Survival and Long-Term Neurodevelopmental Outcome of Extremely Premature Infants Born at 23–26 Weeks’ Gestational Age at a Tertiary Center

Ronald E. Hoekstra, MD*; T. Bruce Ferrara, MD*; Robert J. Couser, MD*; Nathaniel R. Payne, MD*; and John E. Connett, PhD‡

ABSTRACT. **Objective.** Long-term outcome, including school-age function, has been infrequently reported in infants born at ages as young as 23–26 weeks’ gestation. The objective of this study is to report outcome on a large cohort of these infants to understand better the risks and factors that affect survival and long-term prognosis.

**Methods.** Records from 1036 infants who were born between January 1, 1986, and December 31, 2000, were analyzed retrospectively by logistic regression to correlate multiple factors with both survival and long-term outcome. A total of 675 surviving infants were analyzed at a mean age of 47.5 months for developmental outcome. A subset of 147 surviving infants who were born before 1991 were followed through school-age years using the University of Vermont Achenbach Child Behavioral Checklist and Teachers Report Form. Longitudinal follow-up was performed comparing 1-year outcome with school-age performance.

**Results.** Gestational age and recent year of birth correlated highly with survival. Maternal nonwhite race, female sex, inborn status, surfactant therapy, single gestation, and secondary sepsis also correlated positively with survival. Normal cranial ultrasound results, absence of chronic lung disease, female sex, cesarean delivery, and increased birth weight correlated favorably with long-term outcome. Infants who were born at 23 weeks were more likely to have severe impairments compared with those who were born at 24–26 weeks. Early follow-up identified most subsequent physical impairments but correlated poorly with school-age function.

**Conclusions.** Survival continues to improve for infants who are born at extremely early gestational ages, but long-term developmental concerns continue to be prevalent. Early outcomes do not reliably predict school-age performance. Strategies that reduce severe intraventricular hemorrhage and chronic lung disease will likely yield the best chances to improve long-term outlook. Pediatrics 2004;113:e1–e6. URL: http://www.pediatrics.org/cgi/content/full/113/1/e1; prematurity, outcome, neurodevelopment, survival, follow-up.

ABBREVIATIONS. GA, gestational age; NICU, neonatal intensive care unit; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; CLD, chronic lung disease; SD, standard deviation; OR, odds ratio.

A

Advances in perinatal and neonatal care during the past 2 decades have improved the prognosis for most preterm infants. Concomitant with these advances, the limits of viability have been lowered to the point where routine resuscitation of infants whose gestational age (GA) is as low as 23 weeks is now occurring in many perinatal centers. Despite this practice, many unanswered questions remain regarding outcome of these extremely preterm infants. Most outcome reports contain relatively few patients.1–4 Survival statistics vary and do not always account for the aggressiveness of support, which can also vary between centers. Long-term outcome information seems unfavorable compared with more mature preterm infants,5,6 but intact survival with normal cognitive function has been reported.7,8 Added benefits of prolonging gestation by weekly increments, when possible, are unclear. This information is crucial when physicians and parents are asked to make important decisions regarding obstetric interventions and neonatal resuscitation. To address these issues better, we report on both survival and neurologic outcome of a cohort of >1000 infants who were born at ages between 23 and 26 weeks’ gestation over a 15-year period and also evaluate factors that have a significant impact on these findings.

METHODS

The Institutional Review Board approved medical record analysis used for this report. Medical records of 1036 infants who were born at GAs between 23 and 26 weeks and cared for at the perinatal center of Abbott Northwestern Hospital and Children’s Hospitals and Clinics of Minneapolis between January 1, 1986, and December 31, 2000, were reviewed retrospectively. Included in this analysis were 901 inborn infants and 135 infants who were transferred to Children’s neonatal intensive care unit (NICU) after outborn birth. Twenty-three infants (1.6 per year) who died in the delivery room are not included in the analysis. GA assessment was based on obstetric dating including prenatal ultrasound and was confirmed by postnatal physical examination. A staff neonatologist, who routinely provided aggressive stabilization measures, including endotracheal intubation, attended all inborn deliveries unless parents, before birth, refused such measures. A total of 881 inborn infants received surfactant in the delivery room, either as part of randomized studies before 1990, under a Treatment Investigative New Drug protocol, or as part of routine care after Food and Drug Administration approval. All infants who survived delivery room resuscitation were admitted to the
NICU. All infants who survived to discharge had cranial ultrasound scans graded for intraventricular hemorrhage (IVH) using the criteria of Papile et al.12 Echoencephal abnormalities that evolved into cystic changes were classified as periventricular leukomalacia (PVL)12.13 Chronic lung disease (CLD) was defined as the need for supplementary oxygen at 36 weeks postconceptional age. Survival was defined as being alive at discharge to home.

A team that included a certified nurse practitioner, an occupational therapist, and a neonatologist, all of whom were aware of the infants’ NICU experience, performed postdischarge follow-up evaluations. Infants were initially evaluated at 6 months’ corrected age and every 6 to 18 months thereafter as indicated. Age was adjusted for prematurity until a chronological age of 36 months was attained. Evaluations during the first 36 months included a detailed interval health history, Bayley Scales of Infant Development II13 performed by certified testers, and both physical and neurologic examinations. Infants were classified as normal up to 3 years of age when they had normal physical and neurologic examinations and Mental Developmental Index and Psychomotor Developmental Index scores within 1 standard deviation (SD) of the mean (±86) on the Bayley Scales of Infant Development II. Isolated muscle tone abnormalities, unilateral blindness, hyperactivity, or developmental scores between 1 and 2 SDs below the mean categorized infants as having mild to moderate impairment. Infants with severe impairment had spasticity, severe hypotonia, blindness, deafness, or severe developmental delay with developmental test scores >2 SDs below the mean.

For infants between 3 and 6 years of age, the Denver Developmental Screening Test12 was used in conjunction with the Early Language Milestone Scale14 and the Zimmerman Preschool Articulation Test.14 Between 3 and 6 years of age, infants who were classified as normal had normal physical and neurologic examinations and passed all items on the Denver Developmental Screening Test, Early Language Milestone Scale, and Zimmerman Preschool Articulation Test to a level within 6 months of their chronological age. Infants who were classified as having mild to moderate impairment had normal physical and neurologic examinations or examinations with only minor abnormalities and developmental assessments that were 6 to 12 months below their chronological age. Infants who were judged to have severe impairment at 3 to 6 years of age may have had severe abnormalities on physical and neurologic examinations and/or abnormalities on developmental assessment >1 year below their chronological age.

Older children who had completed at least the first grade were evaluated using the University of Vermont Achenbach Child Behavior Checklist and the Teacher’s Report Form15 with both parents and teachers completing the Problem Scales questionnaire. School-age children were classified as normal when they had normal physical and neurologic examinations, had normal Achenbach scores, and were enrolled in the appropriate grade for age in all subjects. These children could be somewhat below average in no more than 1 subject. Children were classified as having mild to moderate impairment when they had normal physical and neurologic examinations, were enrolled in the appropriate grade for age, but were performing somewhat below grade average in >1 subject but not far below average in >1 subject, or had below-normal Achenbach scores. Classification in the severely impaired category included any child with spasticity, severe hypotonia, blindness, or hearing loss. Any child who repeated a grade, required special education, was far below grade average in >1 subject, or had Achenbach scores far below normal was considered to have severe impairment even when their physical and neurologic examinations were normal.

The relationships between multiple risk factors with survival and neurodevelopmental outcomes were analyzed by logistic regression. Year of birth and GA were entered as controlling factors in all models, and additional risk factors were entered individually to determine how much additional risk they conferred. The results of these analyses were summarized in terms of odds ratios (ORs) for survival or neurodevelopmental normality, with 95% confidence intervals for true ORs. ORs >1 indicated that survival or normality was more likely when the risk factor was present, whereas an OR <1 indicated that these were less likely to occur when the risk factor was present. All computations were done using the PROC LOGISTIC in the SAS statistical package.14 A 2 × 2 analysis was used to compare the relationship between survival and both GA and year of birth.

RESULTS

Demographic characteristics of all infants included in the cohort are shown in Table 1. Of the 1036 infants admitted to the NICU, 778 (75%) survived until discharge. Survival improved from 53% in 1986 to 89% in 2000 (Fig 1). Figure 2 demonstrates survival by GA. The relationship between survival and both GA and year of birth was highly significant (P < .0001). After controlling for birth year and GA, factors that significantly affected survival included sex, mother’s race, inborn/outborn status, birth weight, multiple or single gestation, surfactant therapy, and secondary sepsis (Fig 3). Including the 23 delivery room deaths, overall survival for 23 to 26 weeks was 73% (778 of 1059) and was 47%, 66%, 80%, and 86% at 23, 24, 25, and 26 weeks, respectively.

Of the 778 survivors, 675 (87%) were seen at follow-up at a mean of 47.5 months. Sixty-three percent were classified as normal, 17% as mildly to moderately abnormal, and 20% as having severe impairment. Controlling for both birth year and GA, factors that significantly affected neurodevelopmental outcome included sex, birth weight, mode of delivery, cranial ultrasound findings, and CLD (Fig 4). Infants with normal cranial ultrasound findings had significantly better neurodevelopmental outcome than those with cranial ultrasound abnormalities (P < .0001). Of infants with normal cranial ultrasound findings, 73% were later classified as normal with 12% severely impaired. In contrast, only 27% of infants who had grade 3 to 4 IVH or PVL were normal at follow-up, and 52% were considered to have severe impairment. Of 44 infants with isolated grade 3 IVH, 36% were classified as normal and 34% as having severe impairment; whereas of 39 infants with isolated grade 4 IVH, 21% were normal and 67% had severe impairment. Of 32 infants with isolated PVL, 25% were normal and 64% had severe impairment. Infants who had isolated PVL and were found to be normal at follow-up usually had small, isolated cystic ultrasound findings located adjacent to the frontal horns of the lateral ventricles. Compared with infants who were born between 24 and 26 weeks, those who were born at 23 weeks were less likely to be classified as normal and more likely to be classified as having severe impairment (Table 2). In infants who were not seen in follow-up, there was no difference in the occurrence of grades 3 to 4 IVH, PVL, CLD, sex, or birth weight compared with those who were seen.

### TABLE 1. Clinical Description of Patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
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<tr>
<td>No. of infants admitted to NICU</td>
<td>1036</td>
</tr>
<tr>
<td>No. of inborn</td>
<td>924</td>
</tr>
<tr>
<td>Died in delivery room</td>
<td>23</td>
</tr>
<tr>
<td>Admitted to NICU</td>
<td>901</td>
</tr>
<tr>
<td>No. of outborn</td>
<td>135</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>744 ± 162</td>
</tr>
<tr>
<td>GA (wk)</td>
<td>24.8 ± 1.04</td>
</tr>
<tr>
<td>Male</td>
<td>536 (52%)</td>
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<tr>
<td>White race</td>
<td>860 (83%)</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>265 (26%)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>564 (54%)</td>
</tr>
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Values shown are mean ± SD, number, and percentage of occurrence.
A total of 316 of the overall cohort of 1036 infants were admitted to the NICU before December 31, 1990. Of these, 203 (64%) survived until discharge and 147 (72%) were seen at a mean age of 8.25 years. Outcome at this age was similar to that at 47.5 months with 62% classified as normal, 21% as having mild to moderate delays, and 17% as having severe impairment. Similar to earlier evaluations, infants who were born at 24 to 26 weeks’ gestation had better outcomes compared with those who were born at 23 weeks (Table 3). Factors that showed a trend toward affecting outcome at this age included cranial ultrasound results, CLD, sex, GA, and mother’s race (Fig 5).

A total of 126 (86%) of the 147 infants who were seen at school age had previously been evaluated at 6 to 12 months of age. A total of 103 of these infants were believed to be normal at the initial evaluation. At school age, 18 infants had dropped into the mild to moderate delays category and 8 into the severe impairment category. Twenty-five of these 26 infants who changed categories did so on the basis of cognitive abnormalities. Only 1 child who was initially believed to be normal had a physical disability (cerebral palsy) as the basis for inclusion in the severe impairment group. Thirteen infants were classified as having severe impairment at 6 to 12 months; 10 of these infants continued in this category at school age, all of them having cerebral palsy.
DISCUSSION

As technology and sophistication of both obstetric and neonatal care has advanced over recent years, resuscitation and aggressive support of extremely preterm infants has become routine in most perinatal centers in the United States. Changes in perinatal care, such as more frequent antenatal steroid administration given earlier in pregnancy, and postnatal interventions including use of surfactant have improved survival in this population. Despite the more routine nature of this care at earlier ages, many important questions remain. Is it appropriate to resuscitate aggressively all preterm infants? Do the neonatal benefits of prolonging pregnancies’ short periods of time outweigh maternal risks incurred in all instances? Which factors correlate best with good or bad long-term outcome? Previous reports address concern regarding long-term neurologic outcome of extremely preterm infants. Vohr et al, 17 in a follow-up report of 1151 infants who were born be-
between 1993 and 1994 with birth weights between 401 and 1000 g found that 49% had abnormal neurodevelopmental and/or sensory findings at a corrected age of 18 to 22 months. Hack and Fanaroff reported subnormal cognitive function at 20 months' corrected age in 48% of 112 infants who were born between 1993 and 1995 with birth weights <750 g. Although most reports demonstrate no significant change in morbidity despite increased survival, the absolute number of infants who survive in this population has increased, placing a greater burden on early intervention programs and educational institutions.

The favorable overall survival statistics that we report in this large cohort could be accounted for by several factors. As expected, survival in our cohort also improved with advancing GA and year of birth. Female sex, surfactant use, and inborn status correlated with improved survival as were previously reported to be associated with increased survival in preterm infants. The finding of secondary sepsis as a positive factor influencing survival in our cohort was unexpected but can be explained by the fact that the majority of deaths that occur in these infants occur shortly after birth. Infants who live long enough to acquire a secondary infection have an improved chance of survival by virtue of the fact that they have survived the critical period that occurs after birth. High rates of inborn birth, maternal steroid use, prophylactic use of surfactant immediately after delivery, and an aggressive approach to resuscitation likely improved the overall survival rate compared with other reports. In addition, 24-hour coverage by experienced neonatologists has recently been shown to be a factor associated with increased survival in extremely preterm infants. Although delivery room deaths were not included in the analysis, overall survival results were not significantly affected by this omission.

Factors that positively influenced neurologic outcome at 47.5 months included female sex, cesarean section, normal cranial ultrasound results, and absence of CLD. We were unable to demonstrate a difference in outcome related to sociodemographic
factors at 8.25 years as has been previously reported. Gross et al27 recently reported that, with the exception of severe cranial ultrasound abnormalities (grades 3 and 4 IVH, PVL), perinatal medical complications were poor predictors of school-age outcome. Conversely, they found a significant correlation between parental education and marital status at the time of birth and school performance at 10 years. Hille et al28 found a 5-fold increase in the rate of school failure and a 7-fold increase in need for special education at 9 years among preterm children with low socioeconomic status. In contrast, Taylor et al29 found in a group of infants whose birth weights were <750 g that neonatal risk factors were the most consistent predictors of outcome and the need for special education placement. In our cohort, it is likely that the socioeconomic composition is too homogeneous, with few unmaried, poorly educated, non-white mothers, to detect differences in outcome that could be attributed to these factors.

Neurologic outcome differences in our surviving infants were present between those who were born at 23 weeks of gestation compared with those who were born beyond 23 weeks. Conversely, there was little difference in outcome beyond 24 weeks. Although overall survival improves incrementally with each advancing week, long-term neurologic improvements are not demonstrated to improve in the same incremental manner. Similarly, although multiple gestation decreases the likelihood of survival at these early ages, it does not have an adverse impact on subsequent neurologic outcome. Two factors acquired in the newborn period correlate with subsequent outcome. Cranial ultrasound results and presence or absence of CLD strongly correlated with outcome at 47.5 months and trend toward influencing outcome at 8.25 years. It seems that these are areas where improvement in neonatal care could have a large impact on long-term outcome.

Limitations of this study include the retrospective nature of data retrieval and the lack of term, age-matched control subjects. In addition, detailed psychometric testing was not done at school age. We attempted to compensate for physician examiners’ not being blinded to the neonatal status at the time of follow-up examinations by using a stringent classification for outcomes. Strengths of this study include the large number of patients, high rate of follow-up, and age at follow-up evaluations. We consider that this is a “single center” cohort to be a strength of the study. It is on the basis of such data that decisions will be made regarding site of delivery. Our data emphasize the caution of extrapolating early follow-up results with long-term outcome. Although physical disabilities are usually recognized in the first year of life, school-age function cannot be predicted by early evaluation.

In conclusion, it is apparent that children who seem entirely normal at early follow-up remain at risk for developing significant social and educational problems later in life. Prevention of severe IVH and reduction of CLD seem to be key factors in improving the long-term neurologic outcome of these vulnerable infants.

REFERENCES
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