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Release of Oxytocin and Cortisol Is Associated With Neurobehavioral Patterns in Premature Infants

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ABSTRACT

Objective: To examine relationships among salivary oxytocin and cortisol levels in parents and preterm infants and neurobehavioral functioning in preterm infants after skin-to-skin contact.

Design: A secondary analysis of a randomized crossover study.

Setting: NICU.

Participants: Twenty-eight stable premature infants and their mothers and fathers.

Methods: Participating infants contributed 108 saliva samples that we collected 45 minutes after skin-to-skin contact and tested for oxytocin and cortisol. We randomized data collection by whether the infant was held first by the mother or by the father. We conducted linear regression to test if summary scores on the NICU Network Neurobehavioral Scale were associated with salivary oxytocin and cortisol levels.

Results: We found a significant negative relationship between infant oxytocin levels and the Stress scores ($b = –0.07$, $p < .01$) and the Excitability scores ($b = –1.12$, $p = .04$) among infants held skin-to-skin with their mothers. We found a significant positive relationship between infant oxytocin levels and the Self-Regulatory scores ($b = 0.38$, $p = .05$) among infants held skin-to-skin with their mothers. We found a significant positive relationship between infant cortisol level and the Stress scores ($b = 0.05$, $p = .04$), Excitability scores ($b = 1.06$, $p = 0.05$), and Asymmetrical Reflexes scores ($b = 1.21$, $p = .03$) among infants held skin-to-skin with their mothers. We only found a negative significant relationship between infant cortisol levels and the Stress scores ($b = –0.03$, $p = .04$) among infants held skin-to-skin with their fathers.

Conclusion: We found that oxytocin is an important biomarker that may improve infant neurobehavioral functioning. The data showed a difference in oxytocin responses after skin-to-skin contact with mothers compared to fathers.

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More than 15 million premature infants are born annually around the world. Although survival rates of critically ill infants are steadily improving, the incidence of developmental disabilities for preterm infants remains high (O'Reilly et al., 2020; Spittle & Treyvaud, 2016). It has been incorrectly proposed that healthy preterm infants without major complications eventually catch up developmentally to term infants (Duncan & Matthews, 2018; Hodel et al., 2017). Long-term implications for survivors of prematurity are related to differences in brain development that have the potential to affect cognition and behavioral factors such as differences in social and emotional regulation (Chan et al., 2016).

As premature infants grow and develop into school-age children and adolescents, the consequences of early birth continue to influence their neurodevelopmental outcomes (Allotey et al., 2018; Chan et al., 2016). Despite advances in care with preterm infants, it remains difficult to accurately predict which preterm infants will have adverse neurodevelopmental outcomes (Spittle & Treyvaud, 2016). Although some developmental differences and challenges seen in children born premature can be explained by the cumulative effect of medical complications associated with preterm birth and early life experiences, many sequelae of prematurity are not easily explained by medical complications alone

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Skin-to-skin contact facilitates the release of oxytocin and improves preterm infant neurobehavioral functioning.

(Spittle & Treyvaud, 2016). The mechanisms regarding how maternal education affects infant outcomes are unclear, yet a positive relationship between education for pregnant women and infant health outcomes has been documented (Cochrane et al., 1982; Shrestha, 2020).

Until specific and consistent evidence regarding the drivers of poor neurodevelopment after preterm birth is established, a critically important intervention with the potential to reduce some of the adverse consequences of prematurity is parent touch, particularly during skin-to-skin contact (Boundy et al., 2016; Feldman et al., 2014; Kostandy & Ludington-Hoe, 2019). Skin-to-skin contact is an evidence-based holding strategy that increases the parent's proximity to the infant. This physical proximity with direct dorsal contact allows for a continuously interactive environment known to enhance infant physiologic stability and affective closeness between parent and infant (Akbari et al., 2018; Linnér et al., 2020; Shattnawi & Al-Ali, 2019). Evidence suggests that skin-to-skin contact facilitates cortisol regulation and may be a successful intervention to reduce infant stress (Pados, 2019; Vittner et al., 2018).

The infant's disorganized behavioral patterns during early dysfunctional contact between the infant and parent can lead to poor attachment and behavioral problems in childhood (Feldman, 2015). Conversely, early, responsive, synchronous contact between the infant and the parent can positively influence cognitive and developmental outcomes for the child (Golds et al., 2022). Moreover, it is becoming better understood how the oxytocinergic system plays a crucial role in bonding and parenting (Scatliffe et al., 2019; Yirmiya et al., 2020). Oxytocin is also involved in controlling stress, anxiety, and autonomic functions such as heart rate, and high oxytocinergic activity is stress relieving and anxiolytic in animals and humans (Uvnäs Moberg et al., 2020). Conversely, acute stress causes an increase in salivary cortisol, and thus, salivary cortisol is frequently used as a biomarker of psychological stress (Gonzalez-Cabrera et al., 2014).

Vittner et al. (2018) suggested that oxytocin is an important neuromodulator that influences the neurobiological reciprocity and synchronicity with mother–infant and father–infant interactions that could influence their developing relationships and attachment. Skin-to-skin contact activates salivary oxytocin in mothers, fathers, and infants; decreases salivary cortisol in infants; and decreases anxiety in parents (Cong et al., 2015; Vittner et al., 2018). In a previous study, we found that activation of the infant's oxytocinergic system with a similar neurobiologic response did not differ when the infant was held in skin-to-skin by the mother or the father (Vittner et al., 2018, 2019). Therefore, the purpose of this study was to examine relationships among salivary oxytocin and cortisol levels in parents and preterm infants and neurobehavioral functioning in preterm infants after skin-to-skin contact.

Methods

Design

This is a secondary analysis using data from a randomized crossover design study in the NICU that was conducted during a 3-day time frame (Vittner et al., 2018). We collected the data reported in this article in conjunction with the original research to examine differences in biobehavioral mechanisms of skin-to-skin contact for mothers and fathers with healthy preterm infants (Vittner et al., 2018). Relationships to neurobehavioral functioning were not examined in the prior study. Institutional review board approval was received before enrollment and data collection.

Setting

We conducted the study at a Level III/IV NICU affiliated with an inner-city freestanding children's hospital in southern New England.

Participants

The sample consisted of 28 stable preterm infants (30 0/7 to 34 6/7 weeks gestation and between 3 and 10 days old) held skin-to-skin by the mother and father.

Procedures

After informed consent, we randomly assigned each triad to one of two sequences: skin-to-skin contact with the mother on study Day 1 and skin-to-skin contact with the father on study Day 2 or skin-to-skin contact with the father on study Day 1 and skin-to-skin contact with the mother on study Day 2, completed within 3 to 10 days of life. We determined that a single day was a sufficient period to avoid carryover effects between study

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Day 1 and study Day 2 for all participants. Skin-to-skin contact is the current standard of care in this NICU environment; as such, skin-to-skin contact was not restricted because of participation in this research. Each infant was held skin-to-skin daily after study participation through the remainder of the hospitalization. All participants used a skin-to-skin wrap to ensure infant safety and to secure the infant to the parent's chest during skin-to-skin contact procedures. The infant neurobehavioral assessment was completed by trained personnel before the hospital discharge on study Day 3; parents were present for the assessment. Research personnel were unaware of salivary oxytocin and cortisol results before the administration and scoring of the infant neurobehavioral assessment.

Measures

We collected demographic data from the infant's electronic health record. We used the Score for Neonatal Acute Physiology With Perinatal Extension II (SNAPPE-II) to determine preterm infant stability for participation in this study (Richardson et al., 2001; Vittner et al., 2018). The SNAPPE-II score is a valid indicator of an infant's severity of illness and predictor of mortality and morbidity risks using data collected shortly after admission to the NICU; it has a composite range of 0 to 162 (Özcan et al., 2017; Richardson et al., 2001).

In the original study, we collected saliva samples from infants before skin-to-skin contact, 60 minutes during skin-to-skin contact, and 45 minutes after skin-to-skin contact to determine salivary oxytocin and cortisol levels at each time point (Vittner et al., 2018). In this study, we used only saliva sample data that were collected 45 minutes after skin-to-skin contact. We collected saliva with an infant swab. Typically, using swabs for 5 minutes can obtain at least 120 μL of saliva, whereas the minimum saliva needed for testing salivary oxytocin is 70 μL. The swab was 5 mm × 90 mm, an appropriate size for the mouth of a young infant, and the infants were not disturbed by the sampling process. We placed the saturated oral swabs in a small insert tube with a snap cap and immediately stored them in a –80 °C freezer until they were thawed for analysis.

We collected and analyzed salivary oxytocin via an enzyme immunoassay (Assay Designs, Ann Arbor, Michigan). This method is similar to that specifically developed and validated for salivary oxytocin (Kommers et al., 2017). The sensitivity limit without correcting for the concentration is at 11.7 pg/mL, and the lower limit of sensitivity is at 2.0 pg/mL with correction for the extraction. The intra- and interassay coefficients of variation were 4.8% and 8%, respectively. We collected and analyzed salivary cortisol via an enzyme immunoassay (Salimetrics, State College, PA) with a detection limit of <0.007 μg/dL. The average intra- and interassay coefficients of variation were 4.13% and 8.89%, respectively. We assessed the normality of salivary oxytocin and cortisol samples.

We conducted the neurobehavioral assessment of the infants using the NICU Network Neurobehavioral Scale (NNNS) in the NICU just before the infant's hospital discharge (Lester & Tronick, 2004). The NNNS is a valid and reliable instrument that is used to assess and score the full range of infant neurobehavioral performance, including infant stress, neurologic functioning, evaluating behavioral states, and infant regulation, within the lens of a social context (Lester & Tronick, 2004). McGowan and colleagues (2022) further tested the NNNS to examine associations between the NNNS and infant neurobehavioral outcomes. The NNNS portrays a comprehensive and integrated picture of the infant without weighting specific functional domains, and it assumes that an accurate assessment of the infant includes evaluation of classical reflexes, tone, posture, and social and self-regulatory competencies, as well as signs of stress (McGowan et al., 2022). The NNNS has 115 items that are administered and computed into 13 summary scale scores that include Habituation, Attention, Handling, Quality of Movement, Regulation, Nonoptimal Reflexes, Asymmetric Reflexes, Stress/Abstinence, Arousal, Hypertonicity, Hypotonicity, Excitability, and Lethargy scores (Lester et al., 2004; McGowan et al., 2022). The NNNS is used to assess and score a range of neurobehavioral performance, including infant stress, abstinence, withdrawal, neurologic functioning, and a few features of gestational age assessment (Lester & Tronick, 2004). Despite collecting our data from a sample of participants who had a younger corrected postmenstrual age than the sample used to establish the NNNS summary score values, there were no significant differences noted with our data and the published normative NNNS summary score values (Lester et al., 2004).

Analysis

We calculated descriptive statistics for the demographic variables. We conducted a series of

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We identified a significant relationship between salivary oxytocin and cortisol levels and multiple infant neurobehavioral summary scores after skin-to-skin contact with mothers.

linear regression models with each of the infant's NNNS neurobehavioral summary scores used as the response variables. We hypothesized that the measurements of salivary oxytocin and cortisol levels after skin-to-skin contact were the most relevant to the NNNS summary scores. Therefore, our regression models included four potentially explanatory variables of infant neurobehavioral functioning: salivary oxytocin and cortisol levels after skin-to-skin contact, one collected with mothers, a second collected with fathers, and two measures (the third and fourth) for each infant after a skin-to-skin episode with their mother and father. We applied a squared root transformation to these predictors to reduce the impact of extreme values on the models and standardized them to make the regression coefficients comparable with each other. We adjusted the regression models for infant corrected postmenstrual age and maternal education. We used corrected postmenstrual ages to adjust for differences in prematurity of the infants at the time the NNNS was completed. We adjusted for maternal education because although the mechanisms for the relationship between maternal education and infant outcomes are unknown, evidence suggests a strong relationship (Shrestha, 2020). The threshold for statistical significance was a two-sided *p* value of .05. We analyzed the data using R version 4.0.3 (Chan, 2018).

Results

Participating infants were born at a mean of 33 weeks (*SD* = 1.57) postmenstrual age (Vittner et al., 2018). Most infants were White (61%) males (68%). The infants were relatively healthy, with a mean SNAPPE-II score of 3.93. Most parents were White (61%) and college educated (93% of mothers and 89% of fathers). The mothers' mean age was 32 years, and the fathers' mean age was 33 years. Sample characteristics are described in Table 1. The infant sample NNNS summary data showed competence with Self-Regulation summary scores as well as yielding no statistical differences to published normative data (Lester et al., 2004). The Self-Regulation summary

Table 1: Characteristics of Participating Infants (*N* = 28)

Characteristics	*n* (%)	*M*	*SD*
Sex			
Female	9 (32)		
Male	19 (68)		
Race and ethnicity			
Asian	2 (7)		
Black	4 (14)		
Hispanic	5 (18)		
White	17 (61)		
Gestational age at birth, weeks		33	1.57
30–30 6/7	4 (14)		
31–31 6/7	5 (18)		
32–32 6/7	1 (3)		
33–33 6/7	3 (11)		
34–34 6/7	15 (54)		
Weight, g		1,882	416.66
900–1,300	3 (7)		
1,301–1,700	5 (18)		
1,701–2,100	12 (43)		
2,101–2,500	5 (18)		
2,501–2,900	3 (3)		
SNAPPE II		3.93	7.78
0	21 (75)		
7–10	3 (11)		
18–21	3 (11)		
22–27	1 (3)		
Apgar score at 1 minute		7.11	2.04
0–4	4 (14)		
5–7	7 (25)		
8–10	17 (61)		
Apgar score at 5 minutes		8.29	1.27
0–4	1 (3)		
5–7	4 (14)		
8–10	23 (87)		
Mode of birth			
Vaginal	11 (39)		
Cesarean	17 (61)		

Note. SNAPPE II = Score for Neonatal Acute Physiology With Perinatal Extension II.

Table 2: Means and Standard Deviations of the NNNS Summary Scores

NNNS Summary Scale	*M*	*SD*
Habituation score	6.64	1.78
Attention score	5.19	1.09
Arousal score	3.48	0.43
Regulation score	5.01	0.61
Handling score	0.51	0.20
Quality of Movement score	3.97	0.61
Excitability score	3.71	1.74
Lethargy score	4.68	2.20
Nonoptimal Reflexes score	5.25	1.84
Asymmetry score	1.43	1.60
Hypertonicity score[a]	0.00	0.00
Hypotonicity score	0.75	0.97
Stress/Abstinence score	0.21	0.10

Note. NNNS = NICU Network Neurobehavioral Scale.
[a]No infants in the sample had a Hypertonicity score.

score indicates the infant's ability to initiate coping behaviors—for example, the infant spontaneously brings their hands to their mouth and sucks on their fingers. Table 2 describes the infant NNNS summary scores for the 13 subscales.

We collected the saliva samples for this study from 28 mother–infant pairs and 28 father–infant pairs after skin-to-skin contact, which yielded 108 saliva samples that were used in the analysis. One infant had missing values for salivary oxytocin levels when held by the mother and the father and for salivary cortisol levels when held by the father. This infant was excluded from our regression analysis; hence, most of the regression models were fitted based on 27 infants. In addition, one infant had a missing value for the Attention summary score, and 14 infants were awake at the beginning of the neurobehavioral assessment and, thus, were not tested for the Habituation summary score, which tests the infant's ability to sustain sleep with a variety of visual and auditory stimuli. These infants were excluded from regression analysis of the Habituation score. Table 3 summarizes the significant findings from the adjusted regression models.

Infants Held Skin-to-Skin by Mothers

We found a significant negative relationship between infant oxytocin levels and the Stress summary scores ($b = -0.07$, $t = -3.43$, $p < .01$) and between infant oxytocin levels and the Excitability summary scores ($b = -1.12$, $t = -2.26$, $p = .04$) among infants held skin-to-skin with their mothers. We found a significant positive relationship between infant oxytocin levels and the Self-Regulatory summary scores ($b = 0.38$, $t = 2.10$, $p = .05$) among infants held skin-to-skin with their mothers. We also found a significant positive relationship between infant cortisol level and the Stress summary scores ($b = 0.05$, $t = 2.16$, $p = .04$), the Excitability summary scores ($b = 1.06$, $t = 2.12$, $p = .05$), and the Asymmetrical Reflexes summary scores ($b = 1.21$, $t = 2.41$, $p = .03$) among infants held skin-to-skin with their mothers.

Table 3: Summary of Adjusted Regressions Between NNNS Summary Scores and Infant Oxytocin and Cortisol Levels (*N* = 27)

NNNS Summary Scores	Variable	*b*	*SE*	*t*	DF	*p*	95% CI
Self-Regulation	Oxytocin (M)	0.38	0.18	2.10	19	.05	[0.00, 0.75]
Excitability	Oxytocin (M)	–1.12	0.49	–2.26	19	.04	[–2.16, –0.08]
	Cortisol (M)	1.06	0.49	2.12	19	.05	[0.01, 2.10]
Asymmetric Reflexes	Cortisol (M)	1.21	0.50	2.41	19	.03	[0.16, 2.26]
Stress/Abstinence	Oxytocin (M)	–0.071	0.021	–3.43	19	<.01	[–0.11, –0.03]
	Cortisol (M)	0.05	0.02	2.16	19	.04	[0.00, 0.09]
	Cortisol (F)	–0.03	0.01	–2.25	19	.04	[–0.06, 0.00]

Note. Models were adjusted for maternal education and postconceptual gestational age. DF = degrees of freedom; CI = confidence interval; NNNS = NICU Network Neurobehavioral Scale; cortisol (M) = infant cortisol level when held by mother; oxytocin (M) = infant oxytocin level when held by mother; cortisol (F) = infant cortisol level when held by father.

Infants Held Skin-to-Skin by Fathers

We found no significant relationships between infant oxytocin levels and any of the NNNS summary scores among infants held skin-to-skin with their fathers. However, we found a negative significant relationship between infant cortisol levels and the Stress summary scores ($b = -0.03$, $t = -2.25$, $p = .04$) among infants held skin-to-skin with their fathers.

We found no significant relationships between oxytocin and cortisol levels (maternal, paternal, infants held skin-to-skin by mother, and infants held skin-to-skin by father) and the NNNS summary scores for Habituation, Arousal, Quality of Movement, Lethargy, Nonoptimal Reflexes, and Hypertonicity. There were no infants in the study sample that had Hypertonicity summary scores; hence, no relationships were identified for this summary score.

Discussion

Our study provides evidence of significant relationships between salivary oxytocin release and later infant neurobehavioral functioning that might be considered predictive. Oxytocin is a hormone that acts as a neurotransmitter and is considered critical to parent–infant experiences during sensitive periods of development (Carter, 2014; Feldman, 2015). Oxytocin availability is critical to the limbic and neocortical systems and the nervous system structures involved in emotion that depend on early caregiving experiences (Scatliffe et al., 2019). The oxytocinergic system plays a pivotal role in parent–infant bond formation and overall parenting competence, especially during sensitive periods of development (Feldman, 2015; Uvnäs Moberg et al., 2020). Oxytocin facilitates the high levels of social sensitivity and attunement that are necessary for developing relationships and nurturance, which emerge as intellectual development (Feldman, 2015). Early life experiences that used interventions such as skin-to-skin contact provide opportunities for nurturance and reciprocal trust to enhance developing relationships (Vittner et al., 2018, 2019). The findings of our study are an important step in the exploration of oxytocin release as a potential moderator of improved infant neurobehavioral outcomes, and they add to the already documented benefits of skin-to-skin contact among mothers, fathers, and infants (Hardin et al., 2020).

Oxytocin levels for infants held skin-to-skin by mothers were significantly associated with the Self-Regulatory summary score, yet the relationship between variables was stronger for mother–infant skin-to-skin contact than father–infant skin-to-skin contact. The data showed a difference in oxytocin response after skin-to-skin contact with mothers compared to fathers. Evidence suggests that paternal psychobiological axes are sensitive to fathers' experiences interacting with their infants and may provide insights into individual differences in fathers' biology related to postpartum parenting (Gettler et al., 2021). Gettler and colleagues found that in father–infant interactions, oxytocin reactivity was associated with testosterone and cortisol reactivity, respectively, in predicting father–infant outcomes months later (Gettler et al., 2021). Results suggested significant crossover interactions for oxytocin and testosterone in predicting fathers' later postpartum involvement and bonding with their infant (Gettler et al., 2021). Consistent with these findings, the data from our study show that the salivary oxytocin response of infants held skin-to-skin by their fathers was more variable and lower overall compared to infants held skin-to-skin by their mothers.

Parent–infant relationships are difficult to establish when infants confront challenges during the early postpartum period (Golds et al., 2022). Salivary cortisol levels for infants significantly decreased for infants held by their mothers and fathers (Vittner et al., 2018). As expected, infant salivary cortisol levels were significantly correlated to higher Stress summary scores, indicative of behavioral patterns of infant stress and disorganization. Consistent with the evidence in the literature and of clinical concern as well, early dysregulated behavior of premature infants within this sensitive period of development may affect long-term academic, home, and social functioning (Linsell et al., 2019).

In our study, infant oxytocin levels were significantly associated with Regulation summary scores, which is consistent with previous evidence (Shattnawi & Al-Ali, 2019; Shorey et al., 2016). Throughout the life span, oxytocin increases social sensitivity, modulates reactivity to stressors, and contributes to individual differences in social behavior and coping (Carter, 2014). Of concern, the increased acuity and complexity of NICU care creates challenges for

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health care professionals to navigate competing demands and provide opportunities for skin-to-skin contact that can facilitate oxytocin release (Vittner et al., 2015, 2021).

The process of infant behavioral assessment has shifted over the years to embrace a range of competencies that build on strengths. The infant's functional competence leads to the integration of the infant's regulatory efforts—specifically, the infant's capacity to cope with the experiences and stressors they encounter (Vittner & McGrath, 2018). In their seminal work, Lester and colleagues (2004) identify that high-risk infants can be viewed as struggling to maintain a balance between the competing demands of the interaction and environment. Specifically, the preterm infant attempts to maintain physiologic homeostasis while simultaneously being influenced by external stimulation. The infant's abilities to control or regulate their own level of arousal and to habituate is considered a rudimentary form of learning, with recognition of the functional competence that leads to the development of assessments of these more complex forms of behavior (Lester et al., 2004).

Limitations

The generalizability of the findings is limited by the crossover study design and small sample size. Because we fitted regression models for multiple NNNS outcomes, there was a multiplicity issue, but we could not address the issue because of the limited sample size. Therefore, some of our significant findings could be false positives. It is possible that there were carryover effects of skin-to-skin contact; all infants were held skin-to-skin daily from the point of study participation by the mother or the father. With these carryover effects, the regression estimates may not represent pure effects of mother–infant skin-to-skin contact or father–infant skin-to-skin contact. The sample consisted of healthy premature infants, and further research is needed with a broader, more diverse sample of preterm infants and their parents.

Implications

Our findings are consistent with those in the previous literature that support the relationship between infant neurobehavioral functioning and biomarkers of coping and stress in preterm infants. Neurobehavioral patterns shown by the NNNS, particularly increased excitability, arousal, hypertonicity, and stress behaviors, are associated with lower quality of movement scores, orientation, and self-regulation that are predictive of adverse outcomes (McGowan et al., 2022). NNNS profiles discriminate among infants with medical and behavioral issues through four and a half years of age (McGowan et al., 2022). These findings imply a significant relationship between skin-to-skin contact and infant neurobehavioral functioning in addition to validation that neurobehavioral assessments can and should be incorporated into the care of preterm infants to identify individualized plans of care to support the unique strengths of the infant's level of behavioral functioning.

Health care professionals can use skin-to-skin contact to activate oxytocin and enhance developmental outcomes for preterm infants.

Conclusion

Despite advances in NICU care practices, premature infants remain at risk for adverse neurodevelopmental outcomes. Our findings are a first step in exploring oxytocin as a biomarker and provide evidence of potential improvement in infant neurobehavioral functioning. Oxytocin release and availability are critical to the limbic and neocortical systems and those nervous system structures related to emotion that depend on early caregiving experiences. Health care professionals can use skin-to-skin contact to activate oxytocin and enhance infant neurobehavioral functioning. In conjunction with recommendations from the American Academy of Pediatrics, our results suggest that all preterm infants and their parents should have the opportunity for skin-to-skin contact every day, which may lead to the activation and release of oxytocin and decreased levels of cortisol in the infant.

CONFLICT OF INTEREST

The authors report no conflicts of interest or relevant financial relationships.

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