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Lex W. Doyle and Saroj Saigal

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Long-term Outcomes of Very Preterm or Tiny Infants

Lex W. Doyle, MD,
FRACP,* Saroj Saigal, MD,
FRCP(C)[†]

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Drs Doyle and Saigal
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Objectives After completing this article, readers should be able to:

1. List the survival rates for very preterm or tiny babies.
2. Describe potential neurologic impairments and disabilities seen in very preterm or tiny babies.
3. Delineate other long-term health problems in school-age children who were born very preterm or tiny.
4. Discuss health problems in early adulthood of children who were born very preterm or tiny.

Abstract

Survival rates have improved dramatically in recent years for very preterm or tiny infants. However, such infants remain at significant risk for a wide array of long-term morbidities that are mostly inversely related to gestational age. In early childhood, neurodevelopmental disabilities and recurrent health problems take a significant toll. Subsequently “hidden disabilities” such as school difficulties and behavioral problems become apparent and persist through adolescence. Reassuringly, however, most children born very preterm adjust remarkably during their transition to adulthood. As mortality rates continue to fall, the focus for perinatal interventions must be strategies to reduce long-term morbidity. In addition, follow-up to middle age and later adulthood is warranted to determine the risks, especially for cardiovascular, respiratory, and metabolic problems, and other lifestyle issues likely to be confronted by very preterm or tiny survivors.

Introduction

Long-term outcomes for very tiny or preterm infants are of increasing concern as their survival rates have risen in recent times with the advent of modern neonatal intensive care. (1) Even in the era before assisted ventilation, it was clear that outcomes beyond the nursery were important, particularly if obstetric or pediatric management was changing. Kitchen and Campbell (2) reported improved survival rates with a package of intensive care that comprised primarily the ability to infuse glucose and bicarbonate and to monitor the partial pressure of oxygen from arterial blood samples. However, such survival came with the price of a higher rate of long-term impairments among the survivors of those treated with the intensive care package. (3) The need to know about long-term outcomes of very preterm or tiny infants has increased as the rate of preterm birth in developed countries has risen, rather than fallen. (4)

The purpose of this article is to review the data on long-term outcomes of very preterm or tiny infants, including survival and neurodevelopmental, educational, behavioral, psychosocial, growth, and health outcomes of the most preterm (<30 weeks gestational age) or very low birthweight

Abbreviations

BPD: bronchopulmonary dysplasia
ELBW: extremely low birthweight
IQ: intelligence quotient
VLBW: very low birthweight

*The Royal Women's Hospital; Departments of Obstetrics and Gynaecology, and Paediatrics, the University of Melbourne; Murdoch Children's Research Institute, Melbourne, Australia.

[†]Department of Paediatrics, McMaster University, Hamilton, Ontario, Canada.

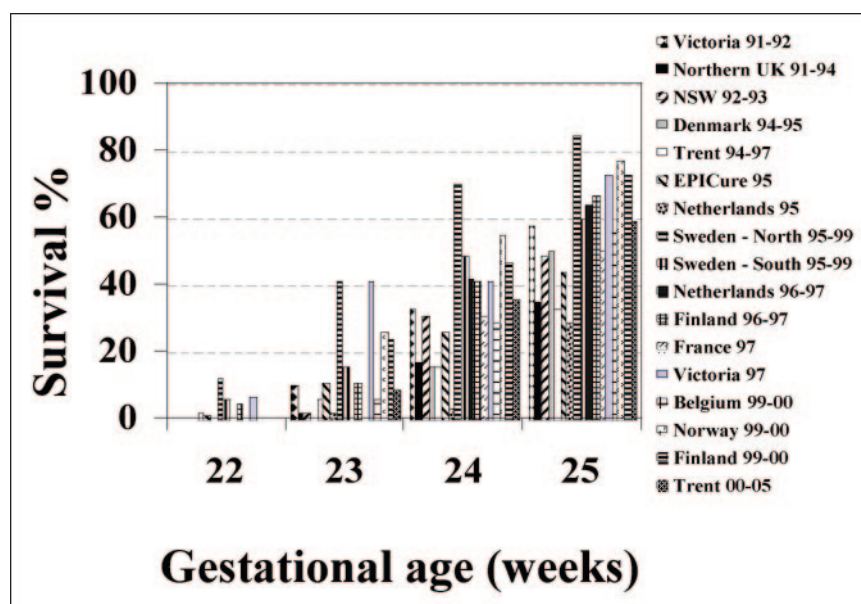


Figure. International survival rates of preterm infants according to gestational age in weeks in the 1990s through 2000. NSW=New South Wales, UK=United Kingdom

(VLBW) (<1,500 g) or extremely low birthweight (ELBW) (<1,000 g) infants at various ages from infancy to adulthood.

This article is based on our recent review of the topic, to which interested readers are referred for more details of methodologic issues, how we have searched for relevant articles, and more detailed data on some outcomes. (1) This article updates that review with more recent data on some outcomes, where available.

Mortality

Gestational age exerts the greatest influence on outcomes for preterm births. There were few survivors before 28 weeks' gestation prior to the widespread use of assisted ventilation in the 1970s, and many more mature babies died from respiratory distress caused by lack of pulmonary surfactant. However, by the mid-1990s, survival rates for very preterm births, especially before 28 weeks' gestation, had improved dramatically, and deaths from surfactant deficiency in infants born after 27 weeks' gestation were uncommon. (5)

Survival rates for infants of borderline viability from geographically determined cohorts are lower at each week than those from single- or multihospital studies primarily because regional cohorts include deaths that never reach tertiary centers for care. Survivors at 22 weeks' gestation are rare, and survival rates increase with increasing gestational age: up to 40% at 23 weeks,

40% to 60% at 24 weeks, 60% to 80% at 25 weeks, and 70% to 80% at 26 weeks from regional cohorts born in the 1990s. (1)

Since that review, Field and associates (6) have reported survival rates to hospital discharge of infants born in 2000 to 2005 in the Trent region of England of 9% at 23 weeks, 36% at 24 weeks, and 59% at 25 weeks, which is at the lower end of the rates reported from Scandinavian countries and Australia for births in the 1990s (Figure). Significant variations exist between regions in survival rates of infants of borderline viability, explained primarily by different attitudes to offering intensive care, both before and after birth. (7) Not having growth restriction, being female, and being born in a hospital that has a neonatal intensive care nursery are among

the variables related to higher survival rates among very preterm infants. (1)

Neurodevelopmental Outcomes in Early Childhood

Neurodevelopmental impairments in the early years include cerebral palsy, developmental delay or intellectual disability, and visual and auditory deficits. Approximately 25% of very preterm survivors in regional cohorts have substantial neurologic morbidity (Table). (1) However, 4% of normal birthweight, nonpreterm controls also have substantial neurosensory disability using the same criteria as for very preterm infants. (7)

Of the impairments leading to disability, cerebral palsy rates are significantly increased in very preterm survivors, increasing inversely with diminishing gestational age. Gestational age-specific prevalences per 1,000 livebirths for cerebral palsy for 1991 to 1994 in Sweden were: 85.5 for gestational ages less than 28 weeks, 60.4 for 28 to 31 weeks, 6.2 for 32 to 36 weeks, and 1.3 for 37 weeks or more. (8) In a recent study from Norway linking various national registries, the gestation-specific rates of cerebral palsy per 1,000 survivors for 903,402 livebirths free of congenital anomalies born between 1967 and 1983 reported in early adulthood (ages 20 to 36 years) were 91.2 for 23 to 27 weeks', 59.9 for 28 to 30 weeks', 19.0 for 31 to 33 weeks', 3.5 for 34 to

Table. Reported Outcomes for Very Preterm or Tiny Survivors Compared With Term Infants

- Substantial neurodevelopmental morbidity in 1 in 4 compared with 1 in 25
- Cerebral palsy in 10% compared with 0.1% to 0.2%
- School difficulties in up to 3 in 4 compared with 1 in 8
- In adulthood
 - Intellectual disability in 1 in 22 compared with 1 in 250
 - Behavioral or psychological problems in 1 in 40 compared with 1 in 500
 - Vision or hearing problems or epilepsy in 1 in 25 compared with 1 in 500
- Hospital readmissions 2 to 3 times more frequent in early childhood, especially for respiratory illnesses
- Higher systolic blood pressure in early adulthood
- Reductions in airflow on respiratory function testing in early adulthood
- Weigh less on average through childhood and into adulthood, but on average reach genetic height potential
- More restrictions in daily living and self-care abilities
- Self-reported health-related quality of life similar

36 weeks', and 1.3 for 37 weeks' or more gestation. (9) These rates were similar to the Swedish study.

Studies on time trends in the prevalence of cerebral palsy in very preterm or VLBW survivors have been conflicting, with reports of no change, a significant decrease, or a significant increase. (1) The two most recent regional studies highlight the different directions in trends. In Nova Scotia, as mortality rates declined significantly from 256 to 114 per 1,000 livebirths for infants of less than 31 weeks' gestation born between 1993 and 2002, the prevalence of cerebral palsy increased from 44 to 100 per 1,000 livebirths. (10) In contrast, the prevalence of cerebral palsy among VLBW infants weighing less than 1,500 g born in Europe decreased from 60.6 per 1,000 livebirths in 1980 to 39.5 per 1,000 livebirths in 1996. (11) In the Norwegian study, the absolute risk of cerebral palsy in adulthood for those of 23 to 27 weeks' gestational age increased for births between 1967 and 1983. (9)

In addition to motor problems caused by cerebral palsy, even extremely preterm infants who have normal intelligence and are free of cerebral palsy have higher rates of developmental coordination disorder, presenting with gross and fine motor problems in childhood. (12)

School Difficulties and Higher Cognitive Function

In a meta-analysis of studies of very preterm children born before 1990 that described cognitive outcomes in 15 studies and behavioral outcomes in 16 studies, Bhutta and associates (13) reported that preterm children had, on average, an intelligence quotient (IQ)

approximately two thirds of a standard deviation below controls, more internalizing and externalizing problems, and higher rates of attention-deficit/hyperactivity disorder. Cognitive and school difficulties were identified in all preterm cohorts in another study of four western countries. (14) There was a higher prevalence and more severe deficits in the smallest birthweight groups compared with those who were heavier. (1) Such disorders persist into high school. In one study, 72% of adolescents who weighed less than 750 g at birth, 53% of those whose birthweights were 750 to 1,000 g, and 13% of normal-birthweight controls experienced school difficulties,

which were apparent even in children who did not have neurosensory impairments and had normal IQs, and were more prevalent among males. (15)

Very preterm survivors also have much higher rates of problems in other cognitive areas, such as attention, visual processing, academic progress, and executive function. (16)(17) In one study, infants whose birthweights were less than 1,000 g or who were born before 28 weeks' gestation scored significantly below normal-birthweight controls at age 8 years on all indices of executive function assessed, and the findings were consistent with global impairment rather than deficits in specific executive domains. (17) These children also performed significantly worse than normal-birthweight controls on tests of academic achievement, such as reading, spelling, and arithmetic. (16) Similar deficits in executive function and in mathematics have been reported for infants of less than 750 g birthweight. (18) The cognitive disadvantage for very preterm survivors persists into late adolescence and early adulthood. (15)(19)(20) In the Norwegian national survey of livebirths from 1967 to 1983, rates of intellectual disability per 1,000 survivors in early adulthood fell significantly with increasing gestational age from 44.2 for 23 to 27 weeks', 17.8 for 28 to 30 weeks', 9.7 for 31 to 33 weeks', 6.9 for 34 to 36 weeks', and 4.2 for 37 weeks' or more gestation. (9)

Behavioral and Psychological Problems

Very preterm infants are at higher risk for behavioral problems such as attention-deficit/hyperactivity disorder in early childhood. (21) They are also particularly

vulnerable to **problems related to inattention, hyperactivity, and emotional difficulties at school** age that interfere with academic functioning. (16) In addition, preterm infants have been reported to have traits such as shyness, anxious/withdrawn, unassertiveness, and social maladaptation. (21) In a recent study, adults who had been ELBW infants and had no major impairments were more cautious, shy, and risk-averse and less extroverted than normal-birthweight controls. (22)

Botting and associates (23) reported a higher prevalence of anxiety and depression, as perceived by 12-year-olds who had been VLBW infants, compared with controls. Several other studies that had longer follow-up revealed that many of the previously noted problems persisted into adolescence and young adulthood. However, there were differences between respondents' reports: parents reported teens who had been ELBW infants to have significant difficulties with attention-deficit/hyperactivity disorder, but the same teens did not perceive themselves to be different from controls. (24) Similarly, parents of young adults who were VLBW infants reported more difficulties than parents of control young adults with thought problems in men and significantly higher scores on the anxious/depressed, withdrawn, and attention scale for women. (25) Both men and women reported lower rates of delinquency and risk-seeking behaviors. (19)(26) In the Norwegian national survey of livebirths from 1967 to 1983, rates of disorders of psychological development, behavior, or emotion per 1,000 survivors in early adulthood fell significantly with increasing gestational age from 24.9 for 23 to 27 weeks', 7.1 for 28 to 30 weeks', 3.5 for 31 to 33 weeks', 3.3 for 34 to 36 weeks', and 2.1 for 37 weeks' or more gestation. (9) In another epidemiologic study of reproductive health of Norwegian infants born 1967 to 1976, women, but not men, who were born preterm were at increased risk of having a preterm birth. (27) A recent report from Helsinki of births from 1978 to 1985 evaluated 162 individuals born VLBW and 188 individuals born at term and free of substantial neurologic morbidity who completed a questionnaire relating to lifestyle and sexual relationships. (28) The VLBW individuals were less likely to leave the parental home, to start cohabiting with an intimate partner, and to experience sexual intercourse. (28)

Other Outcomes in Early Adulthood

In most studies in early adulthood, those who were born VLBW had slightly lower rates of educational achievement, employment, and independent living. (19)(26)

However, few differences were found in young adults born ELBW compared with a relatively advantaged population in Ontario, Canada. (29) In the Norwegian survey of livebirths from 1967 to 1983, rates of completing high school, undergraduate, or postgraduate university degrees or of having lower-paying employment were significantly lower with decreasing gestational age; rates of having higher-paying employment were significantly higher. (9) However, unemployment rates did not vary with gestational age. Decreasing gestational age was associated with lower likelihoods of being a parent, being in a relationship, being divorced, and criminal behavior. (9)

Other Health Outcomes

Children who were born ELBW have more hospital readmissions and other health problems following discharge than do normal-birthweight children, particularly in the first years after birth. In one study, more than 50% of ELBW children were readmitted to the hospital at least once in the first 1 to 2 postnatal years, mostly due to respiratory illnesses, including lower respiratory tract infections. (30) These rates were two to three times the rates of readmission of normal-birthweight children. Even at 10 to 12 years of age, children born before 26 weeks' gestation consumed significantly more services for physician visits, occupational or physical therapy services, nursing or medical procedures, compensatory dependency needs, and services over and above those routinely required by normal-birthweight children (67% versus 22%). (31) By the time ELBW survivors reach adulthood, no differences in acute health problems or use of health resources were found, but chronic health problems remained higher compared with normal-birthweight young adults. (32)

Blood Pressure

Blood pressure was measured at 18 or more years of age in 156 VLBW survivors from one hospital born between 1977 and 1982 and 38 contemporaneous normal-birthweight individuals with both a standard mercury sphygmomanometer and an ambulatory blood pressure monitor. (33) **VLBW survivors had higher systolic and diastolic blood pressures measured by a mercury sphygmomanometer than normal-birthweight individuals as well as significantly higher mean systolic ambulatory blood pressures and for both the awake and asleep periods.** Within the group of VLBW survivors, no significant relationship was apparent between growth restriction in utero and any measure of blood pressure. In another

study, 20-year-old people born VLBW, particularly females, had higher systolic blood pressures than normal-birthweight controls. (34) Higher blood pressure in early adulthood is concerning because cardiovascular diseases related to high blood pressure are a major cause of death in adulthood.

Respiratory Health

Bronchopulmonary dysplasia (BPD) has been described in up to 40% of VLBW survivors, and the rate increases as the birthweight falls below 1,500 g. (35) With increasing survival rates, the prevalence of survivors who had BPD reaching adulthood is approaching 3 to 4 per 1,000, a prevalence greater than that for many childhood diseases known to affect the respiratory system, such as cystic fibrosis, which has a birth prevalence of approximately 0.4 per 1,000 in Caucasians, many of whom do not survive into adulthood.

Lung function has been reported for 147 VLBW survivors born during 1977 to 1982 who had lung function tests at a mean age of 18.9 years. (36) Of the 147 study participants, 33 (22%) had BPD in the newborn period. All lung function variables reflecting airflow were substantially diminished in the BPD group, but lung volumes were not significantly different. More individuals in the BPD group had reductions in airflow in the clinically significant range. Compared with earlier in childhood, some variables reflecting flow deteriorated more between 8 and 18 years in those who had BPD compared with those who did not have BPD. It is possible that individuals who are born VLBW, and those who have BPD in particular, may have an earlier decline in lung function than that expected in nonpreterm individuals.

Other Neurosensory Outcomes

The incidence of blindness among very preterm and very small infants has decreased from 8% to 10% in the 1970s to less than 3% among current survivors, partly due to the increasing use of cryotherapy and laser therapy to prevent retinal detachment. (37) Blindness or severe visual impairment is more common with lower gestational ages, with rates of 1% to 2% for infants whose gestational ages are 26 to 27 weeks and 4% to 8% for those who ages are 25 weeks or less. (31)(38)(39) The requirement for prescription glasses also is related to gestational age, with 24% of 6-year-old children born at fewer than 26 weeks' gestation wearing glasses versus 4% of term controls. (38) In the Ontario study, 36% of adolescents who had been

born ELBW versus 10% of those of normal birthweight were wearing prescription glasses. (40) By adulthood, the corresponding figures were 64% and 37%. (32) Another recently reported adverse outcome is a high rate (4% to 5%) of late retinal detachment among former ELBW infants during their late teens. (32)

Severe hearing impairment in infancy was reported in 7% of infants who weighed less than 1,000 g born in Cleveland in 1990 to 1998. (41) Marlow and associates (38) reported that 6% of 6-year-olds who had been born before 26 weeks' gestation were wearing hearing aids, and another 4% had mild hearing loss compared with 1% of controls. In another study, 5% of 14-year-old children who had weighed less than 1,000 g at birth were wearing hearing aids. (42) At adulthood, only 1.3% of Ontario young adults born ELBW versus fewer than 1% of controls were wearing hearing aids, although a higher proportion reported having difficulties in hearing. (32) In addition to hearing loss, VLBW infants have higher rates of central auditory processing problems, difficulty hearing in noisy places, and poor short-term auditory memory. (43) Hearing difficulties can have cumulative negative effects on the acquisition of language skills and learning at school (18)

In the Norwegian survey of livebirths from 1967 to 1983, rates of blindness, low vision, hearing loss, or epilepsy decreased significantly with increasing gestational age from 41.4 for 23 to 27 weeks', 21.9 for 28 to 30 weeks', 5.3 for 31 to 33 weeks', 3.4 for 34 to 36 weeks', and 2.2 for 37 or more weeks' gestation. (9)

Growth

Infants born VLBW have significantly lower growth attainment in weight and length than their normal-birthweight counterparts during infancy and early childhood. (44) Substantial catch-up occurs by mid-childhood and adolescence, but those born VLBW remain lighter and shorter than normal-birthweight controls. (45)(46)(47) In one study in which parental heights were reported but not measured, ELBW individuals had height z-scores lower than their parents, (46) but in another study where parental heights were measured, ELBW subjects had height z-scores similar to their mid-parental height z-score. (45) However, their mean weight z-score was higher and, hence, their body mass index was relatively higher, which may place the ELBW group at higher risk for later cardiovascular disease and type 2 diabetes.

Functional Limitations and Health-related Quality of Life

Compared with infants born at term, extremely preterm infants have more restriction in activities of daily living and self-care abilities throughout childhood and adolescence and higher rates of chronic health conditions. (31)(40) Such functional limitations and chronic health conditions persist into adulthood. (32)

Saigal and associates (48) reported that although by self-report teenagers who had been born ELBW experienced a greater prevalence and complexity of functional limitations compared with 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. (49) Several studies of former preterm infants at adulthood have shown no differences in the self-reported quality of life despite recognition of their disabilities. (50)(51)(52)

Conclusions

Despite the marked improvement in survival rates in recent years for very preterm or tiny infants, neurodevelopmental morbidity remains high and has not kept pace with improvements in survival. In general, morbidity follows a gestational age gradient that is inversely related to the degree of immaturity. However, no gestational age is completely exempt from neurologic problems, including term. Whether rates of early neurologic impairments and disabilities in very preterm survivors are increasing, diminishing, or staying the same over time, they remain too high compared with term children, and strategies to improve neurologic outcome are urgently required. Several recent positive developments include caffeine therapy for apnea of prematurity, which reduced cerebral palsy and developmental delay at 18 months of corrected age in one trial of more than 2,000 infants, (53) and antenatal magnesium sulfate therapy, which reduced the rate of cerebral palsy at 2 years in a similar-sized trial. (54) More reports of improved outcome from ongoing and future studies of new treatments are eagerly awaited. Further prospective longer-term follow-up to middle age and beyond is warranted to determine whether very preterm or tiny survivors are at increased risk for future cardiovascular, respiratory, or metabolic problems or other adult diseases at earlier ages than would otherwise be expected.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specification

- Know the incidence and range of severity of cognitive impairment in the general population and in high risk groups, including infants with extreme prematurity, or intrauterine growth restriction.



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NeoReviews Quiz

9. Survival rates for infants of borderline viability from geographically determined cohorts are lower at each week of gestation than those from single- or multicenter studies, primarily because regional cohorts include deaths of infants who never reach tertiary centers for care. Of the following, the survival rate, based on regional cohorts born in the late 1990s, for an infant born at 24 weeks' gestation is *closest* to:
 - A. 10%.
 - B. 30%.
 - C. 50%.
 - D. 70%.
 - E. 90%.
10. The rates of cerebral palsy among infant survivors of borderline viability increase inversely with diminishing gestational age at birth. Of the following, the rate of cerebral palsy, based on Scandinavian cohorts born between the 1960s and 1990s, for infants born at gestational ages of less than 28 weeks is *closest* to:
 - A. 5 per 1,000 survivors.
 - B. 30 per 1,000 survivors.
 - C. 60 per 1,000 survivors.
 - D. 90 per 1,000 survivors.
 - E. 120 per 1,000 survivors.
11. Preterm infant survivors of borderline viability at birth are at higher risk for behavioral problems such as attention-deficit/hyperactivity disorder in early childhood. Of the following, the rate of psychological disorders in early adulthood, based on a Norwegian cohort born between the 1960s and 1980s, for infants born at gestational ages of less than 28 weeks is *closest* to:
 - A. 5 per 1,000 survivors.
 - B. 25 per 1,000 survivors.
 - C. 50 per 1,000 survivors.
 - D. 75 per 1,000 survivors.
 - E. 100 per 1,000 survivors.

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