Original Article

Neurodevelopmental outcomes of preterm infants: a recent literature review

Estefani Hee Chung, Jesse Chou, Kelly A. Brown

Homer Stryker MD School of Medicine, Western Michigan University, Kalamazoo, MI, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kelly A. Brown. 1000 Oakland Drive, Kalamazoo, MI 49008, USA. Email: kelly.brown@med.wmich.edu.

Background: Over the past several decades, improvements in technology in the Neonatal Intensive Care Unit (NICU) have led to improved survival of preterm infants. Some studies have found that premature infants are at higher risk of behavioral problems, motor and sensory abnormalities, developmental delay, and poorer academic performance, while other studies have found no significant difference.

Methods: A literature search was conducted through PubMed for articles published between January 2018 and September 2019. Studies that concentrated on preterm infants with relatively uncomplicated NICU courses and without extensive medical interventions were selected.

Results: Historically, preterm infants have been found to be at increased risk for the inattentive subtype of attention deficit hyperactivity disorder (ADHD), depression, anxiety, autism spectrum disorder (ASD), avoidant personality, and anti-social personality, when compared to full term infants. However, some studies found that this difference between the two groups decrease as they enter adolescence and adulthood. Preterm infants are at increased risk for language, cognitive, sensory and motor deficits. Greater gestational age (GA) at birth and higher birth weight is associated with a lower risk of developmental delay. Cohort studies focusing on motor development showed that the degree of impairment decreased over time. Adverse childhood experiences (ACEs) have a negative correlation on multiple domains of development. The overall outcome of these infants may be influenced by socioeconomic status (SES), neonatal morbidities, demographics and parental education. Hearing and vision deficits are relatively infrequent among premature infants. A significant risk factor for hearing impairment involves the use of ototoxic agents such as gentamicin and infants with a patent ductus arteriosus (PDA).

Conclusions: Preterm infants are at higher risk of adverse neurodevelopmental outcomes when compared to their full-term counter parts. However, in recent years it appears that rates of certain neurologic and developmental conditions are occurring in rates lower than historically noted. Premature individuals with possible developmental or mental health concerns should be identified early on so that interventions can be implemented immediately. Those meeting developmental milestone should continue to be monitored closely as deficits may develop later.

Keywords: Preterm infants; prematurity; neurodevelopment; developmental delay

Submitted Sep 27, 2019. Accepted for publication Sep 27, 2019.

doi: 10.21037/tp.2019.09.10

View this article at: http://dx.doi.org/10.21037/tp.2019.09.10

Introduction

Over the past several decades, improvements in technology in the Neonatal Intensive Care Unit (NICU) have led to improved survival of preterm infants. Preterm infant is defined as birth before 37 weeks gestation. This is separated further into extremely preterm (EPI), very preterm (VPI), moderate preterm (MPI), and late preterm (LPI) defined as infants born less than 28, 28 to 32, 32 to 34, and 34 to 37 weeks gestation respectively. EPIs and VPIs are at higher risk of adverse outcomes when compared to MPIs and LPIs (1). Former premature infants who are now children, adolescents, and young adults is an increasing patient population, and their quality of life and neurodevelopmental outcomes are important topics of interest.

A spectrum of neurodevelopmental morbidities is associated with prematurity. Several studies have found that preterm infants are at higher risk of psychiatric problems [autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), anxiety, depression], motor and sensory abnormalities [problems related to vestibular balance, pain processing, deafness, cerebral palsy (CP)], developmental delay (such as problems related to language, cognitive, sensory, and motor development), and poorer academic performance when compared to full term infants. However, while some studies have found no significant difference between preterm infants and full-term infants, other studies found a significant difference at younger ages that diminishes over time, with no significant differences into young adulthood.

This article focuses on the most recent research over the past 2 years that have looked at the neurodevelopmental outcomes in preterm infants at different points in development. We aim to summarize the most recent findings of the neurodevelopmental outcomes for these patients and highlight some recommendations that may improve neurodevelopmental outcomes and enhance the quality of life of former preterm infants into childhood and beyond.

Methods

Search strategy

A literature search was conducted through PubMed with the keywords 'Neurodevelopment' and 'Preterm.' The search was then narrowed to articles published between January 2018 and September 2019. Articles in the reference sections of the articles selected were also reviewed. All relevant articles were assessed with application of inclusion and exclusion criteria.

Inclusion criteria

Studies that concentrated on preterm infants with relatively uncomplicated NICU courses and without extensive medical interventions were selected to minimize possible confounding factors. Selected articles were not restricted to one geographical location. No restriction on extent of prematurity was made. Most articles selected were cohort studies with a few review articles and cross-sectional studies. Studies contradicting the information that most studies supported were found to have a smaller sample size and thus warned readers to interpret information with caution. Also, given that most studies reviewed for this article were cohort studies, many studies had lost some patients to follow-up, and thus there could be concerns of statistical power. Data was collected and summarized independently by two reviewers to minimize selection bias.

Exclusion criteria

Articles that focused on interventional outcomes were excluded in an attempt to focus mainly on the natural outcomes of preterm infants with and without complex neonatal histories. This was done to hone the focus of this article around the natural history of outcomes of preterm infants, while considering possible confounding factors. All editorials, abstracts, case reports, and letters were excluded.

Results

Mental health and/or behavioral problems

Historically, preterm infants have been found to be at increased risk for the inattentive subtype of ADHD, emotional disorders such as depression and anxiety, ASD, avoidant personality, and anti-social personality, when compared to full term infants (1-4). However, other studies contradict this finding, especially as these children enter adolescence and adulthood (2-4).

Johnson *et al.* studied the prognosis of psychiatric disorders in EPI at ages 2.5, 6, 11, 19, and 29 years, born in the United Kingdom and Ireland in 1995, and compared them to term controls. Individuals with a psychiatric disorder at 11 years of age were more likely to have mental health problems that persisted through teenage years,

adjusting for socioeconomic status (SES). The study demonstrated that young adults who were born extremely preterm appear to have a higher prevalence of anxiety, depression, and avoidant personality; however, there was no statistical significance between the preterm and term adults, and researchers concluded that childhood psychiatric disorders do not appear to persist into young adulthood for this population. A limitation to this study was that 42% of participants, which represented a group of lower SES and lower IQ patients with higher cognitive impairment, were lost to follow-up in adulthood. Thus, results may be skewed and may underrepresent the true burden of psychiatric disorders in this adult population (2).

You *et al.* compared 102 LPI infants to 153 term infants born in China at 24 and 30 months of age using the Modified Checklist for Autism in Toddlers (M-CHAT) questionnaire, a Chinese version of the Gesell Development Diagnosis Scale (GDDS), the Sensory Integration Schedule (SIS), and neurological examinations. Infants without neonatal disease and complicated medical course were selected. ASD was diagnosed in 8% of the cohort study, concluding that in their study population of preterm children born without any major problems, patients had a two to four times greater risk for ASD when compared to their full-term peers (3).

Hollanders *et al.* looked at gestational age (GA) and birth weight as independent factors in 705 19-year-old subjects and concluded that these terms are not interchangeable as they result in significantly different outcomes. VPI with very low birth weight (VLBW; defined as ≤1,500 g) reported less internalization behavioural problems and fewer attention problems than VPI with VLBW (5).

Developmental delay

Preterm infants are at increased risk for language, cognitive, sensory, and motor impairment (1-4). These impairments may manifest as poor academic performance or behavioral problems in school-aged children (3,4). Inferior neurodevelopment is multifactorial and is likely a consequence of an immature brain, perinatal risk factors, and environmental exposures. A meta-analysis concluded that environmental factors become more prominent while perinatal factors have less of an impact over time (1). Greater GA at birth and higher birth weight is associated with a lower risk of developmental delay (1,3-8). Preterm infants exposed to corticosteroids or magnesium *in utero* have a lower risk of cognitive delay (7). Perinatal factors that increase the risk of developmental delay are low arterial pH of umbilical cord blood, low Apgar scores, intraventricular hemorrhage (IVH), chorioamnionitis, moderate-to-severe bronchopulmonary dysplasia (BPD), prolonged mechanical ventilation, and seizures (1,4,5,8). IVH and periventricular leukomalacia (PVL) have a strong associate with poorer gross motor function (7,8). Other factors such as such as male sex, spoken language other than English, black race, lower parental education, and SES were found to be associated with poorer developmental outcomes (1,4,5,8). Infants born in underdeveloped countries have a higher prevalence of developmental delay when compared to those in developed countries and has been theorized to be due to lack of resources, inadequate insight, and differences in culture (1). A study conducted on LPI infants at 12 and 18 months of age used Bayley-II scales of infant and toddler development to assess patients and showed significantly lower scores when using chronological age; however, there was no significant difference noted between LPI and full-term infants when using corrected GA (4).

Differences in sensory processing may be due to repeated painful stimulation in the NICU environment and separation from parents. However, even LPI infants not subjected to such environments were found to have abnormalities in sensory processing (3). Premature infants have a 70–80 times greater risk of CP compared to full-term individuals (5). In a large cohort study of EPIs (n=1,113), motor development was analysed utilizing Bayley-III (BSID III) which showed that at the 18–26 months follow-up mark, severe CP decreased 43% and mild CP increased 13% (9). Similarly, moderate to severe neurodevelopmental impairment (NDI) decreased from 21% to 16% in these patients (10).

Do *et al.* investigated the neurodevelopmental outcomes of 184 preterm infants at 2 years of age in a low- and middle-income Vietnamese population using an adapted version of the Bayley Scales of Infant and Toddler Development and the Amiel-Tison's neurological examination method (1). Preterm infants with brain malformations, retinopathy of prematurity, or chromosomal anomalies were excluded. Infants with CP were diagnosed in 7% of infants using the Gross Motor Function Classification System. Preterm infants had higher impairment in cognition, language and motor skills by 17%, 8%, and 4% respectively when compared to the full-term control group (1). Woythaler *et al.* had similar findings of worse cognitive, language, and motor delays in 2-year-old LPI infants using the Bayley scoring system with the greatest impairment in language (4).

Interestingly, Lin *et al.* found that the pooled prevalence of CP in EP infants was reduced compared with previous meta-analysis. This is in the context of improving NICU care alongside better detection capabilities for a wide range of neurodevelopmental disabilities resulting from VPT infants (10). Spittle *et al.* used CP as a proxy for motor impairment to compare an EP group with a term group in Victoria, Australia, finding that the rate of motor impairment in EP children at 8 years of age was higher, but this was in regards to non-CP motor impairment (11).

While many studies, have focused on motor impairment in the context of CP, non-CP motor impairment, such as developmental coordination disorder (DCD), can remain a risk for apparently health EPIs. Bolk *et al.* conducted a population-based cohort study in Sweden that included 441 preterm children and 371 controls. At 6.5 years of age, 37.1% of preterm children had DCD, while 5.5% of the controls had DCD (OR: 7.92). The authors further characterized an increased risk for behavioural problems, executive dysfunction, and other skill impairment (12).

You *et al.* stated that LPIs are increased risk of sensory integration dysfunction, recognition defects and motor disorders despite having any major medical complications. These impairments were more prominent in preterm children with ASD. There is a negative correlation between developmental outcome and twin pregnancies, pregnancy-induced hypertension, and premature rupture of membrane (3).

Hollanders *et al.* found that VPI without VLBW had less hearing loss and higher IQ thus higher educational achievement when compared to VPI with VLBW even after adjusting for demographic and neonatal morbidities (5). Lin *et al.* conducted a prospective cohort study using the Bayley II or Bayley III and Wechsler preschool and primary scale of intelligence-revised (WPPSI-R) on 4,105 2-year-old and 1,427 5-year-old VLBW premature Taiwanese children. Infants with genetic anomalies and major congenital malformations were excluded. Mild delay and moderate-severe delay were referred to as borderline and abnormal outcomes respectively. At 5 years of age 12.05% and 8.67% of participants were found to have borderline and abnormal cognitive development respectively; Of the abnormal and borderline groups, 18.03% and 71.43% had normal or borderline development at 2 years respectively. As age increases, the prevalence of developmental impairment in VLBW preterm children increases. At 2 and 5 years, the incidence of CP was 6.31% and 6.8% respectively. This study did not include the types of early-intervention programs (10).

Li *et al.* conducted a retrospective study on 131 EPIs at 18 and 24 months of age in China. Neurodevelopmental delay was noted in 35.9% of the cohort; Cognition delay, language delay, global developmental delay and moderate-severe CP were noted in 17.5%, 4.6%, 3.2% and 10.7% respectively. After adjusting for the presence of chorioamnionitis, early onset sepsis and bronchopulmonary dysplasia (BPD), prematurity was found to be an independent risk factor for poor developmental prognosis. However, the degree of hypoxia experienced by a neonate appears to have a negative correlation with the severity of developmental impairment. The outcome of infants born in hospitals in a minority/underserved area was found to be worse when compared to those born in more developed areas due to the limited NICU resources. A limitation to this study is lack of knowledge of SES, which is a significant confounding factor (8). Provenzi *et al.* have attempted to further characterize the risk factors for preterm infants by suggesting an epigenetic mechanism. Their 2018 systematic review found that factors such as maternal stress and/or depression, as well as NICU-related stress or pain can have longstanding impacts on the developmental trajectories of preterm infants that can extend through childhood through epigenetic alterations of imprinted and stress-related genes (13).

An additional environmental factor affecting the neurodevelopment of EPs includes maternal education status. Joseph *et al.* followed a group of 873 EPs and assessed neurocognitive and academic outcomes at ten years of age. They controlled for GA and potential cofounders, concluding that maternal education, a proxy for SES of the mother, is associated with significantly poorer neurodevelopment outcomes at 10 years of age. However, children of mothers that were able to advance their education in that 10-year period were associated with modestly improved outcomes (14).

Mother's education status seems to have an impact on EPs' neurodevelopment. The reasons are likely multifactorial, but may partly be explained by the work of Romeo *et al.*, who described the importance of early language exposure in activation of Broca's area. They conducted a functional MRI scan during a story-listening activity and found that in 36 SES-diverse 4–6 years old children, the children with more conversation experience had greater left inferior frontal (Broca's area) activation (15). This is an important factor for any child, preterm or term, but Lean *et al.* contribute to a theory of why this is particularly crucial in preterm. They compared 84 VPT

and 38 demographically matched FT children via the Wechsler Preschool Primary Scale of Intelligence-III, and assessed language with the Clinical Evaluation of Language Fundamentals Preschool-2. Mothers were tested as well. They found a statistically significant connection between mothers' intellectual ability and child intellectual and language abilities. Maternal intellectual ability independently predicts VPT and FT children's intellectual and language outcomes. The genetic basis for heritability of maternal intellectual ability is not fully understood, but prematurity increases the variation in the heritability of intellectual ability. Thus, children born prematurely are more likely to not fully develop intellectually (16). Unfortunately, Field *et al.* found that increased maternal education, along with employment and lower age, were demographic risk factors associated with postnatal anxiety (17).

The relationship between adverse childhood experiences (ACEs) and poor developmental outcomes has been consistently upheld throughout the pediatric literature. Folger *et al.* reified this relationship through their retrospective cohort study that included 311 mother-child dyads and 122 father-child dyads, consistently noting that for both parents the number of ACEs directly correlated to negative impact on child development in multiple domains. Notably, there was an 18% increase in risk of developmental delay for each ACE (18).

Neurosensory impairment

Lin *et al.* found rates of bilateral blindness and severe hearing loss at 2.41% and 0.54 % at 2 years of age and 0.28% and 2.8%, respectively at 5 years of age. The developmental findings at 2 years were found to be less predictive for later learning status, whereas impairments noted at 5 years were suggested to be associated with more challenges later in life (10). Burnett *et al.* further detailed the connection between perinatal factors and neurosensory impairments such as CP, blindness and deafness. Their findings are consistent with Lin *et al.* in that severe hearing and vision deficits are relatively infrequent among EPIs, with rates in toddlers less than 2% and 3%, respectively (10,19). A major risk factor for blindness in preterm infants and retinopathy of prematurity, is receiving medical care in lower resource settings, and these vision conditions have been associated with other medical comorbidities, such as cardiac anomalies. A significant risk factor for hearing impairment involves the use of ototoxic agents such as gentamicin in preterm infants that have an infection. Additionally, VPI with patent ductus arteriosus (PDA) are at increased risk of hearing impairment in toddlerhood (5% compared to 2% risk in infants without PDA) (10,19).

Conclusions

Preterm infants are at higher risk of adverse neurodevelopmental outcomes when compared to their full-term counter parts. However, in recent years it appears that rates of certain neurologic and developmental conditions are occurring in rates lower than historically noted. It is likely that advances in neonatal medical intensive care may be contributing to these improved rates. Premature individuals with possible developmental or mental health concerns should be identified early on so that interventions can be implemented immediately. Even preterm infants that appear to be meeting developmental milestones should continue to be monitored closely as deficits may develop later. This can affect their quality of life all the way into adulthood. Further research on the impact of early-intervention programs on neurodevelopmental outcomes on preterm infants should be conducted, which can provide better understanding of the neurodevelopmental outcomes of preterm infants. Pediatric healthcare providers should continue to schedule follow-up appropriately, closely monitor former preterm infants for developmental delay, and provide appropriate anticipatory guidance to caregivers, ensuring that these vulnerable patients can achieve their greatest potential.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Do CHT, Kruse AY, Wills B, et al. Neurodevelopment at 2 years corrected age among Vietnamese preterm infants. Arch Dis Child 2020;105:134-40.
2. Johnson S, O'Reilly H, Ni Y, et al. Psychiatric symptoms and disorders in extremely preterm young adults at 19 years of age and longitudinal findings from middle childhood. J Am Acad Child Adolesc Psychiatry 2019;58:820-6.e6.
3. You J, Shamsi BH, Hao MC, et al. A study on the neurodevelopment outcomes of late preterm infants. BMC Neurol 2019;19:108.
4. Woythaler M. Neurodevelopmental outcomes of the late preterm infant. Semin Fetal Neonatal Med 2019;24:54-9.
5. Hollanders JJ, Schaëfer N, Van Der Pal SM, et al. Long-term neurodevelopmental and functional outcomes of infants born very preterm and/or with a very low birth weight. Neonatology 2019;115:310-9.
6. Jois RS. Understanding long-term neurodevelopmental outcomes of very and extremely preterm infants: A clinical review. Aust J Gen Pract 2019;48:26-32.
7. McGowan EC, Vohr BR. Neurodevelopmental follow-up of preterm infants: what is new? Pediatr Clin North Am 2019;66:509-23.
8. GuangXi Cooperative Research Group for Extremely Preterm Infants, Li Y, Meng DH, et al. Neurodevelopmental outcomes of extremely preterm infants in southern China: A multicenter study. Early Hum Dev 2019;133:5-10.
9. Adams-Chapman I, Heyne RJ, DeMauro SB, et al. Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network. Pediatrics. 2018;141:e20173091
10. Lin CY, Hsu CH, Chang JH, et al. Neurodevelopmental outcomes at 2 and 5 years of age in very-low-birth-weight preterm infants born between 2002 and 2009: A prospective cohort study in Taiwan. Pediatr Neonatol 2020;61:36-44.
11. Spittle AJ, Cameron K, Doyle LW, et al. Motor impairment trends in extremely preterm children: 1991-2005. Pediatrics 2018;141:e20173410.
12. Bolk J, Farooqi A, Hafström M, et al. Developmental coordination disorder and its association with developmental comorbidities at 6.5 years in apparently healthy children born extremely preterm. JAMA Pediatr 2018;172:765-74.
13. Provenzi L, Guida E, Montirosso R. Preterm behavioral epigenetics: A systematic review. Neurosci Biobehav Rev 2018;84:262-71.
14. Joseph RM, O'Shea TM, Allred EN, et al. Maternal educational status at birth, maternal educational advancement, and neurocognitive outcomes at age 10 years among children born extremely preterm. Pediatr Res 2018;83:767-77.
15. Romeo RR, Leonard JA, Robinson ST, et al. Beyond the 30-million-word gap: children's conversational exposure is associated with language-related brain function. Psychol Sci 2018;29:700-10.
16. Lean RE, Paul RA, Smyser CD, et al. Maternal intelligence quotient (IQ) predicts IQ and language in very preterm children at age 5 years. J Child Psychol Psychiatry 2018;59:150-9.
17. Field T. Postnatal anxiety prevalence, predictors and effects on development: A narrative review. Infant Behav Dev 2018;51:24-32.
18. Folger AT, Eismann EA, Stephenson NB, et al. Parental adverse childhood experiences and offspring development at 2 Years of Age. Pediatrics 2018;141:e20172826.
19. Burnett AC, Cheong JLY, Doyle LW. Biological and social Influences on the neurodevelopmental outcomes of preterm Infants. Clin Perinatol 2018;45:485-500.

Cite this article as: Hee Chung E, Chou J, Brown KA. Neurodevelopmental outcomes of preterm infants: a recent literature review. Transl Pediatr 2020;9(Suppl 1):S3-S8. doi: 10.21037/tp.2019.09.10

