

Mind the Gap: The Unique Neurodevelopment of Extremely Low Birth Weight Infants

Itai Berger MD

Neuro-Fetal Clinic, Pediatric Neurology Unit, Hadassah-Hebrew University Medical Center (Mt. Scopus Campus), Jerusalem, Israel

Key words: extremely low birth weight, prematurity, neurodevelopment, outcome

IMAJ 2008;10:718–721

Prematurity is the main reason for death and for severe long-term disabilities in infants [1,2]. In the past, infants born weighing less than 1000 g were classified as stillborn or considered "pre-viable." Over the decades, the limit of viability was rolled back significantly [3,4]. Two main reasons account for this change. The first is the rising rate of premature births due to the increased use of assisted reproductive technology and advanced maternal age. The second reason is the advances in prenatal and neonatal care due to active management of premature babies, including antenatal steroids, avoidance of postnatal steroids, optimal delivery planning (incorporating training and practice with a tertiary care center), early surfactant administration, new strategies of ventilatory assistance, and performance of bedside surgical procedures, combined with careful and individualized care [5-9]. Together, these factors led to tremendously high birth rates and survival of premature infants, especially among extremely low birth weight infants born weighing less than 1000 g [10,11].

Since the 1990s, survival of ELBW infants has been exceeding 70% in many large centers around the world [7,10,12]. Buchh et al. [13] showed in their study that the number of births of infants weighing less than 750 g has increased over the past 25 years roughly fourfold, the mortality has fallen from about 100% to less than 50% over that time, and the average birth weight of the survivors has decreased from 928 g to 781 g.

Being born ELBW may have a major negative impact on development, even when cognitive and motor performance fall within normal test limits

According to current guidelines developed by the American Academy of Pediatrics [14], it is considered appropriate not to initiate resuscitation for infants younger than 23 weeks of gestational age or those whose birth weight is less than 400 g. However, many caregivers of younger and smaller infants may exert pressure to resuscitate [3,15]. We might still see a reduc-

tion in birth weights and increased survival in the near future. However, together with the increasing survival of ELBW infants, concern has been raised as to the increasing prevalence of adverse neurodevelopmental outcome and quality of life [6,16,17,]. Severe handicaps, such as cerebral palsy, epilepsy and blindness, are diagnosed in as many as 15–25% of ELBW infants [18]. This rate is much higher than in the general population, but it means that most ELBW infants are free of severe disabilities.

The unique neurodevelopmental course of ELBW infants is demonstrated when we track the long-term outcome of the majority of this population. This is where we find the gap. Prematurity alone seems to be a neurodevelopmental risk factor even if the child does not suffer from severe disabilities. Long-term studies of ELBW infants demonstrate that these individuals have difficulties in cognitive, academic and behavioral aspects compared with normal birth weight infants even when they are healthy [17,19,20]. These studies show that most healthy children who were born as ELBW infants study in regular classes in mainstream schools, but at the same time adverse cognitive sequelae are more frequent among them when their outcome is compared to both normal birth weight or to more mature preterm populations [17,19,20]. This is not the case only at the beginning of their school career. Being born an ELBW infant is a developmental disadvantage up to early adulthood [17]. Studies have shown that for the ages 12–25 years extremely premature adolescents and young adults score lower in IQ scores and have lower academic achievements [21,22]. ELBW children exhibited significant deficits across all cognitive parameters assessed, including IQ, writing, reading, mathematics, and executive function tests [23,24], combined with statistically significant higher scores of attention deficit/hyperactivity disorder, psychopathologies and social incompetence [25]. As in severe disabilities, those who were born smaller and more premature suffered more.

Why does that happen?

At least partially, this could reflect multiple central nervous system and non-CNS morbidities. Disorders that are specific for premature infants, including intraventricular hemorrhage, periventricular leukomalacia and bronchopulmonary dysplasia, can cause brain insults and have a significant effect on neurodevelopmental outcome [6,26,27]. When a child suffers from

ELBW = extremely low birth weight

CNS = central nervous system

intraventricular hemorrhage or periventricular leukomalacia it is clear what caused the neurological deficit. But the numbers of infants with these conditions cannot explain the large numbers of cognitively affected children.

Prenatal inflammation is associated with brain damage and defects in long-term neuromotor and neurocognitive outcome [28]. The cause may reflect a response to microorganisms that gain access into the intrauterine space, starting a complex cascade of inflammatory cell recruitment and induction of cytokines and chemokines. The fetal inflammatory response syndrome contributes to white matter damage [28]. But even inflammatory response cannot explain the large numbers of cognitively affected children. There must be something else.

It is suspected that the brain of extremely premature infants develops differently because its growth does not reach expected maturation in the uterus

ELBW infants are vulnerable because their brain is at an early stage of development. Between 29 and 41 gestational weeks, total brain volumes, cortical gray matter and myelinated white matter increase significantly. There are variables that are essential for normal development but are difficult to control outside the uterus [7,29]. Abnormalities in nutrition, metabolic functioning, blood pressure and environmental stresses may disrupt the normal brain development, even when the child does not suffer from major insults [7].

Moreover, specific risk factors are present in the neonatal period. A number of neonatal complications are associated with outcome at school age: hypotension, mechanical ventilation > 14 days, parenteral nutrition > 41 days, patent ductus arteriosus, necrotizing enterocolitis or bowel perforation, low weight gain, slow increase in head growth (< 6 mm per week), and male gender [6,19]. But not all cognitively affected children suffer from these complications.

Perhaps the brain of the extremely premature infants, even those who are healthy, develops differently because its growth does not reach expected maturation in the uterus [30]. We usually assess neonates in the neonatal intensive care units by head ultrasound. But, there are data suggesting that head ultrasonography does not detect the full scope of parenchymal brain injury, and the abnormalities we do find may represent only the tip of the iceberg [31].

The use of more sophisticated methods of neuroimaging in preterm children in middle childhood and adolescence supports the view that prematurity affects brain development, resulting in long-term structural abnormalities. Such studies have reported

disproportionately smaller volumes of the cortex, basal ganglia, amygdala, hippocampus, corpus callosum, an increase in the size of the lateral ventricles and abnormal white matter signal in comparison with term control subjects [7,30,32-34]. There is a direct connection between low IQ and smaller brain volume [35].

Thompson and colleagues [7] extended these findings to demonstrate that preterm infant brains are affected in a regionally specific manner. In their study, deficits in brain volumes appeared to be confined to specific areas (the parieto-occipital, sensorimotor, and premotor regions). The authors concluded that such a regional brain development impact can predict the long-term outcome.

There are sociodemographic factors such as gender, ethnicity, mother's marital status, family structure, language spoken at home, social class, and parental education that also affect neurodevelopmental outcome [36,37]. Several studies proved a correlation between IQ and socioeconomic status among ELBW infants, but in the same studies extremely low birth weight children remained disadvantaged at each socioeconomic level [5,16,36,37]. This means that being born ELBW is a major risk factor. This is the reason for the gap.

Follow-up

We know that these children must be followed. There is a constant debate regarding the predictors of outcome [38]. ELBW children require a thorough long-term diagnostic workup to enable early detection of underlying disorders. Follow-up should start immediately after discharge and should be continued preferably to adulthood. The follow-up should cover all types of possible neurocognitive impairment. This task is gigantic, expensive, and crucial. As in many other medical fields prevention is mandatory.

ELBW children require a thorough long-term diagnostic follow-up to enable early detection and intervention

If ELBW is a risk factor by itself, the best prevention would be to prevent low birth weight by emphasizing prenatal care. We can presume that even with the best prevention methods there will always be premature births. It is advisable to centralize high risk pregnancies and births in tertiary perinatal centers with top-level neonatal intensive care units. Appropriate transport services are essential. Significant improvement can be measured in the mortality and morbidity rates of ELBW infants when referral coordination perinatal services are involved. Appropriate neonatal transport services can reduce the number of stillbirths and non-tertiary hospital births, and thus improve the outcome of the survivors [5,39]. But, this is not enough. Even with the

improvement in the immediate morbidity and mortality rates, long-term follow-up is needed.

In most studies it seems that disability rates are likely to increase with longer follow-up [19,21,36]. Specific cognitive effects such as learning and attention difficulties are not usually recognized until school age. As more of these children are now reaching school age, it is important that the nature of their cognitive deficits be understood. Since even subtle deficits may affect academic achievement, delaying assessments might affect their development.

Conclusions

The relationship between prematurity and cognitive function is complex. The neurodevelopmental course of ELBW premature children is dynamic, complex, and influenced by genetic, perinatal, neurological, social, cultural and environmental factors. The gap means that most ELBW children may have a major negative impact on their development, even when cognitive capacity and motor performance fall within normal test limits. Despite improved treatment and survival, cognitive performance declines as gestational age at birth decreases. The results of most studies strengthen the view that early detection and intervention programs have significant impact on reducing the severity of neurological sequelae in ELBW children. Because of the multiple factors involved, a multidisciplinary group must implement follow-up strategies, providing a medical home for children who were born ELBW, that will manage their special health care needs, coordinate their care, and assist in navigation of the complex national and local systems in order to ensure that they receive appropriate support and intervention services [36,40].

It is surprising how relatively little research is available on this subject. Additional long-term research is needed to determine the specific brain abnormalities underlying the deficits so that preventive strategies can be developed and introduced into clinical practice.

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Correspondence: Dr. I. Berger, Neuro-Fetal Clinic, Pediatric Neurology Unit, Hadassah-Hebrew University Medical Center (Mount Scopus Campus), P.O. Box 24035, Jerusalem 91240, Israel.
Phone: (972-2) 584-4751; Fax: (972-2) 532-8963
email: itberg@hadassah.org.il