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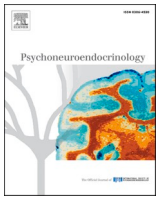

Oxytocin and early life stress in late preterm newborns: an exploratory study

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ABSTRACT

Oxytocin, a neuropeptide traditionally associated with labor and lactation, has been increasingly recognized for its broader roles, including maintaining physiological stability amidst environmental challenges. Previous studies on preterm infants have reported inconsistent results regarding oxytocin responses to maternal contact. The present study investigated peripheral oxytocin levels in late preterm newborns (34^{+0} - 36^{+6} weeks gestation), an epidemiologically relevant and neurodevelopmentally vulnerable subgroup of preterm infants. Fifty newborns (males 56%, median gestational age = 36.1 weeks) were enrolled between April 2022 and September 2023. Timing and type of first maternal contact (within the first hour post-birth or later; skin-to-skin or not), maternal mental health, attachment, and tactile interactions during the first two days of life were assessed using self-report questionnaires. Neonatal oxytocin levels were measured from blood samples collected after 48 h of life. Higher oxytocin levels were observed in twins ($p = 0.05$, $d = 0.67$), newborns delivered by caesarean section ($p = 0.002$, $d = 1.14$), and those who experienced delayed first maternal contact ($p = 0.005$, $d = 1.18$) or lacked skin-to-skin contact ($p = 0.001$, $d = 1.35$). Oxytocin levels were also positively correlated with maternal age ($rho = 0.38$, $p = 0.02$). In multivariate analyses, lack of skin-to-skin contact predicted higher oxytocin levels after 48 h of life ($p = .019$, $\eta^2_p = .27$). Although interpretation is limited by the absence of data on maternal oxytocin administration - which, despite ongoing debate on its placental transfer, may account for the observed differences - our results reinforce previous speculations on the context-dependent nature of oxytocin regulation in preterm infants. Elevated oxytocin levels under stressful conditions may reflect an adaptive neuroendocrine response potentially buffering the developing brain against excessive glucocorticoid exposure.

1. Introduction

Oxytocin, a nine-amino acid neuropeptide, has gained growing recognition for its broad and complex physiological functions, extending well beyond its classical roles in labor and lactation. While traditionally known for stimulating uterine contractions and milk ejection, emerging evidence suggests that oxytocin may also act as an allostatic hormone, contributing to maintaining homeostasis in response to environmental

Abbreviations: **AGA**, Adequate for Gestational Age; **EPDS**, Edinburgh Postnatal Depression Scale; **HPA**, Hypothalamic-Pituitary-Adrenal axis; **LGA**, Large for Gestational Age; **MPAS**, Maternal Postnatal Attachment Scale; **PICTS**, Parent-Infant Caregiving Touch Scale; **SD**, Standard Deviation; **SE**, Standard Error; **SGA**, Small for Gestational Age; **STAI-Y**, State-Trait Anxiety Inventory – Form Y.

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changes (Quintana and Guastella, 2020).

Oxytocin is detectable already during fetal life and is released into the fetal circulation around birth (Chard et al., 1971; Leake et al., 1981; Marchini et al., 1988). During the postnatal period, oxytocin enhances excitatory synaptic transmission and experience-dependent plasticity, particularly within the sensory cortex (Muscatelli et al., 2022), thus marking one of the initial stages of brain-environment integration in human development. Accordingly, understanding which stimuli promote oxytocin secretion during the neonatal period is pivotal to clarifying its role in early brain development and long-term outcomes.

The literature suggests that contact with the mother is a crucial element in regulating the oxytocinergic system during this developmental phase. Animal models indicate that early maternal care can elevate oxytocin levels in pups and foster bonding, while maternal separation may result in reduced oxytocin synthesis and receptor availability, impacting social behavior and stress responses later in life (Onaka and Takayanagi, 2021). Likewise, previous research suggests that affiliative touch, thermal comfort and visual contact (as during skin-to-skin care) may impact short and long-term outcomes through stimulation of oxytocin release in human neonates (Moberg et al., 2020).

Early, uninterrupted mother-infant skin-to-skin contact should be promoted as soon as possible after birth, provided that appropriate monitoring is ensured to promptly identify and manage any signs of maternal or neonatal distress. Indeed, the WHO/UNICEF Baby-Friendly Hospital Initiative (WHO, 2017) recommends initiating skin-to-skin contact immediately or as soon as possible after delivery and continuing it for at least 60 min. Additionally, evidence from a recent Cochrane review (Moore et al., 2025) supports immediate skin-to-skin contact regardless of mode of delivery in healthy full-term and late preterm infants, due to demonstrated benefits including improved exclusive breastfeeding rates, thermoregulation, glycemic stability, and enhanced physiological stabilization.

Skin-to-skin contact is further supported by attachment theory, which posits that early and sustained mother-newborn contact plays a critical role in the establishment of secure attachment and subsequent socioemotional development. Early skin-to-skin contact provides developmentally salient somatosensory, thermal, and affective stimuli that contribute to infant regulation during a sensitive period. These stimuli are thought to act, at least in part, through oxytocinergic pathways and stress-regulatory neuroendocrine mechanisms, promoting dyadic synchrony, maternal sensitivity, and infant bio-behavioural homeostasis. Conversely, maternal separation is increasingly understood as a potential source of biobehavioural stress, a non-neutral event associated with disruptions in offspring autonomic regulation, sleep organization, thermoregulation, and stress-response systems, with potential long-term effects (see review by (Norholt, 2020)).

Nurturescience, a framework proposed by (Bergman et al., 2019), emphasizes the biological importance of continuous mother-infant contact during the early postnatal period. By conceptualizing the mother-infant dyad as a co-regulatory system, nurturescience posits that early nurturing experiences, particularly skin-to-skin care, are fundamental to promoting long-term development, emotional connection and resilience. Emerging evidence also suggests that early tactile experiences may influence epigenetic modulation of stress-response systems, with potential long-term effects: previous research (see review by (Nance et al., 2025)) has shown how early parental care can affect the epigenetic regulation of the oxytocin receptor gene in the offspring, which, in turn, may influence social behavior, stress resilience and susceptibility to mental health disorders later in life.

Studies in preterm infants (i.e., born before 37^{+0} weeks of gestation) have reported inconsistent results regarding the direction of peripheral oxytocin responses to maternal contact, highlighting the complexity of oxytocinergic regulation in this population. For instance, (Vittner et al., 2018) observed a significant increase in neonatal salivary oxytocin levels during 60 min of skin-to-skin contact, suggesting an activation of the oxytocinergic system in response to comforting parental physical proximity. In contrast, (Kommers et al., 2018) reported a decrease in salivary oxytocin levels during kangaroo mother care in preterm twins, which the authors interpreted as a normalization from an initially elevated baseline.

Within the preterm infant population, late preterm infants (i.e., born between 34^{+0} and 36^{+6} weeks of gestation) represent the most epidemiologically significant subgroup, accounting for approximately 70% of all preterm births. Despite the high incidence, this population remains understudied and often overlooked in both clinical practice and research (Fanaroff and Wilson-Costello, 2024). Previously classified as "near--term", late preterms are now recognized as a distinct population, with more favorable outcomes than earlier preterms (Manuck et al., 2016), yet greater physiological immaturity compared to term neonates (Karnati et al., 2020; Sharma et al., 2021). This immaturity increases their vulnerability to both short- and long-term complications. Moreover, between 34 and 40 weeks of gestation, the brain undergoes rapid growth and organization, with significant increases in cortical volume, synaptogenesis, and myelination. Consequently, a late premature birth during this period may still represent a significant risk factor for neurodevelopment, contributing to the adverse neurological and behavioural outcomes frequently reported in this population (Karnati et al., 2020). To mitigate these risks, investigating potential regulatory mechanisms early in life is critical.

The present study adopted an exploratory approach to investigate the context-dependent dynamics of oxytocin regulation during the immediate postnatal period in late preterm newborns, particularly with respect to early maternal interactions. To this end, we considered variables related to early maternal separation, skin-to-skin contact, maternal mental health, and maternal attachment and tactile interactions with the newborn during the first two days of life, as these factors represent key aspects of the early postnatal caregiving environment and offer a useful framework for describing the context in which initial physiological regulation and affiliative processes may develop.

2. Materials and methods

2.1. Study design and setting

The present study is a single-center, observational study conducted in the Well-Baby Unit of the Neonatology and Neonatal Intensive Care Unit of Mangiagalli Clinic, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Italy) in collaboration with the Department of Psychology of the University of Milano-Bicocca (Bicocca Child&Baby-Lab), Milan (Italy).

The Mangiagalli Clinic is a large tertiary referral center for neonatal care overseeing approximately 6000 births per year. The neonatology service is organized into two distinct wards: a Well-Baby Unit (nursery), which provides care for stable term or late preterm newborns, and a Neonatal Intensive Care Unit (NICU), which admits premature and/or critically ill newborns. In recent years, the Clinic has recorded around 450 late preterm births per year, with 80% of all late preterm newborns admitted to our Well-Baby Unit. In accordance with our local clinical protocol, after birth late preterm newborns should remain with their mothers for two hours of uninterrupted skin-to-skin contact. However, if newborns have trouble adapting to extra-uterine life, a neonatal evaluation may be necessary. This could lead to interventions such as blood tests or incubator placement, potentially requiring early separation from the mother. The Well-Baby Unit is equipped with incubators that may be used for otherwise healthy term or late preterm newborns who require limited supportive care during the early postnatal period, such as assistance with adaptation to extra-uterine life or short-term monitoring. Phototherapy can also be provided in the Well-Baby Unit, if clinically indicated. Newborns who develop significant complications requiring more complex medical interventions are instead transferred to the NICU. In the Well-Baby Unit, once the short-term monitoring is complete, newborns proceed to rooming-in with their mother.

This study was approved by the Milan Area 2 Ethics Committee, session held on 14/09/2021. Written informed consent to participate in the study was obtained from both parents of the newborns. Study procedures were conducted in accordance with the Declaration of Helsinki.

2.2. Study population

For the purposes of the present study, we enrolled late preterm newborns (34^{+0}-36^{+6} weeks of gestation) consecutively born at our hospital and subsequently admitted to the Well-Baby Unit of Mangiagalli Clinic, Milan, from April 2022 to September 2023. Maternal exclusion criteria included age < 18 years, limited proficiency in Italian, and known psychiatric disorders. Neonatal exclusion criteria encompassed postnatal complications requiring admission to the NICU, as well as confirmed or suspected congenital malformations or genetic syndromes. Newborns admitted to the NICU were excluded from the study because the greater clinical complexity and more stressful environment could influence the study outcomes.

2.3. Data collection and study procedures

Maternal sociodemographic and clinical data, along with perinatal history and hospitalization details, were collected for all enrolled newborns from electronic medical records (Neocare i&t Informatica e Tecnologia Srl, Italy). All variables collected are reported in Table 1. Recorded hospitalization data included type of feeding (i.e., exclusive breastfeeding, mixed feeding, exclusive formula feeding) and number of skin-breaking procedures performed within the first 48 h of life. These invasive procedures included venipunctures or capillary punctures conducted for various diagnostic purposes, such as the assessment of complete blood count, blood cultures, glycemic monitoring, serum bilirubin monitoring, blood gas analysis, and other biochemical blood tests required by the newborn's medical conditions during its first 2 days of life. Such procedures do not include perinatal non-invasive clinical procedures such as incubator placement to ease adaptation to extra-uterine life or short-term monitoring.

Additional data were derived from questionnaires completed by the mothers. During the birth hospitalization, mothers self-administered 4 validated questionnaires to assess early postnatal interactions and emotional well-being: to measure the frequency of maternal affective touch during the first postnatal interactions, the Parent-Infant Caregiving Touch Scale (PICTS; (Koukounari et al., 2015; Mariani Wigley et al., 2023)); to evaluate mother-infant bonding and attachment, the Maternal Postnatal Attachment Scale (MPAS; (Condon and Corkindale, 1998; Scopesi et al., 2004)); to assess anxiety symptoms, the Spielberger State-Trait Anxiety Inventory – Form Y (STAI-Y; (Spielberger, 1983; Spielberger et al., 1989)); and to screen for post-partum depressive symptoms, the Edinburgh Postnatal Depression Scale (EPDS; (Benvenuti et al., 1999; Cox et al., 1987)). All questionnaires were completed by the mothers online using Qualtrics survey software (Qualtrics, Provo, UT, USA; https://www.qualtrics.com).

Additionally, mothers were asked to complete an online survey

Table 1
Basic clinical characteristics of the study population (N = 50).

Variable		Median	25th Percentile	75th Percentile	N	%
Maternal age		36	34	38		
Primiparity					28	56%
Nationality	Italian				48	96%
	Turkish				1	2%
	Cuban				1	2%
Education	Primary school				19	38%
	Secondary school				14	28%
	University				2	4%
	Preferred not to disclose				15	30%
Occupation[+]	Managers				3	6%
	Professionals				8	16%
	Clerical Support Workers				13	26%
	Service & Sales Workers				1	2%
	Elementary Occupations				3	6%
	Unemployed / Not in labour force				5	10%
	Preferred not to disclose				17	34%
Preeclampsia					5	10%
Hypothyroidism					13	26%
Antenatal corticosteroid therapy (two doses)					13	26%
Mode of delivery	Caesarean section				35	70%
	Vaginal				15	30%
Twins					30	60%
Newborn Sex	Male				28	56%
Gestational age		36,14	35,57	36,28		
1st min Apgar score		9	9	9		
5th min Apgar score		10	10	10		
Birth weight (g)		2473	2260	2720		
Birth weight category	AGA				42	84%
	LGA				1	2%
	SGA				7	14%
Timing of first maternal contact*	After 1 h				18	62,1%
	Within 1 h				11	37,9%
Type of first maternal contact*	Not skin-to-skin				20	60,6%
	Skin-to-skin				13	39,4%
Serum oxytocin (pg/mL)		789	745,9	856,4		
Skin-breaking procedures		5	5	7		
Type of feeding	Mixed feeding				35	70%
	Exclusive formula feeding				8	16%
	Exclusive breastfeeding				7	14%

* Due to missing data, the percentages reported in the table are calculated based on the available sample size for each variable, rather than the total study sample. Abbreviations: AGA, adequate for gestational age; LGA, large for gestational age; SGA, small for gestational age. [+]Occupations have been categorized according to SCO-08 (International Standard Classification of Occupations 2008).

developed in Qualtrics regarding the timing (within the first hour or later) and type (skin-to-skin or not) of their first postnatal contact with their newborn in order to collect information on early mother-infant interactions.

Finally, blood samples for oxytocin measurement were obtained from the newborns enrolled via capillary heel puncture performed as part of routine metabolic screening after the 48th hour of life. At this time, 0.5 mL of capillary blood was collected into a micromethod tube without anticoagulant. As per our study protocol, once collected, the samples were centrifuged at 3000 rpm in a refrigerated centrifuge at 5°C for 10 min, and the resulting serum was aspirated and transferred to microcentrifuge tubes (Eppendorf™) labeled with the appropriate alphanumeric code. The centrifuge is located in a dedicated room in the NICU of our Institution, which is one story below the Well-Baby Unit where sample collection took place. Accordingly, samples were centrifuged within 2–5 min of being collected. Immediately after centrifugation, the serum samples were stored at −80°C until laboratory analysis. At our Institution, the −80°C freezer is located in the basement of the same building as the Well-Baby Unit and the NICU. No repeated freeze-thaw cycles were performed. This handling protocol was applied to all blood samples collected.

Serum was preferred over saliva for oxytocin measurement due to the significant challenges of salivary sampling in newborns. Especially in the early postpartum period, low salivary volume, frequent feeding, and limited cooperation often lead to insufficient sample yield. In contrast, capillary blood sampling, albeit slightly more invasive, ensures adequate volumes without the need for pooling or extensive processing.

2.4. Questionnaires

2.4.1. PARENT-INFANT CAREGIVING TOUCH SCALE - PICTS

The PICTS (Koukounari et al., 2015; Mariani Wigley et al., 2023) is a 12-item self-report questionnaire designed to assess caregivers' self-perceived frequency of behaviors commonly involved in early parent-infant tactile interactions. The questionnaire encompasses 3 domains (each comprising 4 items): Stroking, Holding, and Affective Communication. Parents are asked to rate each behavior on a 5-point Likert scale indicating how frequently they engage in each specified caregiving behavior (1 = never; 5 = very often). A total score (ranging from 12 to 60) is calculated by adding up the responses to all items in the questionnaire. The higher the total score, the more frequently the parent engages in the touch-related aspects of caregiving. Subscale scores can be computed for each of the 3 domains. In our study, the item *I leave my baby to lie down* was reverse-scored (Brzozowska et al., 2021).

2.4.2. MATERNAL POSTNATAL ATTACHMENT SCALE - MPAS

The MPAS (Condon and Corkindale, 1998; Scopesi et al., 2004) consists of 19 items, with response formats varying across 2-, 3-, 4-, and 5-point Likert scales, depending on the item. To ensure equal weighting of questions, all responses are re-coded to a score ranging from 1 (low attachment) to 5 (high attachment). Consequently, the total MPAS score ranges from 19 to 95, with higher scores indicating stronger maternal postnatal attachment to the infant. (Condon and Corkindale, 1998) originally identified three distinct dimensions: pleasure in interaction with the infant, absence of hostility towards the infant, and quality of mother-infant attachment. Conversely, the confirmatory factor analysis performed by (Scopesi et al., 2004) on the Italian version of the MPAS identified a 6-factor structure encompassing: time with the baby, competence, anxiety, burden, detachment, and pleasure in proximity. Since previous studies conducted on the Italian population have used the 3-factor structure (e.g., (Arioli et al., 2025)), in the present study both structures were considered.

2.4.3. SPIELBERGER STATE-TRAIT ANXIETY INVENTORY FORM Y – STAY-Y

The STAI-Y is organized into two separate sets of 20 questions, allowing for a clear separation between stable (STAI-Y Trait) and situational (STAI-Y State) anxiety. The answer to each question is given on a 4-point Likert scale (1 = "not at all"; 4 = "a lot"). A score of 4 indicates the presence of a higher level of anxiety for 10 STAI-Y State (3, 4, 6, 7, 9, 12, 13, 14, 17, 18) and 11 STAI-Y Trait items (2, 4, 5, 8, 9, 11, 12, 15, 17, 18, 20). For the remaining items, the scoring weight is reversed. The total score for each set of questions ranges between 20 and 80, with higher scores indicating greater levels of anxiety.

2.4.4. EDINBURGH POSTNATAL DEPRESSION SCALE – EPDS

The EPDS consists of 10 questions on a 4-point Likert scale assessing depressive symptoms experienced over the previous seven days. Responses range from 0 to 3, with higher scores indicating more frequent or severe symptoms. Three items (items 1, 2 and 4) are reverse-scored. The total score ranges from 0 to 30. Due to inconsistencies in the definition of a cut-off score (Benvenuti et al., 1999; Cox et al., 1987), in the present study EPDS scores were treated as a continuous variable.

2.5. Laboratory analyses

The analyses were conducted at the Clinical Chemistry and Immunochemistry Laboratory of the International Center for the Assessment of Nutritional Status (ICANS), University of Milan, Milan, Italy.

The Human Oxytocin ELISA Kit (Competitive EIA; LifeSpan BioScience, Inc.) was used to measure total serum oxytocin, according to the manufacturer's instructions. Briefly, each well of a microtiter plate is pre-coated with the target antigen. Standards or samples are added to the wells, along with a biotin-conjugated detection antibody. Free antigens (in standards or samples) and antigens bound to the plate compete to bind to the detection antibody. Everything except the bound biotin-conjugated detection antibody is washed away. Next, an avidin-horseradish peroxidase (HRP) conjugate is added, which binds to biotin. Unbound HRP is washed away. A TMB (3.3,5.5′-tetramethylbenzidine) substrate is then added, which reacts with the HRP enzyme resulting in a colorimetric reaction. This reaction is stopped by adding a sulfuric acid solution and the optical density (OD) of the well is measured at a wavelength of 450 nm ± 2 nm. The OD of an unknown sample can then be compared to a standard curve generated using known concentrations of antigen to determine its concentration. After the test is performed, the data is analyzed by plotting a standard curve and calculating the concentration of the target antigen in the unknown samples based on the OD readings. The detection range is 15.625–1000 pg/mL. Sensitivity is < 9.375 pg/mL. Intra-assay coefficient of variation (CV) was < 8%; inter-assay CV was < 10%. The CVs were calculated from replicate measurements and fell within the method's acceptance criteria. The samples were not concentrated.

2.6. Sample size calculation and statistical analyses

Since the study relied on a convenience sample of all eligible late preterm newborns admitted to the Well-Baby Unit during the predefined study period, an *a priori* sample size calculation was not performed, precluding prospective power estimation. However, sensitivity analyses were performed with the G power software (version 3.1.9.4) for each statistical test to determine whether the available sample size provided adequate power (0.80) to detect significant effects and effect sizes.

Descriptive statistics were computed for demographic, clinical, and psychological variables, with continuous variables reported as means and SD or median and interquartile ranges.

The internal consistency of the self-administered questionnaires (STAI-Y, EPDS, PICTS, and MPAS) was assessed using Cronbach's alpha.

To explore the relationship between oxytocin levels and the collected variables we performed either parametric or non-parametric tests, depending on the distribution of each variable. Correlations between oxytocin levels and continuous variables were assessed using Pearson's correlation for normally distributed data and Spearman's rank

correlation for non-normally distributed data, as determined by the Shapiro-Wilk test. Differences in oxytocin levels across binary categorical variables were analyzed using independent samples *t*-tests, whereas categorical variables with more than two levels were analyzed using univariate Analysis of Variance (ANOVA).

Variables showing significant associations with oxytocin levels in univariate analyses (correlations and *t*-tests analyses) were included in a multivariable general linear model to identify independent predictors. Variance inflation factors (VIFs) were computed to assess multicollinearity among the predictors. VIF quantifies how much the variance of a regression coefficient is increased due to correlations with other predictors, which can reduce the precision of the estimated effects and affect the stability of the model. Although no universal cutoff exists, VIF values above 10 are commonly considered indicative of severe multicollinearity (O'brien, 2007). To assess potential correlation between (and confounding effect of) maternal age and the significant categorical predictors we ran a point-biserial correlation.

To assess potential interdependency among the categorical predictors - mode of delivery, timing of first maternal contact, type of first maternal contact, and plurality - chi-square tests of independence with Yates' continuity correction were performed, and effect sizes were quantified using the phi coefficient (φ), an index that measures the strength of association between categorical variables.

All statistical analyses were conducted using the R software (R Core Team, 2023, version 4.3.2., R Foundation for Statistical Computing, Vienna, Austria). A significance threshold of $p < 0.05$ was applied to all analyses.

3. Results

The study sample included 50 late preterm newborns with a median gestational age of 36.1 weeks (IQR 35.5;36.28). Table 1 reports the basic socio-demographic and clinical characteristics of the study population. Mean oxytocin levels were 806.98 pg/mL (range: 544.7–1029.4 pg/mL). Median STAI-Y, EPDS, PICTS and MPAS total and subscale scores are shown in Table 2. The Cronbach's alpha of the questionnaires indicated adequate internal consistency: STAI-Y: 0.95 (standardized: 0.95), EPDS: 0.86 (standardized: 0.85), PICTS: 0.83 (standardized: 0.84), MPAS: 0.70 (standardized: 0.74).

Correlation analyses showed that oxytocin levels were positively associated with maternal age (*rho* =0.38, $p = 0.02$). No significant correlations were found involving birth weight, gestational age, number of skin-breaking procedures and questionnaire-based measures (i.e., EPDS, STAI-Y, PICTS, MPAS; all *ps* > 0.05). Details and results of these analyses are provided in the Supplementary file.

Table 2
Median STAI-Y, EPDS, PICTS and MPAS total and subscale scores.

Variable	Median	25th Percentile	75th Percentile
STAI-Y Total score	76	65	86
STAI-Y STATE	39	33	44
STAI-Y TRAIT	36	32	41
EPDS Total score	7	5	11
PICTS total score	52	46	54
STROKING	16	13	18
HOLDING	17	15	19
AFFECTIVE COMMUNICATION	16	15	17
MPAS Total score	84,6	81,3	86,4
MPAS – QUALITY	40,8	38,2	42,2
MPAS – HOSTILITY	19,6	18,2	21
MPAS – PLEASURE IN INTERACTION	24	23	25
MPAS – COMPETENCE	20,9	20,8	22,2
MPAS – ANXIETY	11	8,2	11
MPAS – BURDEN	13,6	12,2	15
MPAS – DETACHMENT	15	15,0	15
MPAS – PLEASURE IN PROXIMITY	10	9	10

Results from independent samples *t*-test showed no differences in oxytocin levels between newborns whose mothers had received antenatal corticosteroid therapy and those whose mothers had not (t (35) = .48, p = .64).

Oxytocin levels were higher in twins compared to singletons (836.69 pg/mL, SD = 125 vs. 767.99 pg/mL, SD = 59.8, $t(35) = 2.02$, $p = 0.05$, Cohen's $d = 0.67$), and in newborns born by caesarean section compared to those delivered vaginally (842.04 pg/mL, SD = 101 vs. 733.94 pg/mL, SD = 81.2, $t(26.61) = 3.49$, $p = 0.002$, Cohen's $d = 1.14$). Moreover, newborns who experienced the first contact with their mothers after the first hour of life had higher levels of oxytocin compared to newborns who did so within the first hour after birth (857.27, pg/mL, SD = 110 vs. 747.46 pg/mL, SD = 61.4, $t(21.01) = 3.11$, $p = 0.005$, Cohen's $d = 1.18$). Lastly, neonatal oxytocin levels were lower when the first mother-newborn contact was skin-to-skin than when it was not (750.56, pg/mL, SD = 74 vs. 871.90, pg/mL, SD = 98.4, $t(25.29) = 3.71$, $p = 0.001$, Cohen's $d = 1.35$) (Fig. 1).

No significant associations between oxytocin levels and the other categorical variables collected (i.e., primiparity, preeclampsia, hypothyroidism, newborn sex, birth weight category, type of feeding, maternal education, maternal occupation) were observed (all *ps* >.07). Details of these analyses are provided in the Supplementary file.

Multivariate analyses revealed a significant main effect of type of first maternal contact ($b = -141.829$, $t(18) = 2.58$, $p = .019$, $\eta^2_p = .27$), showing that oxytocin levels were higher in newborns who did not experience skin-to-skin as first maternal contact (estimated marginal mean = 885 pg/mL, SE = 37.7) compared to those who did (estimated marginal mean = 743 pg/mL, SE = 30.4). VIF values were 1.04 for age, 3.6 for plurality, 3.35 for mode of delivery, 5.34 for time to first maternal contact and 2.5 for type of first maternal contact.

Chi-square tests revealed strong associations among all categorical predictors. Mode of delivery was significantly associated with timing of first maternal contact: infants born via caesarean section were more likely to have been first held by their mothers after the first hour of life (18 vs. 0 newborns; $\chi^2(1) = 14.62$, $p < .001$, $\varphi = .79$), and less likely to have experienced skin-to-skin contact as their first maternal contact (20 vs. 0 newborns; $\chi^2(1) = 13.07$, $p < .001$, $\varphi = .7$), compared to those delivered vaginally. A consistent pattern was observed for twins, who were more likely to have experienced delayed first maternal contact (i.e., after the first hour of life) (15 vs. 3 newborns; $\chi^2(1) = 15.8$, $p < .001$, $\varphi = .8$) and to not have experienced skin-to-skin contact as their first maternal contact (15 vs. 5 newborns; $\chi^2(1) = 6.6$, $p < .01$, $\varphi = .51$). Additionally, twin births were also more frequently associated with caesarean delivery (27 vs. 8 newborns; $\chi^2(1) = 12.00$, $p < .001$, $\varphi = .53$). Lastly, delayed first maternal contact was strongly associated with the absence of skin-to-skin contact (15 vs. 2 newborns; $\chi^2(1) = 9.41$, $p = .002$, $\varphi = .64$). The heatmap of φ values is presented in Fig. 2, while full contingency tables are displayed in the Supplementary file.

We performed point-biserial correlations between maternal age and the categorical variables mode of delivery, plurality, time to first maternal contact, and type of first maternal contact. None of these correlations were statistically significant (all *rs* <.12, $p > .14$).

Sensitivity analyses, conducted with a power of 0.80 and an alpha level of 0.05, indicated that the available sample size was sufficient to detect large effects (specifically, *rho* = 0.38 and Cohen's *d* values of 0.96 for plurality, 1.12 for mode of delivery, 1.21 for timing of first maternal contact, and 1.13 for type of first maternal contact, and $f^2 = .72$ for the multivariate analysis). This suggests adequate power to detect large effects in all comparisons except those involving plurality, which may have been underpowered.

4. Discussion

The present exploratory study investigated the context-dependent pattern of oxytocin regulation during the first 48 h of life in late

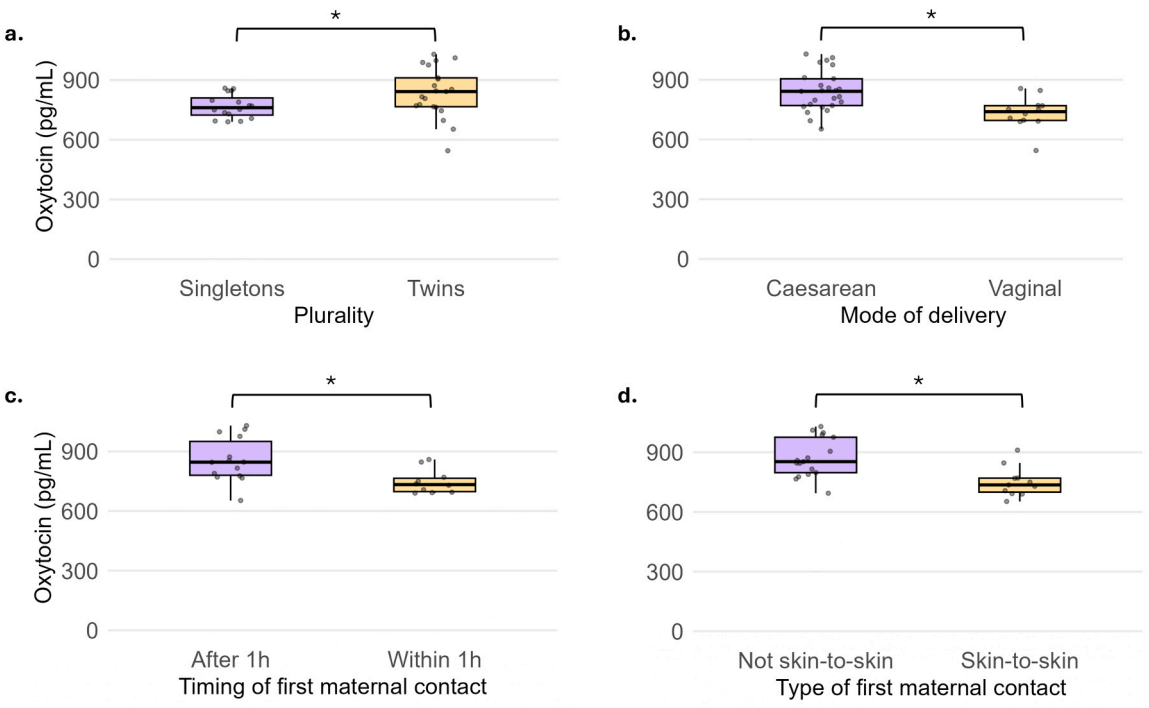

Fig. 1. Box plots illustrating differences in oxytocin levels measured after 48 h of life in late preterm newborns, stratified by: plurality (panel a), mode of delivery (panel b), timing and type of first maternal contact (panels c and d). Black lines represent the medians; boxes indicate the interquartile ranges (IQR); individual data points are shown as dots. *$p < 0.05$.

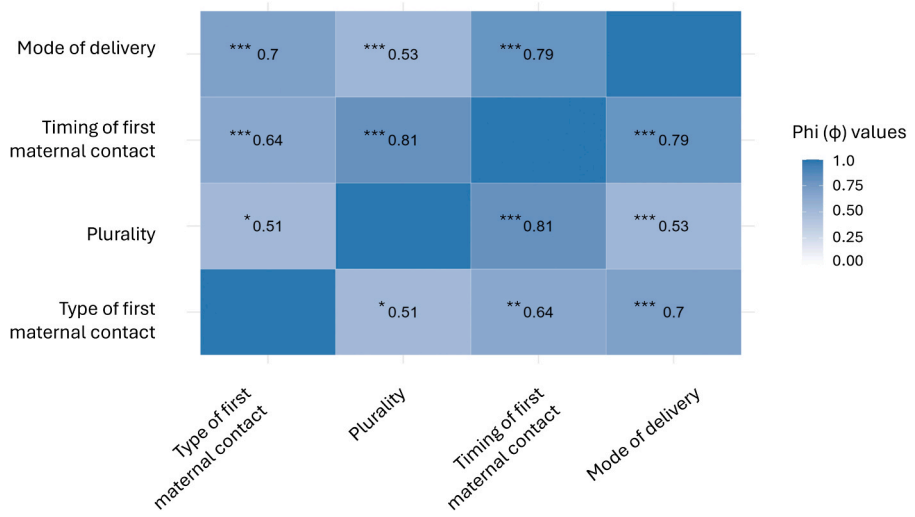

Fig. 2. Heatmap of the associations among timing of first maternal contact, type of first maternal contact, mode of delivery and plurality binomial variables. Phi (φ) coefficients > 0.5 are interpreted as indicating a strong association between variables. *** $p < .001$; **$p < .01$; *$p < .05$.

preterm newborns, with a specific focus on early maternal interactions within the first two days of life. Specifically, we measured neonatal oxytocin levels from blood samples collected after the 48th hour of life and examined their association with perinatal history, hospitalization details, timing and type of first maternal contact (within the first hour post-birth or later; skin-to-skin or not), as well as with maternal mental health, attachment, and tactile interactions during the first two days of life, which were assessed using self-report questionnaires.

Our findings showed that late preterm newborns who experienced delayed maternal holding (i.e. after the first hour of life) or lacked early skin-to-skin contact exhibited higher oxytocin levels after 48 h of life than those held within the first hour of life and/or who had skin-to-skin as their first maternal contact. Although causality cannot be inferred, this may suggest that early mother-infant separation (i.e., within the first hour after birth) may be associated with oxytocin regulation in the first days of life in late preterm infants, as assessed by oxytocin levels after the first 48 h of life. Consistent with this interpretation, the elevated oxytocin levels observed in caesarean-born infants and twins may reflect the lack of early maternal contact in the first hour of life, as these newborns are commonly likely to require perinatal interventions soon after birth (e.g., blood exams, incubator care placement to ease adaptation to extra-uterine life or short-term monitoring) that often lead to early separation from the mother (Crippa et al., 2019). The strong interdependence among the categorical variables considered (i.e., mode of delivery, plurality, timing of first maternal contact, and type of first maternal contact) suggests that these variables may capture overlapping

aspects of early mother-infant interaction (i.e., early separation). Importantly, in the multivariate analysis, the type of maternal contact (i.e., skin-to-skin or not) emerged as an independent predictor of oxytocin levels measured after the first 48 h of life, explaining 27% of the variance. Notably, these results cannot be attributed to maternal age, as, despite correlating with oxytocin levels, it was not found to be associated with any of the aforementioned variables.

Contrary to our hypothesis, oxytocin levels did not correlate with the number of skin-breaking procedures or self-report measures of maternal mental health, attachment and tactile interactions in the first two days of life, suggesting that these potential stressors did not influence oxytocin levels measured after 48 h of life. Therefore, we could speculate that oxytocin regulation in late preterm newborns may be influenced by very early postnatal exposures (i.e, within the first hour after birth), particularly skin-to-skin contact, potentially indicating a sensitive period during which initial caregiving experiences could have a meaningful impact on the newborn, as previously postulated (Widström et al., 2019; Moberg et al., 2020).

Early mother-infant contact plays an important role in regulating both physiological and psychological processes, yet its importance is often overlooked in clinical practice.

Immediate and sustained contact after birth, particularly skin-to-skin, likely facilitates neonatal thermoregulation, improves early physiologic stabilization, and promotes glucose homeostasis in healthy term and late-preterm newborns (Moore et al., 2025), thereby easing the transition to extra-uterine life. It is also likely associated with higher rates of exclusive breastfeeding at hospital discharge to one month postbirth and at six weeks to six months postbirth (Moore et al., 2025). In term newborns, skin-to-skin contact contributes to improved neurobehavioral state organization (Ferber and Makhoul, 2004), and in preterm infants it has been associated with increased vagal tone, interpreted as accelerated autonomic maturation, and improved neurobehavioural status at term (Feldman and Eidelman, 2003). During the early postnatal period, particularly within the first one or two hours after birth, skin-to-skin contact may provide immediate buffering for the newborn, thereby preventing the physiological stress of birth from becoming harmful (Bergman, 2019). Through repeated sensory and emotional co-regulation, these early interactions promote the development of self-regulatory capacities, with evidence of sustained effects on behavioral regulation and cognitive outcomes extending into later childhood in ex-preterm infants (Feldman et al., 2014).

Despite this broad range of benefits, early mother-infant contact is frequently disrupted by routine clinical procedures or organizational workflows, particularly in contexts such as cesarean delivery, where early separation is likely to occur. However, evidence indicates that many of these barriers can be effectively addressed through targeted changes in clinical protocols and staff training, enabling the safe implementation of early skin-to-skin contact even in operative birth settings (Stevens et al., 2014). Importantly, WHO/UNICEF recommend immediate, continuous, and uninterrupted skin-to-skin contact for all mothers and newborns, regardless of the mode of delivery (WHO, 2017).

Early maternal separation has been recognized as a potential source of “toxic stress”, particularly for preterm newborns, with possible implications for later developmental outcomes, thus prompting strong advocacy for a “zero separation” paradigm in post-natal settings (Bergman, 2019). During an early sensitive period, including the perinatal and early postnatal period, even small and brief variations in sensory experience can shape the maturation of basic physiological systems, with cascading effects on social, cognitive, and stress-regulatory development that may persist across the lifespan (see review by (Norholt, 2020)).

Oxytocin synthesis likely begins early during intrauterine life, as it can already be detected in the fetal pituitary gland at approximately 11–15 weeks of gestational age (Leake et al., 1981), and its tissue content increases as gestational age progresses (Burford and Robinson, 1982). In healthy term infants, oxytocin levels are highest at birth and show a rapid decline within the first 30 min (Leake et al., 1981), and then over the first week of life (Kuwabara et al., 1987). A progressive reduction in plasma oxytocin levels has been shown in extremely preterm infants as well from 14 days of life through 34 weeks corrected gestational age (Weber et al., 2017).

In healthy term infants, maternal contact has been hypothesized to influence early oxytocin regulation. However, while biologically plausible and supported by findings from animal models and studies on maternal oxytocin levels (see review by (Moberg et al., 2020), such association is currently supported by scarce and methodologically heterogeneous evidence. In one randomized study, (Hardin et al., 2020) assigned 33 full-term mother-infant dyads to either one hour per day of kangaroo care for six weeks or standard care, and measured infant urinary oxytocin at approximately one week of age and at three months. No statistically significant differences were observed between groups at either time point. Regarding other potential contributors to oxytocin regulation in term newborns, (Leake, 1981) reported no differences in plasma oxytocin levels between breastfed and formula-fed infants during the first 96 h of life.

Studies in preterm infants have yielded mixed results regarding the effect of maternal contact on neonatal oxytocin levels. (Kommers et al., 2018) observed an apparently paradoxical decrease in salivary oxytocin levels during kangaroo mother care compared to the baseline in 11 preterm twin pairs (29–37 weeks of gestation). The authors hypothesized that the oxytocin release triggered by parental co-regulation was less pronounced than the preceding stress-induced surge due to the baseline environment, suggesting that this initial rise, attributed to an overactive sympathetic system, may represent a hormonal request for co-regulation (Kommers et al., 2018). This was further supported by their finding that twins who showed a decrease in oxytocin levels during kangaroo mother care had lower baseline comfort levels, as assessed based on infants’ facial expression and behavior, than those whose oxytocin levels increased. Overall, (Kommers et al., 2018)’s data support the hypothesis that oxytocin levels in preterm infants are context-dependent, rising under stress (e.g., early maternal separation) and decreasing after soothing maternal contact.

Conversely, (Vittner et al., 2018) reported that 60 min of skin-to-skin contact increased salivary oxytocin levels in twenty-eight 3–10 day-old preterm infants ($30–34^{+6}$ weeks of gestation). Oxytocin levels peaked during contact and remained elevated post-contact compared to the baseline. The authors thus concluded that infants’ oxytocinergic system was activated during skin-to-skin contact with a parent, supporting this practice to reduce infant stress responses during NICU stay.

Although the findings of (Kommers et al., 2018) and (Vittner et al., 2018) may appear contradictory, they likely reflect the dynamic and context-dependent nature of oxytocin regulation in preterm infants, influenced by both the infant’s baseline state and the timing and conditions of maternal contact. Additionally, (Vittner et al., 2018)’s study population might have had a more stable baseline and/or a different stage of neuroendocrine maturation compared to (Kommers et al., 2018)’s or our own study sample.

Data from animal models seem to support both the hypothesis proposed by (Kommers et al., 2018) and ours. In rat pups, (Kojima et al., 2012) found that brief maternal separation (1 h) led to marked increases in both hypothalamic (+114.8%) and serum (+125.6%) oxytocin, a finding interpreted by the authors as a neuroendocrinological coping mechanism. However, with continued isolation, while hypothalamic oxytocin remained elevated, serum levels declined, indicating a divergence between central and peripheral oxytocin regulation under prolonged stress. Notably, in (Kojima et al., 2012)’s study, serum oxytocin did not correlate with any of the maternal contact parameters measured. This finding is echoed in our study, where no association was observed between oxytocin levels and PICTS scores. Beyond emotional factors, physical stress may also increase oxytocin levels, as shown by (Nishioka et al., 1998), who reported elevated levels both in the paraventricular nucleus and peripherally in rats exposed to the shaker test. The authors

concluded that oxytocin functions as a stress-responsive hormone, although the underlying mechanisms remain unclear.

Oxytocin has recently been proposed as an allostatic hormone (Quintana and Guastella, 2020), with the ability to modulate both central and peripheral systems to facilitate adaptive responses to environmental challenges. By influencing a wide range of social (e.g., social memory, attachment, aggression) and non-social behaviors (e.g., learning, anxiety, feeding, pain perception), oxytocin may help maintain physiological and behavioral stability in the face of anticipated or ongoing stressors. Evidence from animal (Neumann et al., 2000) and human (Cardoso et al., 2013) studies have shown a functional interaction between oxytocin and the Hypothalamic-Pituitary-Adrenal (HPA) axis, whereby oxytocin counterbalances HPA axis activation by inhibiting glucocorticoid release. In line with these findings, studies in both animals and humans have shown that lactating mothers exhibit attenuated physiological reactivity to stressors (including reduced elevation of cortisol and catecholamines), as reviewed by (Groer et al., 2002). Elevated oxytocin levels during lactation have been suggested as one possible mechanism underlying this effect (Groer et al., 2002). The dampening effect of oxytocin on the HPA axis may play a neuroprotective role in early life, potentially shielding the developing brain from excessive pro-inflammatory glucocorticoid exposure (Zinni et al., 2018). In line with this hypothesis, a study by (Amini-Khoei et al., 2017) reported that intracerebroventricular administration of oxytocin reduced neuroinflammation induced by maternal separation in mice.

Beyond decreased corticosteroid levels, oxytocin administration has also been shown to induce sedation, lower blood pressure, and increase vagal activity in rats (Uvnäs-Moberg, 1997). Furthermore, intraperitoneal injections of oxytocin have been reported to reduce pain sensitivity in newborn rats (Mazzuca et al., 2011). This anti-nociceptive effect may be particularly useful during the early stages of life, contributing to the overall resilience of the developing nervous system against various stressors.

In our study, neonatal oxytocin levels were not associated with factors such as the type of feeding, the number of skin-breaking procedures undergone, maternal mental health, and maternal attachment and tactile interactions in the first 2 days of life (evaluated through the STAI-Y, EPDS, MPAS and PICTS questionnaires, respectively).

The relatively small sample size and the low exclusive breastfeeding rate in our population, consistent with previous reports (Crippa et al., 2019), may explain the non-significant associations. Amidst its many well-documented health benefits, including for preterm infants (Victora et al., 2016; Crippa et al., 2020), breastfeeding is known to provide comfort and soothing to the infant through multisensory stimulation (Maayan-Metzger et al., 2018; Nishitani et al., 2009). Furthermore, breast milk contains measurable levels of oxytocin (Takeda et al., 1986; Zagoory-Sharon et al., 2024), which may be absorbed into the lactating infant's peripheral circulation (Higashida et al., 2017) and potentially influence their social behaviour (Zagoory-Sharon et al., 2024). Nonetheless, during the first days post-partum, when oxytocin levels were measured in the current study, only limited amounts of colostrum are typically available, although biologically essential. Overall, the lack of a statistically significant association between type of feeding and neonatal serum oxytocin levels in our study does not rule out a true association. The potential neuroendocrinological effects of breast milk and breastfeeding in late preterm newborns, and their stress-relieving properties during the early days of life warrant further investigation in future research.

Although painful invasive procedures are recognized contributors to preterm newborns' stress exposure (Vinall and Grunau, 2014), in the present study we did not find a significant association between the cumulative number of skin-breaking procedures and oxytocin levels. However, it may be speculated that response to pain in preterm infants is predominantly phasic (acute), whereas the oxytocin levels measured after 48 h of life may likely reflect a more tonic neuroendocrine state influenced by the broader relational environment, including delayed first maternal contact and lack of skin-to-skin contact. Indeed, it is important to note that the number of skin-breaking procedures is not an exhaustive measure of perinatal interventions or practices that commonly result in early maternal separation but rather represents the cumulative number of invasive procedures performed during the first 48 h of life. As such, it does not capture a range of clinical interventions - such as short-term incubator care - that may involve mother-infant separation without necessarily entailing skin-breaking procedures.

Lastly, regarding the absence in the present study of significant associations between neonatal oxytocin levels and indicators of maternal mental health (EPDS, STAI-Y) or maternal attachment (MPAS), comparison with existing literature is challenging. To the best of our knowledge, no studies have directly examined the association between maternal mental health or attachment and neonatal oxytocin levels in the first 48 h after birth. Conversely, available literature on this topic has primarily looked at maternal oxytocin or oxytocin measured later in infancy or childhood. Importantly, null associations at such an early time point (first 48 h of life) should not be interpreted as evidence against the relevance of maternal mental health or attachment, but rather as consistent with a developmental model in which oxytocinergic regulation is shaped gradually through ongoing relational exposure. Indeed, maternal depression and anxiety can be speculated as influencing infant neuroendocrine regulation at least partly through patterns of caregiving, affective attunement, and repeated dyadic interactions over time. In the first two days of life, these relational processes may not yet be sufficiently established or sustained to yield detectable differences. Similarly, although attachment theory underscores the importance of early caregiver-infant interactions for socioemotional and neurobiological development, attachment-related influences on the infant oxytocinergic system are likely to emerge progressively through ongoing relational experience.

Although limited by a relatively small sample size, the current findings are consistent with a role of skin-to-skin contact in the first hour after birth in the modulation of neonatal serum oxytocin levels in the first two days of life, and suggest that early maternal separation constitutes an important, yet avoidable, stressor for the late preterm newborn soon after birth.

5. Study limitations

Given the exploratory nature of this study, our findings are preliminary and should thus be interpreted with caution. Several factors may limit the generalizability of our findings to a broader population or different clinical settings. Specifically, the monocentric nature of the study and the relatively small sample size, which provided sufficient statistical power to detect only large effect sizes, should be taken into consideration. Moreover, the study design did not allow us to study oxytocin trajectories across the immediate postnatal period, nor did it allow us to draw causal inferences.

Furthermore, difficulties in collecting complete clinical and questionnaire-based data resulted in missing data. However, sensitivity analyses confirmed that the final sample size remained sufficiently powered to detect large effects.

A further consideration in interpreting our findings regards the high serum oxytocin levels found after the 48th hour of life in newborns who had experienced early separation from their mothers. In accordance with our local clinical protocol, this early separation was likely due to perinatal complications requiring immediate therapeutic or supportive interventions (e.g., incubator care, blood tests, glucose administration, etc.). Consequently, this raises the possibility that perinatal stress, rather than maternal separation *per se*, may have contributed to the elevated oxytocin levels observed. Indeed, (Marchini et al., 1988) reported an inverse relationship between umbilical artery pH and oxytocin levels in healthy term newborns: that is, lower pH values (indicative of perinatal stress) were associated with higher oxytocin levels in cord blood plasma. Unfortunately, data on umbilical cord blood gas analysis was not

available in our study population, limiting our ability to assess this potential confounding factor. Notably, though, all enrolled newborns had Apgar scores of 9/10 at 1/5 min, consistent with a stable cardiorespiratory status immediately after birth.

Notably, concurrent neonatal cortisol levels were not measured in the present exploratory study, which was specifically designed to focus on oxytocin dynamics. While this approach allowed targeted investigation of oxytocin regulation, the absence of cortisol measurements limits our ability to contextualize oxytocin levels within the broader physiological stress response and to clearly disentangle oxytocin release associated with affiliative regulation from that occurring in response to stress exposure. Accordingly, our interpretation of elevated oxytocin levels after 48 h of life as potentially stress-related remains necessarily speculative. Future studies should incorporate combined oxytocin-cortisol measurements to more precisely characterize and unequivocally interpret the interactions between these two regulatory systems in the first postnatal days of late preterm infants.

While single measurements of circulating oxytocin are commonly used in the literature as indicators of the physiology of the oxytocin system, questions have been raised on whether they are sufficiently stable to provide valid markers (Martins et al., 2020), especially considering oxytocin's short half-life. Nonetheless, the elevated oxytocin levels after the first 48 h of life observed in our study population may be speculated to reflect an upregulation of its own release through a feed-forward mechanism (Moerkerke et al., 2021), possibly sustained by a persistently stressful environment. Accordingly, we interpreted the observed oxytocin levels after 48 h of life as a reflection of a downstream, context-dependent physiological state shaped by early mother-infant interactions in the immediate post-partum period.

Importantly, data on intrapartum maternal administration of oxytocin were not collected. However, the cross-placental transfer of in-labour administered oxytocin (and its dose-dependance) is still a matter of debate (see review by (Uvnäs-Moberg et al., 2024)). (Malek et al., 1996) showed in-vitro the possibility of bidirectional (i.e., fetus to mother and mother to fetus) placental transfer of oxytocin by simple diffusion, suggesting that maternally administered oxytocin may reach the fetal circulation. Similarly, (Kenkel et al., 2019) reported increased fetal oxytocin levels following maternal administration in an animal model. In contrast, (Patient et al., 1999) reported that maternal oxytocin infusion had no effect on mean oxytocin concentrations in the umbilical artery or vein, nor on the arterio-venous ratio. More recently, (Buckley et al., 2023) showed that synthetic oxytocin infusion during labor increased maternal plasma levels without corresponding increases in neonatal plasma oxytocin, arguing against placental transfer at clinical doses. Given the absence of data on maternal oxytocin administration in the present study and the different hypotheses found in the literature, caution is warranted when interpreting our findings. Future studies on postnatal oxytocin levels in late preterm infants would benefit from systematic recording of maternal oxytocin administration, including dosage and timing, and its association with neonatal levels. The potential effect of maternal post-natally administered oxytocin should also be taken into consideration.

Finally, we acknowledge that reliance on self-reported data from mothers may introduce biases due to social desirability or recall accuracy. Moreover, while the predictive validity of EPDS and STAI-Y in the early postnatal period has been previously demonstrated (Dennis, 2004; Meades and Ayers, 2011), we cannot exclude that results from the MPAS and PICTS in the first days post-partum may reflect transient states rather than stable aspects of maternal attachment and caregiving interactions. These limitations could influence the reliability of the information collected through the questionnaires used in the present study and consequently affect our study results.

6. Conclusions

Our findings reinforce previous speculations regarding the context-dependent nature of oxytocin regulation in preterm infants, with elevations under stressful conditions potentially reflecting an adaptive neuroendocrine response. We hypothesize that this increase may represent a neuroprotective strategy to shield the developing brain from the detrimental effects of excessive glucocorticoid exposure. Furthermore, we emphasize the importance of considering lack of early skin-to-skin contact as a potential source of stress for late preterm newborns. Therefore, we highlight the importance of limiting early maternal separation in both the delivery room and the post-natal unit, favoring maternal presence even when advanced care is necessary, and guaranteeing adequate staffing to facilitate skin-to-skin contact and rooming-in. Further studies with larger, more diverse samples, and longitudinal designs are needed to validate and expand upon our findings, possibly exploring the neurobiological mechanisms underlying our observations and hypotheses.

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CRediT authorship contribution statement

Alessandra Consales: Conceptualization, Methodology, Investigation, Data curation, Writing – Original Draft. **Martina Arioli:** Conceptualization, Investigation, Data curation, Formal analysis, Writing – Original Draft, Visualization. **Margaret Addabbo:** Conceptualization, Investigation, Data curation, Writing – Review & Editing. **Hermann Bulf:** Conceptualization, Supervision, Writing – Review & Editing. **Valentina Silvestri:** Investigation, Data curation, Writing – Review & Editing. **Chiara Turati:** Conceptualization, Supervision, Writing – Review & Editing. **Alberto Battezzati:** Methodology, Supervision, Writing – Review & Editing. **Stefano Ravasenghi:** Methodology, Writing – Review & Editing. **Lorenzo Colombo:** Investigation, Writing – Review & Editing. **Angelo Petrelli:** Investigation, Data curation. **Valentina Tiraferri:** Investigation, Data curation. **Monica Fumagalli:** Supervision, Writing – Review & Editing, Funding acquisition. **Viola Macchi Cassia:** Conceptualization, Project administration, Supervision, Writing – Review & Editing, Funding acquisition. **Maria Lorella Giannì:** Conceptualization, Project administration, Supervision, Writing – Review & Editing, Funding acquisition.

Declaration of Competing Interest

None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2026.107851.

Data availability

Access to the dataset generated and analyzed during the current study is restricted to protect patient confidentiality and participant privacy. The dataset is available from the corresponding author upon reasonable request.

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