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Neurodevelopmental and Functional Outcomes of Extremely Low Birth Weight Infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994

Betty R. Vohr, MD*; Linda L. Wright, MD‡; Anna M. Dusick, MD§; Lisa Mele, MS‖; Joel Verter, PhD‖; Jean J. Steichen, MD¶; Neal P. Simon, MD#; Dee C. Wilson, MD**; Sue Broyles, MD‡‡; Charles R. Bauer§§; Virginia Delaney-Black, MD‖‖; Kimberly A. Yolton, PhD¶¶; Barry E. Fleisher, MD##; Lu-Ann Papile, MD***; and Michael D. Kaplan, MD‡‡‡

ABSTRACT. *Objectives.* **The purposes of this study were to report the neurodevelopmental, neurosensory, and functional outcomes of 1151 extremely low birth weight (401–1000 g) survivors cared for in the 12 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network, and to identify medical, social, and environmental factors associated with these outcomes.**

Study Design. **A multicenter cohort study in which surviving extremely low birth weight infants born in 1993 and 1994 underwent neurodevelopmental, neurosensory, and functional assessment at 18 to 22 months' corrected age. Data regarding pregnancy and neonatal outcome were collected prospectively. Socioeconomic status and a detailed interim medical history were obtained at the time of the assessment. Logistic regression models were used to identify maternal and neonatal risk factors for poor neurodevelopmental outcome.**

Results. **Of the 1480 infants alive at 18 months of age, 1151 (78%) were evaluated. Study characteristics included a mean birth weight of 796 ± 135 g, mean gestation (best obstetric dates) 26 ± 2 weeks, and 47% male. Birth weight distributions of infants included 15 infants at 401 to 500 g; 94 at 501 to 600 g; 208 at 601 to 700 g; 237 at 701 to 800 g; 290 at 801 to 900 g; and 307 at 901 to 1000 g. Twenty-five percent of the children had an abnormal neurologic examination, 37% had a Bayley II Mental Developmental Index <70, 29% had a Psychomotor Developmental Index <70, 9% had vision impairment, and 11% had hearing impairment. Neurologic, developmental, neurosensory, and functional morbidities increased with decreasing birth weight. Factors significantly associated with increased neurodevelopmental morbidity included chronic lung disease, grades 3 to 4 intraventricular hemorrhage/periventricular leukomalacia, steroids for chronic lung disease, necrotizing enterocolitis, and male gender. Factors significantly associated with decreased morbidity included increased birth weight, female gender, higher maternal education, and white race.**

Conclusion. **ELBW infants are at significant risk of neurologic abnormalities, developmental delays, and functional delays at 18 to 22 months' corrected age.** *Pediatrics* **2000;105:1216–1226;** ***extremely low birth weight, neurologic outcome, developmental outcome, functional outcome, prematurity, cerebral palsy, Bayley.***

ABBREVIATIONS. ELBW, extremely low birth weight; NICHD, National Institute of Child Health and Human Development; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; CP, cerebral palsy; SD, standard deviation; OR, odds ratio; CI, confidence interval; CLD, chronic lung disease; SGA, small for gestational age; MDI, mental development index, Bayley II; PDI, psychomotor development index, Bayley II; NEC, necrotizing entercolitis.

The continued improvement in the survival of extremely low birth weight (ELBW) infants in the past decade has been well-documented.[1,2] Specific perinatal and neonatal therapeutic interventions, including antenatal steroids and exogenous surfactants, have contributed to the improved survival.[3–5] As a result, questions have arisen relative to the quality of neurodevelopmental outcome of these new ELBW survivors.[1,6–9] Although a number of studies have reported outcomes of ELBW infants, sample sizes have been limited, and type of assessment, age of assessment, and definitions of outcomes have been variable, resulting in conflicting findings. The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, which was initiated in 1986, currently consists of 14 tertiary care centers in the United States. The NICHD Follow-up Study Group was added to the Network in 1994; it provided a mechanism for conducting longitudinal follow-up studies. Twelve centers participated in this follow-up study. The study group determined a priori that there would be strict standardization of neurologic and developmental assessments, interview formats and age of assessment, and a goal of 80% follow-up compliance for the

From *Women and Infants' Hospital, Providence, Rhode Island; ‡National Institute of Child Health and Human Development, Bethesda, Maryland; §Indiana University, Indianapolis, Indiana; ‖George Washington University Biostatistics Center, Rockville, Maryland; ¶University of Cincinnati, Cincinnati, Ohio; #Emory University, Atlanta, Georgia; **Case Western Reserve, Cleveland, Ohio; ‡‡University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; §§University of Miami, Miami, Florida; ‖‖Wayne State University, Detroit, Michigan; ¶¶University of Tennessee at Memphis, Tennessee; ##Stanford University, Stanford, California; ***University of New Mexico, Albuquerque, New Mexico; and ‡‡‡Yale University, New Haven, Connecticut.

A list of the members of the NICHD Neonatal Research Network appears in the "Appendix."

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Reprint requests to (B.R.V.) Women and Infants' Hospital, 101 Dudley St, Providence, RI 02905. E-mail: betty_vohr@brown.edu

18-month assessment. In addition to the standardized assessments, the NICHD Follow-up Study provides a large cohort. The demographics of the study cohort are shown in Table 1. The number of teen mothers, unmarried mothers, and black mothers are overrepresented in the study cohort compared with the 1996 US annual summary of vital statistics.[10] The range of values, however, reflect the heterogeneity of the individual sites.

The objectives of this report are to describe the neurodevelopmental, neurosensory, and functional outcomes of the ELBW survivors of the participating sites at 18 to 22 months' corrected age and to identify key medical, social, and environmental factors associated with outcome.

METHODS

Participating centers collected pregnancy and delivery data on all live-born infants 401 to 1000 g born between January 1993 and December 1994 and assessed between November 1994 and February 1997. Neonatal outcome data were assessed at 120 days after birth, at discharge, or at the time of death, whichever came first. Data were collected on infants transferred to level II units until discharged from the hospital or to a chronic care facility. All data were abstracted from hospital records by trained study coordinators.

Families at each site were invited to participate in their site follow-up programs after discharge for a comprehensive assessment at 18 to 22 months' corrected age. Participation was considered standard of care at the 12 sites and informed consent was not obtained. Contact to schedule the follow-up evaluation was made by phone call, postcard, or certified letter. Parents were provided with transportation, if needed, and child care for siblings during the assessment. Attrition rates differed by site, and although 8 of 12 sites had compliance rates >80% (range: 80.6–90.7), 4 sites had rates of 75.3%, 61.1%, 62.1%, and 54.4%. The overall follow-up rate was 78%.

The cohort consisted of all 1527 ELBW survivors (63%) of 2498 infants admitted to the neonatal nurseries at the centers. Forty-seven (3%) infants died after discharge and 329 (21%) of 1480 long-term survivors were lost to follow-up, resulting in 1151 infants who were evaluated. Eighty-seven percent were inborn and 12.8% were outborn. There were no mean differences in birth weight (796 g), gestational age (26 weeks), or in grades 3 to 4 intraventricular hemorrhage/periventricular leukomalacia (IVH/PVL; 16% vs 15%) between infants lost and those evaluated, although infants who were lost to follow-up were less likely to have received oxygen at 36 weeks' gestational age (32% vs 40%; $P < .03$). However, mothers of infants who were lost to follow-up or who died were less likely to be married (31.9% vs 37.9%; $P < .001$). Data from the 8 sites achieving an 80% follow-up rate were compared with the 4 sites not achieving 80% follow-up and were found to be comparable. Therefore, the data from all sites were included in the analyses.

TABLE 1. Demographic Characteristics of the Cohort Evaluated at 18 to 22 Months' Corrected Age

Variable	Percentage (Mean)	Range
Less than high school graduate	28	10–46
Infant not living with biologic mother	13	2–22
Not married	49	31–65
Age ≤19 y	18	2–29
Income <$20 000	57	35–73
Medicaid	65	33–79
Race		
Black	51	3–82
White	35	6–78
Hispanic*	12	0–61
Other	2	
Primary language		
English	88	62–100
Spanish	9	0–30
Other	3	0–12

* Hispanic individuals may be of any race—85% were white Hispanics, 3% were black Hispanics, and 12% were unknown.

The assessment consisted of a developmental evaluation, neurological assessment, functional performance, medical and social history, and interviews. This report will focus on the neurodevelopmental and functional outcomes.

Neurologic examinations based on the Amiel-Tison[11] neurologic assessment were performed by certified, masked developmentalists who had been trained on reliability in the examination procedure in a 2-day, hands-on workshop on neurologic assessment. The workshops also established interexaminer agreement on the definitions of specific terms, such as cerebral palsy (CP) and diplegia and subtle findings, such as hypertonia and hypotonia. New neurologic examiners added at a site were trained to criteria by the site-certified examiner. The neurological assessment included an evaluation of tone, strength, reflexes, angles, and posture. Infants were scored as normal if no abnormalities were observed in the neurologic examination. CP was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. In addition, a basic, functional, gross motor skills assessment derived from the work of Russell et al[12] and Palisano et al[13] was completed. Within the functional assessment, children were scored in the following domains: axis-head and neck, axis-trunk, lower limb function-gait, upper limb function, and hand function. All definitions were reviewed and approved by a central review committee.

The Bayley Scales of Infant Development-II,[14] including the Mental Scale, Motor Scale, and the Behavior Rating Scale was administered by testers trained to reliability by 1 of 4 study gold standard examiners. Gold standard examiners were experienced clinicians specifically trained in Bayley Scales of Infant Development-II test procedures. These 4 examiners made tapes of their own evaluations and established initial interexaminer reliability among them. Examiner certification at sites was obtained by the successful completion of 2 videotaped demonstrations of accurate performance and scoring of the Bayley on 18-month-old children. The gold standard examiners reviewed the tapes for accuracy and reliability, granted certification when indicated, and served as a training resource. Bayley scores of 100 ± 15 represent the mean ± 1 standard deviation (SD). A score <70 is 2 SDs below the mean.

The primary caretaker or adult who brought the child for the visit stayed with the child during the Bayley examination, which was administered early in the clinic visit before the medical assessment and interviews. Examiners were not able to successfully administer the Bayley to 95 children seen. The following reasons were given: acute illness ($n = 10$), language barrier ($n = 2$), behavior problem ($n = 24$), developmentally delayed ($n = 18$), and other ($n = 41$). The other category included children with sensory loss (blind or deaf), who could not be administered the Bayley items. Although every effort was made to test children within the window of 18 to 22 months' corrected age, 22 infants were evaluated out of the window because of illness or tracking issues. These data were included because the Bayley II scores were age-adjusted.

Socioeconomic status information, including maternal and paternal education and occupation, marital status, insurance status, income level, and a detailed interim medical history, including data on hearing and vision status, was obtained. Hearing status information was obtained from the parent and follow-up audiologic test results when available. Hearing impairment was defined as any restriction or lack of ability to perform within the normal range and included sensorineural, conductive, or mixed loss. A history of postdischarge eye examinations and procedures was obtained from the parent. In addition, a standard eye examination was completed to evaluate tracking, esotropia, nystagmus, or roving eye movements. Vision impaired was defined as lack of normal vision including use of corrective lenses or contact lenses, blind with some functional vision, or no useful vision.

Statistical Analyses

All outcomes were analyzed by 100-g birth weight intervals. Group differences on continuous measures were examined by the

Wilcoxon rank sum test (2 groups) and Kruskal–Wallis test (>2 groups). Differences on categorical measures were analyzed with χ^2 analyses. Logistic regressions were used to identify associations among biologic, social, and demographic factors, and the major neurologic, developmental, and functional outcomes, and the results expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Maternal and neonatal risk factors known to be associated with increased neurodevelopmental morbidity were entered into the models. Factors examined included outborn status, maternal hypertension, antenatal steroids, maternal education, race, cesarean section, birth weight, surfactant, early-onset sepsis, late-onset sepsis, grades 3 to 4 IVH/PVL, chronic lung disease (CLD; oxygen requirement at 36 weeks), postnatal steroids, small for gestational age (SGA), gender, and adjusted age at time of testing. All data were analyzed at the George Washington University Biostatistics Coordinating Center.

RESULTS

One thousand one hundred fifty-one infants were evaluated at 12 sites. The numbers of infants seen at each center were as follows: University of New Mexico at Albuquerque (n = 38), Yale University (n = 49); Stanford University (n = 75), Indiana University (n = 87), University of Cincinnati (n = 88), Women and Infants' Hospital at Brown University (n = 100), Rainbow Babies' and Childrens' Hospital at Case Western (n = 105), University of Texas, Southwestern Medical Center at Dallas (n = 111), University of Tennessee at Memphis (n = 113), Wayne State University (n = 122), Emory University (n = 132), and University of Miami (n = 131). Ninety percent of the infants evaluated had a birth weight >600 g (Table 2). The percentage of children evaluated in follow-up ranged from 74% for infants born at 801 to 900 g to 83% for infants born at 401 to 500 g. Key prenatal and neonatal characteristics of the sample are shown. Although 18% of the cohort were SGA[15] and 38% had been exposed to antenatal steroids, 73% of infants born at 401 to 500 g were SGA and 60% had been exposed to antenatal steroids. Seventy percent of all infants received surfactant, 40% had CLD, and 18% had grades 3 to 4 IVH/PVL. The median number of days of hospitalization ranged from 73 for infants 901 to 1000 g to 132 for infants 401 to 500 g. There was an overall trend for an increased incidence of CLD, retinopathy of prematurity, receipt of postnatal steroids, and number of days of hospitalization to be associated with decreasing birth weight, whereas grades 3 to 4 IVH/PVL were more evenly distributed among the birth weight groups. Nineteen percent of the children were multiples: 17% were twins and 2% were triplets or greater. Although the data are not shown on Table 2 because the numbers are small, 33 children were diagnosed with an intrauterine infection and 1 infant with a major congenital anomaly. Data collection on anomalies, however, was added as a variable in June 1994.

Table 3 shows the results of the standardized neurologic examination. Forty-one infants did not have a complete neurologic examination, usually because a certified developmentalist was not available to complete the examination. Overall, 75% of infants had a normal examination with a range of 57% (birth weight: 401–500 g) to 79% (birth weight: 801–1000 g). Increased tone in the lower extremities (23%) was more common than in the upper extremities (14%) in all birth weight groups. Although an abnormal neurologic examination was identified in 25% of all infants, CP was diagnosed in 17%. CP categories include 71 quadriplegia, 5 left hemiplegia, 10 right hemiplegia, 90 diplegia, and 11 monoplegia. Seizure disorders were present in 5% of infants and shunted hydrocephalus in 4%. Some degree of vision impairment was present in 9% of the total cohort. It was inversely related to birth weight: 5% at 801 to 1000 g; 10% to 13% at 501 to 800 g; and 21% at 401 to 500 g. Three percent of infants were legally blind in 1 or both eyes. Although the overall incidence of hearing impairment was 11%, only 3% of infants had been fitted with hearing aids at 18 to 22 months. This is in part attributed to the fact that some children were diagnosed with conductive hearing loss.

Table 4 summarizes functional status at 18 to 22

TABLE 2. Characteristics of Study Cohort

Characteristic	401 to 500 g	501 to 600 g	601 to 700 g	701 to 800 g	801 to 900 g	901 to 1000 g	Total
Cohort	18 (1)	119 (8)	271 (18)	324 (21)	403 (26)	392 (26)	1527 (100)
Postneonatal deaths	0 (0)	2 (2)	12 (4)	6 (2)	11 (3)	16 (4)	47 (3)
Evaluated	15 (83)	94 (80)	208 (80)	237 (75)	290 (74)	307 (82)	1151 (78)
Gestational age	25.3 ± 2.2	24.7 ± 1.9	25.0 ± 1.8	26.0 ± 1.8	26.8 ± 1.9	27.6 ± 2.0	26.3 ± 2
Antenatal steroids	9 (60)	37 (39)	67 (33)	94 (40)	99 (34)	132 (43)	438 (38)
Preeclampsia	8 (53)	28 (30)	32 (16)	41 (17)	57 (20)	73 (24)	239 (21)
Surfactant	9 (60)	67 (71)	160 (77)	173 (73)	207 (71)	193 (63)	809 (70)
Oxygen (36 wk)	8 (53)	48 (51)	102 (49)	107 (45)	103 (36)	91 (30)	459 (40)
Oxygen (d)	72 ± 45	77 ± 33	73 ± 35	63 ± 37	49 ± 34	40 ± 35	56 ± 38
Postnatal steroids	8 (53)	64 (68)	123 (59)	119 (50)	111 (38)	87 (28)	512 (44)
Grade 3–4 IVH/PVL	1 (7)	15 (16)	47 (23)	51 (22)	51 (18)	47 (15)	212 (18)
Retinopathy of prematurity (all grades)	12 (80)	84 (90)	167/202 (83)	177/223 (79)	170/267 (64)	141/281 (50)	751/1081 (70)
SGA status*	11 (73)	32 (34)	31 (15)	38 (16)	44 (15)	54 (18)	210 (18)
Male gender	6 (40)	33 (35)	82 (39)	115 (49)	146 (50)	158 (51)	540 (47)
Hospital days (median/range)	132 (87–188)	119 (76–552)	109 (56–507)	99 (47–651)	84 (17–487)	73 (13–1076)	92 (13–1076)
Multiple births	3 (20)	14 (15)	30 (14)	47 (20)	73 (25)	55 (18)	222 (19)

Data expressed as n (%) or mean ± SD.
* Less than tenth percentile for weight using the growth curves by Alexander et al.[15]

TABLE 3. Neurological and Sensory Findings at 18 Months by Birth Weight Category

Birth Weight Category	401 to 500 g	501 to 600 g	601 to 700 g	701 to 800 g	801 to 900 g	901 to 1000 g	Total
Normal neurologic examination	8/14 (57)	67/94 (71)	142/202 (70)	162/224 (72)	213/272 (79)	233/295 (79)	825/101 (75)
CP	4 (29)	16 (17)	42 (21)	38 (17)	42 (15)	45 (15)	187 (17)
Seizure disorder	0 (0)	4 (4)	10 (5)	13 (6)	16 (6)	14 (5)	57 (5)
Hydrocephalus with shunt	0 (0)	2 (2)	8 (4)	10 (4)	11 (4)	11 (4)	42 (4)
Any vision impairment	3/14 (21)	9/93 (10)	25/203 (12)	30/226 (13)	13/273 (5)	14/289 (5)	94/1098 (9)
Unilateral blindness	1 (7)	2 (2)	3 (1)	6 (3)	2 (7)	1 (0.4)	15 (1)
Bilateral blindness	2 (14)	1 (1)	8 (4)	5 (2)	2 (0.7)	3 (1)	21 (2)
Hearing impairment	1/14 (7)	10/90 (11)	27/199 (14)	20/227 (9)	24/270 (9)	20/290 (7)	112/1091 (11)
Wears hearing aids	0 (0)	3 (3)	13 (7)	9 (4)	8 (3)	5 (2)	38 (3)

Data expressed as *n* (%).

TABLE 4. Functional Status by Birth Weight Category

Weight Category	401 to 500 g	501 to 600 g	601 to 700 g	701 to 800 g	801 to 900 g	901 to 1000 g	Total
n	14	94	205	227	276	295	1111
Normal head control	12 (86)	88 (94)	197 (96)	214 (94)	261 (95)	277 (94)	1049 (94)
Sits unsupported	13 (93)	86 (91)	195 (95)	211 (93)	257 (93)	273 (93)	1035 (93)
Sits well alone	9 (64)	82 (87)	171 (83)	195 (86)	234 (85)	260 (88)	951 (86)
Sits unsupported/less secure	4 (29)	4 (4)	24 (12)	16 (7)	23 (8)	13 (4)	84 (8)
Walks	11 (79)	74 (79)	165 (81)	186 (82)	227 (83)	252 (85)	915 (83)
Walks fluently	8 (57)	60 (64)	131 (64)	149 (66)	197 (72)	231 (78)	776 (70)
Walks functional/nonfluent	3 (21)	14 (15)	34 (17)	37 (16)	30 (11)	21 (7)	139 (13)
Normal upper limb function	9 (64)	84 (89)	174 (85)	192 (85)	234 (86)	263 (89)	956 (86)
Bilateral pincer grasp	9 (64)	81 (87)	169 (84)	194 (86)	233 (85)	251 (87)	943 (86)
Independently feeds self	10 (67)	70 (74)	154 (74)	191 (84)	232 (81)	260 (85)	917 (80)

Data expressed as *n* (%).

months of age, including the ability to maintain head control, sit, walk, use a pincer grasp, and feed independently. Lack of head control at 18 to 22 months of age represents severe motor impairment; overall, only 6% of infants had not achieved normal head control, and 7% were unable to sit without support. Infants <500 g were more likely to have abnormal head control (14%) and less secure sitting (29%). Fluent walking and independent eating skills were related to birth weight: 57% of infants 401 to 500 g, 64% of infants 501 to 700 g, 66% to 72% of infants 701 to 900 g, and 78% of infants 901 to 1000 g walked fluently. Eighty-six percent of the cohort had a pincer grasp and 80% fed themselves at 18 to 22 months of age. However, only 64% of infants 401 to 500 g had a pincer grasp, compared with 84% to 87% of infants in all other birth weight groups.

Bayley mental and motor test scores are shown in Table 5. Children were tested at a chronologic age of 22.7 ± 1.5 months (mean ± 1 SD) and a corrected age of 19.5 ± 1.5 months. Mean mental development index, Bayley II (MDI) was 76 ± 17 and psychomotor development index, Bayley II (PDI) was 78 ± 18. Overall, 37% of children had a Bayley MDI <70 and 29% had a PDI <85 (1 SD below the mean); 66% of the cohort had a Bayley MDI <85 and 57% had a PDI <85 (1 SD below the mean). There was a trend for more infants in the lower birth weight categories to have a MDI or PDI <70. Although infants in the lowest birth weight group had an MDI of 78.3 ± 20.4, this was based on a sample of only 13 infants whose mothers had a history of higher education than mothers in the other groups (86.6% vs 71.4% had more than a high school education).

The relationship between Bayley scores and neurologic status was also evaluated. Sixty-nine percent of children with an abnormal neurologic examination had an MDI >2 SD below the norm (<70),

TABLE 5. Bayley II MDI and PDI at 18 to 22 Months' Corrected Age in ELBW Infants

Weight	<500 g	501 to 600 g	601 to 700 g	701 to 800 g	801 to 900 g	901 to 1000 g	Total
Chronologic age (mo)	23.0 ± 2.6	22.9 ± 1.4	22.9 ± 1.4	22.7 ± 1.6	22.8 ± 1.6	22.5 ± 1.5	22.7 ± 1.5
Range	21–31	20–27	20–27	20–28	20–31	20–27	20–31
Corrected age* (mo)	19.3 ± 2.9	19.4 ± 1.4	19.4 ± 1.4	19.5 ± 1.4	19.7 ± 1.5	19.5 ± 1.4	19.5 ± 1.5
Range	18–28	18–23	18–23	18–25	18–24	18–23	18–28
Bayley MDI	78.3 ± 20.4	72.5 ± 16.5	74.3 ± 16.4	74.2 ± 17.0	76.6 ± 16.6	79.4 ± 18.1	76.1 ± 17.2
<85	6/13 (46)	65/93 (70)	139/192 (72)	147/216 (68)	176/264 (67)	163/279 (58)	696/1056 (66)
<70	4/13 (31)	42/93 (45)	78/192 (41)	90/215 (42)	92/264 (35)	86/279 (31)	392/1056 (37)
Bayley PDI	77.3 ± 22.2	75.2 ± 18.7	75.8 ± 18.7	76.8 ± 18.4	79.7 ± 18.0	80.1 ± 17.5	78.1 ± 18.3
<85	7/14 (50)	60/93 (65)	117/190 (62)	127/213 (50)	134/257 (52)	146/275 (53)	591/1042 (57)
<70	5/14 (36)	32/93 (34)	67/190 (35)	65/213 (31)	65/213 (25)	63/275 (25)	297/1042 (29)

Data expressed as mean ± SD or *n* (%).
* Corrected age—22 children were tested after 22 months, 16 at 23 months, 4 at 24 months, 1 at 25 months, and 1 at 28 months. All Bayley scores are age-adjusted.

compared with 26% of children with a normal examination; 73% of the children with abnormal examinations had a PDI >2 SD below the norm, compared with 14% of children with a normal neurologic examination. Severe mental and motor retardation (Bayley scores <50) were present in 35% and 46% of children with abnormal neurologic examinations, respectively, compared with 2% and 3% of children classified as neurologically normal ($P < .0001$). The presence of 1 or more major neurodevelopmental abnormalities, including an abnormal neurologic examination, blindness, deafness, MDI <70, or PDI <70, was identified in 553 of 1122 (49%) of the children.

Logistic regression models estimated the relationships between risk factors and outcomes (CP, Bayley scores <70, independent walking, and independent feeding). Risk factors associated with an abnormal neurologic examination were: grades 3 to 4 IVH/PVL (OR: 3.14; CI: 2.17–4.57), CLD (OR: 1.84; CI: 1.28–2.61), steroids for CLD (OR: 1.89; CI: 1.31–2.75), and necrotizing entercolitis (NEC; OR: 2.36; CI: 1.30–4.22). Significant risk factors for CP were limited to grades 3 to 4 IVH/PVL (OR: 3.05; CI: 2.03–4.57), NEC (OR: 2.01; CI: 1.05–3.73), and surfactant (OR: 1.85; CI: 1.41–3.12). Risk factors associated with MDI <70 and PDI <70 are shown in Figs 1 and 2. Grades 3 to 4 IVH/PVL, CLD, postnatal steroids, less than a high school education, and male gender were all associated with an increased risk for MDI <70. White race and increasing birth weight were associated with decreased risk for MDI <70. Grades 3 to 4 IVH/PVL, CLD, postnatal steroids for CLD, and NEC were also associated with PDI <70. Increasing adjusted age at evaluation was protective. Analyses of the relationship between postnatal steroids and CLD revealed that infants who received postnatal steroids were significantly more likely to be on oxygen at 36 weeks' of age and at discharge. The effects of steroids for a PDI <70 remained, however, after controlling for CLD.

Regression models for 2 important functional skills (independent walking and independent feeding) are shown in Figs 3 and 4. Grades 3 to 4 IVH/PVL, CLD, and postnatal steroids were associated with an increased risk for no independent walking. Grades 3 to 4 IVH/PVL and CLD were also risk factors for no independent feeding, but higher corrected age at time of evaluation was protective.

DISCUSSION

This is the first multicenter, prospective report of outcome at 18 to 22 months' corrected age in a large cohort of ELBW infants born in the 1990s. The large sample provides sufficient numbers to report outcome of the cohort by 100-g birth weight subgroups and to adjust for multiple risk factors for adverse outcome. Only the 401- to 500-g subgroup is too small to be representative. The data were collected at 12 centers across the United States, representing a spectrum of social and demographic characteristics. Fifty-one percent of the cohort had a normal neurodevelopmental and sensory assessment. The probability of being classified as abnormal neurologically increased steadily as birth weight decreased.

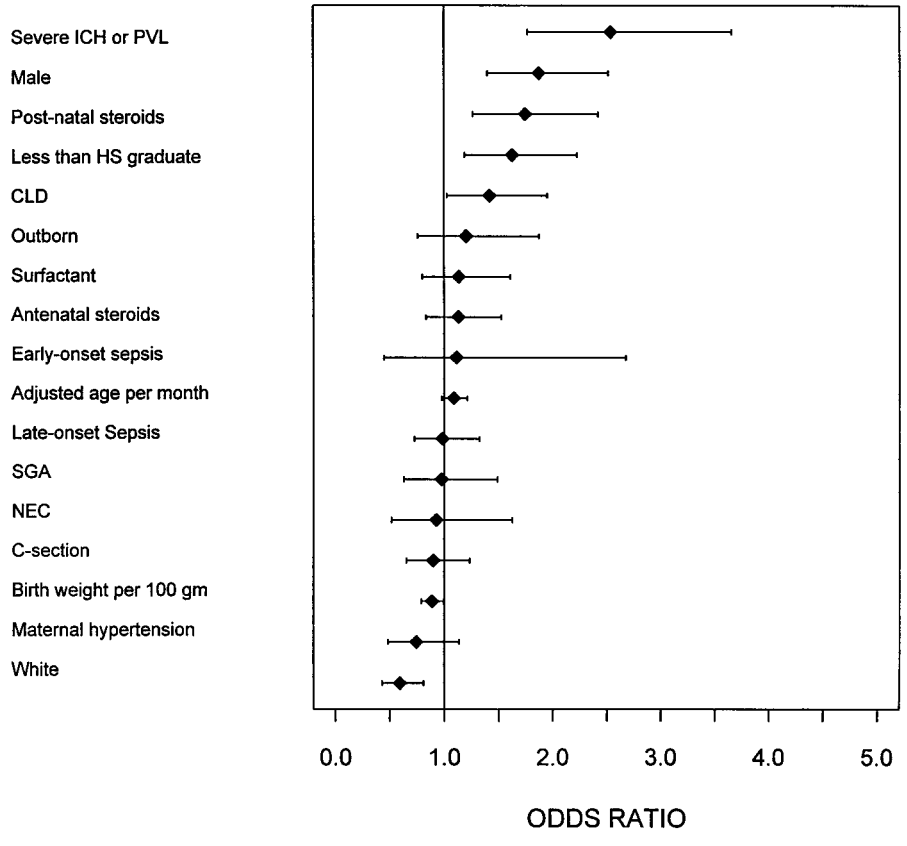

Fig 1. Adjusted risk factors for MDI <70 (ORs and 95% CIs): NICHD Neonatal Research Network. Antenatal steroids indicates β-methasone (2 doses, 12 or 24 hours apart) or dexamthasone (4 doses, 6 hours apart); surfactant, any surfactant preparation given at location (delivery room, neonatal intensive care unit, or referring hospital); early-onset sepsis, positive blood culture result within the first 72 hours; late-onset sepsis, positive blood culture result >72 hours obtained in the presence of clinical signs of septicemia; postnatal steroids, any doses or courses of steroids for CLD.

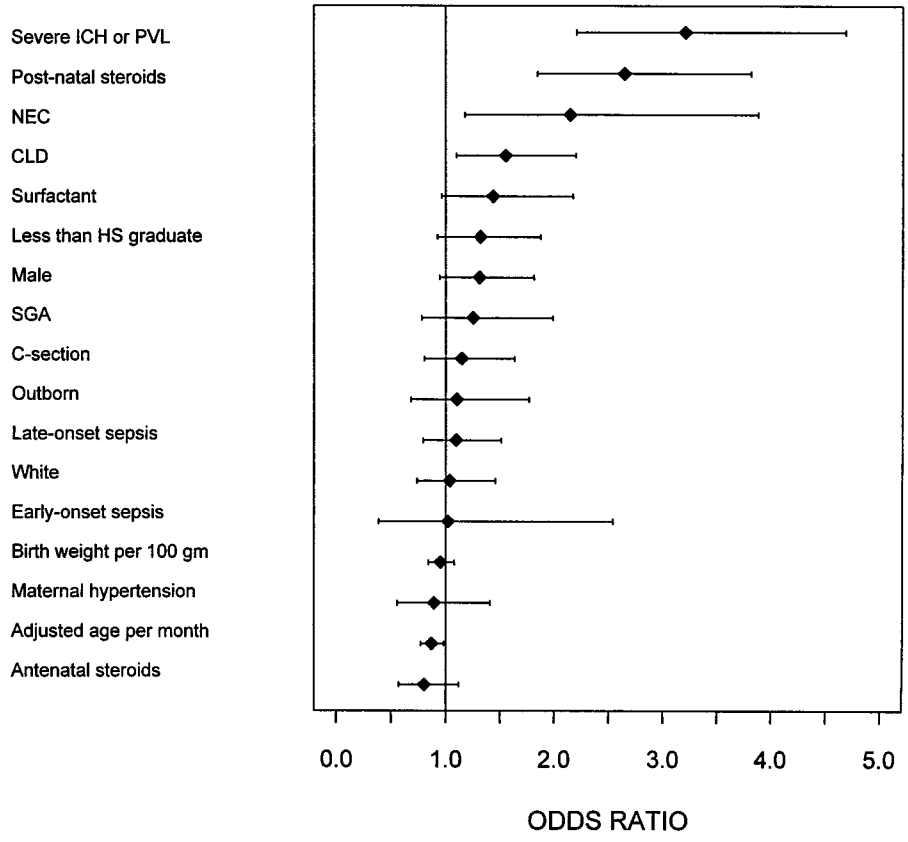

Fig 2. Adjusted risk factors for PDI <70 (ORs and 95% CIs): NICHD Neonatal Research Network.

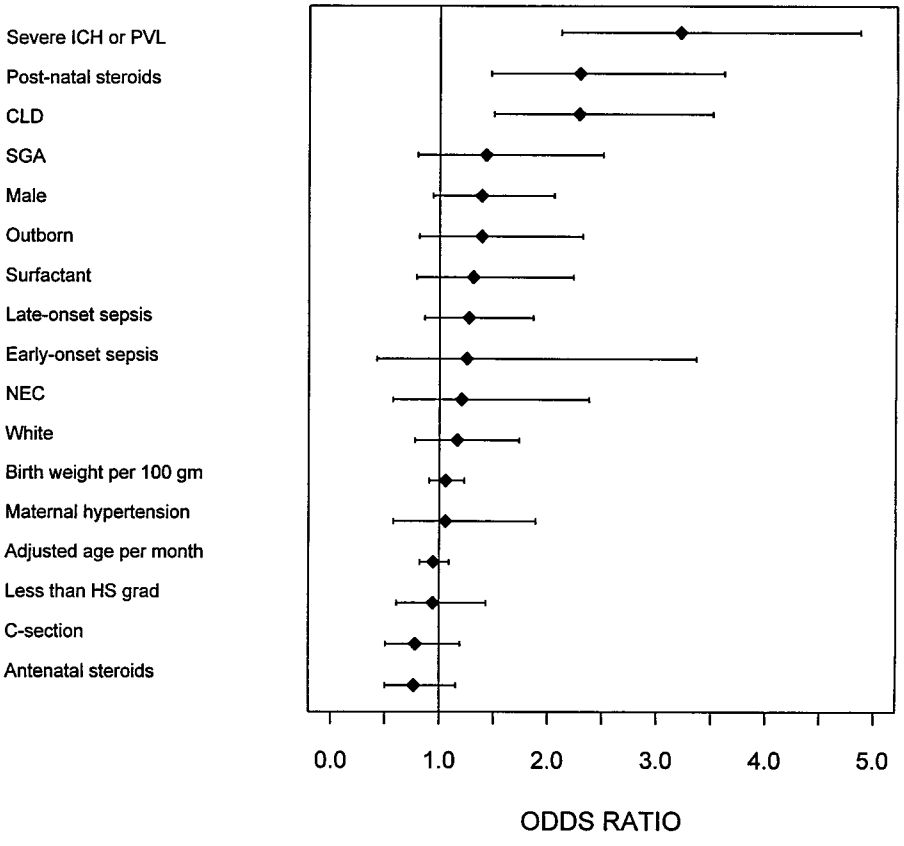

Fig 3. Adjusted risk factors for no independent walking (ORs and 95% CIs): NICHD Neonatal Research Network.

Whereas 25% of infants with birth weights of 901 to 1000 g had abnormal neurologic findings, this increased to 43% of infants 401 to 500 g. A specific diagnosis of CP based on the strict study criteria was made in 17% of the infants (range: 15% for infants 801–1000 g to 29% for infants 401–500 g). This inci-

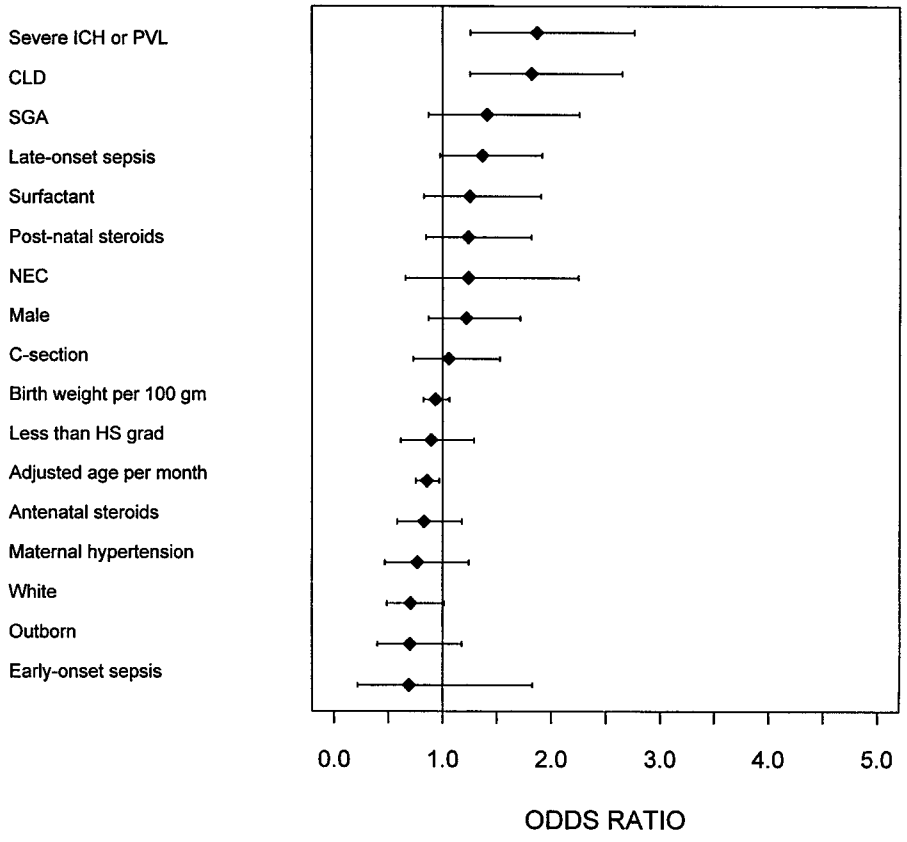

Fig 4. Adjusted risk factors for no independent feedings (ORs and 95% CIs): NICHD Neonatal Research Network.

dence of CP at 18 to 22 months' corrected age is somewhat higher than previous reports (range: 7%–14.8%) of ELBW infants.[16–21] The incidence is similar, however, to the Emsley et al[22] report of infants born at 23 to 25 weeks during 2 periods (1984–1989 and 1990–1994). They found the rate of disability increased from 38% to 68% and blindness increased from 4% to 18%, whereas the CP rate remained relatively stable at 21% and 18%. Disability in their study, however, also included mild findings, such as myopia and strabismus. The NICHD cohort had a mean gestational age of 26 weeks and was born in 1993 and 1994; therefore, they are reasonably comparable in time and gestation to the second period of Emsley et al. The incidence of significant vision impairment (3% blind) and hearing impairment requiring aids (3%) is consistent with other recent reports of ELBW infants,[16,21] although earlier reports often identified greater numbers of visually impaired infants.[6,19] This low incidence of blind infants in our study may be attributed to aggressive ophthalmologic monitoring and management within the neonatal units in the 1990s.

Developmental test scores obtained with the new Bayley II[14] resulted in lower scores than previously reported from these units with the Bayley I. The Bayley II, which is based on new standardization data, was published in 1992. The restandardization was initiated because of evidence of an upward drift[23] in the mean scores on the old Bayley I.[24] The mean scores of the Bayley II MDI and PDI are 12 and 15 points lower, respectively, than the corresponding Bayley I score: the Bayley II mean MDI of 76 is equivalent to a Bayley I MDI of 88 and the Bayley II PDI score of 78 becomes a 93 on Bayley I. This may be a partial explanation for the low test scores reported in this study relative to studies published before 1992, in which the developmental outcomes were overestimated by the Bayley I.

The scores reported in this study are representative of 18 month performance of ELBW infants born in the 1990s. In the current study, 37% of the cohort had a Bayley II MDI more than 2 SD below the mean and 29% had a Bayley II PDI more than 2 SD below the mean (significant cognitive or motor delay). If milder developmental delay (1 SD below the mean) is used, then 66% and 57% of the children are at potential risk of developmental or motor morbidities. As in the functional outcomes, there was a trend for infants of lower birth weights to have lower test scores. An exception was the small subgroup of 14 infants <500 g. Since the subgroup was small and 2 infants in the group were not tested, their mean score may not be representative of infants <500 g. Very little data have been reported on these tiny infants. Most previous studies have reported 20–26% of ELBW infants with Bayley scores <70. Most of these studies, however, report on a total population of infants <1000 g or <1250 g and not on subgroups.[6,19,21] Ment et al[21] reported a rate of 26% for infants <1250 gms. Piecuch et al[25] reported 18-month Bayley outcomes of children born at 24, 25, and 26 weeks' gestation between 1990 and 1994. Forty-two percent of children were administered the Bayley I

and 58% the Bayley II. Scores >2 SD below the mean were identified in 39% of 24-week children, 30% of 25-week children, and 11% of 26-week children. The results support our findings that the lower gestation ELBW children are at increased risk of significant cognitive deficit. The percentage of MDI scores >2 SD below the mean, however, remains higher in our study. Although the low scores at 18 to 22 months' corrected age in our study sample raise great concern, it is unclear whether some of these ELBW infants are still in a catch-up phase or whether they will be destined to long-term learning and performance challenges. Our multivariate analyses did indicate that older age at testing within the 18- to 22-month window was associated with a higher PDI, suggesting motor catch-up is in progress. Assessments at 3 to 7 years of age are required to address this question. Studies in the 1990s reported that ELBW infants followed to school age are at significantly increased risk of academic difficulties, with 45% to 50% receiving resource or special education support services.[26–33]

Functional assessment of daily living skills, including lower extremity mobility (walking) and upper extremity function (pincer grasp and feeding abilities), were also assessed. Overall, 70% of ELBW toddlers were walking fluently, 86% had a pincer grasp, and 80% were feeding independently. In comparison, term children consistently achieve inferior and superior pincer grasp at 9 to 12 months of age, independent walking at 12 to 18 months of age, and independent feeding at 15 to 18 months of age. As with the Bayley, there were similar trends for lower birth weight infants to have less functional skill development. Among 14 infants <500 g, only 57% were walking fluently, 64% had a pincer grasp, and 67% were able to feed independently. Others have shown that functional skills may be delayed in preterm infants.[34] For the total cohort, another 13% of infants had walking skills that were rated as less than fluent. Many of these infants were expected to be walking more fluently within a few months of the study assessment. The data of Msall et al[35] on functional assessments of VLBW infants at 4.5 years of age using the WeeFIM System data suggest that catch-up is still occurring for VLBW infants at 18 months' corrected age.

Although most of the predictors of poor outcomes in the current study were anticipated, the data are unique because they assess the relative impact of multiple risk and protective factors for ELBW infants cared for with current management strategies. Lower birth weight, grades 3 to 4 IVH/PVL,[20,35,37] and CLD[38,40] were all associated with increased morbidity among the ELBW survivors. In addition, steroid treatment for CLD was significantly associated with abnormal neurologic status, Bayley PDI <70, Bayley MDI <70, and no independent walking. Previous studies[40–47] of the use of postnatal dexamethasone for CLD have reported mixed findings. In the randomized, double-masked, controlled trial by Yeh et al,[40,44] early steroid therapy was associated with increased mortality and a significantly higher incidence of neurodevelopmental dysfunction at 2 years' corrected age. In the current study, use of postnatal steroids was associated with prolonged oxygen therapy, suggesting those infants had more severe CLD. The association with poor outcome, however, persisted after adjusting for CLD. It is of interest that although postnatal steroid therapy was a risk factor for an abnormal neurologic examination, it was not an independent risk factor for CP, indicating other factors (ie, IVH/PVL and CLD) are more directly associated. Eight percent of children had other neurologic findings, such as hypotonia, which are known to be associated with CLD and can affect the neurologic examination and motor performance. The mechanism by which postnatal steroids affect neurodevelopment remains unclear. Animal models[46,47] suggest a direct toxic effect; further investigation in the form of prospective clinical trials to test the relative benefits and risks of postnatal steroids are indicated. Surfactant was identified as a risk factor for CP even after adjusting for birth weight and multiple other risk factors. Because the administration of surfactant is based on clinical judgment, and surfactant is given to sicker infants, we speculate that surfactant administration may be a marker for illness severity in the first hours of life.

Another risk factor associated with both an abnormal neurological examination and a low Bayley PDI was NEC. Although the pathophysiology of NEC is not clearly understood, the histologic appearance of the disease includes coagulation necrosis suggesting that ischemic events play a role.[48] It has been suggested that inflammatory mediators associated with bacterial invasion lead to vasoconstriction and hypoxic ischemic events. The associations among NEC, illness severity,[49] infection, surgical intervention, and outcome require further investigation.

Male gender also significantly increased the risk for an MDI <70. Msall et al[50] have previously reported that male gender was a predictor of disability in infants <28 weeks' gestation. Significant protective factors included higher birth weight (MDI), white race (MDI), and higher maternal education (MDI). This is consistent with previous reports showing that social and environmental factors impact on outcome.[51–53] This study demonstrated that a higher level of maternal education had a positive association with Bayley MDI scores as early as 18 to 22 months' of age. The positive effects of white race are also likely secondary to the strong linkage between poverty and black race in the United States.

Because of the known positive effects on survival and pulmonary maturation, we had speculated that prenatal steroid therapy would be associated with better neurodevelopmental outcome. Although prenatal steroid therapy was initially associated with a positive benefit on walking and the presence of a pincer grasp, the adjusted ORs after all risk factors were entered into the model were not statistically significant. Only 38% of the cohort, however, received prenatal steroids. Further prospective evaluation of the long-term effects of prenatal steroids is needed. Finally, although maternal hypertension had previously been shown to have both positive and negative effects on outcome, we identified no clear

association with our outcomes. A known maternal risk factor[54–56] for poor neurodevelopmental outcomes that was not investigated in this study was maternal alcohol and substance abuse. Although the maternal population in this report is at high social risk (65% Medicare and 28% less than a high school graduate), it is difficult and costly to obtain accurate information, and a decision was made a priori not to collect this data. We did, however, include maternal education and race in the logistic regression models. Another risk factor of interest is the 19% incidence of multiples (17% twins and 2% triplets or greater).[57] It is well-known that the incidence of multiples resulting from assisted reproductive technology is increasing[58,59] and that increased short-term and long-term morbidities are associated with higher order multiples.[58,59] The percentage of higher order multiples in the current study was relative low (2%) and may be secondary to current efforts to limit the number of embryos transferred.

The 49% incidence of abnormal neurodevelopmental and/or sensory findings at 18 to 22 months of age supports the need for referral of all ELBW infants for early intervention services. The children at greatest risk for significant delay (MDI or PDI <70) were those with abnormal neurologic examinations.

Although our cohort of 1151 ELBW survivors from 12 tertiary centers is the largest current cohort with comprehensive neurodevelopmental data at 18 months of age, we note that the dataset has limitations secondary to the short duration of follow-up and the 78% follow-up rate. Follow-up to school age, although expensive and fraught with the challenges of long-term tracking of families, would provide additional information on both utilization of special education resources and academic success. In addition, Tin et al[57] identified an increased disability rate among noncompliant families who do not return for follow-up clinic visits, suggesting that the actual morbidity rate may be even higher than our report suggests. However, Tin et al[57] included in his definition of disability all children who died before their second birthday, eg, disabled was defined as death or disability. Most reports in the US literature separate death and disability. Examination of the characteristics of families lost to follow-up in a US population, however, deserves further evaluation. Although we agree that to achieve close to 100% follow-up would eliminate any possible bias of outcome interpretation, this goal remains difficult to achieve.

CONCLUSION

In summary, as increasing numbers of ELBW infants at the limits of viability survive,[56] health care providers must remain cognizant of their increased risk of neurologic, sensory, developmental, and functional morbidity. The neurodevelopment of all ELBW infants must be monitored after discharge to ensure that families receive appropriate support and intervention services to optimize outcome potential.[55]

APPENDIX

NICHD Neonatal Research Network
Betty R. Vohr, MD, Follow-up Study Chair Person
Alan Jobe, MD, Neonatal Network Chair Person
Case Western Reserve University (Grant U10 HD21364)
Maureen Hack, MD
Harriet Friedman, MA**
Bonnie Siner, RN
University of Cincinnati (Grant U10 HD27853)
Jean J. Steichen, MD*
Edward F. Donovan, MD
Tari Gratton, RN**
Emory University (Grant U10 HD27851)
Neal P. Simon, MD*
Barbara J. Stoll, MD
Ellen Hale, RN
George Washington University
Biostatistics Center (Grant U01 HD19897)
Joel Verter, PhD*
Lisa Mele, MS
Indiana University (Grant U10 HD27856)
Anna M. Dusick, MD*
James A. Lemons, MD
Julie Ahlrichs, RN
University of Miami (Grant U10 HD21397)
Charles R. Bauer, MD*
Wendy Griffin, RN
National Institute of Child Health and Human Development
Linda L. Wright, MD*
Sumner J. Yaffe, MD
Elizabeth M. McClure, MEd
University of New Mexico (Grant U10 HD27881)
Lu-Ann Papile, MD*
Jean Lowe, PhD**
Barbara Woodward, MPH, OTR/L
Stanford University (Grant U10 HD27880)
Barry E. Fleisher, MD*
David K. Stevenson, MD
M. Bethany Ball
University of Tennessee at Memphis (Grant U10 HD21415)
Kimberly A. Yolton, PhD*
Sheldon B. Korones, MD
Henrietta Bada, MD
University of Texas Southwestern Medical Center at Dallas (Grant U10 HD21373)
Sue Broyles, MD*
Jon T. Tyson, MD
Jackie Hickman, RN
Wayne State University (Grant U10 HD21385)
Virginia Delaney-Black, MD*
Seetha Shankaran, MD
Debra Driscoll, RN
Women and Infants Hospital (Grant U10 HD27904)
Betty R. Vohr, MD*
William Oh, MD
Terri Leach, MEd**
Yale University (Grant U10 HD27871)
Richard A. Ehrenkranz, MD
Linda Mayes, MD
Elaine Sherwonit, MSN, CPNP

* Follow-up study principal investigator.
** Gold standard certified Bayley examiner.

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BEAUTY IS IN THE EARS OF THE BEHOLDER

A woman in the throes of labor overheard what struck her as the most beautiful word in the English language, and named her newborn daughter "Meconium."

Pinker S. *Words and Rules.* New York, NY: Basic Books; 1999

Submitted by Student

Neurodevelopmental and Functional Outcomes of Extremely Low Birth Weight Infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994

Betty R. Vohr, Linda L. Wright, Anna M. Dusick, Lisa Mele, Joel Verter, Jean J. Steichen, Neal P. Simon, Dee C. Wilson, Sue Broyles, Charles R. Bauer, Virginia Delaney-Black, Kimberly A. Yolton, Barry E. Fleisher, Lu-Ann Papile and Michael D. Kaplan

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