Neonatal Pain and Developmental Outcomes in Children Born Preterm

A Systematic Review

Beatriz O. Valeri, MSc, Liisa Holsti, PhD,† and Maria B.M. Linhares, PhD**

Background: Neonates cared for in neonatal intensive care units are exposed to many painful and stressful procedures that, cumulatively, could impact later neurodevelopmental outcomes. However, a systematic analysis of these effects is yet to be reported.

Objectives: The aim of this research was to review empirical studies examining the association between early neonatal pain experiences of preterm infants and the subsequent developmental outcomes of these children across different ages.

Methods: The literature search was performed using the PubMed, PsycINFO, Lilacs, and SciELO databases and included the following key words: "pain," "preterm," and "development." In addition, a complementary search was performed in online journals that published pain and developmental studies to ensure all of the target studies had been found. The data were extracted according to predefined inclusion and exclusion criteria.

Results: Thirteen studies were analyzed. In infants born extremely preterm (gestational age $\leq$29 wk) greater numbers of painful procedures were associated with delayed postnatal growth, with poor early neurodevelopment, high cortical activation, and with altered brain development. In toddlers born very preterm (gestational age $\leq$32 wk) biobehavioral pain reactivity-recovery scores were associated with negative affectivity temperament. Furthermore, greater numbers of neonatal painful experiences were associated with a poor quality of cognitive and motor development at 1 year of age and changes in cortical rhythmicity and cortical thickness in children at 7 years of age.

Conclusions: For infants born preterm, neonatal pain-related stress was associated with alterations in both early and in later developmental outcomes. Few longitudinal studies examined the impact of neonatal pain in the long-term development of children born preterm.

Key Words: preterm infants, pain assessment, development, systematic review

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From the *Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil; and †Department of Occupational Science and Occupational Therapy, University of British Columbia and Child and Family Research Institute, Vancouver, BC, Canada.

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Reprints: Maria B.M. Linhares, PhD, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Avenida Tenente Catão Roxo, 2650 (Prédio da Saúde Mental, salas 52/53), Campus Universitário Monte Alegre, CEP: 14.051-140, Ribeirão Preto, São Paulo, Brazil (e-mail: linhares@fmrp.usp.br).

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Premature birth is a risk factor which exposes infants to a sequence of adverse events during a period of developmental vulnerability.[1] Despite advances in neonatal care whereby modifications are made in the environment of neonatal intensive care units (NICU), the early, repeated, stressful, and painful procedures continue with potential for subsequent adverse effects on the development of preterm infants.[2] Indeed, NICUs tend to underestimate and to undermanage the pain/stress experiences of preterm infants.[3,4]

Developmental regulation is foundational for good health. It changes from primary biological processes to psychological and social processes in early development.[5] It begins with temperature, hunger, and alert early regulation processes, and progresses to the regulation of attention, behavior, and social interactions. The maturation of self-regulation described by Olson et al[6] includes the following processes: *physiological homeostasis* (birth to 3 mo), refers to modulation and physiological sensory stimuli, such as duration and intensity of crying, time for recovering, ability to calm down, and biochemical responses to stress; *emotional regulation* (3 to 12 mo), when there is an increased ability to adjust the affective responses, attention, and voluntary motor behavior focused on the goal; *behavioral regulation* (first 3 y), refers to the maturation of cognitive and motor skills in children who are already aware of social demands and who can adjust their behavior according to social demands, and *attention regulation*, with the development of symbolic thought and memory; and *self-regulation* (preschool age), whereby the children learn to flexibly adapt to situations and to self-monitor their behavior in different situational demands. The regulation on development is a hierarchical and complex process ensuring physiological, emotional, and behavioral homeostasis.

The very immediate negative impact of acute painful events on developmental regulation of vulnerable preterm infants can be observed in the balance between the reactivity to a painful stressor and the recovery from it.[7] Here, the altered recovery phase through postpuncture responses are seen in changes in facial activity,[8,9] sleep-wake state,[8,10] crying,[11,12] and heart rate[13,14] in preterm neonates. Moreover, the alterations in developmental self-regulation continue to be observed later in childhood in these high-risk infants who present with more difficulties in physiological, emotional, and behavioral regulation than do full-term infants.[15,16] Although these initial findings suggest a long-term impact, developmental processes are complex and, thus, further study is needed to determine the lasting effects of early pain experience.

With regard to neurodevelopment during the neonatal stage, sensory system maturation occurs during a highly sensitive period governed by rapid neuronal plasticity-induced

changes.[17] Early repeated exposure to pain and stress in the NICU can alter the neurological substrate associated with pain processing and consequently lead to changes in somatosensory processing of pain and to altered neurobehavioral responses to pain.[18,19] Repeated experiences of pain in early development can have long-term effects on pain processing,[20] such as decreased pain threshold,[2,21] hyperalgesia,[2,22] and allodynia.[23] However, the type and length of time these effects last likely depend on the developmental maturity of the neonate at the time when the pain occurs, along with other clinical factors, the duration of exposure to the environmental context of pain, and the time of the exposure.[24] Although evidence exists that the early pain experience impacts pain sensory systems, less is known regarding its influence on other aspects of development.

In addition, parents play a pivotal role throughout child development.[25] The parents' behavior can moderate associations between premature risk and child developmental outcomes.[26] Particularly, in a stressful, interactive context, maternal behavior is associated with infant regulatory problems in crying and sleeping.[26] According to the social communication model of pain proposed by Craig,[27] which includes multiple biological, psychological, and social intrapersonal and interpersonal factors influencing pain and pain management, parenting factors influence their children's pain perception and pain reactivity responses.[27]

Although the adverse effects of the early painful experiences in preterm infants are recognized, and a number of narrative topical reviews have been published on the effects on development,[28,29] to the best of our knowledge, no published *systematic* reviews have focused on examining the potential impact of pain on development from the neonatal stage through childhood. Thus, the aim of the present study was to systematically review the empirical findings of relationships between neonatal pain and development of children born preterm who were exposed to multiple painful experiences in a NICU environment.

METHODS

The systematic search strategy, which was based on PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses),[30] was conducted in the following databases: PubMed, PsycInfo, Latin American and Caribbean Health Sciences Literature (LILACS), and Scientific Electronic Library Online (SciELO). In addition, systematic complementary searches were performed in the following online journals: *Early Human Development*, *Infant Behavior and Development*, *Child Development*, *Pain*, *European Journal of Pain*, *The Clinical Journal of Pain*, *and The Journal of Pain*. This last step was performed to confirm that all studies were included in the present review. The searches were restricted to studies published in English, Spanish, or Portuguese, exclusively with human samples, and were not time period limited.

Aligned with the study objective, the search was performed with the following keywords: "pain," "preterm," and "development." The inclusion criteria were empirical studies that assessed neonatal pain and included measures of development outcomes. The exclusion criteria were the following: review studies, letters, case studies, psychometric studies, studies with samples that did not include preterm infants, and studies that did not analyze pain responses in preterm infants and development. To increase the likelihood of finding research on developmental outcomes related to pain in preterm infants, we did not predefine domains of development outcomes for the term "development." Two authors evaluated independently all of the studies to determine that the inclusion criteria had been met. In the case of disagreement, the authors discussed the issue to reach a final decision.

The systematic search of the databases resulted in a total of 137 studies (Fig. 1). After deleting the repeated articles (n = 17), the exclusion criteria were applied, which eliminated a further 108 studies, with 12 studies remaining. Then, of the 235 studies from the search of online journals, 28 were repeated and 206 met the exclusion criteria; 1 study remained. Therefore, the total sample of the present systematic review included 13 articles: 12 (92%) were derived from the databases and 1 (8%) was an additional article from the online journals.

Features of the Studies

The studies employed 3 different designs: cross-sectional studies,[31,32] studies analyzing neonatal pain and short-time outcomes during NICU hospitalization,[33–35] and longitudinal studies.[36–43] One group of studies recorded neonates' immediate biobehavioral pain reactivity-recovery to a skin-breaking stimulus, as measured by standardized scales and physiological indices (eg, Neonatal Facial Coding System scores, sleep-wake state scores, and heart rate). The second group of studies evaluated the cumulative effects of NICU pain on later development. For these studies, pain experience was operationally defined as the numbers of accumulated pain procedures (eg, heel lance) from birth to discharge or term-equivalent age, adjusted for medical confounding variables.

Developmental outcomes were assessed during 2 different phases: early development outcomes during the neonatal phase, ranging from birth to term-equivalent age or 40 weeks postconceptional age, and later development outcomes measured at 4, 8, 12, 18, 24, and 26 months corrected chronological age for prematurity (CCA), and 7 years of age. The range of development outcomes examined in the studies included the following: postnatal growth,[33] neurodevelopment (neurobehavior,[31] cortical activation,[32] brain structures—white and gray matter,[34] corticospinal tract,[35] functional cortical activity,[42] and cortical thickness[43]), cognitive and motor,[36–38] temperament,[39,40] and behavior.[41]

RESULTS

Neonatal Pain and Early Development of Preterm Infants

Table 1 shows that 5 studies found statistically significant associations between neonatal pain experience and early development of preterm infants, including postnatal growth, neurobehavioral, cortical activation, and brain development outcomes. More specifically, neonatal procedural pain was associated with delayed early postnatal body and head growth in preterm infants at 32 weeks postconceptional age, independent of other medical confounding variables.[33] Moreover, a high level of pain in very preterm infants (those born at a mean gestational age [GA] of 29 wk) with no pain management in the NICU setting, was associated with less attention and arousal, more lethargy, and more suboptimal reflexes at approximately 2 months post delivery.[31]

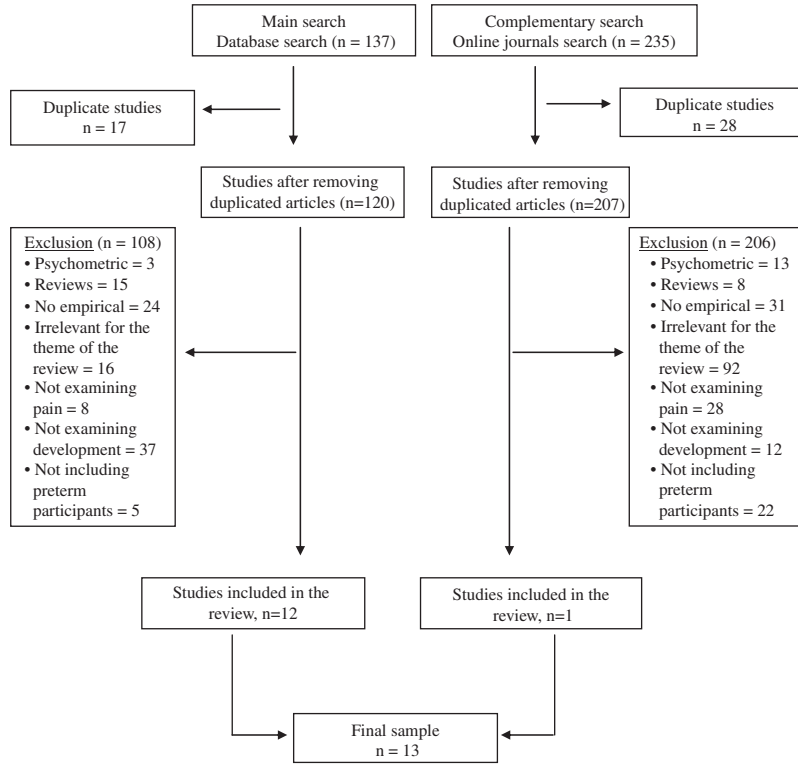

FIGURE 1. Flow diagram of the study selection process.

Furthermore, greater numbers of skin-breaking procedures during NICU hospitalization, which was used as a proxy for early neonatal pain-related stress, was significantly associated with reduced white matter and subcortical gray matter maturation at term age equivalent in very preterm infants.[34] Importantly, the independent association between neonatal procedural pain and early brain development persisted even after controlling for multiple confounding clinical variables, such as infection, illness severity, and analgesic medication. Neonatal pain adjusted for morphine and postnatal infection was also associated with slower rise in fractional anisotropy of the

TABLE 1. Early Development Outcomes of Preterm Infants: Studies Classified by the Phase of Assessment and the Types of Developmental Outcome (n = 5)

Neonatal Pain Assessment		Early Development Outcomes			
Pain Measurement	**Age at Pain Assessment**	**Type of Outcome**	**Measurement**	**Age at Developmental Assessment**	**References**
Number of skin-breaking procedures*	From birth to term-equivalent age	Postnatal growth and weight percentiles	Weight and head circumference	At birth, 32 wk PCA, and 40 wk PCA	Vinall et al[33]
Infant Pain Management Index	Chronological age range 52 to 55 d	Neurobehavior	NICU Network Neurobehavioral Scale (NNNS)	35 to 43 wk PCA	Montirosso et al[31]
Biobehavioral reactivity to pain	Postnatal age >24 h	Cortical activation	NIRS during venipuncture procedure	25-42 h after birth	Bartocci et al[32]
Number of skin-breaking procedures*	From birth to discharge or term-equivalent age	Brain development	White and gray matter MRI, DTI, and MRSI	After birth, and at term-equivalent age	Brummelte et al[34]
Number of skin-breaking procedures*	From birth to discharge or term-equivalent age	Corticospinal tract (voluntary motor pathway)	MRI, DTI	at 32 wk PMA and 40 wk PMA	Zwicker et al[35]

*From birth to discharge or term-equivalent age, adjusted for clinical confounders.

DTI indicates diffusion tensor imaging; HR, heart rate; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectroscopic imaging; NIRS, near infrared spectroscopy; PCA, postconceptional age; PMA, postmenstrual age; SaO_2, oxygen saturation; Wks, weeks.

corticospinal tract.[35] Finally, preterm infants of varying GA responses were compared during venipuncture; the greater the postnatal age, the higher was the cortical activation after the painful procedure.[32] These findings taken together suggest that preterm infants who undergo early repeated painful procedures during NICU hospitalization are at risk for altered brain activation and development.

Neonatal Pain and Later Development of Children Born Preterm

Table 2 shows the associations between neonatal pain and later development of children born preterm at the age of 4 months, 8 months, 12 months, 18 months, 24 months, and 7 years.[36–43] First, we identified 2 methods for measuring neonatal pain in these studies. Six studies evaluated cumulative neonatal pain exposure (the number of skin-breaking procedures, from birth to term age, adjusted for early illness severity and overall intravenous morphine exposure in preterm infants during hospitalization in the NICU) on later development.[36,37,40,42,43] Two remaining studies analyzed the biobehavioral pain reactivity-recovery scores measured in the NICU stay during pain assessment and their association with later infant development.[38,39] Thus, the cumulative repeated pain history measured *how many* pain-related stress events the preterm infants were exposed to during their NICU stay; whereas the pain reactivity-recovery responses focused on *how* the preterm infants reacted and regulated biobehaviorally during daily painful experiences in the NICU and how this regulation predicted later developmental performance.[39]

These studies showed that higher numbers of skin-breaking painful procedures, from birth to term age, in very preterm infants (defined as GA ≤ 32 wk) predicted poorer cognitive and motor development at 8 months and 18 months of CCA, after controlling for early illness severity, overall intravenous morphine exposure, and days on postnatal dexamethasone.[36] Interestingly, lower parenting stress was also associated with better mental development only at 18 months CCA. Moreover, higher neonatal pain-related stress in infants born very preterm was associated with poorer quality of focused attention at 8 months CCA, although it was moderated by maternal behavior; the low level of maternal stress served to buffer this association.[37]

Surprisingly, for extremely preterm infants (≤ 800 g birth weight and 25 wk GA), greater behavioral pain reactivity at 32 weeks of postconceptional age predicted better quality of neuromotor development assessed using the Movement Assessment of Infants Scale (total risk score) at the age of 8 months CCA, over and above other neonatal risk factors.[38] However, there was no significant correlation between pain responses and mental and motor development at 8 months, assessed using the Bayley-II Scales. In extremely preterm infants, greater biobehavioral pain reactivity, or more robust response, appears to indicate a healthy response to adverse events, acting as a protective factor for neuromotor development. This subtle difference was possible to detect because this study measured *how* the infants reacted to pain and not *how many* repeated painful events the infants were exposed to in the NICU and because of the relative sensitivity of the outcome measures used.

In a prospective longitudinal study, preterm infants (30 wk mean GA) were followed from birth to toddlerhood.[39] The neonatal biobehavioral reactivity-recovery responses during acute painful procedures in the NICU predicted the

TABLE 2. Later Development Outcomes of Children Born Preterm: Studies Classified by the Phase of Assessment and the Types of Developmental Outcome (n = 8)

Neonatal Pain Assessment		Later Development Outcomes			
Pain Measurement	**Age at Pain Assessment**	**Type of Outcome**	**Measurement**	**Age at Follow-up**	**References**
Number of skin-breaking procedures*	From birth to term (39 wk and 6 d)	Cognitive and motor development	BSID-II	8 and 18 m CCA	Grunau et al[36]
Biobehavioral Reactivity-Recovery (NFCS; SWS; ECG)	At 32 wk PCA	Motor development	MAI; BSID-II	4 and 8 m CCA	Grunau et al[38]
Number of skin-breaking procedures*	From birth to term (39 wk and 6 d)	Cognitive development	Toy exploration session scored from videotape	8 m CCA	Tu et al[37]
Number of skin-breaking procedures*	From birth to term-equivalent age	Cognitive and behavior	BSID-II; CBCL	18 m CCA	Vinall et al[41]
Number of pain-related and distress-related medical and care procedures	From birth to discharge from NICU (mean = 25 d)	Temperament	IBQ-R; ECBQ	12 and 24 m CCA	Voig et al[40]
Biobehavioral Reactivity-Recovery (NFCS; SWS; ECG)	Mean = 4 d CA	Temperament	ECBQ	25.9 m CCA (mean)	Klein et al[39]
Number of skin-breaking procedures*	From birth to term-equivalent age	Functional cortical activity	MEG; WISC-IV; Beery Perception Subscore†	7.7 y (mean)	Doesburg et al[42]
Number of skin-breaking procedures*	From birth to term-equivalent age	Cortical thickness	MRI; Laplacian streamlines method	7.8 y (mean)	Ranger et al[43]

*From birth to discharge or term-equivalent age, adjusted for clinical confounders.

†Visual Perception Subscore of the Beery-Buktenica Developmental Test of Visual-Motor Integration.

BSID-II indicates Bayley Scales of Infant Development II; CA, chronological age; CBCL, Child Behavior Checklist; CCA, corrected chronological age for prematurity; ECBQ, Early Child Behavior Questionnaire; ECG, continuous electrocardiographic; HR, heart rate; IBQ-R, Infant Behavior Questionnaire-Revised; m, months; MAI, Movement Assessment of Infant Scale; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NFCS, Neonatal Facial Coding System; PCA, postconceptional age; SWS, sleep/waking state; WISC-IV, Perceptual Reasoning Index and Processing Speed Index of the Wechsler Intelligence Scale for Children.

later temperament of toddlers born preterm. Temperament was assessed using the Rothbart approach,[45–47] which includes 3 temperament factors: negative affectivity, surgency, and effortful control, and their dimensions, respectively. More specifically, a greater magnitude of heart rate from baseline to recovery-resting phase, which indicated lower cardiac recovery, predicted higher scores on the surgency temperament factor and on its high-intensity pleasure dimension. In addition, longer duration of preterm infants' crying in recovery-resting phase (postpuncture phase) predicted higher scores on positive anticipation dimension of temperament during toddlerhood. These findings highlight that preterm infants' high behavioral and cardiac autonomic responses after the painful procedures indicate less mature ability to self-regulate and return to their baseline functioning. This very early pain reduced the ability to self-regulate after a painful event and may be part of the core of the surgency temperament factor during toddlerhood.

As described previously, the parenting factors moderated the relationship between neonatal pain-related stress and development. The neonatal distress pain-related procedures predicted the high negative affectivity in the temperament of preterm infants at 12 months but not at 24 months of age.[40] Otherwise, there was a significant interaction between a high level of neonatal pain and distress, a high level of parenting stress, and high levels of negative affectivity in the preterm infants' temperament. These findings demonstrated associations between early neonatal pain and child emotional development, which are moderated by parental stress level.

Furthermore, positive parent interactions buffered the potential adverse effects of neonatal pain on the later development of toddlers born prematurely; neonatal pain was associated with internalizing behavior in toddlers born very preterm (GA $\leq$ 32 wk) at 18 months of chronological corrected age.[41] However, the high parent sensitivity and nonhostility moderated as a protective factor for the relationship between the high number of skin-breaking procedures in the neonatal phase and the internalizing behaviors at 18 months CCA.

Finally, 2 studies reported on the effects of neonatal pain on the later development at school age. After controlling for neonatal confounders, a significant association between the cumulative neonatal pain-related stress and changes in the cortical rhythmicity at 7 years of age was detected.[42] Furthermore, the higher the cortical oscillatory activity, the lower were the visual-perceptual abilities of these children. Most recently, an association between cumulative neonatal pain/stress and cortical thickness was found in children born preterm at 7 years of age; neonatal pain-related stress adjusted for neonatal clinical confounders predicted reduced cortical thickness in 21/66 brain regions.[43]

DISCUSSION

A number of key findings were elucidated in this systematic review of the literature on the association between neonatal pain and developmental outcomes in children born preterm. First, neonatal acute painful experiences have a negative impact on preterm infants' neurobehavioral and postnatal growth, cortical activation, corticospinal tract development, and brain development outcomes, assessed during their NICU hospitalization. In addition, the potential effects of pain-related stress events or reactivity-recovery to painful stimulus on preterm neonates' development were detected at different ages, indicating an early negative impact. Second, neonatal pain experiences have negative effects on attention and cognitive, motor, neurobehavioral, and emotional developmental outcomes in children born preterm at the age of 2 years. Notably, only 2 studies focused on school-age children born preterm showing effects of neonatal pain on later cortical development. Despite the diversity of developmental outcomes measured, these findings contribute to the literature regarding the significant relationship between neonatal pain and development.

With respect to the effects of early pain experience on other aspects of health, such as on pain processing, infants born preterm (28 to 34 wk GA) showed a lower threshold for the flexion withdrawal reflex and gross body movements to cutaneous mechanical stimulation of the heel compared with full-term infants at the age of 1 year.[48] These findings suggest that preterm infants maintained increased pain sensitivity over the first year of age, unlike full-term infants, who do not exhibit this hypersensitivity. The cumulative neonatal pain experience effects brain activation,[49] development of endogenous-gating system,[50] somatosensory perception,[51] and pain sensitivity[43] in experimental pain assessed at later ages (7 to 16 y old). In addition, the early pain-related stress experience in preterm and full-term with NICU hospitalization experience enhanced the perceptual sensitization to prolonged painful stimulation and hypoalgesia to heat pain stimuli in children at school age.[52] Thus, the early, repeated, cumulative pain had a negative impact beyond infancy, altering pain processing in the children's development.

Moreover, the impact of early cumulative pain experience on early brain and cortical activation of preterm infants could have a cascade effect later in development.[53] Compared with children born full-term, those born preterm show neuropsychological impairments at preschool age[54] and at school age.[55] Neonatal pain-related stress was associated with thinner cortex in multiple regions at school age in children born preterm between 24 to 32 weeks GA.[43] Furthermore, very preterm infants (GA $\leq$ 32 wk), who are more vulnerable and exposed to pain-related stress experiences in their NICU hospitalization, are at greater risk for reduced focused attention at 8 months of age compared with full-term infants.[37] In turn, these focused attention problems during early infancy are predictive of cognitive difficulties and hyperactive/impulsivity at preschool age.[44]

Parents provide moderator-buffering effects on the relationships between early neonatal pain and later temperament and behavior of toddlers born preterm.[36,37,40,41] These studies contribute to a better understanding of the complex models of the predictive impact of pain-related stress on the preterm infants' developmental outcomes in the short term. Including proximal parent variables is important when studying the relationships between neonatal pain and development because they help us to understand more clearly the mediator and moderator variables influencing development over time.

As children develop, other variables, such as pain catastrophizing,[56] anxiety,[57] and fear,[58] may interact with the neonatal pain-related stress experiences to contribute to the children's developmental outcomes. In addition, parenting behavior and attitudes influence pain-coping strategies.[59] Caregiver sensitivity and emotional and psychological distress plays a crucial role impacting on infant

pain expression.[60,61] Catastrophizing about their children's pain also impacts on pain estimation; however, unexpectedly, there was less parent-child incongruence in pain ratings.[62] As reported in the findings of the present review, positive mother-child interactions, including high sensitivity and low stress parental profiles, promoted a protective proximal environment for the development of vulnerable infants.[40,41]

Methodological strengths of the studies in this review included data analyses of the relationships between pain and developmental outcomes, which adjusted for confounding variables. The confounding variables that could impact developmental outcomes of children born preterm, such as the severity of clinical status, morphine, and mechanical ventilation, were adequately controlled in 11 studies.[33–43]

The majority of the studies in the present review quantified painful experience as the number of cumulative pain procedures in the neonatal period examined through detailed chart reviews (number of invasive procedures from birth to term age period). As documentation of all procedures by clinical NICU staff may be variable and because the use of nonpharmacological interventions was not recorded, actual exposure could be overestimated or underestimated. Furthermore, not only is the amount of neonatal exposure to painful procedures important, but understanding how the infants reacted to each pain-related stressful experience and how they regulate biobehaviorally in the recovery phase is needed as reports show that neonatal pain reactivity of preterm infants is associated with less emotional regulation in toddlerhood.[39]

The ongoing biobehavioral activation overload from stressful stimuli places these infants at greater risk for other negative outcomes. Exposure to an atypical extrauterine environment and its stimuli triggers physiological responses regulated by the parasympathetic nervous system.[16] These responses play a primary role in the early behavioral regulation, which sustains social interaction, such as sleep-wake states, motor, and emotional activity. In addition, the control of physiological arousal integrates attention processes.[16,63] Children born preterm have a high prevalence of attentional difficulties compared with full-term children.[64] Moreover, children born preterm at preschool age are "at risk" of precursors of attention deficit and hyperactivity disorder, showing difficulties in self-regulation and self-control during calm play activities, both at home and at school.[65] Finally, early differences in biobehavioral neonatal pain reactivity-recovery may reveal variations in the immature preterm infants' emerging regulatory style, resulting in different phenotypic displays of development.

Infants born preterm are exposed to substantial painful and stressful stimuli during a sensitive period of development of nociceptive and nervous system, which are sensitive to changes in sensory experience at this time.[66] In addition, surgery and infection during the neonatal period can affect sensory processing and brain development in this population.[28] The present review included studies showing cortical, attentional, and behavior alterations associated with neonatal pain experience at 4 to 7 years. Thus, pain management during NICU stay plays a crucial role for preventing its adverse effects on the development of the preterm infants.

The results of the present review have several clinical implications that focus on the relevance of developmental care in the NICU and follow-up family support programs postdischarge for infants born preterm. Childhood is a period of both great opportunity and considerable risk, and its influence can extend over a lifetime.[67] Environmental management should aim to moderate and to protect the infant from unnecessary stress. Protective interventions for the brain and for development should begin immediately upon admission to the NICU.[19,67] The Developmental Care Program highlights the positive effects of providing and supporting developmental regulation of autonomic, motor, and attention systems in tiny infants hospitalized in the NICU.[68,69] Here, the health professional team members and parents can act as external coregulators in behavioral, emotional, neuroendocrine, and parasympathetic modulatory response of the neonates; this modulation occurs, in part, through pain and stress management.[70] Protective interventions include not only nonpharmacological interventions for pain relief,[71] but also support for the parents' identifying and modulating self-regulation of the infant to promote synchronous parent-infant interactions, particularly from birth through preschool period.

For this review, it was not possible to apply statistical techniques, such as those used in meta-analysis for the examination of effect sizes and synthesizing the findings, because of the lack of consistency of outcome measures across studies, the variation in statistical analyses performed, and the different designs used. Thus, generalizability of findings may be limited. As we obtain more research with similar methodologies regarding neonatal pain and its impact on child development, meta-analytic studies will be crucial.

Future studies should include analysis of the long-term effects of neonatal pain on preterm children's development, controlling the severity of illness. Further, complex models should be used to examine the effects of the parental psychological and behavior moderator variables and pain history on the relationships between neonatal pain and child development.

In conclusion, neonatal pain has a negative impact on development in the neonatal period and during infancy and toddlerhood through the middle childhood. However, notably few prospective, longitudinal studies were found that analyzed the associations between neonatal pain and developmental outcomes in children born preterm, both in the short term and long term. Longitudinal studies that include developmental assessments at different ages could explore further and clarify the downstream effects of neonatal pain-related stress on the developmental pathway.

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