Chapter 4. Conclusions

Overall

We reviewed a large multiple of citations (>16,000) and included data from 170 articles in the analysis. Among the final articles abstracted for this review, the quality and methodology were variable, as expected, because we incorporated various study designs to address the key questions. Many of the final articles selected were of good to excellent quality. The study question "VLBW with or without other conditions was associated with disability" was a relevant and important question. However, the original intent of the majority (if not all) of the studies that evaluated the association of prematurity or conditions of prematurity with disability did not specifically address this question in this manner. Disability as defined by the U.S. Congress and interpreted by SSA was not the original intent of the studies reviewed. Despite these issues, the evidence of the articles reviewed overwhelmingly support the fact that VLBW with or without specific conditions was associated with increased risk of long-term disabilities. All of the articles reviewed evaluated disabling outcomes that occur ≥12 months of age and were likely to remain disabling ≥1 year. Unfortunately, most of the impairments were lifelong. The evidence to support the association of VLBW with specific outcomes is noted below.

Neurodevelopmental Disabilities

The evidence identified by our search methods clearly demonstrates that VLBW infants have high rates of neurodevelopmental disabilities, including cognitive (MR), neuromotor (CP), neurosensory (visual and auditory) impairments, and communication (language/speech)/ behavioral disorders compared with normal birth weight controls. The review also found evidence that VLBW infants have increased risk of long-term, clinically significant compromise in growth compared with normal birth weight controls. The evidence illustrates that VLBW infants with BPD have increased risk of significant pulmonary impairment that imposes a respiratory disability for variable lengths of time, especially in children who sustained severe BPD during their early neonatal course. The prevalence and severity of all these disabilities is even higher among ELBW infants.

Co-morbidities of prematurity, such as CNS injury, ROP, auditory/communication disorder, BPD, and feeding problems, individually and collectively play significant roles in subsequent, long-term disabilities. The co-existence of these morbidities is precisely the reason VLBW children have multiple handicaps. But even the presence of one handicap, e.g. visual disability, and/or hearing loss, greatly influences other realms of development and growth, and may lead to additional disabilities in speech and language, behavior problems and learning that affect school performance and limit daily function.

Methodologically sound studies demonstrate that a greater proportion of VLBW and ELBW infants have multiple health problems and increased utilization of health care resources compared to full-term controls. These disabilities result in significant tangible and intangible costs to the individual child, its family, and society.

Robust, well designed, and carefully validated predictive models for MR and CP in VLBW infants, constructed with clinical information available at the time of hospital discharge do not yet exist. The ability to accurately predict neurodevelopmental outcome in the individual neonate on the basis of identifiable risk factors has had limited success. However, large and methodologically sound studies performed in a variety of settings have identified several risk factors that appear to have consistent and independent associations with subsequent abnormal cognitive and neuromotor development. In particular, cerebral white matter damage in the form of cystic PVL, severe (grade III or IV) IVH, and ventriculomegaly are the strongest indicators of risk for CP, neuromotor abnormalities, and MR. Timing of cranial ultrasonography is also critical to maximizing detection of the strongest risk factors. The 40-week adjusted gestational age cranial ultrasound had the highest odds ratio for predicting CP.

Increasing evidence indicates that antenatal events contribute to the etiology and sequence of events leading to neurologic impairment, CP, and MR in VLBW infants. Antenatal inflammation, chorioamnionitis, and fetal hypoxia/acidosis may play important roles by stimulating a fetal inflammatory response that injures the immature cerebral white matter. Other antenatal events such as premature rupture of membranes (which may be related to antenatal inflammation and subclinical infection) and abruption have been identified as antenatal risk factors contributing to an increased risk of CP and/or neurodevelopmental disability in premature infants. The degree of prematurity and CNS injury in conjunction with these antenatal factors appear to influence the development of neurologic disability, including CP and MR.

Many studies strongly implicate BPD as an important contributor to subnormal cognitive and motor performance. BPD frequently co-exists with other disabling conditions commonly seen in VLBW/ ELBW infants, such as cerebral white matter damage and IVH, which impact cognitive and motor outcome. Our methods identified many studies documenting a significant independent relationship between bronchopulmonary dysplasia (BPD) and abnormal cognitive development in both VLBW and ELBW infants. Increasingly, evidence supports the association of postnatal administration of corticosteroids (specifically dexamethasone) for the amelioration or prevention of BPD as a contributor, independent of BPD, to developmental delay and CP.

The relationship between biological/medical risk factors and social/parenting risk factors on subsequent neurodevelopmental outcome is complex. The interaction of these factors may have additive or synergistic positive or negative effects on an infant's outcome. Although biomedical risk factors, such as PVL and ROP, are important determinants of subsequent disability in VLBW infants, it is also clear that social/parenting risk factors are critical, independent influences on the outcome of high-risk VLBW children. Neurologic and cognitive abnormalities are higher in infants with adverse parenting factors (e.g. abuse and/or neglect). The evidence illustrates the vulnerability of high-medical risk VLBW infants to parenting, social, and environmental risk factors. It also underscores the importance of having constructive parenting, social, and environmental milieu for children at increased risk for neurodevelopmental problems related to their biomedical risk of being VLBW.

Other risk factors that appear to have associations with cognitive development include race, gender, socioeconomic status as indicated by markers such as mother's level of education, and illness severity as measured by objective scoring systems. The presence of deficits on physical, neurological, visual, auditory, and developmental examinations at 6 or 12 months may significantly refine assessment of risk for sustained neurodevelopmental abnormality. Knowledge of these risk factors encourages the attempt to develop a predictive model(s) using a large cohort of VLBW infants, followed by validation of the model in an independent group.

Speech and Language

Strong evidence indicates increased risk of speech and language delays in VLBW infants. Factors associated with increasing this incidence include patent ductus arteriosus and intracranial ultrasound findings of cerebral white matter damage and IVH, as well as combined neonatal factors of duration of mechanical ventilation, acidosis, seizures, infection and hypoglycemia.

The data on the incidence of hearing loss in ELBW infants are conflicting: four studies report higher incidence ranging 9 to 14% and nine studies report low incidence or rates similar to their full-term controls. This discrepancy may be due to variations in testing methods used, which were frequently not reported in the studies reviewed. Infants with hearing loss are more likely to have had a high illness acuity in their neonatal course with combined exposures to severe hyperbilirubinemia and acidosis, hyperbilirubinemia and aminoglycoside use, elevated creatinine and furosemide use, and aminoglycoside and furosemide use.

The evidence is strong that VLBW infants have increased attention problems and more passive temperament. Intracranial lesions, CP, impaired cognition, and urban socioeconomic setting was associated with the increased incidence.

Available evidence suggests that VLBW infants are at higher risk for learning disabilities and future difficulties in school. Predictors of these problems in VLBW infants include small head circumference and decreased head growth velocity during the first several months of life.

Visual Disability

VLBW infants also are at increased risk for retinal and non-retinal ophthalmic disorders that lead to visual disability. This increased risk is primarily due to complications of prematurity, primarily ROP and CNS injury. The more immature the infant, the greater is its risk for any, as well as for severe ROP and CNS injury. The greater the severity of ROP, the greater is the risk for unfavorable structural and functional outcome (reduced acuity, blindness, abnormal fixation, strabismus, myopia, amblyopia). Infants with threshold (severe) ROP are known to be at very high risk for unfavorable structural and functional ophthalmic outcome. Treatment options for severe ROP, such as retinal ablation with laser therapy, are beneficial, but not always successful. Even when treatment is successful, the long-term visual outcome of infants with severe ROP is not satisfactory. Among threshold ROP eyes that are treated, 40 to 60% of the eyes have unfavorable visual outcome and 20 to 30% of the eyes become blind.

CNS injury is a separate, independent contributor to visual disability that often co-exists with ROP in the premature VLBW infant. The more severe the cerebral white matter damage, as demonstrated by cystic PVL, ventriculomegaly, and IVH, the greater the risk of cortical visual disability. The degree of visual impairment correlates very strongly with the degree of neurodevelopmental impairment. This evidence emphasizes the importance of ocular assessment of VLBW children with CNS damage, and neurodevelopmental assessment in VLBW children with visual disabilities.

The most common visual disabilities in VLBW infants resulting from ROP and/or CNS injury include significant reduction in visual acuity (including blindness), abnormal fixation, strabismus, and severe myopia. Visual fields, contrast sensitivity, and other visual functions may also be impaired. BPD also appears to contribute to greater visual impairment. Thus, ROP, CNS

injury, and BPD individually and collectively contribute to visual disability in the premature VLBW infant.

The first year of life is a critical period for visual development, and vision is a crucial determinant of early motor and cognitive development. Careful assessment of vision in visually high-risk infants is essential during the neonatal and infancy period, and must continue through the first several months and years of life to permit detection of abnormal acuity, strabismus, amblyopia, refractive errors, etc. Studies emphasize that premature infants at risk for ophthalmic disability, and those with documented ophthalmic sequelae early in infancy, require close, long-term follow-up due to evidence that infants may have progressive, ophthalmic deterioration over time. Omission of or inadequate follow-up may contribute to worsening visual outcome or blindness if appropriate timing of interventions for treatable conditions is missed.

No single visual test at one point in time can adequately assess the various multiple visual functions. Meaningful evaluation of visual function requires comprehensive, repeated, long-term assessments for acuity, refractive error, ocular motility, fixation, visual fields, contrast sensitivity, and color vision in conjunction with neurodevelopmental assessment. The specific method and timing of the ocular tests must be in accordance with the infant's age and capabilities. The reality of life-long therapeutic, educational, psychosocial, and socioeconomic significance and costs of visually disabled VLBW children highlights the importance of ocular assessment and appropriate timing of intervention. This, in turn, helps to minimize visual disability and to maximize the adaptation if visual disability exists.

Pulmonary Disability

The studies reviewed indicate that VLBW infants with BPD are at increased risk for long-term pulmonary disability. The greater the severity of BPD, the greater is the association with long-term pulmonary impairment and need for re-hospitalization. On the whole, VLBW preterm infants without BPD are comparable to full-term children in terms of pulmonary outcome. VLBW infants with less severe BPD may have respiratory disability primarily during the first two years of life. VLBW infants with more severe BPD may have persistent lung disease during young childhood and continuing through to their adolescent, young adult years.

Preterm children with chronic lung disease due to BPD vary in their manifestations of pulmonary disability. Lung dysfunction can be demonstrated by formal pulmonary function testing and abnormal physical examination findings. The most frequently described consequences of pulmonary disability are increased respiratory symptoms (e.g. wheezing and cough), respiratory illnesses, and the need for respiratory medications. All of these reflect the underlying physiologic consequences of aberrant growth, development and function of injured premature lungs. Re-admission to the hospital for respiratory illnesses, such as asthma, pneumonia, recurrent bronchitis, and exacerbations of chronic lung disease, is unfortunately common in the first two years of life. The need for hospital admission for issues related to failure- to-thrive due to poor growth, surgeries or other reasons is also increased in VLBW infants with BPD compared to full term infants. Although it appears that premature infants in the current era of neonatal care do not have as severe BPD as in the era prior to the widespread use of antenatal steroids and surfactant, BPD still accounts for significant long-term, multi-system morbidity.

Poor Growth

Recent studies continue to provide evidence that VLBW infants have significantly lower weight and height, and may have abnormal body composition and bone mineralization, during the first years of life compared to children who were born full-term. Growth impairment in VLBW/ELBW infants is due largely to prolonged, acute neonatal illnesses and subsequent chronic illnesses (e.g. BPD, gastroesophageal reflux, short-gut syndrome). But failure to grow (i.e. weight <3rd and <10th percentile through 2 years of age) in high risk VLBW/ELBW infants is also strongly associated with neurosensory developmental abnormalities and motor skills that impact the child's feeding ability. Attainment of appropriate growth and nutrition in VLBW infants is an important challenge that requires conscientious attention over the course of months and years after initial discharge from the neonatal unit. This is particularly true for children who have long-term disabilities related to BPD, short-gut syndrome from necrotizing enterocolitis, and neuromotor, neurosensory, cognitive, and/or neurobehavioral disorders within the context of an adverse social/parenting setting.