3000	*	42.67
		Right DLPRC	1-Hz	1800		20
Cohen et al., 2008 [67]	110%	Right DLPFC	1-Hz	1600	*	1
Monika Klírová et al [68]	100%	Left DLPFC	20-Hz	2000	2 s on 30 s off	15

\* DLPFC: Dorsolateral prefrontal cortex

Study	Motor threshold	Site of Stimulation	Frequency	Number of pulses	Inter-event interval	Number of Session
		Right DLPRC	1-Hz	300	60 s on 60 s off	15
* DLPFC: Dorsolateral prefrontal cortex						

The average improvement in depression showed a decrease rate of 59% for 76 patients, except for a study by Tarhan et al [70], which did not disclose specific HDRS scores of patients. 37% participants showed remission of the depression ( $\text{HDRS-17} \leq 8$ ,  $\text{HDRS-21} \leq 7$ ,  $\text{HDRS-24} \leq 8$ ) and 66% showed responded to rTMS (HDRS score reduced more than 50%). Among the two random clinical trial studies, D. R. Kim et al [67] showed 45.45% response rate for the control group, while response rate of the experimental group is 81% ( $p = 0.088$ ) and remission rate was 18.18% for the control group whereas remission rate of the experimental group is 27.25% ( $p = 0.613$ ), showing a high therapeutic effect. Additionally, another Myczkowski et al [60] showed 7% decrease of HDRS scores in the placebo group, but in the experimental group, they showed a more than 30% decrease rate ( $p = 0.020$ ), similar to antidepressants. In NRS, the response rate of the 56 participants was 33% and the mission rate was 59%. In Garcia et al., 2010 [62], HDRS scores of all participants fall below eight and without 1 participants, all of them experienced their HDRS scores drop by more than 50% and other NRS also revealed significant clinical results. In the case study, nine participants responded (rating scale reduction rate  $\geq 50\%$ ).

Table 3  
Characteristics of result included studies

Study	Instrument	Pre-TMS	Post-TMS	Remission	Response	Side effect (mother)	Infants
D. R. Kim et al., 2019 [59]	HDRS-17	23.18 ± 3.54	9.27 ± 6.05	3	9	1 Patients had headache	3 pre term births
		22.27 ± 2.65	13.18 ± 8.00	2	5		1 shoulder dystocia
Myczkowski et al., 2012 [60]	HDRS-17	29.13 ± 5.64	18.50 ± 9.83	*	*	2 Patients had mild headache	*
		26.67 ± 5.68	24.83 ± 7.60				
D. R. Kim et al., 2011 [61]	HDRS-17	24.4 ± 5.6	9.7 ± 6.1	3	7	4 Patients had mild headache.  1 patients had an episode of supine hypotension	All infants were well-baby nursery
Hizli Sayar et al., 2014 [63]	HDRS-17	26.67 ± 5.58	13.03 ± 6.93	6	12	None	None of baby showed any Abnormalities.
Garcia et al., 2010 [62]	HDRS-24	22.67 ± 6.44	2.14 ± 3.19	8	9	Headache, site pain	*
Tarhan et al., 2012 [70]	HDRS-17	*	*	2	5	None	All gave healthy babies
Zhang et al., 2010 [65]	HDRS-24	35	8	1	1	None	Healthy boy
Tan et al., 2008 [64]	HDRS-17	38	4	1	1	None	No diagnosis of disease
Ferraõ et al., 2018 [66]	HDRS-21	24.33 ± 5.24	7.33 ± 4.03	2	3	2 patients had discomfort at the application site.	Twins were preterm
		12	6	1	1	discomfort at the application site and sore throat	

Study	Instrument	Pre-TMS	Post-TMS	Remission	Response	Side effect (mother)	Infants
Cohen et al., 2008 [67]	HDRS-17	18	6	1	1	*	The infant had a normal neurologic development
Monika Klírová et al., 2008 [68]	MADRS	33	2	*	*	None	Healthy baby
	BDI	29	12	*	*		

## Meta-analysis

### Therapeutic effect

All of the included studies used HDRS to identify degree of depression. The correlation coefficient was 0.5 [71] and because heterogeneity was  $p < 0.001$ ,  $I^2 = 71.933$  the random effects model was applied [72]. rTMS have an effect on mitigating depression with SMD = 1.806, 95% CI: 0.920 – 2.692 and the difference was statistically significant. ( $Z=6.079$ ,  $p < 0.01$ ) [73].

**Abbreviations:** BAI: Beck Anxiety Inventory; BDI: Beck depression Inventory; CGI-S: Clinical Global impression scale; EPDS: Edinburgh Postnatal Depression Scale; HDRS: Hamilton Depression Rating Scale; GAS, Global Assessment Scale; SF-36-V and SF-36-MH: 36-item Quality of Life Health Survey, Vitality and Mental Health scores; IDS-SR: Inventory of Depressive Symptomatology-Self-Report.

Figure 3. Forest plot of therapeutic effect

### Side effect

The rate of occurrence of all side effects from the included studies was determined. The heterogeneity of the studies was  $p = 0.112$ ,  $I^2 = 46.631$  so fixed effect model was applied [72]. The probability of side effects was small (event rate = 0.346,  $Z = -2.696$ ,  $p = 0.007$ ) [73].

Figure 4. Forest plot of side effect

### Sensitivity analysis

Except for Garcia's study, which was too high therapeutic effect compared to other studies, the rTMS Of SMD = 1.074 (95% CI: 0.689 – 1.459,  $Z=5.468$ ,  $P < 0.001$ ) showed significant therapeutic effect for PPD (Figure5).

**Abbreviations:** BAI: Beck Anxiety Inventory; BDI: Beck depression Inventory; CGI-S: Clinical Global

impression scale; EPDS: Edinburgh Postnatal Depression Scale; HDRS: Hamilton Depression Rating Scale; GAS, Global Assessment Scale; SF-36-V and SF-36-MH: 36-item Quality of Life Health Survey, Vitality and Mental Health scores.

Figure 5. Forest plot of therapeutic effect without Garcia study

### Quality of the included studies

According to experimental design, RCT was evaluated ROB2, NRS was ROBINS-I, case study was Methodological quality tool and the detailed domain for the risk of bias assessment is presented in Appendix 3. Figure 7 is funnel plot for the Treatment effect of rTMS in treatment of PPD. The occurrence of asymmetric can be caused by publication bias or other causes.

(A) RCT risk of bias graph; (B) NRS risk of bias graph; (C) case study risk of bias graph

Figure 6. risk of bias graph

## Discussion

Mothers are reluctant to treat antidepressants because they are concerned about the disadvantages of their own side effects, as well as the disadvantages to the fetus [74, 75], and in case of electroconvulsive therapy, only 1.2% of them accept them, and the majority are very negative because ECT has anesthesia process, and people worried about side effects such as post-treatment amnesia [76]. The population of this survey is public and if the population is limited to mothers, it will show lower acceptability. rTMS was also not well-received in the survey because it was not widely known as a recently re-examined treatment method, but after hearing the explanation of the treatment method, the acceptance rate of the mother for rTMS was significantly improved [77], as clinicians generally present the treatment effect while delivering knowledge of the treatment, so the acceptability of the mother acceptance of rTMS is positive.

The size of Therapeutic effect was  $SMD = 1.394$  (95% CI: 0.944–1.843,  $Z = 6.079$ ,  $p < 0.01$ ) which was significant for treating depression [73]. Except for Garcia study [62] which is expected reporting bias because of selection report,  $SMD = 1.074$  (95% CI: 0.689–1.459,  $Z = 5.468$ ,  $p < 0.001$ ) which is meaningful result. The literature not included in the meta-analysis and excluded literature because those are not suitable selection criteria also support the therapeutic effect of rTMS for PPD [64, 66–70, 78–82]. In a studies included systematic review, 36% of the patients with PPD scored the same as the normal person and 66% saw their depression rating scale decrease by more than 50%. In addition, Brock G study showed that 14 out of 19 patients reduced their Edinburgh Postnatal Depression Scale (EPDS) below 8 [80] and Ozmut study also showed that 8 out of 15 patients reduced their EPDS scores by more than 50%. [79]. Other case-reporting [81, 82] also succeeded in improving patients with PPD using rTMS. Although parameters that can affect therapeutic effects such as stimulation site, frequency, and interval time are still being studied, there are not much research data, we have been able to confirm that there is therapeutic effect without relying on multiple parameter settings on the literature collected, and if the protocol becomes more sophisticated, we will have a higher therapeutic effect.

Event rate = 0.346 for side effects, which is statistically small but affected [73]. However, the side effects of rTMS treatment on mothers were minor, such as headaches, discomfort and pain in the stimulation area, and these side effects disappeared at the end of the treatment process. Even this was reported similarly in RCT and is seen as a common side effect of TMS devices, not as a side effect in treating PPD. Supine hypotension was unexpected event [61] but a disease caused by a posture problem during treatment and was able to prevent supine hypotension through postural correction [83]. In case of antidepressants, side effects are commonly known as dizziness, hand tremors, cold sweats, lethargy and anxiety [84]. These side effect are constantly experienced in daily life and it can have a huge impact on pregnant women and mothers who need to take care of their infants [85]. In addition, 2.5% of mothers who suffer from treatment resistant depression and these have to choose a different treatment method [86]. Another treatment ECT was much serious. A direct and indirect study of fetal effects in mothers who was given ECT showed fatal side effects on fetuses and mothers including uterine contraction and vaginal bleeding, and a 7.1% of fetal mortality rate [13]. Compared to these two treatments and based on all the research we've done so far, The side effects of on mothers do not affect their daily lives and are safe.

All children born from mothers with rTMS treatment were born healthy. And In one RCT study in which the child's health condition was determined by appearance-pulse-grimace-activity-respiration scores, the difference between the two group was not significant [experimental group 8.36(1.50), control group 8.73(0.90)  $p = 0.501$ ] [61].

There were five premature births and brachial flexus injury related to fetuses. Five percent of the participants in the study experienced premature birth, but two have already shown signs of premature birth risk in a biomedical test and the average rate of women experiencing premature births worldwide is 9.1 to 13.4% [87], it is unlikely that the causal relationship that rTMS treatment causes premature births will be established and further research is required. It was confirmed that brachial flexus injury was the only side effect that occurred in newborns, including premature births, and that it was not associated with rTMS treatment [59]. There were no actual side effects in the infant. Hizil Sayer performed following study that checked child of mother treated rTMS and reported that the exposure of Rtms during pregnancy did not affect the cognitive or motor development results of the child [88]. Although the results are fully reliable due to the lack of research, the magnetic field affecting fetal development is the lung and immune system [89] and it is also unlikely that rTMS will have a negative impact on fetal development and growth, given that magnetic is associated with diseases such as asthma at frequencies above 40 Hz [90]. Likewise, it could be safe because the maximum electromagnetic field applicable to fetuses is 800mv/m [91], while the electromagnetic field of the rTMS is 100mv/m [92].

In terms of treatment effectiveness and safety as well as economic efficiency, rTMS is more attractive method than other treatment methods. When comparing the economic efficiency of antidepressants and rTMS in a study using cohort model, the use of rTMS can save US\$112 dollars for Quality Adjusted Life Years (QALY), which is more cost-effective [93] and In a Singapore study comparing economic efficiency with ECT, the cost of treating rTMS for one year was \$1850(US\$8515) cheaper than ECT [94]. rTMS treatment not only leads to neurobiological changes through brain stimulation, but also reduces anxiety about the cost which was one of the risk factor that has the greatest impact on pregnant women [95]. Consequently, socioeconomic costs of peripartum depression could be reduced.

Although the analysis showed high heterogeneity, it is assumed that the parameters that affect the treatment of rTMS are different in each study. In case of publication, funnel plot is asymmetric and p-value of Eggar regression is 0.001. However, except for Garcia's research [62], the funnel plot has a symmetrical structure and has no publication bias with Eggar regression p-value = 0.121. In order to do a more accurate study, high quality clinical trial should be conducted to identify the therapeutic effect of rTMS. How to compensate non-treatment groups is an important consideration. In addition, not only the randomization clinical trials but follow up or cohort study about the children born after treatment should also be conducted. Although many studies considered health of fetus [59, 61, 63–67, 70], only Myczkowski et al [60] considered breastfeeding, and only Eryilmaz et al [88] conducted follow up study of children. One of the main advantages of rTMS is that it has negative effect on the baby. Due to practical constraints, this paper cannot provide a comprehensive review of effect of rTMS on growing babies.

In this study, we have identified 11 studies to collect existing research data and use rTMS to treat peripartum depression and five of them are suitable for quantitative synthesis. According to the analysis of the included studies, rTMS is statistically significant effect on the treatment of PPD and had fewer side effect that were minor. From a variety of perspectives, the treatment of PPD using rTMS can be thought to be an attractive treatment to avoid exposure of chemical ingredients to fetuses and severe side effects of ECT.

## Abbreviations

**PPD:** Peripartum depression

**MDD:** Major depressive disorder

**ECT:** Electroconvulsive therapy

**MAO:** Monoamine oxidase

**rTMS:** Repeated transcranial magnetic stimulation

**DLPFC:** Dorsolateral prefrontal cortex

**RCT:** Randomized controlled trial

**NRS:** Non-randomized studies

**DSM-5:** Diagnostic and Statistical Manual of Mental Disorders-5

**HDRS:** Hamilton Depression Rating Scale

**ROB2:** Risk of bias 2

**ROBINS-I:** The Risk of Bias Assessment tool for Nonrandomized Studies

**SMD:** Standardized Mean Deviation

**MARDS:** Montgomery-Åsberg Depression Rating Scale

**BDI:** Beck Depression Inventory.

**EPDS:** Edinburgh Postnatal Depression Scale

**QALY:** Quality adjusted life year

**CGI-S:** Clinical Global impression scale

**GAS:** Global Assessment Scale

**SF-36-V:** 36-item Quality of Life Health Survey Vitality scores

**SF-36-MH:** 36-item Quality of Life Health Survey Mental Health scores

## **Declarations**

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### **Availability of data and materials**

No data or materials were generated for this narrative review.

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#### Contributions

HJ: Conceive the project, search strategy, screening literature, data extraction, bias evaluation, data analysis, and drafting the manuscript and revising JY: Study design, screening literature, bias evaluation, data analysis, drafting the manuscript, and revising the manuscript and SMK supervised the entire procedures and helped to draft the manuscript. All authors read and approved the final manuscript.

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### **Consent for publication**

Not applicable

### **Competing interests**

The authors declare that they have no competing interest

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## Figures

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### Basic information

- Title of the paper, author, year of publication.

### Study Characteristics

- Study design, number of subjects, dropout rate, bias risk assessment factor

### Subjects Characteristics

- Age, primary psychiatric diagnosis, gestational age, and simultaneous treatment

### Treatment Characteristics

- Motor threshold, site of stimulation, frequency and pulse, interval time, number of sessions

### Result Characteristics

- Treatment effect for the mothers, side effects on mothers, side effects on fetuses,
- 

## Figure 1

Data extraction items.

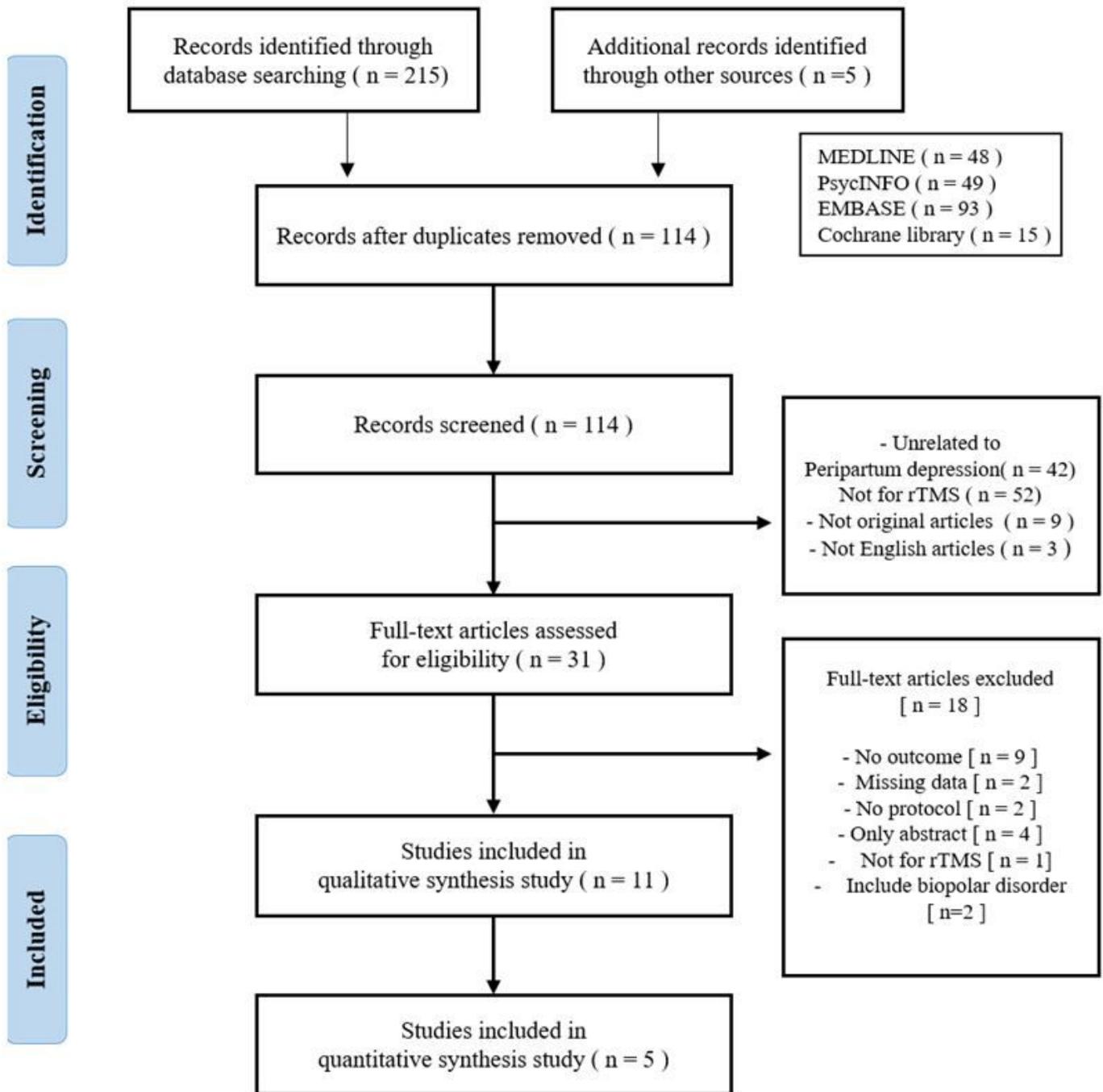


Figure 2

Study Selection PRISMA flow diagram.

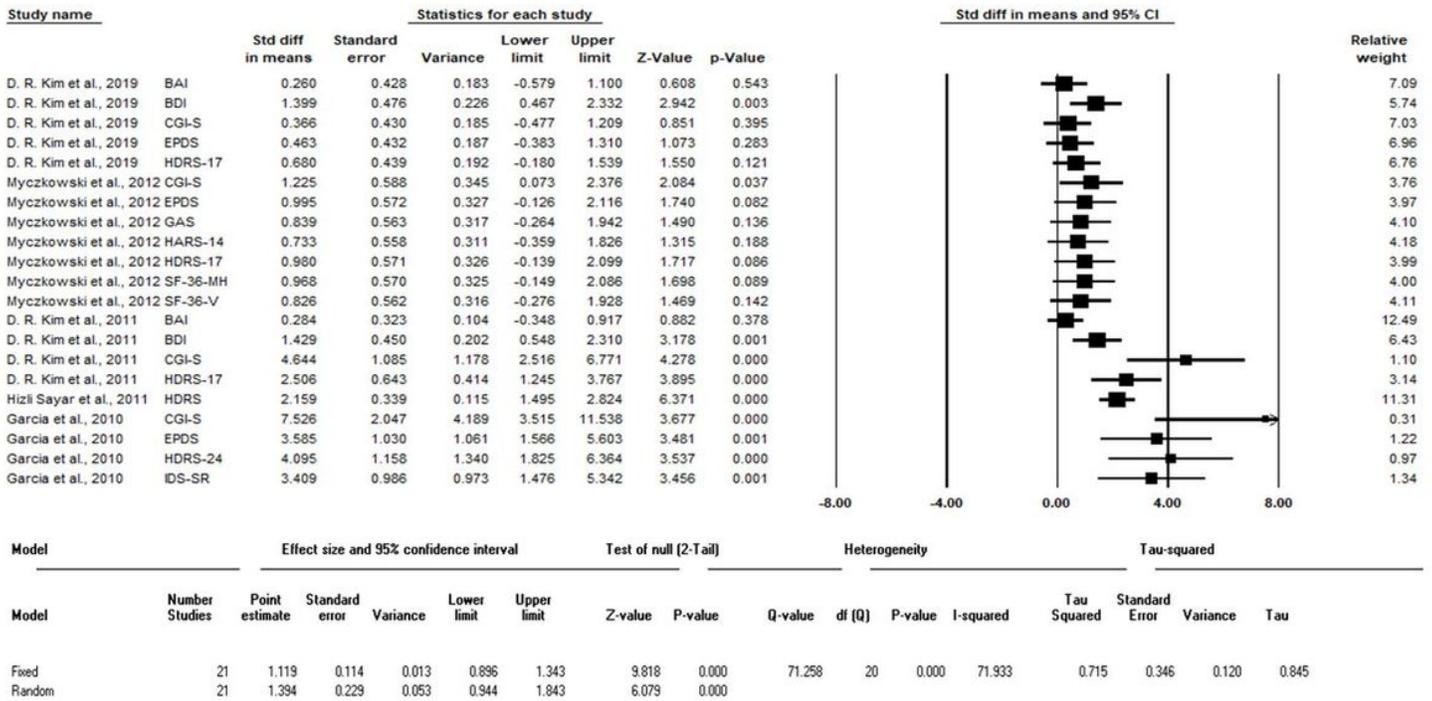


Figure 3

Forest plot of therapeutic effect. Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck depression Inventory; CGI-S: Clinical Global impression scale; EPDS: Edinburgh Postnatal Depression Scale; HDRS: Hamilton Depression Rating Scale; GAS, Global Assessment Scale; SF-36-V and SF-36-MH: 36-item Quality of Life Health Survey, Vitality and Mental Health scores; IDS-SR: Inventory of Depressive Symptomatology-Self-Report.

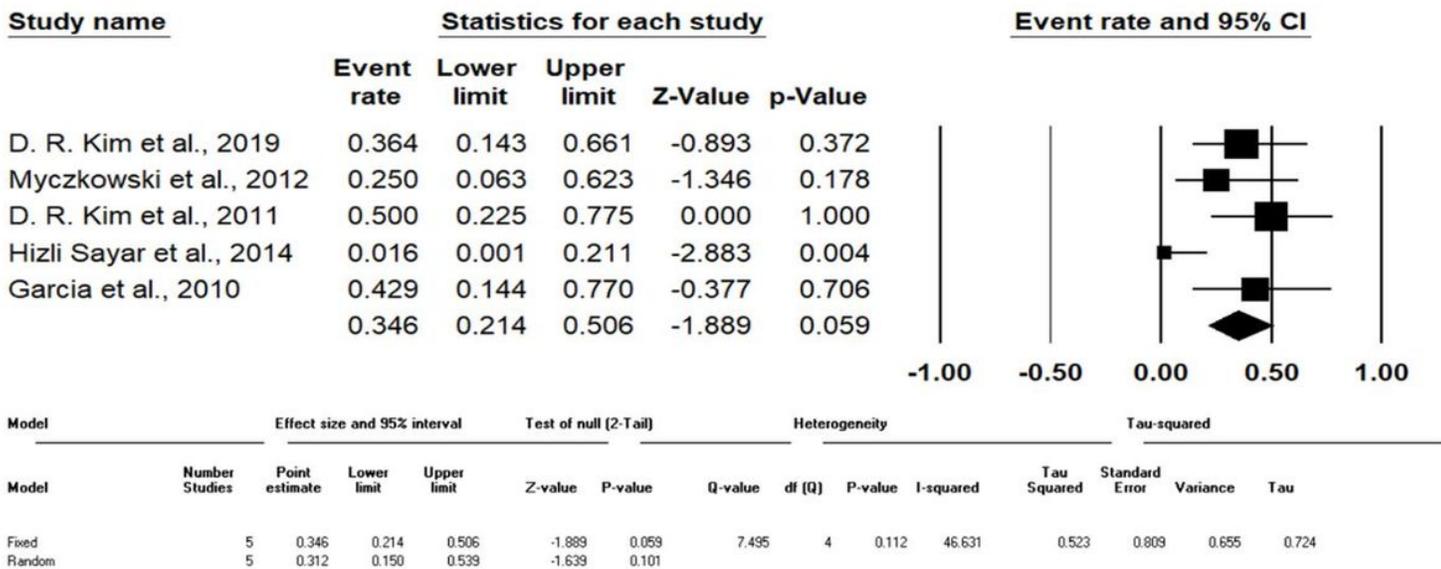


Figure 4

Forest plot of side effect.

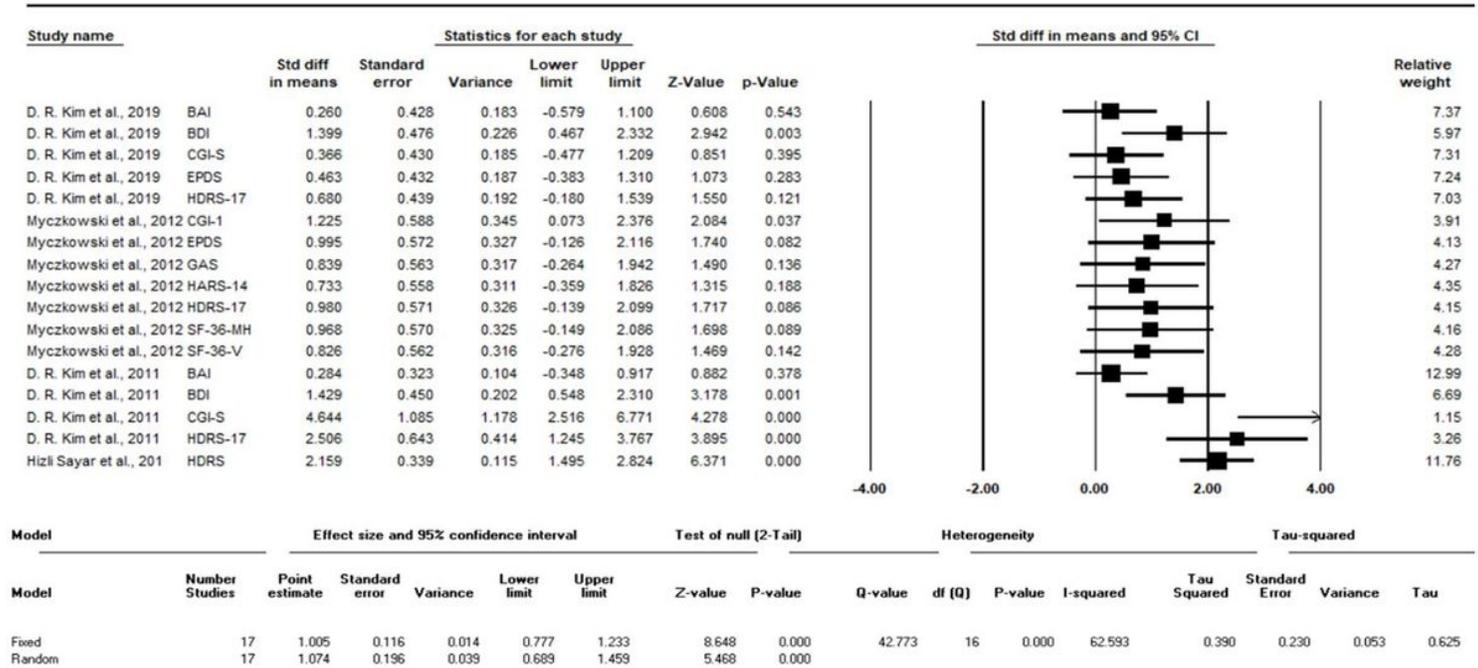


Figure 5

Forest plot of therapeutic effect without Garcia study. Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck depression Inventory; CGI-S: Clinical Global Impression scale; EPDS: Edinburgh Postnatal Depression Scale; HDRS: Hamilton Depression Rating Scale; GAS, Global Assessment Scale; SF-36-V and SF-36-MH: 36-item Quality of Life Health Survey, Vitality and Mental Health scores.

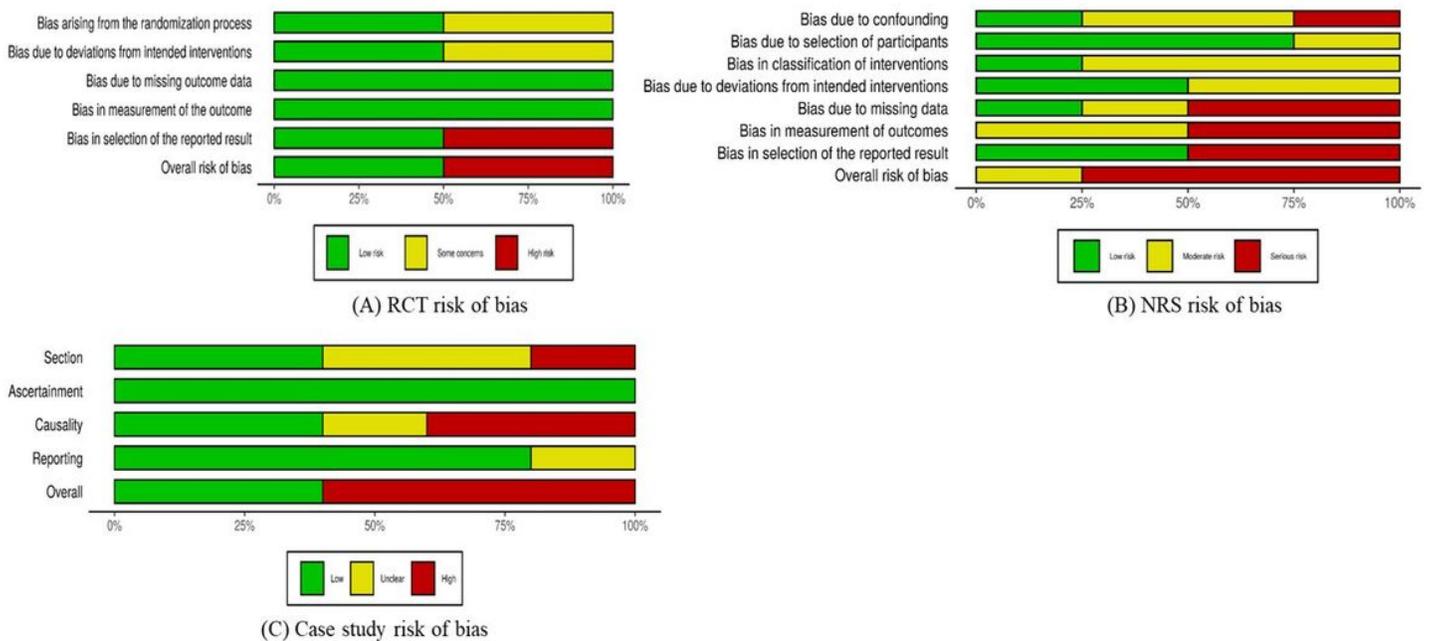


Figure 6

Risk of bias graph. (A) RCT risk of bias graph; (B) NRS risk of bias graph; (C) case study risk of bias graph.

Funnel Plot of Standard Error by Std diff in means

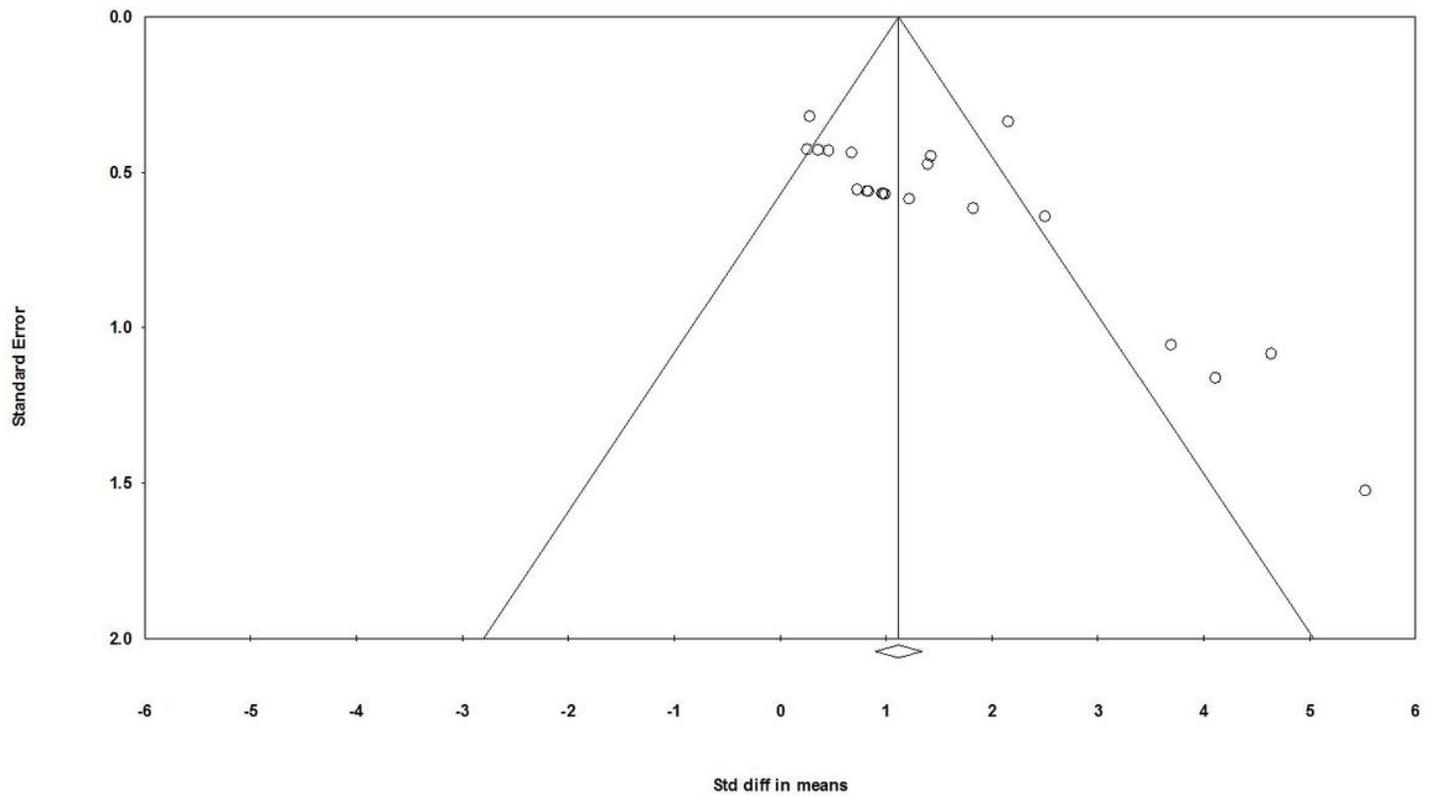


Figure 7

Funnel plot of rTMS effect for PPD.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix4PRISMAchecklist.doc](#)
- [Appendix3Riskofbiasassessment.docx](#)
- [Appendix2Excludedstudies.docx](#)
- [Appendix1Searchingstrategy.docx](#)