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Review

Management and outcome of extremely low birth weight infants

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Proceedings

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Abstract

Survival of extremely low birth weight (ELBW) and extremely premature (EP) infants has shown consistent improvement thanks to advances and innovations in perinatal and neonatal care. Regionalization, with high-risk deliveries in a tertiary perinatal center, offers the coordinated, collaborative, expert and specialized care needed by these mothers and their infants. Despite decreasing rates of the major neonatal morbidities observed in recent years, these continue still to be significant for ELBW/EP infants, impacting their overall prognosis. After NICU discharge and in the first years of life, issues with health, growth and development are common. In school age and adolescence, problems with behavior, socialization and cognition are prevalent. Adult outcomes of ELBW/EP need further clarity, emphasizing the importance for consistent long-term follow-up for this special cohort.

Keywords

ELBW, premature infants, AGA, SGA, IUGR, NICU, management, outcome.

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Introduction

With regionalization of perinatal care, improved technology and better understanding of their pathophysiology and specific needs, the survival of extremely low birth weight infants (ELBW) has improved dramatically [1].

ELBW infants are not a homogeneous cohort. They are best classified into two sub-groups: (1) infants who are extremely premature (EP), and appropriate for gestational age (AGA) and (2) infants with intrauterine growth restriction, being small for gestational age (SGA) but not always very premature (< 27 wks). This distinction is important because of the different pathophysiologic processes at play in these subgroups, with potentially very different consequences on the developing fetus and neonate.

The lowest gestational age and the lightest birth weight at which resuscitation should be initiated remain subjects of considerable debate. National guidelines for the management at the borders of viability are available, including those from the American and Canadian Fetus and Newborn Committees [1].

Perinatal management

Women presenting with complications such as premature labor, premature ruptured membranes, severe growth restriction, should be under the care of a specialist in Maternal-Fetal Medicine (MFM), with consultation to Neonatology. There should be antenatal transfer to a tertiary care perinatal center for optimal management, specifically adequate time for antenatal corticosteroid therapy, magnesium sulfate for neuroprotection, counselling and preparation for premature birth, and also optimal delivery [1-3].

The successful management of the ELBW infant begins in the delivery room. A competent team headed by an experienced neonatologist is essential for the proper management of the very fragile newborn [1]. Resuscitation is initiated using an inspired oxygen concentration of 30-40%, which is rapidly adapted to the infant's condition and the preductal oxygen saturation readings. Continuous CPAP or bag and mask ventilation should be provided. Severely depressed ELBW may require intubation, with subsequent early administration of surfactant.

Intensive care unit management

Expert management in the delivery room and during the first hours after admission to the NICU is of paramount importance in order to prevent immediate and long term complications in the ELBW infant. Acute changes in cerebral blood flow may predispose the very fragile network of periventricular vessels to rupture. It is essential to handle these very fragile infants with extreme care, avoiding unnecessary disturbances and preventing rather than correcting physiological deviations in acid-base balance, blood gases, blood pressure, or body temperature. Also, overly aggressive ventilation either in the delivery room or in the NICU may predispose to significant acute or chronic pulmonary problems such as hyperinflation and loss of elasticity of the alveoli, pulmonary interstitial emphysema, pneumothorax, and eventually chronic lung disease

The vast majority of ELBW infants will require some form of respiratory assistance in order to survive. For vigorous infants, nasal CPAP and other non-invasive respiratory assistance using nasal ventilation or high-flow nasal cannula, are preferred modes of support. Infants requiring more than 40% oxygen, have elevated PCO_2 or marked work of breathing, will require intubation for ventilation and administration of surfactant [4].

A variety of ventilatory strategies have been promoted, including high frequency ventilation, in order to reduce the risk of short and long term complications. Nowadays, with the early administration of surfactant and improvement in lung compliance and the early introduction of caffeine, rapid extubation and placement on nasal CPAP or nasal ventilation is possible in the majority of ELBW infants. However, for infants less than 750 grams, a more progressive weaning process with maintaining respiratory assistance for a few extra days at a very low PIP of 10 to 12 mmHg and rates of 30-40 per minute, may be more efficacious and allow advancement of intravenous and oral nutrition.

ELBW infants enter rapidly into a catabolic stage. Prevention is achieved by the early introduction of parenteral nutrition [5] A percutaneous vascular catheter (PCVC) is inserted as

soon as the baby's condition has stabilized in order to provide parenteral nutrition from the first hours of life. Also, early oral nutrition is currently the focus of active study. Oral immunotherapy (OIT) with colostrum or breast milk which is placed on the baby's lips and oral mucosa every two hours shortly after birth is a common practice. Minimal feedings in stable infants should be started in the first 48 hours of life. For the vast majority of ELBW, breast milk is used and only occasionally premature formula. Breast milk fortifiers are added when the enteral intake is 80-100 mL/kg/day, thus increasing its caloric and nutrient content for optimal growth.

In the vast majority of ELBW infants, the patency of the ductus arteriosus (PDA) becomes a real problem [6]. Although indomethacin was the initial drug of choice, ibuprofen has in recent years, demonstrated superior effectiveness and less side effects. The current debate questions whether therapy is indicated and if so, the selection of the best time for treatment. It should be the clinical picture and the significance of the PDA that dictate the time and mode of therapy. Failure of pharmaceutical closure and/or persistence of a significant PDA may point to the need for surgical ligation, which in turn may increase the risk for neonatal and long-term neurodevelopmental morbidities.

Appropriate management of neonatal pain and stress is a very important aspect of modern neonatal care, not only as humane and ethical practice but also to potentially prevent long term consequences of pain-related stress on neurodevelopment [7]. Global developmental care practices minimize stress on infants, limit sensory overload and may shorten the duration of hospitalization [8]. Partnership with the parents, with their involvement in the care and decision-making, empowers and also prepares them to care for their ELBW infant after NICU discharge [9].

Significant neonatal morbidities

Apnea of prematurity is a feature of nearly all ELBW infants. Incidence and frequency decrease with advancing gestational age, but at times it may be seen up to 42 weeks of postmenstrual age. Caffeine, which stimulates the respiratory center, is the most effective pharmacologic treatment for apnea of prematurity and has long-term neurodevelopment benefits [10]. If caffeine cannot control apnea, high flow nasal cannula, nasal CPAP and nasal ventilation may be additional modes of support. On occasion, persistent apnea may need to be treated with intubation and ventilation.

Another significant neonatal complication is necrotizing enterocolitis (NEC), which selectively affects the premature and sick infants. The incidence of NEC varies widely from center to center and is estimated at between 9 and 25% for ELBW infants [11].

A high index of suspicion with early discontinuation of feedings and naso-gastric decompression, with antibiotics and expert stabilization, will often avert the need for surgery. The current emphasis on breast milk and probiotics may result in significant reductions in NEC [12].

ELBW infants are particularly vulnerable to bacterial, viral and fungal infections. A significant number of premature labors are likely precipitated by infection [13]. Chorioamnionitis is a frequent finding after a premature birth, particularly in the presence of prolonged rupture of the membranes. Group B streptococcal infections have declined with the use of antenatal screening and the use of antenatal antibiotics, but not eliminated.

Nosocomial infections are common in ELBW infants. Aside from the immaturity of the immune system, predisposing factors include ventilator care, total parenteral alimentation via central or peripheral lines, and exposure to extensive handling. In recent years, *S. epidermidis* has emerged as the most common organism [14].

Finally, a significant number of ELBW infants continue to require oxygen supplementation beyond 36 weeks of postmenstrual age [15]. The use of dexamethasone in the past has been criticized for producing neurodevelopmental complications. Adjusted smaller doses of dexamethasone are recommended [16]. In recent years and in many centers, hydrocortisone has replaced dexamethasone with apparently superior outcomes.

Two of the most preoccupying complications in the ELBW infants are intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) [17]. The degree of prematurity is a very strong predictor for IVH. Severe Grade III and IV IVH have been recently reported to be between 5 and 12%. PVL is the other significant injury of the developing premature brain, with an incidence estimated to range from 4 to 15%.

It is also important before discharge from the NICU that all infants have a hearing test. For all degrees of severity of hearing impairment the incidence is estimated at 3.1% and for severe/profound loss at 1.9% [18].

Finally, retinopathy of prematurity (ROP) remains a frequently diagnosed morbidity [19]. However, blindness has become a rare occurrence, with an estimated prevalence of about 2%. Hence, systematic examination of all ELBW by an experienced ophthalmologist is mandatory.

Outcome of ELBW infants

The outcome of ELBW infants is an ever changing picture, reflecting past and current practices. Survival rates have reached a plateau and recent publications on the outcome of the post-surfactant cohorts describe significantly lower rates of blindness, severe developmental delay and severe disability [20]. However, a high prevalence of behavioral, emotional and cognitive problems has been described [21].

Most outcome studies point to an inverse correlation with gestational age and birth weight, though some show no gradient in outcomes with either diminishing gestational age or birth weight [22]. Other factors with negative correlations to outcome include intrauterine growth restriction, perinatal infections, chronic lung disease (CLD), severe intraventricular hemorrhage, cystic periventricular leukomalacia, post-hemorrhagic ventricular dilatation, surgical NEC and PDA, low socio-economic status and low level of maternal education and schooling [23].

The first 2-5 years will disclose the presence of health and neurosensory sequelae for the ELBW. In later years, the challenges from school, adolescence and work may uncover cognitive, behavioral and emotional disorders.

After NICU-discharge, mortality risk is elevated from sudden infant death syndrome (SIDS) and conditions related to prematurity, specifically CLD. Despite a marked decrease in the incidence of SIDS overall, for ELBW/EP infants this rate is 1.23 per 1,000 live births, which is 3 times higher than for infants born at term [24].

More than half of ELBW are re-hospitalized in the first two years and there is a higher use of medical services in the first decade, particularly with CLD and physical disabilities. Respiratory symptoms, such as wheezing, are common in childhood and airway obstructive limitations are observable to adulthood. Elevated blood pressure has been noted in adolescence and adulthood for some ELBW cohorts. Gastro-esophageal reflux and growth problems are prevalent in the first years. Though most ELBW do achieve normal growth and even approximate their genetic potential, their overall physical stature will be toward the lower range for height and weight [25, 26].

Cerebral palsy continues as sentinel morbidity, with an estimated prevalence of 8.5%, with 4.4% non-ambulatory at 18-24 months. Hypotonia, minor motor in-coordination, language and developmental delays are common diagnoses impacting on mobility, function and participation in social activities. Severe disability defined by the presence of at least one of the following: bilateral blindness, hearing impairment requiring amplification, inability to walk 10 steps with support, cerebral palsy or a Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) score of less than 70 using the Bayley Scales of Infant Development II (BSID-II), was observed in 34.2% of ELBW at 18-24 months, with multiple disabilities in about a quarter of these children [27].

Subtle and non-specific neurocognitive disorders have been observed in 50-70% of non-disabled ELBW with normal intelligence, often emerging after starting school [25]. These include disorders with language, visual processing, attention and executive functions. A "preterm behavioural phenotype" characterized by inattention, anxiety and social problems was proposed by Johnston et al. and associated with a specific risk for a triad of disorders, namely autism spectrum disorders (ASD), attention deficit/hyperactivity disorders (ADHD) and emotional disorders [28]. Moster et al. describe a higher rate of autism with lower gestational ages, with a rate of 0.6% at 23-27 weeks gestation compared to 0.05% at term [29]. Emotional disorders in preterm survivors include anxiety, such as separation anxiety, often diagnosed before 10 years of age, whereas depression is often diagnosed in adolescence. Record-linkage studies from Sweden and Denmark indicate a significantly increased risk of mood disorder (predominantly depression) in early adulthood in extremely premature adults and also in adults born moderately or late preterm. More research is needed to clarify if there is an increased prevalence of psychotic symptoms (e.g. schizophrenia) in ELBW survivors [26, 28].

These disorders may readily explain the educational problems seen in this cohort, with grade repetitions, need for remedial assistance and scholastic underachievement. Saigal et al. found that 72% of adolescents with birth weight < 750 grams, 53% with birth weight 750-1,000 g and 13% of normal birth weight controls had school difficulties [25]. Likewise, the underlying problem with inat-

tention and anxiety may underscore the social maladaptation, shyness and unassertiveness. Of note, this population has lower rates of delinquency and risk-taking behaviours in comparison to control adults. Though there are lower rates of educational achievement, employment and independent living for adolescents and adults born very premature and despite higher rates of disability, they did not perceive themselves to be different from their peer controls and reported a quality of life and functional outcomes similar to their peers [25, 30].

Fertility rates of adult survivors of extreme prematurity are lower. In a population-linkage study from Norway, the absolute reproduction rates were 25% for women and 13.9% for men born at 22-27 weeks gestation, compared to rates of 68.4% for women and 50.4% in men born at term [31]. Financial assistance for disability is higher compared to control adults born at term [29]. Though economic productivity, namely employment and earning, was lower in ELBW adults the deficits were not large [32].

The family of ELBW experience significant emotional and psychological distress, greatest in the first month and persistent beyond 3 years of life. Families with low income and less parental education have greater difficulties, more so if there are severe health issues and handicaps in the ELBW child. Divorce is more prevalent in these families, particularly if disability is diagnosed. Parents experience negative consequences in their workplace and a decrease in social activities. Beyond the adolescent years, ELBW families still had greater emotional distress, but also reported positive interactions within the family unit and friends [33, 34].

Long-term follow-up of this high- risk cohort of NICU graduates should be mandatory. It opens the door for the scientific evaluation of the consequences of very premature birth and the factors that can mitigate for the best outcomes. It provides feedback to the perinatal and neonatal care practices that will better define best care approaches. It continues the support and affirmation of the ELBW and their families. It can bridge the transition from neonatal intensive care to the needed continuing health care, education, social services and other societal resources.

Conclusions

The take-home message regarding ELBW remains cautious optimism. Outcomes have not shown worsening, rather gains in most spheres, as the attitudes for care for these infants at the border of viability have become more open. The economic toll on society is significant; the personal toll on the ELBW and their families is significant. More ELBW continue to survive and go home. The majority remains in the mainstream and participate alongside their term-born peers. Despite higher rates of disabilities and challenges in their daily lives, ELBW exhibit resilience, the ability to successfully participate in society and lead meaningful and productive lives.

Declaration of interest

The Authors declare that there is no conflict of interest.

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