Editorial

Follow-up Care and Outcome Evaluation of High-Risk Preterm Infants: A Life-Course Commitment

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Neonatology can be considered as one of the most successful medical innovations of the latter half of the twentieth century. A slow, synergistic accretion of scientific and clinical insights—combined with an evolution in the way physical spaces of hospitals were built and shaped, and the elaboration and articulation of a moral stance toward the activities being developed—eventually led to a new separate field of medicine that drastically improved infant mortality rates throughout the world. Rarely have the processes and products of scientific medicine been as heralded and harangued, as lauded and condemned, and as publicised and misunderstood as they have in the context of neonatal intensive care.[1]

Neonatal care in the last century can be divided into 3 stages. Right up to the 1950s, neonatal mortality was high and those who managed to survive had to be contented with whatever minimal care that was available, and the morbidity was relatively low. Neonatal care then entered into the second stage when heroic attempts were made to salvage high-risk infants without a good understanding of the scientific basis of neonatal disorders. The mortality rates were lowered at great costs of accompanying high incidence of severe disabilities among the survivors. For example, the indiscriminate administration of oxygen to premature babies with respiratory distress had resulted in blindness from retrolental fibroplasia. The subsequent arbitrary restriction of oxygen then resulted in mental retardation and cerebral palsy amongst the survivors. Most opponents to the development of neonatal care nowadays are still referring to the experience during this "dark age" of neonatology history. The development of neonatal intensive care in Singapore in the 1980s took place at the stage of advances in neonatology when significant progress had been made in the better understanding of the pathophysiology of many neonatal diseases such as hyaline membrane disease, periventricular-intraventricular haemorrhage (PIVH), bronchopulmonary dysplasia, necrotising enterocolitis, nutritional deficiencies, hyperbilirubinaemia, and retinopathy of prematurity. Technological innovations had enabled safer and more scientific-assisted ventilation, non-invasive monitoring, and effective nutritional care. These have resulted in better and more precise management of many neonatal disorders and a reduction of iatrogenic diseases. However, proper scientific evaluation of new treatment policies and innovations is mandatory to prevent their ever-enthusiastic implementation and adverse consequences.[2] We have also arrived at a period when we have great opportunities to critically examine the many epidemiological research data worldwide. This will lead to further refinement of prognostication, as well as to allow us to understand the cost-effectiveness of neonatal intensive care.

Advances in neonatal-perinatal care have been responsible for the improved survival of high-risk newborns. Babies who had been born too early have been the major beneficiaries. However, a major concern that newer therapies may result in an increased number of disabled survivors still persists. Neurodevelopmental follow-up is therefore a critical component of the evaluation of the neurological development and ongoing clinical needs of high-risk newborns. A substantial number of these infants will experience later neurological and developmental difficulties that are likely to seriously limit their educational, social, and other life-course opportunities. Unfortunately, it is not always possible to accurately predict—in the neonatal period—which infants will experience these problems and which will not. Furthermore, children's skills and abilities develop with age and experience, with simpler skills often forming the foundation for the learning of more complex skills. Thus, it is often not until a child fails, or is slower to develop a specific skill compared with other children of his or her age, that his or her problems become fully apparent. The developmental timing of this will also depend on the function of interest, with motor deficits tending to emerge in the first year of life, while cognitive and behavioural impairments develop more slowly from early childhood to adolescence. Therefore, high-risk infants require close

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monitoring and developmental surveillance as part of our ongoing responsibility for care and optimisation of their outcomes beyond merely survival and discharge from the neonatal unit.

Neurodevelopmental follow-up is also important for family support. The initial continuity-of-care should be provided by the neonatologist as it is important to reassure the family that the same personnel responsible for the life-saving decisions are continuing to assume responsibility for the child's adaptation into home life. Families want to know if their child is healthy and growing normally, or if problems are likely to be encountered in the future. Such information is valuable for both stress management and family decision-making. It also enables families to proactively plan and advocate for their child's needs. Families also need advice and support at key transition points in a child's life when additional challenges may be encountered by a child, such as starting childcare or enrolling into schools.

Information about high-risk children's outcomes is crucial for the improvement of existing neonatal-perinatal services. Specifically, possible positive and negative effects of different medical interventions on neurological and developmental outcomes may not be apparent in the first years of life. Therefore follow-up data can provide valuable feedback information about the efficacy and potential risks associated with different clinical care approaches beyond survival and short-term health outcomes. Finally, careful follow-up screening helps ensure that problems are detected early so that timely targeted interventions can be instituted to treat or to prevent significant health problems, which may worsen and place the child at increased risk of more complex impairments. Early intervention not only serves to minimise distress and strengthen families, but also to reduce the burden of long-term care on public health, social, and educational services over the child's life span.

Resource availability would determine how extensive and elaborate a follow-up programme would be, but the minimal requirement for the clinical monitoring of outcomes is a periodic assessment of growth and neurosensory development during the first 2 years of life. The ideal is a comprehensive programme involving all aspects of care, including well-baby care, evaluation of outcome, social and educational intervention, and therapy when needed. A home-visiting programme, especially during the early postdischarge period, and parent support groups for selected high-risk conditions (e.g. children with chronic lung disease) could also be considered. Because it is impossible to provide ongoing high-risk follow-up care for all infants treated in the neonatal intensive care unit, specific criteria have been proposed to identify children at greatest risk for sequelae. Traditionally, follow-up programmes primarily targeted children with birth weight of <1500 g (very low birth weight, VLBW) or gestational age of <32 weeks. Increasingly, most reports from developed countries would only cover infants with birth weight <1000 g (extremely low birth weight, ELBW) or gestational age <28 weeks; and even those born at the threshold of viability.

Neurodevelopmental outcome typically refers to cognitive, neurological and/or sensory outcomes. Traditionally in outcome studies, neurodevelopmental impairment has been defined as the presence of 1 or more of the following: a) cognitive delay based on scores on standardised cognitive tests that are 2 standard deviations below the mean (this would correspond to a score of 70 or below on the Mental Developmental Index of the Bayley Scales of Infant Development); b) moderate to severe cerebral palsy defined as a score of >2 on the Gross Motor Function Classification System; c) hearing deficit/loss requiring amplification; d) severe visual impairment with visual acuity of 20/200 or less in the better-seeing eye with best conventional correction (legal blindness). Increasingly, behavioural, psychological and functional outcomes are being recognised as important long-term neurodevelopmental outcomes.

Neurodevelopmental outcomes of several large cohorts of preterm infants around the world have been reported.[3,4,5,6,7,8,9] They are: the Victorian Infant Collaborative Study (VICS) Group; the EPICure 1 and 2 Studies from United Kingdom; Japan Neonatal Research Network; Eunice Kennedy Schriver NICHD Neonatal Research Network Follow-up Study Group; the Extremely Preterm Infants in Sweden Study (EXPRESS); and the Swiss National Cohort Study of Extremely Preterm Infants. What can we learn from their experiences?

Interpretation of the neurodevelopmental outcomes literature on preterm infants is challenging. Differences in defining the study population make comparison of data from different studies difficult. For example, the use of birth weight classification versus gestational age can be problematic as the more mature infants who are small for gestational age (SGA) may be included in a given birth weight category. This may have an impact on the outcome results as the SGA infants are known to have a greater risk of neonatal morbidities and poorer outcomes compared to their appropriate for gestational age (AGA) counterparts.

The assessment tools used in the studies vary. For example, several studies have shown that results from the Bayley Scales 3rd edition (BSID III, 2006) result in higher cognitive scores than the 2nd edition (BSID II, 1992).[10,11] It remains unclear whether the BSID III overestimates or is a more valid assessment of the cognitive performance compared with BSID II.

There are significant differences and changes in perinatal and neonatal clinical policies and practices over time. The

impact on outcome is difficult to accurately ascertain as the improved survival rate has outpaced any concomitant decrease in the rate of long-term neurodevelopmental sequelae. Even in developed countries, there are global and regional differences in their perinatal approach to infants at the threshold of viability, making comparison of survival and outcome data between studies very difficult.

Over the past few decades, several changes in perinatal care are known to have significant impact on the neurodevelopmental outcome of preterm infants—directly or indirectly—by reducing complications such as PIVH. Infants who received antenatal corticosteroids had a lower death rate and a reduced incidence of moderate to severe cerebral palsy. The beneficial effect was dose-dependent and maximal benefit was associated with a complete course of antenatal steroids.[12,13] On the other hand, early administration of dexamethasone (before 8 days of age) was associated with an increased risk of cerebral palsy; although sequelae remain uncertain with late administration or lower doses for shorter duration.[14,15]

The successful introduction of exogenous surfactant for the treatment of hyaline membrane disease had increased survival of extremely preterm infants. Improvements in neonatal-assisted ventilation including non-invasive methods (e.g. continuous positive airway pressure) and improved strategies of mechanical ventilation (e.g. high-frequency oscillation, volume-targeted and synchronised ventilation) have improved survival and reduced morbidities (e.g. pulmonary air leak, bronchopulmonary dysplasia and severe PIVH), with remarkable impact on neurodevelopmental outcomes. Although yet to be universally accepted, clinical trials have shown that preterm infants whose mothers receive magnesium sulphate at impending preterm deliveries have lower risk of cerebral palsy and severe motor dysfunction compared with non-exposed infants.[16,17]

There are also many other confounding factors that may subsequently affect neurodevelopmental outcome, making comparison of results from studies difficult. These are the social and family support ecosystem, ongoing health issues and the access to quality early intervention programmes and early childhood education in the community. These factors are inseparable from the level and standards of neonatal-perinatal care in determining the long-term outcomes of preterm infants. Beyond the conventional 5 to 8 years of follow-up period, they also have strong influences on the child's development of behavioural and psychological problems, functional disabilities, academic achievement and subsequent quality of life.

Despite difficulties in interpreting world literature on the outcomes of preterm infants, some observations are well supported by the current outcome data.

Individuals born preterm are at increased risk for impaired neurodevelopmental outcomes compared with those born at-term. The risk of impairment increases with decreasing gestational age. Former preterm infants are more likely than those born at-term to develop behavioural and psychological problems. These include attention deficit hyperactivity disorder, general anxiety, depression, difficulty in peer interactions, and autism spectrum disorder.[18,19,20] School-age children born preterm are at increased risk of functional disabilities that may cause them problems in managing daily activities. These are subtle problems such as motor coordination (non-cerebral palsy motor impairment), social interactive skills and executive functions (working memory, problem-solving, planning and organisation).[21,22]

There were contrasting reports on the adult outcome of preterm infants. Earlier studies reported lower rates of academic achievement, independent living, lower income and employability in preterm adult survivors compared with those born full-term.[19,20] In contrast, other studies suggest that despite their increased risk of neurodevelopmental disability, adults who were born preterm may overcome their difficulties and become functional young adults at a comparable rate to those who were born full-term in terms of high school graduation, post-secondary education opportunities, employment, independent living, marriage, and parenthood.[23,24] Differences in outcome may be due to higher socioeconomic status of the study population, and access to healthcare and educational support. We hope to have our local data when the 'Quality of Life Study' on children with chronic medical problems and disabilities (sponsored by the National Council of Social Service, Singapore) is completed in 2019. It is equally important to understand that patients and their parents have a better perception of their quality of life than healthcare professionals. Healthcare providers need to be aware of this difference so that they do not only focus narrowly on neurodevelopmental disabilities of their patients but to broaden their definition of outcome to include the ability of the adult survivors to overcome their limitations with a positive self-perception of their quality of life.[25,26]

The notion that increased survival brought an additional burden of disability into the population remains even today. There were local published reports on the survival and neurodevelopmental outcomes of preterm infants.[27,28] The paper on 'Long-term neurodevelopmental outcomes of premature infants in Singapore' published in this issue of Annals, Academy of Medicine, Singapore has given us further reassurance that the increased survival of preterm infants in Singapore has not been accompanied by an increase in adverse neurodevelopmental outcomes among the survivors. The overall neurodevelopmental outcomes over the 10-year period from Epoch I (1994-1995) to

Epoch II (2004-2005) did not worsen despite a lower mean gestational age, with an improvement in long-term visual impairment rates and intelligence quotient (IQ) scores. Notable changes in clinical practice worldwide during this period have been an increase in antenatal corticosteroids use, increased use of exogenous surfactant, saturation targeting to reduce excessive oxygen exposure, and limiting the use of postnatal corticosteroids.

One common limitation of this study and previous reports is that they are essentially data from a relatively small population being cared for in tertiary institutions. The difference in outcomes between the inborn and outborn high-risk infants is well recognised. In Singapore, about 60% of the annual births take place at private hospitals. The major shortcoming of our perinatal care delivery has been our failure in the regionalisation of neonatal-perinatal care—a system with proven cost-effectiveness in most countries. A nationwide perinatal audit and neonatal follow-up network have yet to be formally established to provide a constant feedback mechanism to the existing system, as well as to provide more accurate national data which can then be benchmarked against the well established international networks.

The low follow-up and high follow-up attrition rates introduce another bias issue. Some studies report that infants who fail to keep follow-up appointments, or are followed only with great difficulty, are more likely to have developmental impairment. Many complex socioeconomic and medical factors may be associated with increased attrition—which is of concern not only because of the potential bias introduced but also because those children and families lost to follow-up could potentially benefit most from supports and services. Nevertheless, questions related to generalisability of findings may be inherent, regardless of outstanding follow-up rates. Thus population-based or large regional-based cohorts (eg. VICS, EPICure, EXPRESS), may be considered the ideal model of prospective observational studies of high-risk infants.

Improving the survival rate without increasing the adverse outcomes of the extremely preterm (<28 weeks' gestation) and ELBW (<1000 g) infants—especially those born at the threshold of viability—would be our new frontier in management in the coming decades. They contribute disproportionately to overall hospital days and consume a large percentage of neonatal intensive care unit personnel time, effort, and costs of care. Ethical guidelines on perinatal care at the threshold of viability have been drawn out and will be regularly reviewed.[29] Care of these infants is in constant evolution, as a result of new discoveries in both basic and clinical research as well as growing clinical experience.

The definitions of 'long-term follow-up' are changing, and there is a need for 'long-term' to be even longer. There is a growing reliance on complete evaluation and reporting of neurodevelopmental outcomes in prospective studies and trials and an increasing recognition that it is crucial to fully understand outcomes beyond the initial hospitalisation and even beyond early childhood. Yet, the challenges of following a cohort for years or decades and the potential barriers to achieving reliable results are numerous. Long-term follow-up requires time, dedication, and persistence from both follow-up staff and families. However, data certainly suggests that follow-up until school years is warranted for several reasons. First, infant and early childhood developmental measures are poor to modest predictors of long-term child outcomes, particularly for cognitive scores.[30,31] Second, some developmental disorders cannot be reliably and accurately assessed at a young age, such as executive function impairments, specific learning problems (e.g. dyscalculia, dyslexia), and common mental health disorders such as attention deficit hyperactivity disorder and anxiety disorders. Third, there is an increasing body of data indicating that disability rates change between early childhood and school age.[32,33] A large population-based study of preterm infants followed for 10 years identified that although the majority of these children remained in their 2-year disability category, there were shifts. Early preterm infants showed a small shift from moderate and severe to no or mild disability. In contrast, there was a shift of moderate and late preterm infants with no or mild disability at age 2 to moderate or severe disability at age 10.[34]

The transition of high-risk infants from the neonatal intensive care unit to a comprehensive follow-up programme that involves early interventions, education, and social and family support is almost equivalent to transferring the child to another intensive care environment in the community. Certainly, it is a time- and resource-intensive undertaking. But we are unlikely to truly transform long-term care and improve the lifetime outcomes of high-risk infants without such an investment in the future. Today's neonatologists should go beyond their comfort zone of medical care and continue to be ready to take on the leadership role in ensuring the best possible outcomes of high-risk infants. This will be their life-course commitment.

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