Neurodevelopmental Outcome of the Premature Infant

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- Prematurity • Outcomes • Neurodevelopment • ELBW
- Late preterm

Advances in antenatal medicine and neonatal intensive care, including more aggressive delivery room resuscitation, surfactant use, antenatal corticosteroid utilization, improved ventilatory techniques, and nutritional management have successfully resulted in improved survival rates of preterm infants.[1–11] These improvements have been most dramatic in infants born extremely low birth weight (ELBW, ≤1000 g) and at the limits of viability (22 to 25 weeks).[1–3,5–8] But improvements in survival have not been accompanied by proportional reductions in the incidence of disability in this population.[2,4–7,9–15] Thus, survival is not an adequate measure of success in these infants who remain at high risk for neurodevelopmental and behavioral morbidities. The primary outcome of most neonatal clinical trials is long-term neurodevelopmental outcome.[16] Numerous authors have reported on the developmental outcomes of ELBW infants in infancy and early childhood[2,4–7,9–15,17–21] and there is now increasing evidence of sustained adverse outcomes into school age and adolescence,[22–49] not only for ELBW infants but for infants born late preterm.

EXTREMELY LOW BIRTH WEIGHT AND VERY LOW BIRTH WEIGHT INFANT SURVIVAL RATES

Survival rates for very low birth weight (VLBW; ≤1500 g) and ELBW infants consistently improved during the 1980s and 1990s.[1–4,6,9–11] The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported an improvement in the survival of all VLBW infants from 77% in 1987/1988 to 86% in 1999/2000 in their multicenter network.[1] ELBW infants in the NICHD had similar improvements in survival from 37% in 1991 to 1994 to 43% in 1995 to 1998,[3] and in a single-center report from 49% in 1982 to 1989 to 67% in 1990 to 1998.[4,12] In the early 2000s survival rates have stabilized at approximately 85% for VLBW and 70% for ELBW infants.[12,50]

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Survival remains directly proportional to gestational age and birth weight.[1,2,8,10,11,19,50–54] Although most early follow-up studies reported the outcomes of low birth weight infants weighing less than 2500 g, the improvement in survival has shifted the focus to VLBW infants weighing less than 1500 g, ELBW infants weighing less than 1000 g, and micropremies weighing less than 750 g. From 1987/1988 to 1999/2000, survival of infants weighing 500 to 750 g improved from 44% to 65%; for infants weighing 751 to 1000 g survival improved from 66% to 88%; and for 1001- to 1500-g infants from 87% to 93%, in the NICHD Neonatal Research Network.[1,8] Single centers have reported similar trends. One center reported improved survival of infants born weighing 500 to 749 g from 27% (1982 to 1989) to 48% (1990 to 1998) and infants born weighing 750 to 999 g from 66% to 85%.[4] Another center saw improvements from presurfactant use (1979 to 1985) to universal surfactant use (1989 to 1991) for all ELBW infants proportional to birth weight (500 to 599 g: 26% to 38%, 600 to 699 g: 23% to 62%, 700 to 799 g: 47% to 75%, 800 to 899 g: 63% to 82%, and 900 to 999 g: 83% to 87%). Again, survival rates have stabilized in the early 2000s, and remain directly proportional to gestational age. In a more recent NICHD report, these rates were 55% for 501- to 750-g infants, 88% for 751- to 1000-g infants, 94% for 1001- to 1250-g infants, and 96% for 1251- to 1500-g infants born 1997 to 2002.[50]

As the methodology for assessing gestational age has improved, there have been an increasing number of reports evaluating the effects of prematurity, rather than low birth weight. Preterm is defined as less than 37 weeks', very preterm is less than 32 weeks', and extremely preterm is defined as less than 28 weeks' gestation. Survival has continued to improve for even the tiniest preterm infants born at the limits of viability (22 to 25 weeks, < 800 g).[1,2,5,6] Emsley and colleagues[5] reported an increase in survival of 23- to 25-week infants from 27% (1984 to 1989) to 42% (1990 to 1994). O'Shea and colleagues[6] reported survival at 501 to 800 g improved from 20% (1979 to 1984) to 36% (1984 to 1989) to 59% (1989 to 1994) over a similar time period. In the NICHD Neonatal Research Network from 1987/1988 to 1999/2000, survival at 23 weeks improved from 23% to 30%, at 24 weeks from 34% to 59%, and at 25 weeks from 54% to 70%. For infants born weighing 501 to 600 g, survival increased from 21% to 39%; 601 to 700 g from 33% to 59%; and 701 to 800 g from 53% to 77%.[1] These survival rates vary worldwide, according to reviews of the world literature in 2000 by Hack and Fanaroff[2] and by Lorenz and colleagues.[7] Hack and Fanaroff report a range of survival at 23 weeks from 2% to 35%, at 24 weeks from 17% to 62%, and at 25 weeks from 35% to 72%; survival by birth weight varied similarly, with survival at less than 500 g ranging from 4% to 38%, 500 to 599 g from 4% to 38%, and at 600 to 699 g from 27% to 63%.[2] Lorenz and colleagues[7] reported ranges of survival by gestational age less than 26 weeks (14% to 76%) and birth weight less than 800 g (4% to 81%). Factors related to the variability in survival rates include differences in reporting (inclusion/exclusion of fetal deaths, survival to discharge home versus inclusion of postdischarge deaths), and differences in aggressiveness of antenatal and neonatal management (antenatal steroid use, cesarean section rates, delivery room resuscitation).[2] Survival rates are also consistently higher in girls than boys.[1,2,9,50,51,53] But these documented improvements in survival of VLBW and ELBW infants over the past 20 years have not been accompanied by proportional reductions in the incidence of disability in this population.[2,4–7,9–15]

NEURODEVELOPMENTAL OUTCOME

It has been almost universally accepted that neurodevelopmental outcome after preterm birth is the most important measure of neonatal ICU (NICU) success. Most large clinical trials in the field of neonatology now include a measure of neurodevelopmental outcome. But no one optimal age of assessment has been agreed on. Because of the administrative challenges of long-term follow-up including cost, tracking, and feasibility, most authors have published data on shorter long-term outcomes (18 to 22 months corrected age). But there is now increasing evidence of adverse outcomes into school age and adolescence.[22–49]

NEURODEVELOPMENTAL IMPAIRMENT

Most published reports of neurodevelopmental outcome in infancy focus primarily on the incidence of severe disability, often defined as mental retardation, cerebral palsy, epilepsy, blindness, and/or moderate to severe hearing impairment.[2] This has historically been the neurodevelopmental outcome of interest owing to the severity of the developmental impact of these severe and often combined morbidities. Unlike mortality rates, the incidence of these moderate to severe disabilities has not changed significantly over the past 20 years.[2,4–7,9–15] Rates are highest in ELBW populations, and like mortality rates, rates of disability generally increase with decreasing gestational age and birth weight.[2,4–6,15,17,20] Hack and Fanaroff[2] report worldwide rates of severe disability in infants of 23 to 25 weeks' gestation of 34%, with rates at 24 weeks ranging from 22% to 45%, rates at 25 weeks ranging from 12% to 35%, and rates in infants born of less than 800-g birthweight of 9% to 37%. Lorenz and colleagues'[7] rates were slightly lower, with 22% disability at less than 26 weeks and 24% at less than 800 g. Factors related to the variability in reported rates of disability include variable rates of survival and neonatal complications, socioeconomic status of the population reported on, reporting on chronologic versus corrected age, variability in the definition of disability or in its clinical diagnosis, the child's age at follow-up, and variability in follow-up rates.

In the NICHD Neonatal Research Network, rates of neurodevelopmental impairment (NDI) (defined as the presence of any of the following: moderate to severe cerebral palsy, cognitive or motor scores that fall more than 2 standard deviations below the population mean on standardized testing, bilateral hearing impairment requiring amplification or bilateral blindness) in Network Centers in the 1990s ranged from 28% to 40% in infants born at 27 to 32 weeks and 45% to 50% in infants born at 22 to 26 weeks.[15] Only 21% of all ELBW infants had no impairments (no cerebral palsy, normal cognitive and motor scores, no visual or hearing impairment) at 18 months.[13] Regional and local studies in the 1990s report similar wide ranges of major neurodevelopmental impairment rates, from 20% to 48%.[4,6,9,10,12,17,37]

Center variability in outcomes is related to rates of neonatal morbidities such as sepsis, necrotizing enterocolitis, grade 3-4 intraventricular hemorrhage, and bronchopulmonary dysplasia and differences in management style including rates of administration of antenatal steroids, postnatal steroids, antibiotics, cesarean section rate, and use of ventilators.[21,55]

COGNITIVE OUTCOMES

The most common severe impairment seen in VLBW and ELBW infants at 18 and 30 months is cognitive impairment, defined as scores that are more than 2 standard deviations below the mean on standardized cognitive testing. Most follow-up studies of ELBW infants use the Bayley Scales of Infant Development II as the measure of cognitive functioning between 6 months and 3 years.[56] The Bayley has a mean score of 100 with a standard deviation of $\pm$15. Scores of less than 70 (more than 2 standard deviations below the mean) are considered severely impaired. When scoring a preterm infant using this assessment, corrected age (chronologic age − weeks of prematurity) is most often used until 30 months of age. Average score for ELBW infants at 18 to 22 months corrected age in the NICHD is 76[20] but varies from center to center with a range of 70 to 83.[21] Center and regional reports cite higher average MDIs. Wilson-Costello and Hack[4,10,12] report average MDIs of 84 to 86 in their cohort of infants weighing less than 1000 g born from 1982 to 2002 and 83 to 89 in a subset of infants weighing less than 750 g at 20-month follow-up. Wood and colleagues[57] reported similar results at 30 months corrected age in a cohort of 20- to 25-week infants in the United Kingdom whose average MDI was 84.

Like rates of neurodevelopmental impairment, rates of cognitive impairment vary worldwide, and are inversely proportional to gestational age and birth weight. World-wide rates of cognitive impairment throughout childhood range from 14% to 39% at 24 weeks, 10% to 30% at 25 weeks,[2] 4% to 24% at less than 26weeks, and 11% to 18% at less than 29 weeks.[5,14] In infants born weighing less than 800 g, rates of cognitive impairment range from 13% to 50%,[2,6,7,14,19] and at less than 1250 g the rate is 26%.[14] In the NICHD, rates of cognitive impairment are reported at 37% to 47% in 22- to 26-week infants,[13,15] 23% to 30% in 27- to 32-week infants,[15] and 34% to 37% in all infants weighing less than 1000 g.[20,58] Wilson-Costello and Hack[4,10,12] site 20% to 26% rates of cognitive impairment in their cohort of ELBW infants at 18 months. At 30 months corrected age, 30% of Wood and colleagues'[57] cohort had cognitive impairment.

But cognitive functioning in infancy may not be predictive of cognitive functioning later in life. The assessment of an infant's cognitive function is highly dependent on motor, language, and social-emotional development. Thus, cognitive assessment in infancy is not as accurate as cognitive assessment later in life. In fact, Hack and colleagues[30] found that MDI at 20 months corrected age was not predictive of cognitive functioning at 8 years of age in their cohort of 330 ELBW infants. Although mean MDI at 20 months was 76, mean cognitive score at 8 years was 88. Rates of cognitive impairment dropped from 39% at 20 months to 16% at 8 years. The positive predictive value of having a low cognitive score at 8 years (<70) given a low cognitive score at 20 months (<70) was only 0.37. Ment and colleagues[33] had similar findings in a cohort of VLBW infants. Mean expressive language scores increased from 88 at 3 years to 99 at 8 years of age and full-scale IQ increased from 90 to 96.

At school age, cognitive functioning is assessed using a variety of different measures including the Stanford Binet Intelligence Scale–4th edition, the Wechsler Preschool and Primary Scales of Intelligence–3rd edition (WPPSI), the Wechsler Intelligence Scale for Children (WISC-III), the Woodcock-Johnson Psycho-Educational Battery–Revised, the Differential Abilities Scales, the McCarthy Scales of Children's Abilities, the British Abilities Scale, and the Kaufman Assessment Battery of Childhood. Each of these assessments provides an intelligence quotient (IQ) and subtest scores that allow for a limited assessment of specific areas of strengths and weaknesses. These tests, like the Bayley, have a mean of 100 with a standard deviation of 15 in the general population. Mean IQ for VLBW and ELBW infants at school age (5 to 14 years) ranges from 82 to 105.[22–24,26,27,30,33,34,41–43] Although the mean IQ is within the average or low average range for children born ELBW or VLBW, they have significantly lower IQ scores than their normal birth weight peers (0.5 to 1.0 SD lower)[22,23,26,27,31,34,41–43] and significantly higher rates of cognitive impairment.[23–25] Cognitive scores are significantly correlated with gestational age and birth weight.[22,26,28,41] Although environmental factors such as type of health insurance, bilingual household, income level, single parent, teenage mother, and level of maternal education are known to have an impact on intelligence, differences in IQ between preterm and term controls persist after adjustment for these confounders.[59]

Although measures of intelligence in children at school age provide a reliable assessment of general cognitive functioning, they do not identify specific learning disabilities. In addition to impairments in global cognitive functioning, more subtle cognitive impairments are often detected in school age. These higher prevalence, lower severity dysfunctions reportedly occur in 50% to 70% of children born VLBW.[37] Children born VLBW or ELBW have relative impairments of executive functioning,[29,41,60,61] visual-motor skills,[61] and memory,[29,41] especially verbal memory.[32] They score lower on tests of academic achievement,[29,30,42] perceptual-organizational skills,[31,41] visual processing tasks,[31,41] and adaptive functioning[29,41] compared with their normal birth weight peers. Even ELBW infants without neurosensory or cognitive impairment have higher rates of learning disabilities,[26,27] especially in math,[31,41,43,62] ranging from 25% to 40%.[26,31]

Thus, it is not a surprise that ELBW infants have higher rates of academic underachievement and need for special education services.[25,26,34] While ELBW infants have mean scores on formal tests of academic achievement that fall within the normal range (94 to 105), they score lower than normal birth weight peers.[26,34] Teachers of VLBW infants report rates of below average school performance in all academic areas, ranging from 24% to 41%.[25,26,38,42] Approximately 25% of VLBW infants and 25% to 62% of ELBW infants receive special education services.[25,34,35,40,41,45] Between 15% and 34% required grade repetition.[35,36,41,43]

An increasing number of investigators have reported on cognitive and academic abilities of former VLBW and ELBW teenagers and young adults.[24,28,29,32,35,41,61,63] ELBW teens continue to have mean cognitive scores in the average to low average range but persist in having significantly lower cognitive and academic scores than teens born normal birth weight,[44–46] and significantly higher rates of cognitive impairment.[45,46] Cognitive differences are greatest in areas of visual-perceptual tasks.[44] Academic differences are seen in reading and mathematics.[44] As a result, only 56% to 74% of preterm children, significantly fewer than normal birth weight teens, graduate from high school.[45,46] Hack and colleagues'[46] report on a single-center cohort of VLBW infants showed significant gender differences in graduation rates: 66% of VLBW males compared with 75% for term males and 81% for VLBW females compared with 90% for term females.

MOTOR OUTCOMES

Another outcome of major concern is cerebral palsy. Extremely preterm infants are born during a period of active brain development and maturation, placing them at extremely high risk for brain injury from hypoxia, ischemia, undernutrition, and infection, which are associated with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). PVL is injury to the periventricular white matter as a result of hypoperfusion and infarction. It is visualized radiographically as echolucency, echodensity, or cystic degeneration. Although IVH, ventriculomegaly at term, and cystic PVL are all associated with cerebral palsy, cystic PVL is the strongest predictor.[64]

Cerebral palsy is typically defined as a disorder of movement and posture that involves abnormalities in tone, reflexes, coordination and movement, delay in motor milestone achievement, and aberration in primitive reflexes.[64] Rates of cerebral palsy in ELBW vary from 5% to 30%[2,4–7,10,12–15,17–21,23,24,57,64,65] but are most commonly sited at 15% to 23%.[13,15,17,20,23,24,57,64,65] The most common form of cerebral palsy in this population is spastic diplegia, accounting for 40% to 50%

of all cases, followed by spastic quadriplegia, and hemiplegia.[17,57,64] This is not surprising, as PVL lesions involve injury to the white matter that contains the descending motor tracts for the lower extremities. More extensive lesions also involve upper extremity motor tracts.

Arguably more important than the location of impairment is the functional level of the affected infant. Level of gross motor function can be assessed and categorized using Palisano's Gross Motor Function Classification System.[66] This system was developed as a method for assessment of a child's motor function by direct observation of the child's gross motor performance. It describes a child's function, not the fluidity of his or her movements. Palisano's system classifies gross motor function on a 5-point scale. Normal function at 18 to 24 months is defined as Level 0 and involves the ability to walk at least 10 steps independently. An infant at Level 1 can sit with hands free, creep or crawl on hands and knees, pull to stand, and cruise or walk with hands held. Those at Level 2 use their hands for sitting support, creep on their stomach, and may pull to stand; those at Level 3 require external support to sit, roll, and may creep; and those at Level 4 maintain head control in a supported sitting position and can roll prone to supine. Level 5 is the inability to maintain antigravity movements of the head and trunk.[64,66] Although 27% of a cohort of ELBW infants diagnosed with cerebral palsy at 18 to 22 months had moderate to severe gross motor function (Level 3 to 5), 28% had gross motor function consistent with level 0 or 1 and were ambulatory.[64] It is important to remember that a diagnosis of cerebral palsy includes a wide spectrum of motor performance.

Although cerebral palsy is the most well known and potentially most disabling motor abnormality associated with prematurity, infants born preterm often demonstrate less severe differences in their neurologic development. During the first year of life, transient dystonia is a common deviation in the motor development of VLBW infants.[67–69] Transient dystonia was first described in 1972 by Drillien[68] as transient abnormalities on neurologic examination in close to half of all low birth weight infants (<2000 g) in the first year of life. The motor features described included increased extensor tone of the trunk and lower extremities and increased adductor tone in the lower extremities leading to shoulder retraction and hip rotation, persistent primitive reflexes, head lag on pull to sit, and delayed supportive responses. These signs disappear gradually between 8 and 12 months of age in 80% of infants in which they occur. The other 20% often go on to be diagnosed with cerebral palsy. More recently these transient findings have been re-described as occurring in 21% to 36% of preterm infants with a peak incidence at 7 months corrected age.[67,69] The presence of findings consistent with dystonia increases the risk of later cognitive and motor problems including cerebral palsy but have a low specificity, as they are transient in most infants.

At school age, low birth weight infants are more likely to have subtle neurologic impairment than their normal birth weight peers.[61,70] On exam, 10% to 11% of low birth weight infants have neurologic soft signs, a twofold increased risk compared with their normal birth weight peers.[23,71] Soft signs are defined as deviations in speech, balance, coordination, gait, tone, or fine motor or visual motor tasks that do not signify localized brain dysfunction. These soft signs are associated with an increased the risk of subnormal IQ, learning disabilities, attention deficit disorder, and internalizing and externalizing behaviors at 6 and 11 years.[71]

Assessment of motor outcomes should be performed at each follow-up visit with a formal neurologic exam. Many centers use a variation of the Amiel-Tison neurologic assessment.[72] This assessment includes a standardized evaluation of muscle tone, strength, reflexes, joint angles, and posture.

NEUROSENSORY OUTCOMES

Although much less common than cognitive and motor disabilities, rates of neurosensory disabilities are higher in ELBW infants than the general population. Unilateral or bilateral blindness occurs in 1% to 10% of ELBW infants.[2,4,6,7,10,12–15,17,19–21,57] Milder visual impairments including myopia and strabismus occur at rates of 9% to 25%.[5,20,21,57]

Hearing impairment requiring amplification is reported in 1% to 9% of ELBW infants.[2,4,5,10,12–15,17,19–21,57] Milder hearing impairment has been reported in 11% to 13%,[20,57] and when transient conductive or unilateral hearing loss is included, rates of milder impairment are as high as 28%.[21] These rates of neurosensory impairment persist at school age.[23,24,40] with some studies reporting even higher rates of hearing impairment of 14%.[30]

BEHAVIORAL AND PSYCHOLOGICAL SEQUELAE

Evaluations of behavior are routinely obtained in infancy and childhood by parent, teacher, or subject interviews with standardized measures of behavior, attention, adaptive skills, and depression. The Child Behavior Checklist[73] is a questionnaire designed to describe social competencies and emotional/behavioral issues of children and is commonly used in follow-up studies. It has a version for 1.5- to 5-year-olds and a version for ages 4 to 18, which has scores that were derived for withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior, and the presence of any behavior problem. The Conners Rating Scales[74,75] are questionnaires designed for parents or teachers to describe symptoms of inattention, hyperactivity, and oppositionality in school-age children. Multiple different measures of childhood depression exist and have been studied in this population.

VLBW has been associated with a wide variety of behavioral and psychological diagnoses and disabilities. Recent concern has arisen that rates of Autism Spectrum Disorder (ASD) may be higher in ELBW infants than previously thought. Although low birth weight (< 2500 g) may result in a two- to threefold increase in the risk of ASD,[76,77] true risk of ASD in very preterm infants is unknown. Two prior studies have investigated rates of autistic characteristics in children born VLBW (<1500g). Indredavik and colleagues[48] demonstrated a trend toward higher scores on the Autism Spectrum Screening Questionnaire in a population of 56 children at 14 years of age who were born VLBW compared with full-term controls. Limperopoulos and colleagues[78] recently reported 25% of VLBW infants screen positive on the Modified Checklist for Autism in Toddlers (M-CHAT). However, the M-CHAT was developed for use in the general population and not for a high-risk population such as VLBW infants. In addition, no diagnostic confirmation was performed.[78] Further studies are needed to determine the true risk of autism in this population.

At school age (8 to 12 years old), parents and teachers of VLBW/ELBW infants report higher rates of inattention and hyperactivity,[22,25–27,36,39,41,47,48] with rates of 23% to 27% in VLBW and 33% to 37% in ELBW infants.[25,27,47,48] One quarter to one half of VLBW/ELBW infants have symptoms of anxiety and/or social withdrawal,[25,27] and at 12 to 14 years old, 8% to 14% meet criteria for generalized anxiety disorder, compared with 1% to 4% of peers.[47,48] At 12 to 14 years old, 25% to 28% of VLBWs meet criteria for a psychiatric disorder compared with 7% to 10% of peers.[47,48] At 17 and 20 years of age, ELBWs continue to score higher on measures of inattention, anxiety/depression, withdrawn behavior, and social problems.[44,49]

At 14 and 17 years of age, VLBW children score significantly lower on measures of self-esteem.[43,44] They report less confidence in their athletic, school, romantic, and job-related abilities.[44] At the age of 20 years, VLBW adults report lower rates of alcohol and drug use, sexual activity, and pregnancy than adults born normal birth weight.[46,49]

FUNCTIONAL OUTCOMES

A practical and clinically relevant approach to evaluating a child's neurodevelopment is to provide information on functional skills in daily living and health care status. Functional assessment is the process of determining a child's ability to perform the tasks of daily living and to fulfill the social roles expected of a physically and emotionally healthy child of the same age and culture. This includes tasks of feeding, dressing, bathing, maintaining continency, mobility, communication, play, and social interaction. The social roles expected include involvement with peers.

As a result of the high rates of cognitive, motor, neurosensory, and behavioral difficulties seen in children who were born VLBW, even in those without severe impairments, these children have higher rates of functional limitations than children who were born normal birth weight.[40]

Four functional outcome measures are currently available:[79–81] the Pediatric Evaluation of Disability Inventory (PEDI) for children 6 months to 7.5 years;[79] the Functional Independence Measure for Children (WeeFIM)[80,81] for children with and without disabilities through age 8 years; the Vineland Adaptive Behavior Scale (VABS), which measures communication, daily living, socialization, and motor skills in children birth to 18 years;[82] and the Battelle Developmental Inventory for children age 0 to 8 years.[83,84]

Although 93% of ELBW infants achieve sitting balance, 83% walk, and 86% feed themselves independently by 18 to 22 months corrected age, more subtle functional deficits become apparent later in life.[20] At 10 to 14 years of age, 27% of children who were VLBW and 32% of those who were ELBW report restricted physical activity; and 24% of VLBW and 29% of ELBW report they are unable to participate in sports.[40] Functional outcomes are considered particularly important by parents.

FACTORS ASSOCIATED WITH OUTCOME

Recent studies support that a combination of biologic and environmental factors contribute to survival and outcome of preterm infants. Tyson and colleagues[85] evaluated the effects of both low gestational age and gender on outcomes of ELBW infants. In a cohort of 4192 22- to 25-week gestation infants for whom the outcome was known at 18 to 22 months, 73% had died or had NDI. Factors significantly associated with an increased likelihood of a favorable outcome for infants 22- to 25-weeks' gestation who received intensive care were higher gestational age, higher birth weight, female gender, singleton, and antenatal steroids, all factors present at birth.

Multiple birth is an important risk factor for both death and NDI among VLBW infants.[18,86] In a recent NICHD Neonatal Network study, ELBW twins born from 1997 to 2005 were at increased risk of moderate to severe cerebral palsy (8.4% versus 6.3%), MDI less than 70 (39% versus 29.9%), NDI (45.1% versus 36.0%), and death or NDI (64% versus 53%) compared with singletons.[87]

Common neonatal morbidities, including bronchopulmonary dysplasia (BPD), retinopathy of prematurity, necrotizing enterocolitis, and infection, have also been associated with poor cognitive function and academic abilities in infancy and at school age.[55,88–94] Rates of neurodevelopmental impairment at 18 to 22 months corrected age is directly proportional to duration of need for mechanical ventilation in the

NICU.[18,55] BPD has been implicated as a risk factor for cerebral palsy in multiple studies.[91–93] It also has an independent negative effect on motor outcome at 3 years.[88]

Cranial ultrasound abnormalities including severe intraventricular hemorrhage (IVH), hydrocephalus, and periventricular leukomalacia (PVL) are the strongest predictors of cerebral palsy.[91–95] Multiple authors have reported a two- to sixfold increased risk of cerebral palsy associated with grade 3 to 4 IVH,[13,15,19,93,96,97] and a 3- to 10-fold increased risk of cerebral palsy associated with cystic PVL.[13,15,19,97] The presence of hydrocephalus may increase the risk by 12.2 times,[93] and the presence of PVL and hydrocephalus by 15.4 times.[97] According to results from the Indomethacin trial, 60% of ELBW infants with grade 3 to4 IVH had cerebral palsy at 5 years of age and 92% required special services.[98]

Yet ultrasound, although helpful, lacks both sensitivity and specificity. In fact, IVH grade has been shown to account for only 5% of the variance in predicting major handicap.[92] Additionally, 6% to 9% of ELBW infants who demonstrate no abnormalities on cranial ultrasound have cerebral palsy at 18 to 22 months corrected age.[18,99] Recent studies have suggested that MRI may be more predictive of neurodevelopmental outcomes in preterm infants than cranial ultrasound.[100,101] But although MRI identifies more subtle white matter lesions than cranial ultrasound, it remains controversial whether MRI is superior in predicting outcomes.[102–105] In addition, MRI is expensive and less practical, requiring transportation and often sedation of the infant. Thus, more investigation into the identification of those individual infants who will most benefit from intervention services is needed.

LATE PRETERM

Although most neonatal outcomes research has focused on the ELBW infant, more recent studies have brought a long neglected population of infants to our attention, the late preterm population. During the 1990s the rates of delivery at 40 or more weeks' gestation decreased while rates of deliveries between 34 and 36 weeks increased steadily.[106] From 1990 to 2005 the rate of late preterm births increased from 7.3% to 9.1% of all births.[107] Compared with term infants, these late preterm infants have higher mortality rates.[108–110] They also have higher rates of neonatal morbidities such as respiratory distress, temperature instability, hypoglycemia, kernicteris, apnea, seizures, infection, and feeding problems.[107–109,111,112] All of these morbidities have the potential to have long-term neurodevelopmental sequelae. In addition, the brain of the late preterm infant is more immature than the term infant's brain. At 34 weeks there are significantly fewer gyri and sulci, and the brain weighs an estimated 60% of that of a term infant.[111] Although there is a large body of literature that addresses the neurodevelopmental outcome of VLBW and ELBW infants, there is a paucity of information published about the neurodevelopmental sequelae of late preterm birth. Infants born at 34 to 36 weeks are 3.39 times as likely as term infants to develop cerebral palsy and 1.25 times as likely to have cognitive impairment.[113] They are more likely to qualify for special needs preschool and are more likely to have problems with school readiness.[114] In kindergarten and first grade they have lower reading scores, teachers report math skills below those of their full-term peers, and they are more likely to qualify for special education services.[115]

SUMMARY

As more and more preterm infants are born and survive, more is known about their short- and long-term neurodevelopmental outcomes. Infants born preterm are at significantly higher risk for neonatal morbidities and subsequent adverse neurologic, developmental, learning, and behavioral sequelae.

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