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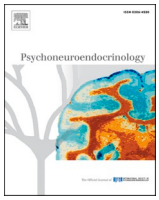

# Intranasal oxytocin increases breast milk oxytocin, but has a reduced effect in depressed mothers: A randomized controlled trial

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ABSTRACT

Oxytocin (OT) plays pivotal roles in stress regulation, mother–infant bonding, and breastfeeding, all of which are adversely impacted by postnatal depression (PND). In a double-blind, randomized controlled trial, we assessed endogenous OT concentrations first in the breast milk of new mothers at baseline, and second following the administration of exogenous OT compared to a placebo delivered via a nasal spray.

*Method:* Participants were mothers (N = 62, aged 23–42 years) and their infants (aged 3–9 months). Each mother underwent screening for PND symptoms using the Edinburgh Postnatal Depression Scale (EPDS). N = 26 mothers scored above the cut-off point (≥9) on the EPDS, and N = 36 mothers scored below. Breast milk samples, collected during breastfeeding, were assayed for OT content.

*Results:* Baseline endogenous OT concentration in breast milk was not associated with maternal low mood. Exogenous OT administration was associated with a significant increase in breast milk OT, but with reduced effect in mothers experiencing symptoms of PND compared to control mothers.

*Conclusions:* Future studies should test if breast milk OT exhibits a protective role against the developmental disadvantages of maternal PND on children. The current findings may reflect a possible disruption of the interaction between the central and peripheral OT pathways during breastfeeding in mothers experiencing symptoms of PND. These insights shed new light on the potential biological mechanisms involved in the transference of mental health vulnerabilities from mothers to infants.

## 1. Introduction

Breastfeeding has been found to have a positive effect on the mother–infant relationship and children's development (Feldman and Eidelman, 2003; Oddy et al., 2010; Sanefuji et al., 2021). In addition, breastfeeding can be protective against perinatal mental health difficulties developing in new mothers (Wang et al., 2021). However, mothers who intend to breastfeed during pregnancy, and do not go on to, are twice as likely to experience symptoms of postnatal depression (PND) in the year following childbirth, compared to mothers who did not plan to breastfeed, and do not (Borra et al., 2015). Women experiencing PND who do breastfeed their infant also often report increased negative breastfeeding experiences and early weaning (Hahn-Holbrook et al., 2013; Watkins et al., 2011). This may be because PND is associated with mothers finding it stressful to connect intimately with their infant (Santona et al., 2015), or because PND is associated with greater difficulties in lactation (Brown et al., 2016; Nagel et al., 2022; Stuebe et al., 2012).

The directionality of the relation between PND and reduced breastfeeding likely varies between cases. However, given that negative breastfeeding experiences and early weaning can reduce maternal self-efficacy (Ahmadinezhad et al., 2024), and increase feelings of shame and guilt in mothers who conceptualize breastfeeding as personally important in their new maternal role (Jackson et al., 2021) – each of

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which can trigger or worsen a depressive state – it is important to better understand the relation between PND and reduced breastfeeding. It is likely that social factors influencing the mother's depression contribute to this, considering that breastfeeding mothers typically receive more social support compared to non-breastfeeding mothers (Pope et al., 2016). Although, it is also likely that neuroendocrine mechanisms integral to both stress regulation and breastfeeding physiology, such as oxytocin (OT), prolactin, the hypothalamic-pituitary-adrenal (HPA) axis, gonadal steroids, and the thyroid, are also involved (Stuebe et al., 2013, 2012).

To delve deeper into this, the current study explores the association between oxytocin (OT) levels in breast milk and PND. OT, a neuropeptide hormone, has received less research attention than reproductive and other stress hormones in the etiology of PND. However, in recent years there has been a surge of interest in OT due to its involvement in the regulation of social and parenting behavior, anxiolytic effects, pair bonding (including mother−infant bonds), and lactation for breastfeeding, each of which are areas in which women experiencing PND have difficulties (Grewen et al., 2010; Jobst et al., 2016). Notably, the infant's OT system also develops in the context of the early parent−child relationship, and has been found to be altered in the children of mothers who experienced PND (Priel et al., 2019). However, little is known about the relation between OT during breastfeeding and PND. The present study aims to fill this gap.

Central OT is produced in the hypothalamus and communicates through neurons with OT receptors distributed across the brain, which influence a range of affective, cognitive and social-cognitive processes (Moses et al., 2024; Ross and Young, 2009; Triana-Del Rio et al., 2022). OT is also released from the hypothalamus into the bloodstream, where it binds to peripheral OT receptors located throughout the body, including on the skin, oral mucosa, and mammary glands (Uvnäs-Moberg and Prime, 2013). This is referred to as peripheral OT. During breastfeeding, the infant's suckling typically activates peripheral OT receptors on the mammary alveoli of the mother's breast. This stimulation of the OT receptors by the infant suckling then induces contraction of the myoepithelial cells that cause the milk ejection for lactation (Lincoln and Paisley, 1982). In addition, the sensory nerves stimulated in both mothers and infants during skin-to-skin contact and infant suckling during breastfeeding activate peripheral OT receptors in these areas (on the skin, infants' oral mucosa, and mothers' mammary glands). This sensory information is then conveyed via spinal cord nerve fibers back to the hypothalamus, which prompts the central release of OT in both mothers and infants separately (Uvnäs-Moberg and Prime, 2013).

It has been proposed that this interplay between the central and peripheral OT pathways functions as a feedback loop during breastfeeding that promotes sustained lactation in the mother, and induces a biobehavioral coordination between mother and infant during breastfeeding. For example, mother–infant skin-to-skin contact and infant breast-seeking behavior has been found to increase maternal OT (Matthiesen et al., 2001; Yokoyama et al., 1994). Furthermore, this central−peripheral OT feedback loop interacts with OT receptors in the dopaminergic neural reward pathway and the amygdala, which induces an anxiolytic effect in mothers during breastfeeding (Niwayama et al., 2017). This in turn triggers a reward response in both mothers and infants that reinforces mutual engagement and fosters the development of the infants' stress regulation system and social brain network (Altemus et al., 1995; Feldman, 2015; Heinrichs et al., 2001). Consistent with this, breastfeeding mothers on average show lower cortisol levels, blood pressure and heart rate compared to non-breastfeeding mothers (Ebina and Kashiwakura, 2012; Ohmura et al., 2023). In addition, maternal mood scores tend to improve after breastfeeding (Heinrichs et al., 2001), and elevated salivary OT in mothers after breastfeeding is associated with enhanced recognition of positive facial expressions and reduced recognition of negative facial expressions (Matsunaga et al., 2020).

Recent research using hyperscanning has also identified inter-brain synchrony between mothers and infants during breastfeeding in the ventral prefrontal cortex, that regulates emotional responses and decision-making in relation to threat (Minagawa et al., 2023), and where central OT receptors are prevalent (Lee et al., 2017). This study by Minagawa et al. (2023) further found that neural activity during breastfeeding is greater in mothers in brain areas involved in reward processing (right orbitofrontal cortex), and is greater in infants in part of the early social brain network (left temporoparietal junction) involved in processing language, as well as social orientation (Minagawa et al., 2023), the latter of which is related to OT (Clark et al., 2013; Lindley Baron-Cohen et al., 2024).

Given this evidence, OT may therefore be a promising pathway through which breastfeeding confers advantages for infant brain and social development, and may also be useful in understanding the psychobiological effects of clinical conditions such as PND. Levels of OT have been found to be reduced in both mothers who experienced PND and their children, compared to controls, as measured in saliva, plasma, and urine (Apter-Levy et al., 2013; Pratt et al., 2015; Stuebe et al., 2013). Moreover, dysregulation of the OT system has been shown to mediate the relation between maternal depression and child development over time, particularly by restricting synchrony and mutually regulated mother–child interactions that typically facilitate social learning (Priel et al., 2019). In addition, breast milk OT has been found to support the infant's emerging immune system (s-IgA) (Zagoory-Sharon et al., 2024), which is disrupted in both mothers with PND and their children (Ulmer-Yaniv et al., 2018). Despite these findings, the evidence remains limited regarding the relation between OT during breastfeeding and PND. Stuebe et al. (2013) reported a negative correlation between plasma OT during breastfeeding and maternal PND symptoms at 2 months postpartum. However, this observation was not confirmed in later studies, which reported no difference in plasma OT during breastfeeding between depressed and non-depressed mothers (Lara-Cinisomo et al., 2017; Whitley et al., 2020).

It should be noted that these studies that measured the relation between plasma OT during breastfeeding and maternal PND included mothers who were given the choice of breastfeeding or bottle feeding their infant with formula during the testing session. Therefore the definition of breastfeeding in these investigations is perhaps misleading. In Stuebe et al.'s (2013) study, some of the mothers also used an electronic pump to express their milk for the observed infant feeding, which has been found to be associated with negative experiences in some women, including triggering distress, anxiety and pain (Bartels et al., 2020; Stuebe et al., 2013). In Whitley et al.'s (2020) study, some of the mothers had also stopped lactating by the time of data collection. Given the inconsistency of findings between these studies and how breastfeeding was defined, it is therefore still unclear whether plasma OT is affected by PND during breastfeeding or not.

Since OT is directly related to lactation and is activated in the brain via OT receptors that are stimulated by infant suckling during breastfeeding, breast milk OT may provide a more relevant measure for examining the relation between OT and PND during breastfeeding. However, to date, no research has directly measured OT in the breast milk of women experiencing PND. The current study aims to investigate this relation for the first time, since if it is found that women experiencing PND have lower concentrations of OT in their breast milk, it may suggest that the reduced incidence of breastfeeding among such women, compared to controls, might be due to a disruption in the peripheral OT pathways leading to breastfeeding difficulties. Furthermore, while previous research has investigated the role of salivary and plasma OT in social relationships, OT in breast milk may offer a more sensitive index of bonding within the mother−infant relationship, for mothers who breastfeed. The present study does not address each of these points, but begins this line of inquiry by examining the relation between breast milk OT and symptoms of PND in new mothers.

In addition to exploring the relation between naturally occurring levels of OT and PND, we adopted an experimental approach to explore

how intranasal administration of exogenous OT relates to levels of endogenous OT in breast milk, and whether this relation is moderated by PND. Intranasal administration of OT acts directly on the brain (Quintana et al., 2021), and by measuring OT in breast milk, this approach aims to investigate the coordination between the central and peripheral OT pathways in relation to breastfeeding. Given that previous research has demonstrated that intranasal administration of OT induces lactation within 70 seconds of inhaling a 5IU dose (Huntingford, 1961), OT administration could potentially offer benefit to new mothers experiencing PND who would like to breastfeed but are also encountering lactation difficulties.

### 1.1. Aims and hypotheses

This study had two primary objectives: (1) To investigate the relation between endogenous OT in breast milk and maternal mood at baseline. We predicted that endogenous breast milk OT would be negatively associated with symptoms of PND, measured across a continuum of low mood. Additionally, we predicted that OT concentrations in breast milk would be lower in women experiencing PND compared to mothers in the control group. (2) To test for change in endogenous breast milk OT concentrations following the administration of exogenous OT via a nasal spray, in comparison to baseline levels and following placebo administration. We predicted that endogenous OT levels in breast milk would increase in both mothers experiencing PND and those in the control group, following the administration of intranasal exogenous OT, relative to baseline levels and placebo administration.

## 2. Material and methods

Participants comprised breastfeeding mothers ($N = 62$, mean age = 33.38, SD = 4.35, ranging from 23 to 42 years old) and their infant (mean age = 4.73, $SD = 1.69$, ranging from 3 to 9 months old). Recruitment took place in community settings. Mothers were included in the study if they were in a pattern of breastfeeding their infant at the time of taking part, either exclusively or in combination with other food, and between 3 and 9 months postpartum. Mothers provided demographic information through a questionnaire, which included data on age, marital status, mental health history, birth control usage, menstrual cycle, pregnancy duration, childbirth, and breastfeeding patterns. The detailed demographic characteristics of the participants are reported in Table 1. Further details on sample recruitment can be found in Lindley Baron-Cohen et al. (2022).

The study excluded mothers who were younger than 18 years old or currently pregnant. All participants were evaluated for symptoms of postnatal depression (PND) using the Edinburgh Postnatal Depression Scale (EPDS, range = 0–24, mean = 8.35, $SD = 5.80$) (Cox et al., 1987). The participants were subsequently divided into two groups based on their EPDS scores: a group of probable PND cases ($N = 26$) and a low PND control group ($N = 36$), using an EPDS score of $\geq 9$ as the clinical threshold (Cox et al., 1987). This EPDS cut-off point was based on the recommended level for clinical referral of PND and in cultural contexts where PND is under-reported in community settings (Cox et al., 1987; National Childbirth Trust, 2017, 2021; Smith-Nielsen et al., 2018). The sample sizes were determined based on a power calculation which suggested that with $N \geq 24$ per group, the study would have 80 % power to detect a significant difference between groups, with a medium effect size ($d = .60$) and a 5 % Type 1 error probability.

### 2.1. Protocol

The study employed a double-blind, placebo-controlled, case-controlled, randomized controlled trial, within-subjects, cross-over design. Data was collected at a research laboratory at three different time points: at baseline and after the administration of both exogenous oxytocin (OT) and a placebo via a nasal spray. Each of these sessions

**Table 1**
Participant demographic characteristics.

| Category | | Total Sample (N = 62) % | Probable PND cases (N = 26) % | Low PND Controls (N = 36) % |
|---|---|---|---|---|
| Marital status | Married | 79.3 | 73.1 | 83.3 |
| | Cohabiting | 9.5 | 11.5 | 8.3 |
| | Single | 11.1 | 15.4 | 8.3 |
| Sexual orientation | Heterosexual | 88.9 | 88.5 | 91.7 |
| | Bisexual | 3.2 | 7.7 | 0.0 |
| | Missing | 7.9 | 3.8 | 8.3 |
| Parent to other children | Yes | 15.9 | 11.5 | 19.4 |
| | No | 84.1 | 88.5 | 80.5 |
| Educational level | University | 79.3 | 84.6 | 77.9 |
| | College | 1.6 | 0.0 | 2.8 |
| | School | 1.6 | 3.8 | 0.0 |
| | Missing | 17.5 | 11.5 | 19.5 |
| Birth control use | Non-hormonal | 85.7 | 84.6 | 86.1 |
| | Hormonal | 14.3 | 15.4 | 13.9 |
| Menstruating at Baseline | No | 96.8 | 96.2 | 97.2 |
| | Yes | 3.2 | 3.8 | 2.8 |
| Menstruating at the time of Placebo administration | No | 98.4 | 100.0 | 98.4 |
| | Yes | 1.6 | 0.0 | 1.6 |
| Menstruating at the time of OT administration | No | 98.4 | 100.0 | 98.4 |
| | Yes | 1.6 | 0.0 | 1.6 |
| Breastfeeding | Exclusively | 82.5 | 80.8 | 86.1 |
| | In combination | 17.4 | 19.2 | 13.9 |
| | No | 0.0 | 0.0 | 0.0 |
| Self-report of recent formal diagnosis | Postnatal depression | 12.7 | 30.8 | 0.0 |
| | Postnatal anxiety | 14.3 | 34.6 | 0.0 |
| | Psychosis | 0.0 | 0.0 | 0.0 |
| | Post-traumatic stress disorder | 1.6 | 3.8 | 0.0 |
| | Borderline personality disorder | 3.2 | 7.7 | 0.0 |
| Mental health history | Depression | 20.6 | 38.5 | 8.3 |
| | Anxiety | 12.7 | 23.1 | 5.6 |
| | Psychosis | 1.6 | 3.8 | 0.0 |
| | Post-traumatic stress disorder | 1.6 | 3.8 | 0.0 |
| | Borderline personality disorder | 3.2 | 7.7 | 0.0 |
| Currently receiving mental health treatment | Talking therapy | 11.1 | 26.9 | 0.0 |
| | Antidepressant | 3.2 | 3.8 | 2.8 |
| | None | 85.7 | 69.2 | 97.2 |
| Previous mental health treatment | Talking therapy only | 15.9 | 30.8 | 5.6 |
| | Antidepressant only | 1.6 | 0.0 | 2.8 |
| | Talking therapy and antidepressant | 6.3 | 11.5 | 2.8 |
| | None | 76.1 | 57.7 | 88.9 |
| Pregnancy length | Full term | 79.4 | 80.8 | 80.6 |
| | Premature | 12.7 | 15.4 | 11.1 |
| | Missing | 7.6 | 3.8 | 8.3 |
| Birth delivery | Vaginal | 68.2 | 73.1 | 63.9 |

(continued on next page)

**Table 1** (*continued*)

| Category | | Total Sample (N = 62) % | Probable PND cases (N = 26) % | Low PND Controls (N = 36) % |
|---|---|---|---|---|
| | C-section | 31.7 | 26.9 | 36.1 |
| Birth delivery was induced | Yes | 34.9 | 46.2 | 27.8 |
| | No | 57.1 | 53.8 | 61.1 |
| | Missing | 7.9 | 0.0 | 11.1 |
| Epidural during delivery | Yes | 54.0 | 53.8 | 55.6 |
| | No | 38.1 | 46.2 | 33.3 |
| | Missing | 7.9 | 0.0 | 11.1 |
| Primary nationality | British | 52.4 | 42.3 | 61.1 |
| | Non-British | 47.6 | 57.7 | 38.9 |
| First language | English | 71.4 | 73.1 | 72.2 |
| | Other | 28.6 | 26.9 | 27.8 |

were scheduled about one week apart and conducted at the same time of day. The same data collection procedures were followed for each condition. Mothers and their infants were given privacy to breastfeed. Four minutes after the start of breastfeeding, a researcher entered the room to collect a sample of breast milk. This timing was chosen based on previous studies showing that mothers' plasma OT levels spike approximately 4 minutes after the start of breastfeeding at 3–4 months postpartum (Uvnäs-Moberg et al., 1990).

Mothers were asked to manually express 5 ml of breast milk into a 50 ml polypropylene conical centrifuge tube for the sample. They were instructed to continue breastfeeding while expressing the milk sample, by switching the side from which the infant was feeding and expressing milk from the breast the infant had just been feeding from. All collected samples were immediately placed on ice and the total duration of the feed was recorded. The collected breast milk samples were processed using a centrifuge twice for 5 minutes each at 16.1rcf at a temperature of 4°C. The samples were then divided into 1 ml volumes and stored at −80°C on the same day as collection until analysis.

For each of the sessions involving exogenous OT and placebo nasal spray administration, a single dose of either OT or placebo was given prior to breastfeeding. This involved administering 3 actuations (4IU, 6.72 μg each) to each nostril. After the nasal spray was administered, participants were invited to rest for a period of 35–45 minutes. This allowed time for the pharmacokinetics of OT to cross the blood-brain barrier (Quintana et al., 2021). Following this rest period, breast milk samples were collected using the same protocol as described for the baseline session. The nasal sprays used in the experiment either contained 24IU OT (40.32 μg, Syntocinon) or a placebo. Both types of nasal spray were dispensed by independent pharmacists in identical bottles to ensure blinding of the content.

The order in which the active and placebo sprays were administered for each participant was randomized using a computer-generated list. This list ensured the order of nasal spray administration was counterbalanced across the participant sample. The codes that were used to identify the content of the nasal sprays were unblinded only after the data collection period for the entire sample had been completed.

### 2.2. Measures

#### 2.2.1. Endogenous breast milk OT concentration

At the time of analysis, the breast milk samples were transported at −80°C to the Feldman Lab, where they continued to be stored at −80°C until the day of analysis. On this day, the assaying sample was thawed completely and centrifuged again, before being transferred into clean tubes. Determination of OT concertation was performed by using a commercial OT Enzyme-Linked Immunosorbent Assay (ELISA) kit (Assay Design, ENZO, New York, USA). The inter-assay coefficients of the controls and samples were less than 10.6 % and 16.8 %, respectively.

#### 2.2.2. Mood measure

Participants' baseline mood was assessed using a self-report questionnaire, the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). The EPDS is a ten-item scale that is widely used to screen for symptoms of postnatal depression and anxiety. Respondents rate each item on a four-point scale (0−3), with higher total scores indicating greater severity of symptoms experienced over the past seven days. Mothers who score ≥9 in total or ≥1 on question 10 indicating risk of self-harm are recommended to be referred for clinical assessment (Cox et al., 1987).

### 2.3. Data analysis

The data was analyzed using a series of mixed-model analyses of variance (ANOVAs) with group (probable PND vs low PND controls) as the between-subjects factor and condition (baseline, post-OT, post-placebo) as the within-subjects factor. Post-hoc t-tests were conducted to compare groups at each condition. Correlational analyses were conducted to examine the relationship between mood measures and OT concentrations. All analyses were performed using SPSS version 26. There was attrition of $N = 5$ participants in the low PND control group (see CONSORT diagram), so some of the analyses were based on a sample of $N = 24$ probable PND cases and $N = 32$ low PND controls.

## 3. Results

### 3.1. Associations with demographic variables

The distribution of endogenous breast milk OT concentrations was not normal, marked by a skewness of 4.68, $SE = .32$, and a kurtosis of 23.37, $SE = .62$. Upon the identification and winsorization of two outliers ($SD > 4$), the distribution normalized, with the skewness reducing to.79, $SE = .32$ and kurtosis falling to.54, $SE = .62$. For the primary analysis, the winsorized data was used, while the raw data was employed for secondary analyses. Various demographic variables were probed for any potential association with endogenous breast milk OT, using Spearman's correlation tests (see Table 2). Spearman's correlation revealed a negative relation between endogenous breast milk OT and infant age. Independent Samples t-tests found there was a significant group difference in maternal age, history of depression, current and previous use of mental health treatment, between mothers experiencing PND and low PND controls. See Table 3 for group means and standard deviations.

### 3.2. Associations between endogenous breast milk OT and maternal mood

Given that maternal EPDS scores did not follow a normal distribution (skewness of .85, $SE = .30$, and a kurtosis of .43, $SE = .60$) Spearman's correlation was employed to investigate their relationship with endogenous breast milk OT. No significant correlation was found, $r_s(55) = .16$, $p = .24$. Furthermore, independent samples t-tests revealed no significant differences in breast milk OT between mothers experiencing PND and low PND controls: $t(55) = 1.32$, $p = .19$; with a mean OT concentration of $M = 227.47$, $SD = 54.47$ in probable PND cases, compared to $M = 209.20$, $SD = 50.34$ in low PND controls. These findings were further corroborated by the Bayes Factor Independent Samples test, setting the Bayes factor to $BF_{01}$ to indicate the strength of evidence in favor of the null hypothesis, which showed evidence supporting the null hypothesis that maternal PND does not affect breast milk OT concentration (Bayes factor = 2.31).

Similar results were obtained when tests were rerun using the unprocessed data: Spearman's correlation, $r_s(55) = .16$, $p = .23$; independent samples *t*-test, $t(55) = -.59$, $p = .56$; with a mean OT concentration of $M = 227.47$, $SD = 54.47$ in probable PND cases,

**Table 2**
Correlation Matrix for Associations between Maternal Breast Milk OT and Demographic Variables.

| Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Breast milk OT | | | | | | | | | | | | |
| 2. Infant Age | −.36** | | | | | | | | | | | |
| 3. Infant Weight | −.31 | .51** | | | | | | | | | | |
| 4. Maternal Age | .18 | −.17 | −.19 | | | | | | | | | |
| 5. Marital Status | .14 | .24 | .01 | −.24 | | | | | | | | |
| 6. Sexual Orientation | .20 | .05 | −.04 | −.04 | .16 | | | | | | | |
| 7. Hormonal Birth Control Use | .04 | −.18 | −.11 | −.11 | .12 | .18 | | | | | | |
| 8. History of Depression | −.05 | .09 | −.04 | −.05 | .02 | .14 | −.11 | | | | | |
| 9. History of Anxiety | .10 | .02 | .03 | −.07 | .05 | −.08 | −.17 | .51 | | | | |
| 10. Currently Receiving Mental Health Treatment | .13 | −.09 | −.11 | −.12 | .11 | .19 | .22 | .36** | .23 | | | |
| 11. Previously Received Mental Health Treatment | .02 | −.07 | −.07 | .04 | −.04 | .24** | .07 | .58** | .08 | .41** | | |
| 12. Gestation Duration | −.11 | −.15 | .03 | .01 | −.26 | .08 | −.11 | −.29* | −.26* | .07 | −.02 | |
| 13. Degree of Breastfeeding in Relation to Other Foods Provided for the Infant | −.13 | .05 | .09 | .05 | −.11 | −.42** | −.08 | −.28* | −.07 | −.07 | −.29* | .23 |

*p < .05, **p < .005.

**Table 3**
Means and standard deviations of demographic variables.

| | *Probable PND cases Mean (SD)* | *Low PND control group Mean (SD)* | *Independent Samples t-test* |
|---|---|---|---|
| *Infant Age* | *4.87 (1.97)* | *4.59 (1.44)* | $t(44) = .60$, $p = .56$ |
| *Infant Weight* | *6.57 (1.19)* | *6.62 (1.90)* | $t(50) = -.11$, $p = .92$ |
| *Maternal Age* | *32.02 (4.34)* | *34.89 (4.11)* | $t(55) = -2.56$, $p = .01$* |
| *Marital Status* | *1.42 (.76)* | *1.27 (.63)* | $t(57) = -.84$, $p = .41$ |
| Sexual Orientation | *1.08 (.28)* | *1.00 (.00)* | $t(56) = 1.45$, $p = .16$ |
| Hormonal Birth Control Use | *.15 (.37)* | *.15 (.36)* | $t(53) = .02$, $p = .98$ |
| History of Depression | *.38 (.50)* | *.09 (.29)* | $t(38) = 2.68$, $p = .01$* |
| History of Anxiety | *.23 (.43)* | *.06 (.24)* | $t(37) = 1.81$, $p = .08$ |
| Currently Receiving Mental Health Treatment | *.35 (.56)* | *.06 (.35)* | $t(40) = 2.28$, $p = .03$* |
| Previously Received Mental Health Treatment | *.65 (.98)* | *.21 (.65)* | $t(42) = 2.00$, $p = .05$* |
| Gestation Duration | *.84 (.37)* | *.88 (.33)* | $t(56) = -.42$, $p = .68$ |
| Degree of Breastfeeding in Relation to Other Foods Provided for the Infant | *.28 (.68)* | *.12 (.48)* | $t(56) = 1.04$, $p = .30$ |

compared to $M = 252.37$, $SD = 210.23$ in low PND controls; and Bayes Factor Independent Samples test, bayes factor = 4.29. Taken together, these analyses show that in this study, maternal mood as observed by PND status is not associated with the concentration of OT in breast milk.

### 3.3. Impact of exogenous OT administration on endogenous breast milk OT

To examine the changes in endogenous breast milk OT following exogenous OT nasal administration relative to baseline and placebo administration, repeated measures three-way interaction ANOVA tests were applied, comparing condition (exogenous OT and placebo), maternal endogenous breast milk OT, and group (probable PND cases and low PND controls). The within-subject variables incorporated in this analysis included endogenous breast milk OT at baseline, exogenous OT and placebo administration conditions, across three within-subject factor levels. We observed a significant main effect of condition, $F(2,84) = 7.16$, $p = .001$, $n_p^2 = .15$, along with a significant interaction between condition and group, $F(2,84) = 3.39$, $p = .04$, $n_p^2 = .08$. Intranasal OT administration influenced endogenous breast milk OT in both groups. As illustrated in Fig. 1, the influence of condition on endogenous breast milk OT was predominantly driven by exogenous OT administration in the low PND control group. The tests were re-run using the raw data, which reinforced the initial trend in results, demonstrating a significant effect of condition, $F(2,84) = 7.97$, $p < .001$, $n_p^2 = .16$, and a significant interaction between condition and group, $F(2,84) = 3.92$, $p = .02$, $n_p^2 = .09$. Therefore, exogenous OT administration appeared to modulate endogenous breast milk OT concentration, with this effect being driven by the low PND control group. To examine any possible confounding effects of associated mental health conditions, maternal self-reported diagnosis of anxiety, post-traumatic stress disorder and borderline personality disorder were added into the original model as covariates. However, none of these factors significantly influenced the model and the main effect of condition remained significant ($F(2,78) = 5.35$, $p = .007$, $n_p^2 = .12$), although the effect of the interaction between condition and group became non-significant ($F(2,78) = 2.60$, $p = .08$, $n_p^2 = .06$).

## 4. Discussion

This paper reports an initial investigation of OT in breast milk among mothers experiencing symptoms of PND at varying levels. Contrary to our predictions, there was no significant association between endogenous breast milk OT and maternal mood at baseline. Similarly, there was no significant group difference detected in the baseline concentration of endogenous breast milk OT between women experiencing PND and mothers who reported symptoms of PND below the clinical threshold. This potentially suggests that the negative breastfeeding experiences and premature weaning often reported by women with PND may be more attributable to psychological factors, influenced by the mother's depressive state, rather than to biological factors such as OT. However, further investigation is needed to test if these results replicate before ruling out the possibility of an association between maternal mood and breast milk OT, and to examine other potential interactions with related biological factors that were not measured here. For example, it is possible that plasma OT compared to breast milk OT may have different associations and biological effects related to maternal mood during breastfeeding.

When the effect of exogenous OT nasal administration on endogenous breast milk OT was tested, it was found to have a significant effect that was more pronounced in the low PND control group. Considering past research has documented increases in both salivary and breast milk endogenous OT following exogenous OT nasal administration in healthy populations (Huntingford, 1961; van Ijzendoorn et al., 2012; Weisman et al., 2012), the reduced effect in mothers experiencing PND may suggest a potential disruption to the OT system in this group. This could occur either in the central or peripheral pathways, or in their coordination, particularly in the context of breastfeeding. This is worthy of further investigation.

Disparities in the location of potential disruption within the central

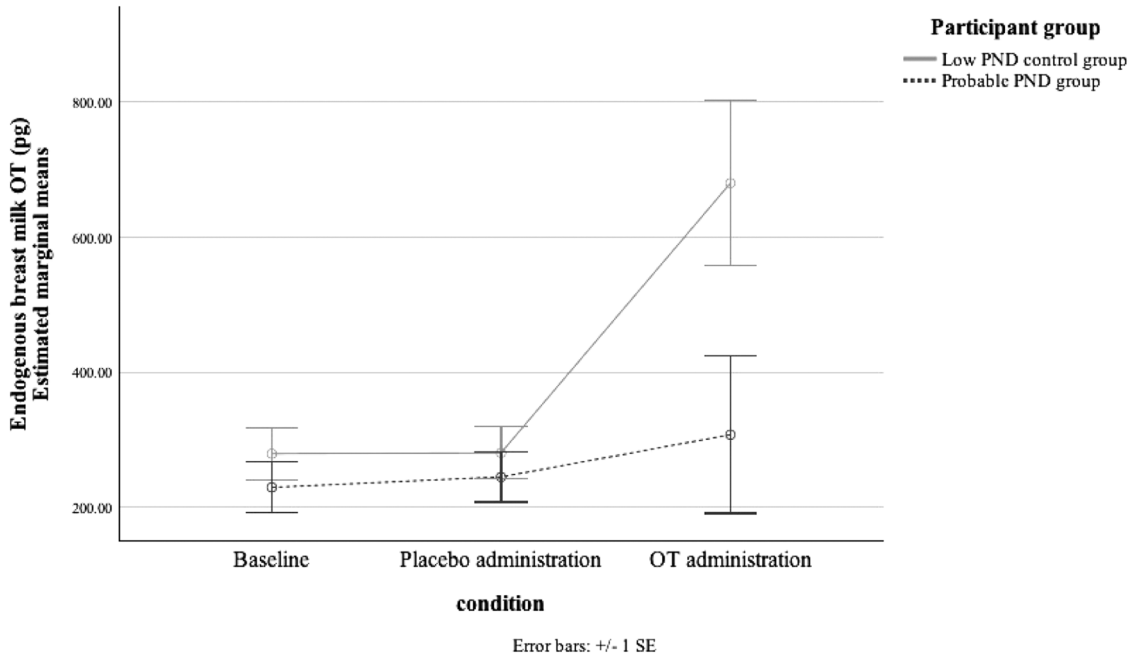


**Fig. 1.** Line graph showing endogenous breast milk OT concentration by group and condition.

and peripheral OT pathways may also account for differences in the profiles of mothers experiencing PND, given that some women experience lactation difficulties accompanying their low mood, while others do not. Although the absence of an association between endogenous breast milk OT and maternal EPDS scores at baseline might suggest that OT receptors in the mammary glands are unaffected by maternal low mood, this may reflect an evolutionary adaptation to ensure that women encountering low mood post childbirth are still able to lactate milk to feed their infant. If this is the case, breast milk OT could serve as a critical source for building the infant's OT system, if maternal OT pathways are compromised due to the mother's depression. However, if there is a disruption to the central–peripheral OT feedback loop during breastfeeding in women experiencing PND, this could also account for why such women, despite being able to lactate milk to feed their infant, do not report the anxiolytic or reward effects related to breastfeeding, as do women who are not experiencing PND. In line with this hypothesis, past research suggests that neither plasma OT concentration during breastfeeding nor PND symptoms are influenced by the duration of breastfeeding or the volume of milk released (Stuebe et al., 2013; Uvnäs-Moberg et al., 1990). This therefore hints that the primary disruption to the OT system in mothers experiencing PND may be linked to the central pathways. This should be investigated further.

In addition, our finding that exogenous OT administration significantly impacted endogenous breast milk OT in the low PND control group only supports previous research that has demonstrated inconsistent effects of OT administration, and which suggested that a single dose of 24 IU OT may have reduced effects in severe cases of psychopathology (Lindley Baron-Cohen et al., 2022). Whether this could be due to less plasticity of the OT system, or reduced OT receptor responsivity in more severe clinical cases (Feldman, 2020, 2021) remains unknown. In either scenario, a stronger dose of OT might be required to see substantial effects of OT administration in mothers experiencing PND. Again future research should investigate this.

Understanding the mechanisms through which mental health vulnerability is transferred from mother to child in the context of PND is an important question that remains open. Given that previous research has identified altered OT in depressed populations in both the central (Purba et al., 1996) and peripheral pathways (Scantamburlo et al., 2007), and the potential for this disruption to specifically impact the mother–child relationship (Apter-Levy et al., 2013), the absence of a baseline association between maternal mood and breast milk OT in our study should be interpreted cautiously until it is replicated. At this stage, it is not possible to conclude whether the lack of association we found is because OT pathways in breast milk are unrelated to maternal mood. It is important to note that OT concentrations in breast milk are lower than in other fluids such as saliva and plasma (Feldman et al., 2011; Takeda, 1986; Uvnäs-Moberg et al., 2020). However, it is also possible that plasma OT might be associated more with maternal physiology and psychological functioning than breast milk OT, and this could be investigated further.

Several limitations of our study warrant consideration. First, whilst our sample size was based on a power analysis and consistent with other studies that reported differences in OT administration between mothers experiencing PND and controls (Fortunata Donadon et al., 2020; Mah et al., 2013), the group sizes were still relatively small. Given that OT concentrations in breast milk are smaller than in other fluids (Uvnäs-Moberg et al., 2020), we acknowledge that our analyses could have lacked the power necessary to detect significant small effects between groups at baseline. As such, our findings should be viewed as tentative until they are replicated in larger studies. In addition, it should be noted that we decided to analyze OT at a single consistent time point, rather than analyzing multiple samples across a feeding session. While each milk ejection is directly tied to OT release and follows a consistent pattern within an individual's profile across the first nine months of lactation (Uvnäs-Moberg and Prime, 2013), measuring OT at a single time point during breastfeeding can only provide indication of a state marker within a short time-interval (Martins et al., 2020). Future research could therefore enhance our understanding of the relation between breast milk OT and PND by comparing averages of breast milk samples across the duration of feeding, as well as in comparison with plasma OT concentration during breastfeeding. Finally, we defined PND cases using a clinical cut-off point from self-reported scores on the EPDS. Although the EPDS is a well-validated screening measure for PND (Martin and Redshaw, 2018), future studies could enhance validity by defining cases using formal clinical diagnoses.

Despite these limitations, our study provides the first test of OT in breast milk in mothers experiencing PND and offers valuable insight into the potential protective role of breast milk OT for building the infant's

OT system and buffering against the adverse effects of maternal depression on infant development. The findings also identified a potential disruption in the interaction between the central and peripheral OT pathways in mothers experiencing PND in the context of breastfeeding that has not been studied before. This could have relevance for research investigating new treatments to support women experiencing PND. The results warrant replication in a larger study. Nevertheless, these findings provide a new direction for research to investigate and deepen our understanding of the mechanisms underlying intergenerational vulnerability during the postnatal period, and the most effective areas to target in PND treatment to support both mothers and their children. Understanding how breast milk OT can be affected in PND may also offer a new direction for future research exploring some of the adverse effects of PND on children's early development. Specifically, if infants are deprived of one potential source of OT – from breast milk – that would typically help regulate stress and social orientating within the mother–infant relationship, this could have important developmental implications.

## Ethical approval

Ethical approval was obtained by the Health Research Authority (212606, 17/EE/0082) and the study is registered at http://www.clinicaltrials.gov (NCT04745494).

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## CRediT authorship contribution statement

**Lindley Baron-Cohen, K:** Conceptualization, Funding acquisition, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Fearon, P:** Methodology, Resources, Supervision, Writing – review & editing. **Feldman, R:** Methodology, Resources, Supervision, Writing – review & editing. **Hardiman, P:** Resources. **Zagoory-Sharon, O:** Resources, Data curation, Writing – review & editing. **Meins, E:** Supervision, Writing – review & editing. **Fonagy, P:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2025.107374.

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