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Early neurodevelopmental outcomes of extremely preterm infants

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ABSTRACT

Infants born at extreme preterm gestation are at risk for both death and disability. Although rates of survival have improved for this population, and some evidence suggests a trend toward decreased neuromotor impairment over the past decades, a significant improvement in overall early neurodevelopmental outcome has not yet been realized. This review will examine the rates and types of neurodevelopmental impairment seen after extremely preterm birth, including neurosensory, motor, cognitive, and behavioral outcomes. We focus on early outcomes in the first 18–36 months of life, as the majority of large neonatal studies examining neurodevelopmental outcomes stop at this age. However, this early age is clearly just a first glimpse into lifetime outcomes; the neurodevelopmental effects of extreme prematurity may last through school age, adolescence, and beyond. Importantly, prematurity appears to be an independent risk factor for adverse development, but this population demonstrates considerable variability in the types and severity of impairments. Understanding both the nature and prevalence of neurodevelopmental impairment among extremely preterm infants is important because it can lead to targeted interventions that in turn may lead to improved outcomes.

Introduction

Infants born at extreme preterm gestation are at risk for death and medical complications, as well as short and long-term developmental impairments in survivors. While prematurity is defined as birth prior to 37 weeks' gestation by the World Health Organization (WHO), extreme prematurity refers to birth at the earliest gestational ages, defined as less than 28 weeks. In 2013, more than 1 in 10 babies in the world were born prematurely, while in the United States the rate was greater than 11%.[1,2] This account for almost 15 million births worldwide, and is a major cause of death for children. The majority of preterm babies are born between 34 and 37 weeks, with 1.92% born less than 32 weeks and approximately 0.73% of all births were born prior to 28 weeks. Whereas extreme prematurity accounts for a small percentage of overall preterm deliveries, it does account for a larger percentage of long-term complications and short- and long-term resource utilization, including hospital readmissions and healthcare costs. Additionally, while the overall preterm birth rate has been declining in the last decade, the rate of extreme preterm birth has remained relatively unchanged.

Resources play a role in the rates of survival after preterm birth, as 90% of infants born <28 weeks gestation in resource-challenged settings will die compared with 10% in

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high-income settings.[1] Understandably, then, countries with higher rates of earlier preterm survival may report higher rates of medical and neurodevelopmental complications of prematurity, thus making worldwide comparisons challenging. It is reported that in some countries, such as the United States, 22–24 gestational weeks is considered to be a limit of viability whereas in other low-resource countries, it is considered rare for an infant born less than 32 weeks to survive.[1,3,4] Survival and severe morbidities are considered competing outcomes, and thus many studies and trials that include extremely preterm infants use a composite outcome of death or "neurodevelopmental impairment." However, neurodevelopmental impairment is itself a composite outcome, including neurologic, cognitive, and sensory elements, and has been defined differently across studies and epochs. This necessarily leads to challenges in interpretation, as well as applicability. Although information is often presented to families in terms of rates of this composite outcome either in the antenatal or postnatal setting, this may not be meaningful to them. The value of each of the component outcomes may vary broadly for each individual and family, outcomes may be conceptualized differently, and statistics can be difficult to grasp.[5,6] Understanding the context of both a family facing a decision about initiating or continuing intensive care for their extremely preterm infant and these inherent difficulties in interpreting outcomes studies is critical in neonatology.

Neurodevelopmental impairment is risk after preterm birth and is multifactorial, resulting from and influenced by a myriad of antenatal, perinatal, and postnatal causes. Antenatally, maternal diabetes has been associated with poorer neurodevelopmental outcomes, for example, as well as inadequate prenatal care, maternal infections, and malnutrition, while maternal pre-eclampsia does not appear to increase risk over the risk of prematurity alone. In the perinatal period, neurodevelopmental outcomes have been reported to be associated with gestational age at birth, clinical stability, medical comorbidities, and acquired brain injury such as intraventricular hemorrhage (IVH) or white matter injury. Postnatally, long-term medical complications such as requiring supplemental oxygen or tube feedings as well as a family's socioeconomic status and access to developmentally supportive therapies have been shown to be connected to rates of impairment. "Intact" survival usually refers to survival without major medical or neurodevelopmental complications, which typically including visual impairment, hearing impairment, gross motor delays, or deficits in cognitive ability, although this outcome, too, has been defined variably across studies.

Survival vs. "intact survival" rates

The rates of survival at extreme preterm gestation have improved significantly over the past decades, likely as a result of advances in both perinatal and neonatal care as well as changes in the approach to resuscitation among "periviable" infants, infants born less than 26 0/7 weeks gestation as recently defined by a Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD) workshop on the topic of extreme prematurity.[7] Several large cohorts have clearly demonstrated these improvement in survival rates at the earliest gestational ages, including the NICHD Neonatal Research Network (NRN) which recently showed that among infants born between 22 and 29 weeks gestation, overall survival increased from 70% in 1993 to 79% in 2012. The greatest gains in survival rates in that time period were for infants born at 23 and 24 weeks.[8] The NICHD NRN consists of large, academic quaternary care centers that are selected by National Institutes of Health (NIH) peer review. The NRN cohort has rigorous follow-up standards and protocols, but is not population-based, and also may not reflect community practice in non-academic environments.

Population-based cohorts in Sweden and the Netherlands have also shown increased survival rates at periviable gestation.[9,10] The Swedish EXPRESS group has shown that in their most recent era after adopting a national centralization of services for possible preterm delivery, and a more active approach to perinatal management, survival at 23 weeks gestation increased from 8% to 52%, from 28% to 67% at 24 weeks, and that babies born at 25 and 26 weeks have a one-year survival rate of 81% and 85% respectively. After the Netherlands Association of Pediatrics and the Netherlands Association of Obstetrics and Gynecology modified the national policy toward more active intervention at periviable gestational ages, the Dutch group saw increased survival from 30% to 56% at 24 weeks, and 54% to 73% at 25 weeks over two epochs spanning 11 years. Similarly, EPICure, a UK population-based cohort, showed increase in survival over two epochs, while EPIPAGE-1 and -2, a French population-based cohort, did not show increased survival rates less than 25 weeks over its two epochs, but did show improvements at gestational ages above 25 weeks.[11,12] The Neonatal Research Network of Japan recently reported survival rates higher than other cohorts, with overall survival to 3 years between 22 and 25 6/7 weeks of 74%, including 36% survival at 22 weeks and 63% at 23 weeks.[13] Finally, a series of population-based cohorts of extremely preterm infants from the state of Victoria, Australia, followed by the Victoria Infant Collaborative Study (VICS) group showed that survival less than 28 weeks increased between epochs in the 1990s and have stayed relatively stable in epochs since.[14–16]

Several large cohorts have shown these improved rates of survival have been accompanied with increased rates of complications related to preterm birth. The incidence of some short-term morbidities such as retinopathy of prematurity and bronchopulmonary dysplasia are directly related to decreasing gestational age, and more survivors at these extremely young gestational ages result in increased prevalence of these co-morbidities, although changes in definitions and enhanced surveillance protocols over time may also contribute to an increase in reporting.[17] In the neonatal period, infants are also susceptible to brain injury, including IVH, posthemorrhagic hydrocephalus, and white matter injury, which are also associated with decreasing gestational age.[11] Additionally, survivors of extreme prematurity may have other early childhood or life-long medical difficulties, such as significant respiratory health problems, feeding difficulties, and increased risk for emergency hospital readmission.[18–20]