Preterm Birth 3

An overview of mortality and sequelae of preterm birth from infancy to adulthood

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Survival rates have greatly improved in recent years for infants of borderline viability; however, these infants remain at risk of developing a wide array of complications, not only in the neonatal unit, but also in the long term. Morbidity is inversely related to gestational age; however, there is no gestational age, including term, that is wholly exempt. Neurodevelopmental disabilities and recurrent health problems take a toll in early childhood. Subsequently hidden disabilities such as school difficulties and behavioural problems become apparent and persist into adolescence. Reassuringly, however, most children born very preterm adjust remarkably well during their transition into adulthood. Because mortality rates have fallen, the focus for perinatal interventions is to develop strategies to reduce long-term morbidity, especially the prevention of brain injury and abnormal brain development. In addition, follow-up to middle age and beyond is warranted to identify the risks, especially for cardiovascular and metabolic disorders that are likely to be experienced by preterm survivors.

Introduction

As Goldenberg and colleagues1 outline earlier in this series, the rate of preterm birth in developed countries has risen, rather than fallen, over time. Moreover, the survival rates for very early preterm births have increased because of technological advances and the collaborative efforts of obstetricians and neonatologists. However, biologically, preterm infants are more susceptible than their term counterparts. Although most organs are immature, the brain2 and lung3 are especially susceptible to the consequences of preterm birth, which leads to high rates of long-term neurological and health problems. Because of increasing costs of providing neonatal intensive care and social and economic burden of disabilities, the debate continues about whether intensive care is justified for infants of borderline viability. Clinicians will increasingly be exposed to survivors of preterm birth; therefore, they need to be aware of the changing outcomes and the long-term effect of disabilities and health problems on the survivors, their families, and society.

Here we review data for the mortality and both short-term and long-term sequelae of preterm birth in developed countries. The focus will be on a broad range of outcomes, such as neurodevelopment, education, behaviour, psychosocial matters, growth, and health of the most preterm (<30 or <32 weeks’ gestational age) infants, at various ages from infancy through to adulthood. Whenever possible, we will add the few data available for similar outcomes in infants closer to term, sometimes referred to as late preterm births. For most outcomes, we will rely on the more plentiful data reported by birthweight, either for infants of very low birthweight (VLBW, birthweight <1500 g) or extremely low birthweight (ELBW, birthweight <1000 g).

The methodological issues that prevent valid comparisons of outcomes between different centres and different countries include heterogeneity of the cohorts under consideration (geographically-defined vs multicentre vs single-centre studies); reporting of outcomes by birthweight versus gestational age; varying ages of reporting outcomes; different assessment techniques; inconsistencies in definitions and severity of reporting disabilities; and high attrition rates.1,6

Outcomes of preterm infants

Late preterm births

Although preterm births at 32–36 weeks’ gestation are five times more common than births before 32 weeks’ gestation, their public-health effect has not been well studied.7 In 2003, 12.3% of births in the USA were preterm (defined as <37 weeks’ gestation).4 What is of concern is that since 1981 there has been a 31% increase in the preterm birth rate in the USA, of which two-thirds were late preterm births (34–36 completed weeks’ gestation).4

The mortality and neonatal morbidity of late preterm births are substantial. Compared with infants born at term, preterm infants have higher rates of temperature instability, respiratory distress, apnoea, hypoglycaemia, seizures, jaundice, kernicterus, feeding difficulties, periventricular leukomalacia, and rehospitalisation.8,9 Preterm infants also make up an important fraction of infant deaths.7

In a British study, up to a third of 7-year-old children born at 32–35 weeks’ gestation were reported by their teachers to have difficulties in motor skills, speaking, writing, mathematics, behaviour, and physical education.8 Thus elective deliveries of infants born near term are not without

Search strategy and selection criteria

In writing this review, we did a Medline search for articles reported over the past decade. We used the following medical subject headings to search for articles: “premature”, “preterm”, “low birthweight”, “follow-up”, “cerebral palsy”, and “outcomes”. We focused on studies that reported comprehensive, long-term outcomes in geographically-defined cohorts, with few or no exclusions because they are likely to be least biased.

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increased risk of mortality and morbidity, which have significant implications for educational services and costs.

Very preterm births

There is little doubt that gestational age exerts the greatest influence on outcomes of preterm births. Before the widespread use of assisted ventilation in the 1970s, there were few survivors before 28 weeks’ gestation, and many more mature babies died from respiratory distress caused by absence of pulmonary surfactant. With increasing and earlier use of antenatal corticosteroids, assisted ventilation, and surfactant, and changing attitudes towards intensive care, survival rates for very preterm births, especially those born before 28 weeks’ gestation, had improved strikingly by the mid-1990s.

Survival rates for infants of borderline viability from geographically-determined cohorts born after 1990 are lower at each week than those from the single-hospital or multihospital studies, mainly because the regional cohorts include deaths that never reach tertiary care. Variations exist between regions in neonatal intensive care, which is highest for hospitals without a neonatal intensive care unit than for those with intermediate or non-tertiary care. Differences in mortality have also been noted by level of neonatal care, which is highest for hospitals without a neonatal intensive care unit than for those with intermediate or non-tertiary care.

Regionalisation encompasses the transport of sick infants from community hospitals to tertiary care centres, and transfer of high-risk mothers to the perinatal centre before delivery. The outcome of ELBW infants is more favourable with maternal transfer rather than transfer after birth.

Mortality

Differences in mortality have also been noted by level of neonatal care, which is highest for hospitals without a neonatal intensive care unit than for those with intermediate or non-tertiary care. In a Swedish national study of ELBW births in 1990–92, infant mortality was 30% for infants born at level III (tertiary care centres), 46% at level IIa (with full perinatal service), and 55% at level IIb (basic neonatal service). Similar differences in perinatal (79% vs 45%) and neonatal (59% vs 32%) survival of ELBW infants were reported in tertiary-care and secondary-care hospitals in Finland in 1996–97. A more striking example is the widening difference in mortality rates between ELBW infants born in level III perinatal centres compared with those born elsewhere during successive eras from 1979–97 in the state of Victoria, Australia; the absolute difference in survival rates increased from 12% in 1979–80 to 45% at level IIa (with full perinatal service), and 55% at level IIb (basic neonatal service).
to 44% in 1997. Samuelson and colleagues speculated, on the basis of the assumption that mortality differences are related to the level of care, that about 16–23% of neonatal deaths could be prevented if most infants born in hospitals without neonatal intensive care units were delivered in regional perinatal centres in Georgia, USA. In the EPICure study of births in the UK and Ireland in 1995, survival to discharge was low for all weeks of gestation (table 1), partly because of lack of regionalisation. Large variations in infant mortality rates exist between countries (table 1), between different geographic regions within the same country, and between various racial and ethnic groups. In the USA, although black preterm infants seem to have a survival advantage over white preterm infants, the rates of preterm birth for black babies are more than double those of Hispanic or white babies and overall the neonatal mortality continues to be higher in black infants than in white infants.

The most pronounced changes in survival have taken place in infants born before 26 weeks’ gestation during the 1990s (table 1), such as changes within the same region during 5–6 years. In another region there was a non-significant increase in survival in 3 years, counteracted by a rise in some neonatal morbidities, such as intraventricular haemorrhage. Over a longer time, the survival rate for ELBW infants in Victoria, Australia, increased almost three-fold from 25% in 1979–80 to 73% in 1997.

Neurodevelopmental sequelae

Examples of neurodevelopmental impairments in the early years are cerebral palsy, mental retardation, and sensory impairments (such as visual and auditory deficits). Many infants might have important developmental lags that are not classified as impairments. Several groups have reported rates of neurosensory disabilities in regional cohorts of very preterm infants born after 1990. The definitions of the disabilities and their severity are not uniform, which makes interpretation difficult, but about a quarter of survivors have substantial neurological morbidity (table 2). Although the rates seem high, they are highest in the same region during 5–6 years. In another region there was a non-significant increase in survival in 3 years, counteracted by a rise in some neonatal morbidities, such as intraventricular haemorrhage. Over a longer time, the survival rate for ELBW infants in Victoria, Australia, increased almost three-fold from 25% in 1979–80 to 73% in 1997.

Cerebral palsy is generally used as a marker of quality of care and to document time trends in prevalence; however, differences in prevalence might be related to population characteristics (regional or single hospital), aggressiveness of intervention, new therapies (postnatal steroids), or changes in mortality rates. The prevalence of cerebral palsy is inversely related to gestational age. Hagberg and colleagues reported data from Sweden on gestational age-specific prevalences for cerebral palsy per 1000 livebirths during 1991–94: 85·5 for gestational ages of less than 28 weeks, 60·4 for 28–31 weeks, 6·2 for 32–36 weeks, and 1·3 for at least 37 weeks. In a Swedish national ELBW cohort of births in 1990–92, the frequency of cerebral palsy was 14%, 19%, and 3% for infants born at 23–24, 25–26, and after 27 weeks’ gestation, respectively.

Studies of time trends in the prevalence of cerebral palsy have shown no change, a reduction, or an increase. Two studies showed the different directions in trends; in Nova Scotia as the mortality rates declined from 256 to 114 per 1000 livebirths for infants born before 31 weeks’ gestation between 1993 and 2002, the incidence of cerebral palsy increased over time from 44 to 100 per 1000 livebirths. By contrast, the trends in prevalence of cerebral palsy in the latest 16-European centre study of VLBW infants born between 1980 and 1996 are encouraging. The birth prevalence fell from 60·6 (99% CI 37·8–91·4) per 1000 livebirths in 1980 to 39·5 (28·6–53·0) per 1000 livebirths in 1996. Even more reassuring is the fact that although the decline was initially seen in infants with a birthweight of 1000–1499 g, it was also apparent in ELBW infants. Irrespective of whether the risk of cerebral palsy in survivors remains constant throughout time, a reduction in neonatal mortality will result in an increase in absolute numbers of cases of cerebral palsy as a function of an increase in survivors. Preterm infants also have a high prevalence of minor neuromotor dysfunction and poor coordination. Even extremely preterm infants with normal intelligence and no cerebral palsy can present with gross and fine motor difficulties.

Most studies of VLBW infants show continued sequelae such as cognitive deficits, academic underachievement, grade failures, and the need for increased remedial assistance during mid-childhood and adolescence. In a comparative study of four western countries, cognitive and school difficulties were identified in all cohorts. These problems fall along a gradient, with a high prevalence and severe deficits in the smallest birthweight group. Saigal and colleagues showed that 72% of adolescents with a less than 750 g birthweight, 53% with a birthweight of 750–1000 g, and 13% of normal birthweight controls had school difficulties. These difficulties were apparent even in children without neurosensory impairments and normal intelligence quotient (IQ), and were more prevalent in boys.

Behavioural sequelae

Very preterm survivors also have high rates of dysfunction in other cognitive areas, such as attention, visual processing, academic progress, and executive function (which refers to processes that bring about purposeful behaviour, important in a child’s cognitive functioning, behaviour, emotional control, and social interaction). Anderson and colleagues reported that ELBW infants or those born before 28 weeks’ gestation at age 8 years scored less than controls of normal birthweight on full-scale IQ and on all indices of executive function that were assessed; the sizes of the differences were between a half to three-quarters of a SD and suggested general impairment rather than deficits in specific executive domains. These infants also fared worse than did the normal birthweight cohorts.

Table 2: Neurological disability rates for survivors of borderline viability by gestational age from geographically defined cohorts

<table>
<thead>
<tr>
<th>Disability diagnosis</th>
<th>Rate of disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or enabling cerebral palsy, visual acuity ≤6/60 in at least one eye, sensorineural deafness with hearing aids, special school education†</td>
<td>21% (18/86)</td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy, visual acuity ≤6/60 in better eye, sensorineural deafness with hearing aids, developmental quotient ≤−2 SD relative to controls</td>
<td>21% (46/219)</td>
</tr>
<tr>
<td>Cerebral palsy, visual acuity ≤6/24 in better eye, hearing loss more than 60 dB, Griffiths scale &lt;70 or developmental quotient ≤−2 SD, any growth measurement ≤−2 SD, epilepsy requiring regular medication, any other serious condition</td>
<td>35% (19/55)</td>
</tr>
<tr>
<td>Not stated</td>
<td>26% (13/50)</td>
</tr>
<tr>
<td>Cerebral palsy, visual acuity ≤6/60 in better eye, hearing aids, developmental quotient ≤−2 SD (Griffiths)</td>
<td>29% (74/255)</td>
</tr>
<tr>
<td>Unable to walk without assistance, blind, impaired hearing uncorrected with hearing aids, no clear speech</td>
<td>23% (64/283)</td>
</tr>
<tr>
<td>Cerebral palsy, developmental quotient ≤−2 SD (Bayley I)</td>
<td>35% (9/26)</td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy, severe visual impairment, deafness with hearing aids, epilepsy, shunted hydrocephalus, intelligence quotient &lt;50</td>
<td>25% (25/102)</td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy, visual acuity ≤6/60 in better eye, sensorineural deafness with hearing aids, developmental quotient ≤−2 SD relative to controls (Bayley II)</td>
<td>28% (41/148)</td>
</tr>
</tbody>
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Outcomes assessed largely by questionnaires, with no formal cognitive assessment. †Corrected for prematurity.

on tests of academic achievement, such as reading, spelling, and arithmetic. Similar deficits in executive function and in mathematics have been reported for infants with birthweights of less than 750 g, which remained even when controlled for IQ. The cognitive disadvantage between VLBW and ELBW infants seems to persist into late adolescence and early adulthood. However, cognitive dysfunctions are moderated by environmental factors such as parental socioeconomic status and education, two-parent family, neighbourhood effects, schooling, and social and racial backgrounds. Whether cognitive deficits improve or worsen over time is not clear.

The risk of behavioural problems, such as attention deficit hyperactivity disorder, is increased by 2–6–4–0 times in very preterm infants in early childhood. They are also especially susceptible to difficulties related to inattention and hyperactivity, and have emotional troubles at school age that affect academic functioning. These have been identified even in children without neurodevelopmental impairments, and seem to be universal despite crosscultural differences. Additionally, preterm infants tend to have traits such as shyness, unassertiveness, and social maladaptation, and are anxious and withdrawn. Botting and colleagues reported a higher prevalence of anxiety and depression as perceived by VLBW 12-year-olds than that by controls. Long-term follow-up revealed that many of the difficulties persisted into adolescence and early adulthood.

Parents of ELBW teenagers reported difficulties such as attention deficit hyperactivity disorder; however, the same teenagers did not perceive themselves to be different from controls. Similarly, parents of VLBW young adults reported more difficulties than parents of control young adults, with thought problems in men and higher scores on the anxious or depressed, withdrawn, and attention scale in women than in men. However, both VLBW men and women reported lower rates of delinquency and risk-seeking behaviours than did control young adults.

In most studies, VLBW young adults had slightly lower rates of educational achievements, employment, and independent living than normal birthweight controls; however, few differences were reported in ELBW young adults from an advantaged population in Ontario. Despite the high rates of disabilities and educational and behavioural problems encountered during their years of growing up, most young adults in all studies showed surprisingly good recovery in adapting to roles of adult functioning and were doing better than had been predicted.

Other sequelae

ELBW children have more hospital readmissions and other health problems in the weeks after discharge than do those of normal birthweight children. In a review, more than a half of ELBW children were readmitted to hospital at least once in the first 1–2 years of life, mostly as a result of respiratory illnesses, including lower-respiratory-tract infections; these rates were 2–3 times the rates of readmission of normal birthweight children. Respiratory syncytial virus also increases the risk of rehospitalisation, especially in very premature infants. Others have also reported high rates of ill health and increased use of outpatient health care in the early years in survivors who were very preterm at birth. Even at 10–12 years of age, children who had been born before 26 weeks’ gestation had greater needs for services such as physician visits, occupational or physical therapy, nursing or medical procedures, and compensatory dependency than did children of normal birthweight (67% vs 22%). A reduction in both the prevalence of health disorders and use of health-care resources by ELBW adolescents has been reported. By the time ELBW children reached adulthood,
there were no differences in acute health disorders or use of health resources compared with normal birthweight adults, but chronic health disorders remained higher than in young adults of normal birthweight. Special health-care needs and equipment were necessary only for a very few ELBW adults. Several studies have reported a high systolic blood pressure in VLBW young adults.

Bronchopulmonary dysplasia has been described in up to 40% of VLBW survivors, and the rate rises as the birthweight falls below 1500 g. ELBW survivors with bronchopulmonary dysplasia have even more ill health and hospital readmissions in early childhood than do ELBW survivors without bronchopulmonary dysplasia; however, as children with a history of bronchopulmonary dysplasia enter school age, the risk of rehospitalisation can be similar to that for their peers who have non-bronchopulmonary dysplasia. In a study of VLBW survivors (mean age 18–9 years), all lung function variables related to airflow were substantially diminished in the bronchopulmonary dysplasia group.

Retinopathy of prematurity continues to be one of the most common morbidities in infants born before 26 weeks’ gestation. In the 1990s, there was a remarkable reduction in the frequency of blindness from 8–10% in the precryotherapy era to less than 3% in present survivors. Gestational age affects the rate of blindness or severe visual impairment, or both, with rates of 1–2% for infants with a gestational age of 26–27 weeks, and 4–8% at 25 weeks or below. Myopia and hypermetropia arise in at least a quarter of children born before 28 weeks’ gestation. The need for prescription glasses is also related to gestational age and the age of children at the time of reporting, with 24% of 6-year-old children born before 26 weeks’ gestation wearing glasses versus 4% of term controls. In the Ontario study, 36% of ELBW adolescents versus 10% of normal birthweight adolescents were wearing prescription glasses and by adulthood, the figures were 64% versus 37%, respectively. Another adverse outcome was a high rate (4–5%) of late retinal detachment in ELBW infants during their late teens.

Although rates of hearing impairments in VLBW infants have been generally stable at around less than 3–5%, variations are related mainly to differences in the definitions and age at reporting. Severe hearing impairment in infancy was reported in 7% of VLBW infants born in Cleveland during 1990–98. Marlow and colleagues reported that 6% of 6-year-olds born before 26 weeks’ gestation were wearing hearing aids, and another 4% had mild hearing loss compared with 1% of controls. Similar figures were cited for 11-year-old children born before 26 weeks’ gestation in the Swedish cohort. Doyle and colleagues reported that 5% of 14-year-old ELBW children were wearing hearing aids. At adulthood, only 1–3% of ELBW young adults versus less than 1% of controls were wearing hearing aids, although a higher proportion reported having difficulties in hearing. VLBW infants have central auditory processing difficulties, including difficulties discriminating simple speech sounds and worse auditory recognition than their full-term counterparts. Hearing impairments have a cumulative detrimental effect on the acquisition of language skills and learning at school.

Infants born with VLBW have lower growth attainment in weight and length than their normal birthweight counterparts during infancy and early childhood. Although by mid-childhood and adolescence substantial catch-up starts, at every age the VLBW group had lower growth variables than did the normal birthweight group. Despite their small size at birth, ELBW survivors did achieve adult stature mostly within the normal range, but remained disadvantaged in their height compared with controls of normal birthweight. In a study in which parental heights were reported but not measured, ELBW survivors had height Z scores lower than their parents, in another study in which parental heights were measured, ELBW survivors had height Z scores that were not different from their mid-parental height Z scores. Body-mass index (BMI) Z scores for the ELBW group showed a sustained increase from age 3 years to adulthood, in which both sexes normalised to above zero. Thus the growth failure during infancy followed by accelerated weight gain and crossing of BMI percentiles at adolescence can place the ELBW group at high risk for later cardiovascular disease and type 2 diabetes.

Functional outcomes

In the past two decades, the importance of including functional measures to define the effect of impairments, such as cerebral palsy and cognitive and other deficits on the individual’s ability to do the essential tasks of daily living, is being increasingly recognised. Several investigators have shown that compared with infants born at term, as a group, extremely preterm infants have a higher prevalence of mental and emotional delays, visual deficits, and restriction in activities of daily living and self-care abilities throughout childhood and adolescence.

Additionally, the rates of chronic health disorders were also higher in the preterm group than in the term group. These findings of functional limitations and chronic health disorders persist into adulthood.

An innovative development in health care has been the growing recognition of the importance of understanding the effect of treatment and interventions on the lives of patients. Traditionally, clinicians relied on parental reports to obtain information on the health of children because of the longstanding misconception that children are neither reliable nor valid reporters. Saigal and colleagues noted that although by self-report ELBW teenagers had a greater prevalence and complexity of functional limitations than did control teenagers, as a group they placed a high valuation on their health-related quality of life. Parents also reported a higher prevalence of functional limitations for their ELBW children than parents of control teenagers. However, the corresponding mean health-related quality of
life scores, although lower than those provided by control parents, were higher than those provided by the ELBW teenagers for their own health status. 132

Several studies of preterm infants at adulthood have shown no differences in the self-reported quality of life despite recognition of their disabilities. 133–135 Although this high rating of quality of life by people with disabilities is well recognised and described as a disability paradox, 136 the validity of these studies continues to be challenged. 137

Saigal and colleagues 138 showed that systematic differences exist between proxies and other respondents in reporting of health status, valuations, or both. ELBW and control adolescents and their parents provided higher ratings of health-related quality of life for severely disabling hypothetical health states than did health professionals. This discrepancy in the valuation between patients and health professionals is in accord with other studies in adults. 139 Thus, eliciting self-reported quality of life provides valuable complementary information to the traditional objective assessments by researchers and health professionals to understand people's lives as they experience and value them.

Effect on families
Clearly from all studies, prematurity and its associated sequelae have an enormous negative psychosocial and emotional effect on the family. 140–142 The effect of psychological distress was greatest for VLBW high-risk infants in the first month of life and persisted during the first 2 years of life. By age 3 years, although there were no differences in distress symptoms, parent stress remained greater than for normal birthweight infants. 140 The effect seems to vary according to medical risk factors, developmental outcome, family environment, and age at reporting. 141,142,143 Higher effect was associated with low family income, less parental education, and the severity of the child's functional handicap. 144 Drotar and colleagues 145 showed the negative effect of low socioeconomic status and abnormal neurodevelopmental status on the child of school age, and reported that the effect was more pronounced for the underprivileged Cleveland ELBW cohort than that reported in other international studies.

At adolescence, although families of ELBW infants reported greater emotional distress in the past than families of normal birthweight controls, they also showed resilience by having positive interactions with friends and within the family unit, enhanced personal feelings of mastery and accomplishment, and both positive and negative effects on the marital relationship. Other negative effects on work and finances were no longer factors by adolescence. 146

Economic considerations of neonatal intensive care for the tiniest babies
The increasing effectiveness of neonatal intensive care for the smallest and most preterm infants is well established, but of importance is whether or not the resources have been spent efficiently and whether those who need intensive care are getting it. In a study of the economics of ELBW livebirths in the state of Victoria over four different eras from the late 1970s to the late 1990s, 147 the effectiveness of neonatal intensive care was shown by the stepwise increase in survival rates from about one in four in the late 1970s to three in four in the late 1990s. At the same time the efficiency of neonatal intensive care remained stable between successive eras, costing about AUS$5000 per year of life gained with each stepwise increase in survival. Although expensive, economically, neonatal intensive care compares favourably with many other health-care programmes, not only hospital-based and intensive programmes, but also many ambulatory and non-intensive programmes. 148 The proportions of ELBW infants offered intensive care increased over time and more were born in level III perinatal centres, increasing from 70% in 1979–80, to 91% by 1992. 149 The outcome for babies born in level III perinatal centres was progressively much better than for those born elsewhere. 150

Conclusions
Although work on strategies for prevention or reduction, or both, of the frequency of prematurity continues, future directions for neonotologists include modifying the antecedents of brain injury, achieving the best neonatal and postnatal care for infants, and providing greater support and resources to parents to help them achieve the best potential for their children. Additionally, further prospective long-term follow-up to middle age is warranted to establish whether preterm infants are at risk for future cardiovascular and metabolic disorders related to their small size at birth and subsequent rapid catch-up in growth.

Conflict of interest statement
We declare that we have no conflict of interest.

References


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