

REVIEW

Outcome of extreme prematurity: as information increases so do the dilemmas

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Application of technology in neonatal intensive care has been very successful in reducing mortality, particularly in extremely low birthweight infants. As survival has improved, the need for accurate studies of long term outcome has increased. This need has been met by studies that are larger, more inclusive, and address a wider variety of later outcomes. Rather than a comprehensive quantitative review of these studies, this article uses a smaller number of studies that focus on infants of borderline viability, to illustrate current dilemmas and challenges in interpretation, and the actions, both individual and societal, that may be prompted by these interpretations.

It can be reasonably claimed that the application of technology in neonatal intensive care has been one of the most successful of all innovations in medicine in reducing mortality, particularly in extremely low birthweight (ELBW) infants. However, death in itself is an inadequate measure of outcome, and survival in a severely impaired state is considered by many to be equally undesirable. As survival has improved, our need for accurate studies of long term outcome has increased.

This need has been answered by recent studies which are indeed larger, more inclusive, and address a wider variety of later outcomes. In considering how to respond to and use the results of these studies, we have not attempted a comprehensive quantitative review of the type published by Lorenz *et al.*¹ Bhutta *et al.*² Hack and Fanaroff,³ and Ho and Saigal.⁴ Rather we have used a smaller number of articles that focus on this complex group of infants of borderline viability, to illustrate current dilemmas and challenges in interpretation, and the actions that may be prompted by these interpretations.

CHANGES IN SURVIVAL

The improvement in survival over the three decades from the 1970s to the early 1990s has been well documented by Lorenz *et al.*¹ Continued improvement in infants weighing 500–999 g born in a single perinatal centre between the 1980s and 1990s was recently shown by Wilson-Costello *et al.*⁵ with an increase in survival from 49% to 67%. Serenius *et al.*⁶ also reported relatively high survival rates of 43% of live births at 23 weeks gestation, 61% at

24 weeks, and 77% at 25 weeks from a regionalised programme in Sweden. Comparing data between northern and southern Sweden, Håkansson *et al.*⁷ reported that survival was significantly higher in the region where there was a combination of proactive resuscitation and a high degree of centralised management.

On the other hand, two large population based studies using national data provide contrasting results. In the EPICure study, Costeloe *et al.*⁸ found substantially lower survival rates in the United Kingdom and Ireland than did Markestad *et al.*⁹ from Norway. Although both studies describe the results in national populations, survival rates appear to be at least one third higher in Norway, regardless of the denominator (table 1). The Norwegian cohort was born four to five years later, but this seems unlikely to be responsible for such major differences. It is more likely that a more aggressive approach to management with a much higher use of antenatal steroids and a higher caesarean section rate in Norway, together with a much greater degree of regionalisation, may have played a role. In contrast, intensive care was provided in the United Kingdom in 137 out of 266 hospitals in which the infants were born (51%). A surprisingly high proportion of infants were cared for in units with fewer than 10 births in this weight range, and only 15 hospitals had 10 or more intensive care cots. Even in low risk populations, regionalisation has been shown to be associated with lower mortality,¹⁰ and repeated studies have shown improved survival and lower morbidity of preterm and low birthweight infants born and treated in tertiary care centres.^{11–13}

These studies exemplify some of the problems with interpretation and generalisation of the data. Inception cohorts vary; studies may report death rates using various denominators, which range from all live births in a region, all births in a perinatal unit, or all admissions to a neonatal intensive care unit. Although increased use of ultrasound has allowed gestational age to be defined more accurately, variations in reporting, such as rounding off the week of gestational age as opposed to completed weeks of gestation, continue to be responsible for some degree of variation. Finally deaths may be reported as occurring by hospital discharge or up to 1 or 2 years of age.¹⁴

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ELBW, extremely low birthweight; IQ, intelligence quotient; VLBW, very low birthweight

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Table 1 Comparison of survival rates of national studies from the United Kingdom and Norway

Gestational age (weeks)	EPICure ^a		Markestad <i>et al</i> ^b	
	Live births	NICU admissions	Live births	NICU admissions
23	26/241 (11%)	26/131 (20%)	9/55 (16%)	9/28 (39%)
24	100/382 (26%)	100/298 (34%)	35/80 (44%)	36/58 (60%)
25	186/424 (44%)	186/357 (52%)	55/83 (66%)	55/69 (80%)

Data are survival to discharge.
NICU, Neonatal intensive care unit.

CHANGES IN MORBIDITY

Infancy

In contrast with the improvements in survival rate, shorter term morbidity at 18–30 months appears to have changed very little. Combined morbidity—cognitive, sensory impairment, or cerebral palsy (and sometimes including isolated seizures and hydrocephalus)—is much more difficult to compare than is mortality because of the multiplicity of, and variations in, diagnostic criteria. A comparison of the results from different programmes over time by Lorenz *et al*¹ concluded that, with improved survival and constant impairment rates, the absolute numbers of infants with impairment have increased with time. It is important to note, however, that the absolute number of infants free from impairment has also increased. Lorenz *et al*¹ found that the rate of cerebral palsy for infants born between 1977 and 1994 was not significantly different in the ELBW infant from that previously reported in very low birthweight (VLBW) infants. On the other hand, cognitive impairment was somewhat more common and accounted for most severe disabilities.

Most large follow up studies in the early 1990s were consistent in showing no increase in the prevalence of early long term morbidity.^{15–17} However, a recent large scale study reporting secular change in a population of infants born at 500–999 g from a single perinatal unit³ found an increase in the prevalence of morbidity, with neurodevelopmental impairment rising from 26% to 36%. In this study, however, there was a clear increase in the number of deliveries during the later period, which may have represented changes in obstetric referral patterns and therefore in underlying risk. A somewhat more optimistic, albeit still disturbing, picture is seen in the report by Vohr *et al*¹⁸ of outcomes in infants over three two-year epochs (1993–4, 1995–6, 1997–8). This very large multicentre study involving 3785 infants of 22–26 weeks gestation found a significant reduction in neurodevelopmental impairment from 50% to 45% with specific declines in Bayley mental and physical developmental index scores <70. The decline in neurodevelopmental impairment almost exactly balanced the increase in survival (from 55% to 61%), and consequently the absolute number of children with impairment remained unchanged. A 45% rate of impairment, however, is still a cause for much concern. An even more pessimistic outcome was provided by Rijken *et al*¹⁹, with 92% of 23–24 week gestation infants, and 64% of those born at 25 weeks, having adverse outcomes. However, these outcomes were based on only 11 survivors in each gestational age group, in an area with a relatively low degree of regionalisation (only 63% were born in the perinatal centre).

Morbidity at mid-childhood

Longer term outcome at school age allows the inclusion of a wider range of problems including poor growth, chronic ill health, educational delay, and behavioural and emotional disorders. In addition, it provides an opportunity for assessment of the predictive value of abnormalities found at earlier follow up. A formal meta-analysis of school age

outcome by Bhutta *et al*² concluded that preterm birth is associated with lower cognitive scores and increased risk of attention deficit/hyperactivity disorder (ADHD) and other abnormal behaviours, and that there was a significant inverse correlation between lower birth weight or gestational age and cognitive test scores. However, they also point out that numerous studies have shown a significant effect of demographic and environmental factors, such as age, sex, race and socioeconomic status, on both cognitive and behavioural development.

Davis²⁰ has produced an extensive summary of recent (1996–2002) studies of developmental and behavioural outcomes at school age or older. These outcomes ranged from educational attainment and cognitive function to behaviour, attention problems, psychiatric problems, and risk taking and criminal behaviours. She concluded that, in addition to the increased rates of neurodevelopmental and sensory disability, there was a high proportion of ELBW children who, despite functioning within the normal range on intelligence quotient (IQ) tests, exhibited a wide variety of more subtle motor and behavioural problems. Although methodological differences make comparisons difficult, it appears to be a common finding that approximately half of ELBW children require additional educational services. For example, Buck *et al*²¹ found that 47% of infants under 28 weeks gestation required school based rehabilitation services (compared with 18% of controls). Taylor *et al*²² determined that 63% of infants with birth weight under 750 g had at least one functional impairment compared with 18% of controls. They also found an increased prevalence of ADHD in these children. Breslau and Chilcoat²³ also found ADHD to be twice as common in urban low birthweight children than in controls. Schraeder *et al*²⁴ in New Zealand reported a very high rate of problems, with 71% of infants with birth weight under 1500 g having problems in at least one area of behaviour, cognition, school performance, and special education (compared with 42% of controls); 71% of VLBW infants versus 29% of controls required special academic assistance in maths or reading. It is noteworthy that, in all of these examples, the control group included a significant number of infants with problems in these domains.

The extent to which environmental factors dominate is unclear. Gross *et al*²⁵ in a study of 10 year olds in 1985 born at less than 32 weeks gestational age suggested that family factors were stronger predictors of school performance than were perinatal complications. On the other hand, Wolke and Meyer,²⁶ also reviewing a group of infants born at less than 32 weeks gestation, concluded that perinatal and neonatal factors, rather than the postnatal social environment, were more related to outcome.

Only a few studies have examined the predictive value of findings at earlier follow up. Marlow *et al*,²⁷ following the EPICure cohort, found rates of severe disability (cerebral palsy, blindness, severe deafness, and IQ less than 55) to be consistent at 6 years of age with the findings at 30 months²⁸: 86% of infants who had severe disability at 30 months still

had moderate to severe disability at the older age. In contrast, rates of other moderate and mild disabilities at 6 years of age were very much higher and poorly predicted by the examination at 30 months. Although 80% of survivors had a least some form of disability, it is important to note that 34% of these were in the mild category and included such problems as mild hearing impairment, squint, or refractive error. A second interesting finding by Marlow *et al*²⁷ was the importance of the appropriate control group for defining cognitive impairment. Using the original test standardisation norms, 11% of ELBW children had cognitive impairment, defined as an IQ of more than 3 standard deviations below the mean. In contrast, when compared with their classmates and using the same cut-off value, this figure doubled to 21%. Depending on which criterion was used, the proportion of children with severe disability could be described as either 13% or 22%. Although the higher figure represents a true comparison of the difficulties faced by these children when compared with their peers, it must also be admitted that this comparison group of classmates attending normal schools were, in effect, pre-selected for normality.

Hack *et al*²⁹ were also able to compare the performance of a cohort of ELBW survivors at the ages of 20 months and 8 years. They found that the Bayley scales of infant development were a good predictor of outcome at the later age only when neurosensory impairment was present. In the absence of physical disability, prediction was poor, and indeed, under these circumstances, cognition function appeared to improve over time; the proportion of children with mental developmental index scores <70 was 29% at 20 months, and the proportion with Kaufman assessment battery for children scores <70 was 7% at 8 years.

Similar findings of a change in cognitive scores over time have been reported by Ment *et al*.³⁰ Median scores on the Peabody picture vocabulary test-revised increased from 88 at 36 months to 99 at 96 months; a similar increase was also noted in full scale and verbal IQ. These improvements were significantly associated with two-parent households and higher maternal education. However, for children with significant central nervous system injury, the scores declined over time. Whether early cognitive scores improve, remain stable, or worsen over time is not yet clear.³¹ These findings illustrate the impreciseness of early cognitive development scores in predicting later outcomes.^{29, 32}

The issue of prediction is further confounded by the fact that not only are different tests administered at different ages, but these tests tap different conceptual variables at the younger age versus the older age. Thus, strictly speaking, we are not assessing the same skills at each age, as in developmental terms children are moving targets. In addition, secular trends of an increase in IQ of 0.2–0.5 point per year have been reported.³³ Other issues on the “conundrum” of prediction have been succinctly highlighted by Aylward.^{31, 32} Regardless of improvements in IQ scores, a low score in infancy is a marker of subsequent risk of neuropsychological problems, learning disabilities, and attentional and behavioural disorders.^{22, 31}

Morbidity at adolescence and beyond

Further follow up to adolescence presents a mixed picture in different domains. In terms of cognitive abilities, most studies on VLBW and ELBW children show that the deficits persist to adolescence, with mean IQ between 8 and 13 points below that of the control subjects. Taylor *et al*²² reported a 21 point difference in IQ between subjects with a birthweight <750 g and controls. In general, comparisons between cohorts in different studies do not provide a helpful reflection, as some studies report the IQ on all survivors,^{22, 34} whereas others report only on those in mainstream education.³⁵ In the study by

Saigal *et al*³⁴ there was an improvement in mean IQ from 89 to 99 when subjects with neurosensory impairments and IQ <85 were excluded. Also, whereas Saigal *et al*³⁴ have shown stability in IQ between age 8 and 14 years, Botting *et al*³⁵ reported a significant fall from 108 to 90 in mean IQ scores for the VLBW group as measured by the Wechsler preschool and primary scales of intelligence at age 6 years and the Wechsler intelligence scale for children-III at 12 years. However, some of the decrease was accounted for by the revised standardisation of the test.^{35, 36}

In addition, all studies report significantly poorer performance in VLBW/ELBW subjects on tests of academic achievement compared with controls.^{34, 35} In fact, Botting *et al*³⁵ reported lower performance by VLBW subjects even though they were in the mainstream educational system. Taylor *et al*²² performed an analysis on the sub-sample of children ≤750 g who had no neurological impairments and had an IQ ≥80. Even children in this “normal” subgroup performed significantly less well, with lower IQ and poorer maths skills and tests of executive function.

In keeping with the significant deficits in cognition and achievement measures, VLBW children more often required remedial assistance and repeated a grade (20–50%).^{34–37} Once again, even VLBW children from mainstream schools required more remedial education than their peers (35% v 14%).³⁵ Unfortunately, further longer term follow up studies report that the educational disadvantages associated with being VLBW seem to persist well into late adolescence and young adulthood.^{38–40}

A review of the studies on behavioural and emotional problems show that VLBW adolescents were still at risk of a wide array of these disorders.^{40–46} However, a decrease in the prevalence of ADHD has been reported in some studies.^{46, 47} Interestingly, Saigal *et al*⁴⁶ found that, although parents reported significant differences in ADHD and depression, the teenagers themselves did not perceive any differences compared with controls.

On the positive side, several studies have reported some catch up growth by adolescence^{48–50} and, despite a consistent burden of neurosensory impairments, there was a decrease in the utilisation of healthcare resources, except home care services.⁴⁹ Most importantly, VLBW teenagers appeared to have a very positive perception of their health and abilities,³⁸ their self esteem,⁵¹ and health related quality of life,⁵² and had a lower incidence of risk taking behaviours.^{40, 41} These perceptions differ from that of parents³⁸ and health professionals⁵² and underscore the considerable resilience demonstrated by ELBW/VLBW survivors.

DISCUSSION

We have referred to the problems in comparing different studies that arise from lack of standardisation of the age of assessment, the nature of the tests performed, and the reference norms used for the tests. An additional problem arises from the use of different definitions of impairment and, ever more so, in the labelling of severity.

The issue of the values inherent in these measurements is a useful segue to the issue of the use of data produced by follow up programmes. Of the many functions of follow up programmes, the most common uses of long term outcome data are probably in the process of making decisions about the initiation or continuation of intensive care for individual patients or for the allocation of healthcare resources from a societal perspective. For information to be helpful for individuals, it needs to be accurate, comprehensible, and appropriate to the specific situation. Accuracy will always be limited to some extent by the time lag inherent in conducting follow up. Even though information about survival may be very current, information about performance at school age is

necessarily about 10 years out of date at the time of its use. For information to be appropriate to the situation, the denominator used must be comparable with clinical circumstances. Thus antenatal counselling and decision making in a perinatal unit should be based on data using the outcomes of all live births in such units, not just the outcome of admissions to the neonatal intensive care unit; it does not, however, require population based data. Decision making after admission to intensive care may reasonably use outcomes based on intensive care admissions. However, for other purposes, such as planning health and education services after discharge, population based data are essential, as they are for determining temporal trends and comparing results of regional programmes.

Comprehensibility requires the use of patient friendly language or terminology and some consideration of the relative values of parents, particularly as these are known to vary systematically from the values of health professionals.⁵³ The global expression of disability or impairment, and its severity, necessarily incorporates values, which are probably those of healthcare professionals. Some individual domains, however, may be valued differently by parents, and global expressions of risk may not mirror the distribution of parental values.

The most contentious issues arising from the use of follow up data is that of policy decisions to restrict or deny resuscitation or intensive care. The demonstration by Rijken *et al*¹⁹ of a very high rate of impairment in 23–25 week survivors, despite a very small sample size, appears to have already had an impact on social policy in Holland.⁵⁴ Such global policies result not only in intensive care being withheld from those who are likely to be severely disabled, but also from those who are potentially healthy surviving children. Financial savings, admittedly only one stimulus for such policies, may not be particularly high. Stotz and McCormick⁵⁵ have shown that the savings in intensive care unit costs that accrue from withholding intensive care for infants of birth weight less than 600 g amount to only 3.2%, and would reduce the annual number of survivors in the United States by only 575. These calculations do not, however, include the costs of long term care accrued by families later in life, nor do they include the indirect costs incurred by families, even in countries with universal health insurance. There is a considerable non-financial toll on families after the birth of an ELBW infant, especially in the early years.⁵⁶ Even so, the long term negative effects on families of ELBW survivors may be overestimated. Saigal and others^{57–58} have shown that, although many parents of ELBW children feel that it has taken a considerable toll on their emotional health, a higher proportion of parents with ELBW children with impairments than parents of non-impaired children reported that the experience had improved their feelings about themselves, and brought parents closer together. It is well recognised that the values of healthcare practitioners vary systematically from those of parents in general, and even more so from the parents of EBW infants.⁵² It would seem to be crucial therefore that such parents be involved, not only in individual decision making, but also in the development of guidelines on the delivery or withholding of intensive care. The absence of parental involvement risks imposing standards that are more restrictive, as healthcare practitioners tend to be more pessimistic than parents.⁵⁹

Birth weights and gestational age are strong predictors of outcome and therefore likely to be the variables that will generate such policies. However, it must be remembered that other variables, including sex and ethnicity, will also modify outcome. The use of gestational age or birth weight criteria alone will discriminate against those who would have relatively better outcomes, such as female infants, and those

who may have better outcomes as a result of medical treatment such as antenatal steroids. Hack *et al*⁶⁰ are correct in reiterating that major clinical decisions on whether to institute or forego intensive care in infants of borderline viability should not be made solely on data based on early cognitive assessments, which generally appear to provide a pessimistic picture; data on longer term outcomes should be considered in the equation.

The wide national variations in approaches to management and attitudes of health professionals demonstrated by the Euronics study⁶¹ mean that it is inappropriate, and indeed may even be considered impertinent, to make recommendations for any society but one's own. Given the limitations of generalisability and extrapolation from follow up data, it would seem unwise to impose substantive changes in policy about resuscitation and withholding of intensive care. Rather, it would be preferable to use the data to: promote optimal access to effective care, by maximising perinatal regionalisation; maintain informed but individualised decision making by parents; advocate the services—medical, social, and educational—that many ELBW children will require in the future.

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