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The role of early developmental intervention to influence neurobehavioral outcomes of children born preterm



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ABSTRACT

Children who are born preterm are at risk of adverse long-term neurobehavioral outcomes, including cognitive, motor, and behavioral impairments. Early developmental interventions that commence within the first year after preterm birth have a preventative focus, with the aim to positively influence the developmental trajectory. While there is a great deal of heterogeneity in the research trials to date, there is evidence that early developmental interventions have a moderate effect on cognitive and behavioral outcomes up to preschool age, with some evidence for improved motor outcomes. This review discusses key components of early developmental interventions including commencing the intervention as early as possible, ideally in the neonatal intensive care unit, and promoting developmental skills overtime with an appropriate enriched environment. The importance of involving and supporting parents in early intervention is also highlighted, particularly given the influence of the parent–infant relationship on developmental outcomes and higher rates of mental health problems in parents after preterm birth.

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Introduction

Children who are born preterm (<37 weeks' gestational age) are at increased risk for a range of neurobehavioral impairments compared to their peers born at term.¹ Rates of major neurobehavioral impairments such as cerebral palsy, autism,

attention hyperactivity disorder (ADHD), blindness, and deafness are higher in children born preterm, occurring in up to 15% of preterm children.^{1–3} The rates of milder neurobehavioral impairments in areas including language,⁴ attention,⁵ social–emotional development,³ executive function,⁶ and developmental coordination disorder (DCD)² also occur at

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much higher rates in children born preterm, with over half of these children having one or more neurobehavioral impairments.⁷ The range of neurobehavioral impairments for children born preterm is diverse, but they all may have significant effect on quality of life and academic performance.⁸ Further, preterm children have up to a 4–6-fold increase in psychiatric disorders including anxiety and depression.^{9,10} Long-term, neurobehavioral impairments in adults born preterm including lower intelligence and academic achievement are associated with lower wages and decreased wealth.¹¹

The risk of neurobehavioral impairments not only increases with decreasing gestational age, but is also related to perinatal (e.g., brain injury and infection) and environment influences (e.g., lower socio-economic status and parenting). Although the effects of neurological and medical factors play an important role, overtime environmental and social factors become increasingly important.¹² Despite many advances in obstetric and neonatal care that have improved neurobehavioral outcomes for preterm children over the past few decades,¹³ the rates of impairments remains too high, and early developmental interventions are needed not only during the neonatal intensive care period but also during the first years of life to optimize outcomes.

It is commonly assumed that providing early interventions will benefit all children at high risk of neurobehavioral impairments, but the evidence for this is variable.^{14,15} Although the definition of early intervention is inconsistent in research and clinical practice, it has broadly been defined as “multidisciplinary services provided to children from birth to 5 years of age to promote child health and well-being, enhance emerging competencies, minimized developmental delays, remediate existing or emerging disabilities, prevent functional deterioration and promote adaptive parenting and overall family function.”¹⁶ For the purpose of this review, we have restricted early developmental interventions to the first year after birth, as the theoretical and biological constructs of starting intervention in the first year during key periods of brain and musculoskeletal development, and the nature of the parent–infant relationship are different compared with later in childhood. In this review, we will summarize the state of the evidence for early developmental interventions for preterm infants across the range of neurobehavioral impairments including cognitive, motor, and behavioral domains and the theoretical frameworks for these programs. We will also discuss the important role parents have in early developmental intervention programs.

Critical periods of brain development and early intervention

There is increasing evidence both from animal and human models that the early environment (including parenting behavior) and experiences shape brain development.^{17,18} For example, childhood maltreatment (such as abuse or neglect) has been associated with smaller brain volumes in children,¹⁹ while higher levels of early maternal supportive behavior has been associated with larger hippocampal volumes.²⁰ Infants born very preterm are exposed to the extra-uterine environment during an important period of brain development in the

late 2nd trimester or early 3rd trimester. The last trimester of pregnancy is associated with a rapid period of brain development, with white matter increasing 5-fold and gray matter increasing 4-fold.²¹ Infants born early are susceptible to alterations in brain development not only due to the disruption of genetically programmed patterns of brain genesis, but also due to experiences such as neurological insults including intraventricular hemorrhage and periventricular leucomalacia, biological influences such as infection and bronchopulmonary dysplasia, and environmental influences such as altered auditory and visual stimuli, along with physical separation from their parents.^{22–24}

Although the developing brain is vulnerable, this rapid plasticity in the brain means that there is also potential for early experiences and the environment to positively influence brain development. For example, in feline models of early intervention for motor impairments, it has been shown that better functional outcomes are obtained when intervention occurs early while the cortico-spinal tract is developing rather than later when the cortico-spinal tract is complete.¹⁴ By training early, there is reactive synaptic plasticity resulting in brain structure reorganization and hence improved outcomes. The same principles underlie early developmental interventions for preterm infants, so that by training early the aim is to improve brain connections during key periods of brain development, rather than waiting for an impairment to occur once altered brain connections have developed. Importantly, training must not be passive but rather it needs to be active so that the infant is learning (i.e., development, alteration, and/or selection of neural circuits) through their experiences.

The role of parents and the child's early environment in early intervention

Within an ecological framework, parents and the home environment have the strongest, most proximal, and enduring influence on child development,²⁵ even after taking other environmental factors such as socio-economic status (SES) and parental education into account.²⁶ There is also evidence that even for preterm children with great exposure to medical risk factors such as neurological abnormality, a stimulating home environment and sensitive parent–infant relationship are associated with better neurodevelopmental outcomes.^{27–29} More negative and intrusive early parenting is associated with poorer developmental outcomes for very preterm children across childhood.^{27,30} Conversely, warm and sensitive parenting and a positive family environment can have a protective effect on the development of preterm children, even after accounting for the influence of medical risk factors such as brain injury.^{27,28,31} Thus the parent–infant relationship and the parenting environment of the infant is considered to be one of the primary mechanisms through which many early intervention programs have a positive effect on preterm children, and is a focus of many programs [e.g., mother–infant transaction program (MITP)].^{32,33} Indeed, our Cochrane review on early intervention programs for preterm infants concluded that early intervention programs that focused on the parent–child relationship were more

effective than programs focused on the child or the parent alone.¹⁵ However, it is interesting to note that the state of the evidence for such programs to actually change observable parenting behavior or the parent–infant relationship is variable. For example, while one systematic review³⁴ showed that early intervention programs can positively change the parent–infant relationship in preterm infants, another systematic review and meta-analysis³⁵ found no overall change in maternal sensitivity after early intervention. Methodological differences between studies including the nature of the intervention and measures used to assess parenting and the parent–infant relationship are likely to be factors influencing this inconsistency. In order to develop interventions for preterm children that focus on the most effective mechanism for change, it is important that future studies examine whether the parent–child relationship and parent-based factors such as behavior and attitudes are altered by the intervention, and whether they do indeed mediate the relationship between the intervention and child outcomes.

Key features of successful early developmental intervention programs for preterm infants

Given the wide range of developmental problems preterm infants may face, it is not surprising that there is great diversity in the range of early intervention programs available for infants born preterm. Our Cochrane review of early developmental interventions for preterm infants to improve cognitive and motor outcomes included 25 randomized and quasi-randomized trials that commenced within the first year following preterm birth.¹⁵ The trials varied greatly with regard to when the intervention commenced (immediately after birth versus post-hospital discharge), delivery of the intervention (clinic based versus home based), professional delivering the intervention (e.g., nurse, psychologist, physical therapist, and pediatrician), focus of the intervention (e.g., infant and parent–infant relationship), inclusion criteria (e.g., low-risk versus high-risk infants), dosage (e.g., 4 sessions versus >100 sessions), and length of follow-up (3 months–18 years). A meta-analysis of trials found the early developmental interventions improved cognitive outcomes during infancy and at preschool age with a moderate effect size but the effects were not sustained at school age.¹⁵ Further, there was a small effect of early developmental interventions on motor outcomes in infancy. However, of the small number of studies that reported long-term motor outcomes, only one has shown gains beyond infancy.³⁶ Another systematic review of behavioral outcomes following early intervention for preterm infants found a small but significant effect of parenting interventions on child behavior, with evidence of persistence into early childhood for some programs.³⁷ In the following section, we highlight the successful components and key ingredients of successful early developmental intervention studies.

When to commence early intervention?

Early developmental intervention can begin in the neonatal intensive unit (NICU) from birth, although most intervention

studies have commenced at least a few weeks after an infant is born. Interventions that start in the NICU and continue after discharge are ideal for families as there is continuity of care, and have also been shown to have a larger effect on cognitive outcomes than when commenced post-discharge.¹⁵ There have been multiple NICU-based interventions trialed including Creating Opportunities for Parent Empowerment (COPE),³⁸ Newborn Developmental Care and Assessment Program (NIDCAP),^{39,40} massage therapy,⁴¹ and different components of developmental care.⁴² These interventions have shown short-term improvements in neurobehavioral outcomes,⁴³ although the longer-term benefits remain unclear.⁴⁰ Early developmental intervention alone in the NICU is unlikely to be enough to offset the negative consequences of preterm birth for most children and their parents and thus there is a critical imperative for it to continue post-hospital discharge.

Where to deliver early intervention?

Early intervention can occur in the home, hospital outpatient clinic, or in the community. A recent study from Taiwan investigated the effect of early developmental interventions delivered in an outpatient hospital clinic or home-based compared with usual care.⁴⁴ Both clinic-based and home-based interventions were better than usual care (which involved general health, immunization, nutrition and growth surveillance) in improving cognitive, motor, and behavioral outcomes with the effects mediated by mother–infant interaction and infant emotional regulation. This suggested that location of intervention delivery did not necessarily strongly influence efficacy, but again highlighted the importance of ensuring there is a focus on the parent–infant relationship. Further research comparing the effectiveness of different formats, locations, and delivery modes of intervention is needed to understand whether some are more effective for certain populations or families.

Who should receive early intervention?

Although it is recommended that all very low birth weight infants have early intervention initiated within 2 months of a suspicion or diagnosis of a delay in an area,⁴⁵ there is a role for preventative early intervention in preterm children. The aim of preventative care is to modify the development trajectory, which is often delayed in preterm infants in most domains of neurobehavior compared to term-born peers, by enriching the environment, enhancing physical and cognitive development, and promoting resilience in the early stages of development.^{43,46} One of the challenges in the perinatal care and subsequent development over the first-year post-term is identifying which infants are delayed or have a specific diagnosis, which often results in interventions commencing late rather than early.⁴⁷ The majority of research on early developmental interventions over the past decade has focused on infants born very preterm (<32 weeks' gestation) given the high rates of neurobehavioral challenges in this population.¹⁵ Very preterm infants without known risk factors for adverse neurological outcomes in the perinatal period such as intraventricular hemorrhage and periventricular

leukomalacia, experience positive benefits on cognitive,⁴⁸ motor,^{49,50} behavior,^{51,52} and language development⁵³ in early childhood as a result of preventative early developmental interventions.

For most early developmental interventions for preterm infants, research trials have been designed as *preventative* interventions particularly when commenced in the first few months after birth.¹⁵ Early identification of infants at risk for specific neurobehavioral impairments, such as cerebral palsy, often does not occur until the second or third year,⁵⁴ although there are tools such as neuroimaging (e.g., cranial ultrasound and magnetic resonance imaging) and early standardized neurological/neurobehavioral assessments (e.g., General Movements Assessment) that can be used to identify children at high risk.^{55,56} There has recently been a shift in the early intervention field for children at high risk of cerebral palsy to be identified within the first few months of life and enrolled in cerebral palsy motor specific training trials to improve the evidence base.¹⁴ Infants born preterm, with a diagnosis of cerebral palsy in the first year, are likely to benefit more from intensive, goal-orientated, task-specific training than traditional preventive care programs for preterm infants to improve motor outcomes.^{15,57} Early identification of other neurobehavioral impairments in preterm infants, including cognitive and behavioral impairments, is challenging but also possible using standardized neurobehavioral assessments such as the NICU Network Neurobehavioral Scale and neuroimaging.^{58,59} However, to date, there have not been any targeted early developmental intervention randomized controlled trials in preterm infants focused on identifying and treating cognitive and behavioral impairments based upon specific assessment findings in the newborn period.

What should early intervention involve?

Several reviews have concluded that the greatest improvements in the developmental pathways for preterm infants are associated with developmental interventions that focus on parent–infant relationship and infant development.^{15,32,60} Interventions that focus primarily on responsive parenting, which supports the conditions for the child’s development through the dyadic relations in the family have the greatest effect on cognitive outcomes.⁶⁰ The MITP is the most well studied and widely used of these programs and involves improving parent–infant interaction by enabling parents to appreciate their infant’s unique characteristics, sensitize parents to infant cues and readiness for interaction, along with a focus on parental grief, guilt, and anxiety related to preterm birth.^{33,61,62} Similarly, within the limited number of interventions that have improved motor outcomes of preterm infants, those that have had a positive effect, involved physical therapists working within a model involving the parent–child dyad.^{36,44}

How long should early intervention occur for?

The length and dosage of interventions varies within the literature. The shortest intervention involved 4 sessions and although it had short-term positive effects on cognitive outcomes, its efficacy in long term has not been investigated.³⁸

On the other hand, the Infant Health Development Program (IHDP) involved intensive intervention for 3 years, and while it has also shown short-term benefits, in long term these effects were not sustained at school age.⁶³ There is no clear dose–benefit relationship investigated to date, but several programs with similar theoretical construct to the MITP, involving 7–12 sessions over the first 6–12 months have been shown to have a positive effect on cognitive, behavior and/or cognitive outcome.⁶⁰

Consideration of parental mental health

Given the critical role that parents have for early intervention with preterm infants, it is important to consider factors that may negatively influence parental functioning and ability to engage with early intervention for their child. One of these factors is parental mental health problems. Parents of preterm infants are more likely to experience symptoms of depression and anxiety in the first few years after birth compared with parents of term-born infants.⁶⁴ For example, a recent study finding that 40–50% of mothers and fathers of infants born <30 weeks’ gestation reported clinically significant depression and anxiety within the first few weeks after birth.⁶⁵ The high rates of distress in parents of preterm infants has implications for children’s development, as maternal post-natal depression has been associated with higher rates of child behavior and emotional problems, and poorer language and cognitive development across childhood and adolescence.⁶⁶ Similar associations between parental mental health problems and poorer child development have also been identified for very preterm children.^{67,68} However, preterm infants may be more vulnerable in some areas to the negative influence of parental mental health, with evidence that if parents experience anxiety or depression, preterm children are at greater risk of developing mental health problems than term-born children.⁶⁹

One of the mechanisms through which parental mental health problems influence child outcomes is through parenting behavior. Maternal post-natal depression has been associated with increased maternal negativity, unresponsive or negative maternal–child interaction, impairment in ability to recognize infant cues, and providing fewer learning opportunities.⁶⁶ Considering the critical importance of the parent–infant relationship in promoting optimal outcomes for preterm infants, early interventions to improve parental mental health are also likely to be an important component of any approach to improving child outcomes after preterm birth. While few early intervention programs for parents after preterm birth include a specific focus on parental mental health, some include broader psychosocial support and education for parents. Evidence from 2 systematic reviews indicates that early intervention programs after preterm birth that include parental psychosocial support (and often developmental support for the infant) are associated with lower symptoms of maternal depression and anxiety.^{35,70} Heterogeneity between interventions (timing, focus, and length) increases the challenges with identifying the key components of effective interventions that promote parental mental health. However, given the high rates of depression

and anxiety in this population of parents and the significant impact this can have on parenting and child development, developing, and assessing interventions with a significant focus on parental mental health is critical in order to maximize the impact of early intervention programs on child outcomes.

Limitations of current research

There have been a large number of randomized controlled trials on early developmental interventions to improve outcomes for infants born preterm, yet there are many limitations in the literature to date.^{51,71} One of the limitations in the research involving randomized controlled trials is standardization of the control group, with many control groups ultimately receiving intervention due to ethical concerns of providing no intervention, potentially reducing the effect size of successful interventions being tested.⁷¹ This is particularly problematic in long-term follow-up studies (e.g., at school age) investigating the effects of an intervention in the first year, given that those children who go on to have later neurobehavioral impairments during the preschool years or school years should ideally have received some intervention. Thus, it is not surprising that the effects of early developmental interventions are not sustained at school age, but this should not mean that these interventions are not part of clinical care.^{36,72} Rather, early developmental interventions can provide a positive start for infants born preterm but further intervention may be required if a child has a specific neurobehavioral impairment. Finally, the majority of research to date has focused on cognitive outcomes, with fewer studies assessing motor and behavioral outcomes longer-term, restricting conclusions about the broader effect of early intervention across multiple developmental domains.

Future research directions

Despite early developmental interventions having a positive effect on neurobehavioral outcomes, their use in clinical practice is limited due to the cost, particularly for home-visiting programs.⁴³ However, there have been few cost-benefit analyses of early developmental interventions for preterm children, and this must be part of the research agenda for future studies. For instance, a recent review on a new intervention approach called Family Nurture Intervention (FNI) estimated that cost of autism related to preterm births <34 weeks' gestation was \$US 16 billion per year in the United States.⁴³ If their intervention was implemented as standard care, at a cost of \$100 million per year in the United States, they estimated an ultimate project return on investment of 16–1.⁴³ Understanding the costs and benefits associated with early interventions will be critical in effective translation into standard clinical practice. Future interventions and trials should also consider options for the mode of intervention delivery. With advancements in technology, there may be a role for web-based intervention given that these have also been shown to be effective in other populations at improving mental well-being⁷³ and child outcomes in

other populations.⁷⁴ Further, specialist electronic toys, such as the CareToy™, which is an intelligent system inspired by baby gyms are being trialed to examine their feasibility and validity in providing intensive home-based intervention for preterm infants.⁷⁵ Finally, we still know little about the right dosage of intervention and when the intervention should start. Although there is some evidence that the earlier the intervention starts, the better the child's outcome will be, there is little research on what the most effective dose of intervention might be and whether longer and more intense intervention is necessarily the most clinically and cost-effective approach.

Clinical implications

It is essential that early interventions are targeted to the child and family's needs,^{45,57} and include and involve parents. For preterm infants at high risk of cerebral palsy, identified with neuroimaging and/or neurobehavioral examination ideally in the first few months of life, task-specific, goal-orientated interventions involving families are recommended.⁵⁷ Where possible it is ideal that early developmental interventions can extend from the NICU into the home. However, given different funding models in clinical practice world-wide this is not often possible.³² Thus clinicians in both hospital and community based services should focus on transition of care, acknowledging the important milestone the infant and family has achieved to be discharged from hospital whilst also recognizing that discharge from hospital is not always the end point of care and follow-up of long-term neurodevelopmental development is needed.²² When early development intervention is not commenced in the NICU, it is important that appropriate follow-up services are in place so that intervention can be commenced in a timely manner.

Conclusions

There is increasing evidence that early developmental interventions with a preventative focus improved cognitive, behavior, and motor outcomes for infants born preterm. For those children or parents with a specific impairment, such as a child with cerebral palsy or parent with significant postnatal depression, targeted intervention programs are needed. Early interventions with parents of preterm infants to support their mental health and parenting may promote positive brain development processes and result in better outcomes for these vulnerable children. It is important to note that while this review has focused on early intervention in the first year of life, the effects of preterm birth are long term, and further intervention,⁷² including possible "booster" sessions or special education support, may be required at school age.

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