Current therapies to reduce the risk of brain damage associated with preterm birth

Eliza Clotea 1, Roxana Georgiana Bors 1, Vlad Dima 2, Mihaela Plotogea 3, Valentin Varlas 1,4

1 Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania
2 Department of Neonatology, Filantropia Clinical Hospital, Bucharest, Romania
3 “Nicolae Malaxa” Clinical Hospital, Bucharest, Romania
4 “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Premature birth is an important public health problem associated with increased perinatal morbidity and mortality rates. Due to the triggering mechanisms of premature birth as well as the immaturity of the fetal brain, it is more prone to injury. Thus, these premature babies have an increased risk of immediate neurological complications as well as late neurodevelopmental abnormalities, which can have lifelong repercussions. Prompt identification of fetal brain injury and their treatment, as well as the supervision at regular time intervals of the neurodevelopment of children born prematurely, are a real challenge for the medical system.

Keywords: preterm birth, brain injury, follow-up, neurological outcomes, therapy

INTRODUCTION

Premature birth is defined as birth before completing 37 weeks of gestation. According to WHO, across the world, the rate of preterm birth is rising and varies from 5% to 18%. While the mortality associated with preterm birth has declined steadily in the last years, complications of prematurity are the main cause of death among children aged 5 and below and continue to lead to high rates of neurodevelopmental disability, including cerebral palsy [1].

Cortical maturation begins in intrauterine life, from 34 weeks of pregnancy, and progresses until the age of 30. Oligodendrocytes are the cells most responsible for myelination and are cellular targets in premature brain injury. Neurodevelopment depends on cortical maturation as well as connectivity of cortical structures. The morphometric and structural modification of the cortex is associated with developmental, neurological, and behavioral disorders [2,3]. Thus, due to the immaturity of the brain, premature babies are at risk of developing neurological disorders throughout their lives, a risk inversely proportional to their maturity at birth [2].

Etiological factors for neurodevelopmental disability in preterm babies are still only partially understood, and the dysfunction is considered to be multifactorial. These factors affect the development of oligodendrocytes, thus influencing the myelination of the white matter and the cortical gray matter [3].

Among the factors that increase the susceptibility of a premature baby's brain to injury are: vascular fragility, effects on the function of the blood-brain barrier, decreased functioning of developing neuroglial cells, damage to the process of oligodendroglial maturation, and the selective vulnerability of certain brain regions [4].

Hypoxia-ischemia in the perinatal period is known to cause brain injury in preterm infants at the level of the white matter, subsequently affecting the gray matter, with neurodevelopmental impairment. Antenatal hypoxia can be found in fetuses with growth restriction or those small for gestational age, these disorders are predisposing factors for cerebral palsy and developmental disorders. Also, during the delivery, they can be exposed to acute asphyxia. Postnatal hypoxia can occur secondary to apnea associated with prematurity or bronchopulmonary dysplasia (BPD) [5,6].

The vascularization of the premature brain is underdeveloped, thus the germinal matrix, the most vascularized structure, is also the most prone to hemorrhages, especially in premature infants under 32 weeks, hemorrhage that progresses to the level of the lateral ventricles and can even cause periventricular hemorrhagic infarction [7].
Brain injury is also linked to infection and/or inflammation during pregnancy. Chorioamnionitis, the infection of the fetal membranes, is an important cause of perinatal morbidity and mortality. The incidences of chorioamnionitis vary during pregnancy, occurring in 4% of term deliveries compared to 94% of deliveries at 21-24 weeks of gestation [8]. When chorioamnionitis occurs, the fetal immune system responds by secreting pro-inflammatory cytokines, especially interleukin-6 (IL-6), leading to a fetal inflammatory response syndrome, including cerebral inflammation with impaired neurodevelopmental outcomes and damage to hematopoiesis, thus, the risk of intraventricular hemorrhage and cerebral palsy increases [2,9].

Postnatal factors involved in the occurrence of brain injury in premature infants are hemodynamic instability, mechanical ventilation, stress, or sepsis, which maintain peripheral and cerebral inflammation [2].

In this article, we wanted to present the main mechanisms of brain injury in premature infants, neurological outcomes, and the main therapies available to prevent and treat neurological injuries.

**NEUROLOGICAL OUTCOMES FOLLOWING PRETERM BIRTH**

Since preterm infants are at increased risk of neurological complications, close monitoring of the neurodevelopment of at-risk patients is necessary both in neonatal intensive care units and in pediatric services.

Infants born prematurely have a higher risk of developing neurological disorders, one of the most important being cerebral palsy [10]. Premature birth affects every aspect of neurologic development. Those exposed at greatest risk are extremely premature infants, born before 28 weeks of gestation, who register the highest rates of neurodevelopmental impairment, hearing loss, or retinopathy of prematurity. Neonatal intensive care unit (NICU) admission for more than 5 days carries a significant risk for auditory impairment, and up to 7% of preterm infants born extremely premature need amplification [7,11].

Imaging techniques highlight the effects of preterm birth on the premature brain. Overall brain size is smaller in preterm infants, and these differences persist with time, into adolescence and adulthood, influencing later cognitive function [13]. Scans show that the white matter diffusivity of premature infants is altered when compared to that of term infants, examined at equivalent ages. These anomalies reflect the compromise of white matter structure, often seen in disorders of the nervous system, such as cerebral palsy [14].

Infants exposed to chorioamnionitis have an increased risk of cognitive impairment at the age of 18-22 months secondary to exposure to inflammatory cytokines [15].

Late preterm infants have a 3-fold increased risk of being diagnosed with cerebral palsy by age 5 years compared to full-term infants, based on predictive factors such as resuscitation at birth, administration of antibiotics, low Apgar score at one minute, and intracranial hemorrhage [16,17].

Late preterm birth is associated with speech, cognitive and motor delay, cerebral palsy, attention deficit hyperactivity disorder, and autism. Speech and language delay and the need for speech therapy is a debatable topic, the data in the literature being contradictory regarding its benefits [18,19,20]. Using cognitive tests at different chronological ages to identify cognitive delay reveals lower scores in late preterms compared to full-term infants [21,22]. In addition, the average locomotor score is significantly lower in late preterms [22].

Attention deficit hyperactivity disorder (ADHD) is another problem that can appear in premature infants as late as two years of age and can be objectified using questionnaires, stimulant medications, or diagnostic codes [18,23].

**CURRENT TREATMENTS FOR PRETERM INFANTS TO REDUCE BRAIN INJURY**

**Antenatal treatment**

Maternal glucocorticoid therapy is indicated when preterm labor is anticipated to promote fetal lung development. A Cochrane meta-analysis published in 2017 evaluating the effects of a single course of antenatal corticosteroids administered to the mother in case of threatened preterm labor concluded that current evidence supports this practice, and it should be considered routine in case of preterm labor. Maternal glucocorticoid therapy is linked to a reduction in a vast majority of adverse outcomes, such as perinatal death, neonatal death, intraventricular hemorrhage, necrotizing enterocolitis, need for mechanical ventilation, and systemic infection up to 48 hours after birth. However, there were no significant differences in long-term outcomes, such as chronic lung disease, death, or neurodevelopmental delay during childhood [24].

A systematic review with meta-analysis comparing dexamethasone and betamethasone administration in case of preterm birth concluded that glucocorticoid therapy has proven beneficial effects when compared to placebo and also revealed no significant differences between the two treatments for outcomes such as neonatal death, neurodevelopmental impairment, weight at birth or intraventricular hemorrhage [25].

Among important antenatal therapies in preterm labor is the administration of magnesium sulfate.
The mechanisms underlying the neuroprotective effect of magnesium sulfate are not fully understood; however, there are several hypotheses for this effect: Magnesium acts as an anti-excitotoxic agent via the N-methyl-D-aspartic acid (NMDA) receptor and reduces thus extracellular glutamate. Moreover, magnesium reduces oxidative stress and lowers the level of pro-inflammatory cytokines, thus exhibiting anti-inflammatory effects. The overview of current data indicates that antenatal magnesium sulfate is essential for preventing cerebral palsy in premature infants, and the benefits of postnatal administration should be investigated in randomized clinical trials [26].

Postnatal treatment

In the case of premature babies, brain lesions develop after a few hours after birth, up to a few weeks, so the prompt initiation of treatment is essential. From the first minutes of life, premature babies receive intensive neonatal care, with respiratory support, control of blood pressure and blood sugar levels, as well as ensuring an electrolyte balance [2].

In moderate-severe hypoxic-ischemic lesions, therapeutic hypothermia is recommended, maintaining a brain temperature of 33.5 ± 0.5°C, in the absence of infections. It starts in 6 hours of life and is maintained for 72 hours, having an immunosuppressive effect and thus reducing brain damage, with a small risk of intracranial hemorrhage. Unfortunately, there is not enough data in the literature regarding its benefits in extremely premature babies [27].

In preterm infants, the incidence of bronchopulmonary dysplasia (BPD) is high. For example, 50% of premature infants born before 28 weeks and approximately 80% of those born before 25 weeks develop BPD [28]. As BPD is associated with strong inflammation, the use of postnatal glucocorticoids has initially been a widespread practice. However, recent data indicate that, at least in some cases, the use of postnatal glucocorticoids in high doses is associated with developing cerebral palsy [29,30]. The balance between risks and benefits depends mostly on timing, dose, and underlying relative risk of developing cerebral palsy.

A Cochrane review published in 2017 concluded that the benefits of corticosteroid therapy administered early after premature birth (<7 days) do not outweigh possible adverse effects. However, hydrocortisone was linked to promising short-term outcomes improvement without adversely impacting long-term neurodevelopmental outcomes [31]. Another Cochrane review investigating late postnatal systemic corticosteroid therapy started after 7 days of life found that this strategy may lower neonatal mortality without significant adverse effects on long-term neurodevelopmental outcomes. As highlighted in a meta-analysis done by Onland et al., the most important conclusion is that postnatal corticosteroid therapy increases the risk of developing cerebral palsy in preterm infants in the low-risk category for bronchopulmonary dysplasia. On the opposite side, it reduces the risk of cerebral palsy among high-risk infants with bronchopulmonary dysplasia [32].

Epileptic seizures have a high incidence in the neonatal period, especially in prematurity [33]. In addition, neonatal seizures are linked to poor neurodevelopment, and seizures in the preterm infant are associated with worse outcomes than in the term infant [34]. According to a survey of 193 neonatologists, phenobarbital and phenytoin rank among the most common medications to treat neonatal seizures [35]. Both of them, like other GABAergic drugs, exhibit potential adverse effects on brain development, short-term but also long-term. Moreover, recent data indicate that less than half of the neonates treated with barbiturates respond to the treatment, and the mechanism might be more because of a sedative effect rather than by modulating seizure activity and reducing underlying brain dysfunction [36]. Considering the potential adverse effects and modest response, treating seizures in neonates, especially preterm infants, is currently a challenge, and further studies are needed to improve current practice.

Future directions in the postnatal treatment of brain injury focus on the intranasal administration of stem cells for rapid absorption in the brain. These cells have immunomodulatory, neuromodulatory, and regenerative potential [5,37].

Other promising treatments with a fetal neuroprotective role are the administration of melatonin, erythropoietin, and vitamin D. Maternal vitamin D deficiency is associated with premature birth, so newborns also have a high chance of having vitamin D deficiency. Vitamin D plays a role in the normal development of the fetal brain. Animal studies have shown that vitamin D supplementation has anti-inflammatory, neuroprotective, and immunomodulatory effects, even preventing the phenotype of autism [5]. Erythropoietin used to prevent postnatal anemia has a neuroprotective effect by reducing inflammation and oxidative stress. Exogenous melatonin dissolved in ethanol or combined with erythropoietin has proven its neuroprotective effect in animal studies, but still, the administration of ethanol as a treatment in children is not yet an accepted idea. More clinical studies, with a larger number of patients and with long-term follow-up, should be performed to strengthen the idea of Aly et al. regarding the benefits of melatonin administration combined with therapeutic hypothermia in reducing seizures and the absence of neurological abnormalities in preterm infants [5,38].
CONCLUSIONS

Premature birth and its complications on the fetus and neonate continue to be a challenge for both obstetricians and neonatologists. The fetal brain is an organ prone to complications, some of which have resounding effects on the child’s life. Timely administration of neuroprotective therapies in the case of brain injuries can have excellent effects on the long-life neurological outcome of premature children.

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