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REVIEW

Oxytocin and Women Postpartum Depression: A Systematic Review of Randomized Controlled Trials

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Abstract: Previous studies have demonstrated that oxytocin was a viable therapy option for postpartum depression. However, the role remains controversial. To evaluate the efficacy of oxytocin on women postpartum depression, we searched PubMed, Web of Science, Cochrane Library, and EmBase for literatures from inception of the database to April 18th, 2022. Randomized controlled trials (RCTs) that investigated the effects of oxytocin on postpartum depression were selected for this study. Six RCTs (195 women) were gathered. The effects of oxytocin were roughly divided into emotion and cognition. The modulation of oxytocin to women's emotion was demonstrated in four of the trials. The results were conflicting: One trial showed that oxytocin alleviated the depressive mood; two trials showed that oxytocin had no effect (but reduce negative thoughts in healthy mothers, or decrease the narcissistic trait); another trial showed that oxytocin aggravated depression. Women's cognition was shown to be regulated by oxytocin in four of the trials. In general, oxytocin enhanced postpartum depressive women's perception of their relationship with the infants. This systematic review showed that the effect of oxytocin on postpartum depression is still uncertain. We partly support that exogenous oxytocin might improve the cognition of women with postpartum depression to their infants, while the effect on emotion is still controversial. Further RCTs with larger samples and more diversified evaluation criteria are needed to better reveal its efficacy on postpartum depression.
Keywords: oxytocin, postpartum depression, postnatal depression, systematic review, randomized controlled trial

Introduction

Postpartum depression (PPD) is defined as depression in women after delivery.[1] The PPD patients may have negative emotions such as melancholy, anxiety, disappointment, and so on. Serious cases even commit suicide.[1] The global prevalence of PPD is around 15%.[1] Maternal brain reactions and behaviors are compromised in PPD. PPD may last for a long period. It severely harms women's ability to take care of their infants.[2] It also affects the relationship of women with their spouses. PPD is becoming a major public health issue. It has a complex pathogenic mechanism that has yet to be fully clarified.[3] Withdrawal of gonadal steroid hormone and dysregulation of the hypothalamic pituitary-adrenal axis are reported to play major roles.[3] High-risk pathogenic factors are familial inheritance, hormone-level changes, neurotransmitter levels or activity changes, inflammation, and so on.[4–6] Treatment of PPD frequently involves antidepressant medications and psychotherapy.[7] Brexanolone, a positive allosteric modulator of Gamma Absorptiometry Aminobutyric Acid (GABA) A receptors, was approved in 2019 by the Food and Drug Administration (FDA) as the first drug to be expressly prescribed for treating individuals with PPD.[8]

Oxytocin (OT) is a hormone synthesized in paraventricular nucleus (PVN) and supraoptic nucleus of hypothalamus.[9] It is necessary for maternal functions including labor and lactation. OT is commonly administered to women to help them labor and avoid postpartum hemorrhage.[10] It has also been linked to a variety of behavioral and neuropsychiatric conditions, including postpartum depression.[11–13] Skrundz[14] found that enhancing the release of OT during pregnancy

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might serve as a potential target for the prevention of prepartum PPD. This could help to minimize the negative consequences of PPD on the mother-child connection. Apter-Levy[15] reported that oxytocin-based intervention had the potential to improve child social outcomes under the negative influence of chronic maternal depression. Our previous study[16] also revealed that OT protected against PPD by inhibiting NLRP3 inflammasome activation in a PPD mouse model. It was reported in several studies[17,18] that there was a negative association between OT and depressive symptoms, as evidenced by lower plasma OT concentrations in women with PPD. Conversely, Dai[19] discovered a higher expression of PVN OT in the postmortem patients with mood disorders than in control groups, which might be contrary to our conventional speculation.

Previous studies have demonstrated that OT is a viable therapy option for PPD.[20] A previous review reported the relationship between both endogenous and synthetic OT and PPD. It focused on the studies about the correlations between the intrapartum intravenous OT and the occurrence of PPD.[20] The administration of OT for the treatment of PPD, on the other hand, still remains controversial. This systematic review summarized all randomized controlled trials (RCTs) that have been conducted so far to assess the effectiveness of OT treatment for PPD.

Methods

Sources and Search Strategy

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] We searched PubMed, Web of Science, Cochrane Library, and EmBase for literatures without language or publication status restrictions from inception of database to April 18th, 2022. RCTs that investigated the effect of oxytocin on postpartum depression were selected for this study. The search was undertaken in the databases using medical subject heading (MeSH) terms, title or abstract or keywords, and their combinations: "Oxytocin" and "Depression, Postpartum" as the MeSH, "Ocytocin/Syntocinon /Pitocin" and "Postnatal Depression/Depression, Postnatal/Post-Partum Depression /Depression, Post-Partum/Post Partum Depression/Postpartum Depression/Post-Natal Depression/Depression, Post-Natal/Post Natal Depression" as the entry terms used for queries. Take "web of science" as an example, the retrieval formula is: (TS=(Oxytocin) OR AB=(Oxytocin OR Ocytocin OR Syntocinon OR Pitocin)) AND (TS=(Depression, Postpartum) OR AB=(Depression, Postpartum OR Postnatal Depression OR Depression, Postnatal OR Post-Partum Depression OR Depression, Post-Partum OR Post Partum Depression OR Postpartum Depression OR Post-Natal Depression OR Depression, Post-Natal OR Post Natal Depression)). More retrieval formulas were shown in Table S1. Further qualified studies were manually searched from the references of relevant original and review articles. The theme, design, participants' characteristic, intervention, controls, and outcomes were collected to identify possibly relevant studies. Two researchers reviewed titles, abstracts, and full-text articles independently.

Study Selection

During the process of study selection, we were to include all studies that investigated the effects of oxytocin on patients with postpartum depression. The following were the criteria for inclusion: a) a randomized control design was required; b) the participants were diagnosed with postpartum depression; c) depressive symptoms were assessed using a questionnaire or a diagnostic interview; d) participants were given oxytocin therapies or a placebo; and e) there were available data concerning the efficacy of oxytocin. The article was not included if it was not available.

Data Extraction and Quality Assessment

The study design, age, postpartum period, diagnostic criteria, treatment reagent, treatment duration, and outcome results were collected. The methodological quality of included studies was made decisions according to the Cochrane criteria guidelines. Two researchers extracted the data independently. Any disagreements in the evaluation of the research were investigated further using the above criteria until a consensus was established. Each trial was allocated a risk of bias. A low/ unclear/high risk of bias was assigned if the risk of bias was deemed low, unclear or high.

Statistical Analysis

Flow diagram was made using Review Manager 5.4.1 software. The risk of bias assessment was made using Cochrane Risk of Bias tool (RoB 2.0).[22] The clinical heterogeneity was significant as the outcomes of six RCTs were diverse from each other. Therefore, we did not do meta-analysis with forest plot. Statistical analysis was not involved.

Results

Selection of Studies

As shown in Figure 1, the search provided 517 citations (PubMed, 145; Web of Science, 180; Cochrane Library, 56; Embase, 136). After duplicate publications removal, 296 articles were screened by titles and abstracts. After screening titles and abstracts, 289 articles (Not RCTs, 285; Not relevant to this analysis, 4) were excluded for not meeting the inclusion criteria. Among the 7 RCTs, Li's research[23] was conducted in males. As we focused on women postpartum depression, after detailed evaluation, six publications[24–29] were obtained ultimately and included in the systematic review.

Study Characteristics

In this systematic review, a total of 195 participants were selected. Four studies[24,25,27,29] of the PPD patients were diagnosed according to Edinburgh Postnatal Depression Scale (EPDS). Two studies[26,27] of the PPD patients were diagnosed according to Beck's criteria scale[30] or Diagnostic and Statistical Manual of Mental Disorders (DSM). The outcome measures were as follows: Positive and Negative Affect Scale (PANAS);[24] facial emotion recognition (FER), Postnatal Negative Thoughts Questionnaire (PNTQ);[25] EPDS, Hamilton Depression Rating Scale (HDRS), Affective Neuroscience Personality Scale (ANPS), Shedler–Westen Assessment Procedure (SWAP);[26] Maternal Sensitivity, Cry paradigm;[27] Enthusiastic Stranger Paradigm (ESP);[28] Self-Assessment Manikin (SAM), Controlled Oral Word Association Test (COWAT), Five Minute Speech Sample (FMSS).[29] The main characteristics of the included six studies are shown in Table 1.

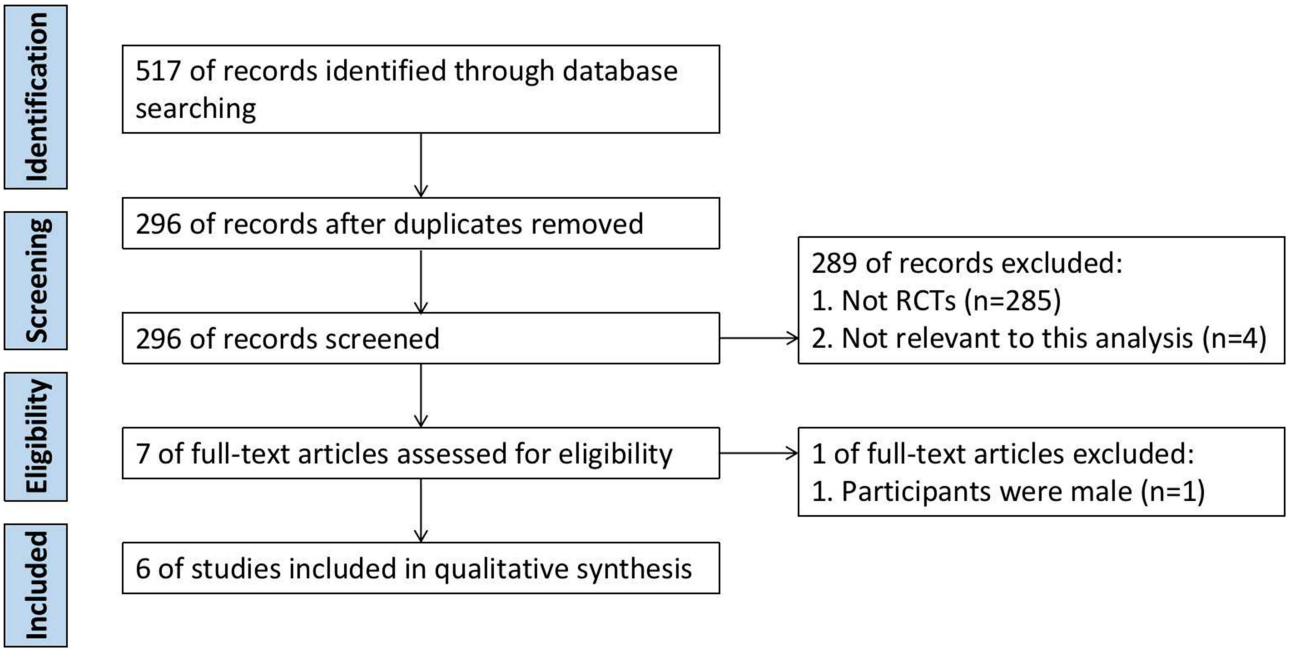

Figure 1 PRISMA flow-diagram of selection process.
Abbreviation: RCT, randomized controlled trial.

Table 1 Characteristics of the Selected Studies

First Author, Year	Study Design	Sample Size		Age	Postpartum Period	Diagnostic Criteria	Intervention	Control	Outcomes (Measures)	Time of Outcome Assessment
		Oxytocin	Control							
Lindley Baron-Cohen 2022[24]	Crossover	26	32	33.62 ± 4.48	4.70±1.71 months	EPDS ≥ 9	Oxytocin, 24IU, once	Placebo	PANAS	35–45 min post-treatment
Donadon 2021[25]	Crossover	20	35	> 18	2–12 weeks	SCID-5-CV; EPDS ≥ 10;	Oxytocin, 24IU, once	Placebo	FER, PNTQ	30 min post-treatment
Clarici 2015[26]	Parallel	5	11	36.5 ± 5.6	4.5 ± 1.2 months	Beck's (2001) criteria scale	Oxytocin, 16IU, once daily for 12 week; + psychodynamic psychotherapy	Placebo; + psychodynamic psychotherapy	EPDS, HDRS, ANPS, SWAP	End of treatment
Mah 2017[27]	Crossover	Roughly half of 25	Roughly half of 25	28.24 ± 5.93	Unknow (infant aged: 6.22 ± 2.44 months)	EPDS ≥ 12	Intranasal oxytocin administration, 24IU, once	Placebo	Maternal Sensitivity, Cry paradigm	35–50 min post-treatment
Mah 2015[28]	Crossover	Roughly half of 16	Roughly half of 16	26.5 ± 4.71	Unknow (infant aged: 3–11 months)	DSM	Oxytocin, 24IU, once	Placebo	ESP	55 min post-treatment
Mah 2013[29]	Crossover	13	12	28.24 ± 5.93	Unknow (infant aged: 6.22 ± 2.44 months)	EPDS ≥ 12	Oxytocin, 24IU, once	Placebo	SAM, COWAT, FMSS	45 min post-treatment

Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; PANAS, Positive and Negative Affect Scale; SCID-5-CV, Structured Clinical Interview for the DSM-5; FER, facial emotion recognition; PNTQ, Postnatal Negative Thoughts Questionnaire; HDRS, Hamilton Depression Rating Scale; ANPS, Affective Neuroscience Personality Scale; SWAP, Shedler–Westen Assessment Procedure; DSM, Diagnostic and Statistical Manual of Mental Disorders; ESP, Enthusiastic Stranger Paradigm; SAM, Self-Assessment Manikin; COWAT, Controlled Oral Word Association Test; FMSS, Five Minute Speech Sample.

Risk of Bias Assessment

A summary report of the risk of bias is presented in Figure 2 according to the Cochrane criteria guidelines.[22] Five of the studies had random sequence generation. The other one did not provide enough information and was graded as unclear. Allocation concealment was found in five of the investigations, while the remaining one lacked sufficient information. Three of the studies provided measures using blind outcome assessors; one study described measures using unblind outcome assessors; the other two studies did not show enough information. All studies had a low risk in performance, attrition, reporting, and other bias.

Effects of Oxytocin on Postpartum Depression

Lindley Baron-Cohen[24] conducted a trial to investigate whether OT administration decreased poor mood in women with PPD and across the low mood range. The study included 58 mothers who were 3 to 9 months postpartum. The PPD group consisted of 26 patients who scored ≥9 of EPDS, while the control group consisted of the rest 32 participants. After rating mood at baseline and after the administration of OT or placebo, PANAS was recorded. Researchers discovered that

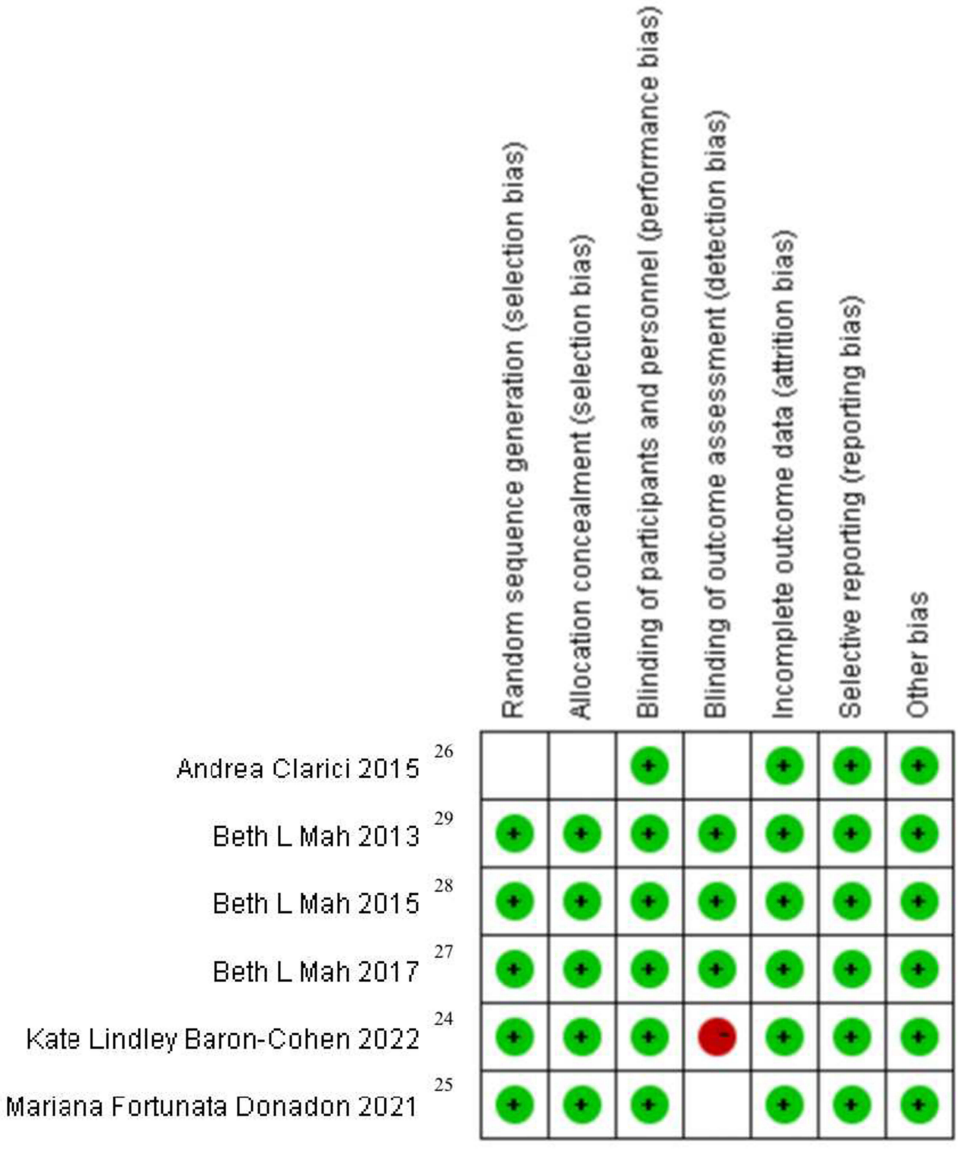

Figure 2 Risk of bias assessment of included studies.

whereas OT had no effect on mood in PPD women (26/58), it greatly lowered negative mood in the control group (Negative PANAS Score in control group: Baseline = 11.64 ± 1.81, Placebo = 11.28 ± 2.04, OT = 10.69 ± 1.40). A significant effect was shown among conditions including baseline, OT and placebo ($p < 0.0001$). And there was a slightly significant interaction effect among "Condition" and "Group" ($p < 0.059$). The findings imply that OT may be beneficial in the treatment of mothers with moderate sub-clinical depression.

Donadon[25] conducted a crossover-designed trial to assess the roles of intranasal OT on FER of baby faces alongside with passive thoughts in PPD mothers. A task of FER of baby faces and a questionnaire of postpartum passive thoughts were completed by participants. Researchers found that women with PPD exhibited higher ratings of passive thoughts about motherhood and their infants, but no deficits in FER, when compared to the control group. As compared to placebo ($p = 0.02$), OT (20/55) was related with a significant reduction in the frequency of the passive thoughts (Score of PNTQ-BRM-NT in PPD group: OT = 5.33 ± 4.43, Placebo = 2.13 ± 6.13). The results suggest that OT may have positive impacts on mother–infant interactions, maternal affiliative behavior and maternal care as evidenced by changes in several cognitive aspects.

Clarici[26] conducted a study to assess whether OT had therapeutic effects on PPD women with depressive symptoms. A total of 16 mothers participated in the trial. The women were given a daily dose of OT or placebo for 12 times weekly, as well as a brief psychoanalytic psychotherapy. Researchers discovered that after oxytocin was administered during psychotherapy (5/16), there was no significant difference in depressive symptomatology compared to the placebo group (11/16) (Changes of EPDS before and after administration: OT = 3.4, Placebo = 3.93). They also found that only those who took OT (5/16) in a personality characteristic evaluation had a lower narcissistic trait ($p = 0.019$) (Changes of SWAP before and after administration: OT = 1.6, Placebo = −1.6). The findings imply that PPD may entail narcissistic affective balance abnormalities and that OT supplementation can help to alleviate this form of affective disturbance.

Mah[27] tested the effects of OT on sensitive caregiving. Apperceptive and caring responses to pre-recorded cry sounds of infants, as well as maternal sensitivity, were used as outcome measures. Researchers found that mothers with PPD were more likely to assess the infant scream as a more urgent event in the OT condition (Roughly half of 25. The precise number was missing.) ($p = 0.04$), and they were more inclined to response by choosing a harsh parenting method ($p = 0.03$). OT had no influence on mothers' sensitive interaction with their infants ($p = 0.36$ for maternal sensitivity, $p = 0.45$ for non-intrusiveness). The results suggest that OT has a significant impact on the impression of urgency and a caring strategy for the crying of infants in PPD mothers.

Mah[28] conducted a pilot study to ascertain whether administration of intranasal OT to mothers with PPD would boost protective behaviors toward their infants. The study included 16 mothers who had been diagnosed with PPD. In the presence of a stranger with social aggressivity, mothers' protective behavior toward their newborn was assessed. Researchers found that in the presence of an aggressive stranger, the enthusiastic stranger paradigm enhanced mothers' protective responses to the infants. The protective reaction of mothers with PPD was increased after the administration of OT (Roughly half of 16. The precise number was missing.) ($P = 0.036$). The results suggest that OT improves the protective response of PPD mothers.

Mah[29] conducted a clinical study to evaluate whether intranasal delivery of OT to mothers with PPD would affect their parenting-related expressed emotion. A total of 25 mothers with PPD took part in the research. FMSS, SAM, and COWAT were used as outcome measures. Researchers discovered that mothers in the OT condition (13/25) were more sorrowful ($p = 0.01$) and described raising their infants as a difficulty more frequently ($p = 0.038$), but the quality of their interaction with their infants was more positive ($p = 0.036$). The findings imply that while OT does not make depressed mothers feel happier, it improves their perceptions of the interaction with the infants.

Discussion

PPD has serious consequences for women's health, and negatively impacts the capacity to care for their infants. The damages of PPD include difficulties with breastfeeding, behavioural functions, social interaction, and so on.[31,32] The pathological mechanism of PPD is multifactorial that has yet to be fully clarified. Disruption of the oxytocinergic system has received less attention until recently.[13]

There has been a growing body of evidence that OT is associated with PPD. A study[33] suggests that oxytocin receptor epigenetic variation could be a key mediator of mood-related neuroactive steroid synthesis. It was also reported in an animal study that injection of OT into paraventricular nucleus alleviated depressive-like behaviors in a PPD rat model.[34] PPD has been demonstrated to be inversely associated to plasma OT levels both throughout pregnancy and after delivery.[14,35]

In this systematic review, six randomized controlled trials were included to evaluate the effect of exogenous OT on PPD. The effects of OT were roughly divided into emotion and cognition. Four of the trials showed the regulation of OT to women's emotion. However, the results were conflicting: One trial showed that OT alleviated the depressive mood of PPD (22/55);[25] two trials showed that OT had no effect on PPD (but reduce negative thoughts in healthy mothers (26/58), or decrease the narcissistic trait (5/16));[24,26] One trial showed that OT aggravated depression as mothers with OT administration was more sorrowful than control group (13/25).[29] Four of the trials showed the regulation of OT to women's cognition. In general, oxytocin enhanced postpartum depressive women's perception of their relationship with the infants (Roughly half of 25; Roughly half of 16; 13/25).[27–29] However, it was also reported that there were no effects of OT on facial emotion recognition (20/55) and maternal sensitivity (Roughly half of 25).[25,27] Furthermore, an MRI experiment[23] showed that intranasal OT markedly enhanced the BOLD fMRI response of fathers to seeing pictures of own infants within the caudate nucleus, visual cortex, and the dorsal anterior cingulate (dACC). It suggests that intranasal oxytocin induces more activations of brain regions in human fathers involved in reward, empathy and attention.

Among the six studies, five[24,26–29] of them assessed depression status in the late (more than 6 weeks) postpartum period, while the postpartum period of the other one[25] is uncertain (2–12 weeks). This reminds us that if mothers use OT in the early postpartum period, it may enhance the benign relationships between mothers and their infants, and thus to prevent the occurrence of PPD. On the other hand, a recent cross-sectional study indicated that maternal and paternal depression were positively associated in the early postnatal period.[36] We speculate that the use of OT by couples may be better than that by mothers alone. These may be the directions for future studies.

Collectively, our systematic review partly supports that exogenous OT may improve the cognition of women with postpartum depression to their infants, while the effect on emotion is still controversial. However, there are some limitations: (1) There are extremely few RCTs that are relevant to our topic. Furthermore, half of the six RCTs are from a same laboratory, which could lead to biased conclusions. (2) There is relatively high clinical heterogeneity among the trials, notably in terms of clinical response. The outcome measures of each article are distinct, which makes it difficult for intercomparison and inductive summary. (3) The sample sizes of the studies are small, resulting in limited conclusion power. Further RCTs with larger samples and more diversified evaluation criterias are needed to better reveal the potential efficacy of OT on PPD.

Abbreviations

ANPS, Affective Neuroscience Personality Scale; COWAT, Controlled Oral Word Association Test; dACC, dorsal anterior cingulate; DSM, Diagnostic and Statistical Manual of Mental Disorders; EPDS, Edinburgh Postnatal Depression Scale; ESP, Enthusiastic Stranger Paradigm; FDA, Food and Drug Administration; FER, facial emotion recognition; FMSS, Five Minute Speech Sample; GABA, Gamma Absorptiometry Aminobutyric Acid; HDRS, Hamilton Depression Rating Scale; MeSH, medical subject heading; PANAS, Positive and Negative Affect Scale; PNTQ, Postnatal Negative Thoughts Questionnaire; PPD, Postpartum depression; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PVN, paraventricular nucleus; RCTs, Randomized controlled trials; SAM, Self-Assessment Manikin; SWAP, Shedler–Westen Assessment Procedure.

Ethics Approval

Ethics approval was not required, as all data were gathered from previous published studies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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