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# Facing the outcome of prematurity – opinions from the general practitioner

Otilia NOVAC[1], Maura Adelina HINCU[2,3], Anda-Ioana AVASILCAI[3], Vlad DIMA[4], Gabriela Ildiko ZONDA[2,3], Luminita PADURARU[2,3]

[1]Department of Preventive Medicine and Interdisciplinarity, Division of Family Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[2]Department of Mother and Child Care, Division of Neonatology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[3]"Cuza-Voda" Clinical Hospital of Obstetrics and Gynecology, Iasi, Romania
[4]Filantropia Clinical Hospital, Bucharest, Romania

## ABSTRACT

*Preterm birth is a leading cause of neonatal mortality and morbidity, affecting more than 15 million babies worldwide each year. Preterm infants also have higher rates of motor, functional, and cognitive deficits. Modern imaging has contributed significantly to a better understanding of the etiology of various forms of brain injury in neonates. The follow-up of premature newborns is essential to prevent and diminish neurological sequelae in time. A multi-disciplinary team is needed to adequately monitor this category of children, in which the family doctor has a significant role. The variety of adverse events that preterm infants can be exposed to before, during, and after birth poses significant obstacles to developing therapeutic interventions to prevent brain damage, including developmental vulnerability to injury during a particular gestational age. In addition, several procedures required for neonatal critical care, reduce mortality but increase the risk of brain injury. This review is aimed to update the reader about the complications of preterm birth, current therapeutic uses, imaging techniques, as well as present and future research on preterm birth.*

**Keywords:** preterm, neurological development, neonatal care, imaging techniques

Prematurity is a significant worldwide health issue and the leading cause of mortality among children under five years old [1]. Before 37 weeks of gestation, brain development occurs optimally in the intrauterine environment. According to CDC data from 2016, 10% of births in the United States occurred before 37 weeks of gestational age, with 2.76 % occurring before 34 weeks [2]. 64% of infants born between 22 and 24 weeks of gestation die, while 43% of survivors suffer from neuromotor impairment [3].

Identifying the sequence of events that contribute to proper brain development during the intrauterine period is a technical challenge, as imaging studies are hampered by reduced resolution due to fetal mobility and maternal tissue insertion. Experiences resulting from sensory stimulation and deprivation and interaction with the external environment have lasting effects on connection maturation, synaptogenesis, and cell differentiation. Therefore, the early extrauterine experience can potentially interfere with the normal progression of brain maturation [4].

Early exposure of preterm infants to the external world (gravity, sensory experience) affects neurological and musculoskeletal development. Those born ex-

*Corresponding authors:*
Gabriela Ildiko Zonda
*E-mail:* ildikozonda@yahoo.com

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tremely preterm and with very low birth weight (VLBW) who develop perinatal complications, have an increased risk of motor impairment, as motor acquisition during the first two years of life is directly related to gestational age at birth [5]. Although extreme deficits at 30 months of age are strong predictors of chronic symptoms at 6 years of age, children with less severe disabilities remain at risk. In addition, mild or severe motor abnormalities are associated with lower academic performance and less involvement in social activities compared with children without motor impairment [6]. Cerebral palsy is more common in preterm infants than in term babies, and the risk increases directly to the decreasing of gestational age. Moreover, low birth weight, multiple pregnancies, intrauterine infection, placental abruption, premature rupture of membranes, respiratory distress, postnatal corticoid treatment, and neonatal sepsis are all risk factors for cerebral palsy [4].

Preterm infants examined at term equivalent age show widespread alterations in white matter, suggesting lower white matter integrity commonly seen in neurodevelopmental disorders such as cerebral palsy. In extremely preterm infants of full correction age, the amount of cerebral cortex and deep nuclear gray matter decreased, and the amount of cerebrospinal fluid increased [7].

Very preterm neonates (infants born at < 32 weeks of gestation) had significant white matter (31.6%) and gray matter (21.1%) abnormalities on MRI. Repeated MRI scans of extremely preterm neonates (gestational age 23–30 weeks) showed that 49% have changes in brain structure and regional volume early postpartum, increasing to 92% by the end of gestation. The nature of brain pathology changes over time, as indicated by the appearance of hemorrhagic lesions (embryonic matrix and intraventricular), changes in signal intensity (indicative of necrotic or demyelinating processes), and ventricular dilatation [7]. However, moderately premature newborns or those delivered before 35 weeks are also at risk. Therefore, the closer the due date, the better the future development [8].

The neuropathological substrate, mainly for premature infants born at less than 32 weeks gestation, consists of cerebral white matter injury and dysmaturational events. Subsequent data now suggests that although white matter injury is an important and likely initiating event, multiple following dysmaturational events are most critical in determining the outcomes. However, as these events evolve over a prolonged period (several months), a relatively long time window exists for interventions to prevent, counteract, or reduce immaturity [9].

The somatosensory and pain perception circuits are intact but undeveloped. Later in pregnancy, the taste and smell systems are fully developed. Together, they form the eating behavior and brain connections that govern hormonal appetite regulation [10]. There is evidence that some pathologies encounter enteral feeding. Long-term nasogastric tube feeding in children may delay early oral food, alter immune responses, and affect long-term feeding behavior. Numerous studies have shown that exposing preterm infants to breast milk shortens the time to transition to oral feeding and, thereby shortens hospital stay [4].

Numerous clinical, epidemiological, and experimental researches highlight the need for proper nutrition throughout the preterm period for optimal neurodevelopmental outcomes and the detrimental consequences of postnatal malnutrition [7,8,11].

Due to its high total antioxidant capacity, breast milk can protect the auditory system of preterm infants. However, regardless of other conditions, newborns that need more than 5 days of intensive care have an associated risk for hearing loss. The incidence of congenital hearing loss is 1 in 1000 newborns and it increases significantly in relation to the number of days spent in the NICU. The high prevalence of hearing loss in preterm infants, especially born at less than 32 weeks, can be explained by the immaturity of the auditory system and the frequent coexistence of additional risk factors, such as background noise in neonatal intensive care units, congenital Cytomegalovirus infection, hypoxia, or intracranial hemorrhage. The noise in the neonatal critical care unit is high-frequency and high-intensity and the arrhythmic sounds may interfere with proper hearing development and have psychological consequences. Studies show that children with a history of premature birth should have an extended audiological follow-up and delayed indication for cochlear implantation [12].

Preterm infants are admitted to the NICU regularly throughout the neonatal period to improve their chances of survival. The NICU is a protective environment, but it is also stressful with intrusive and uncomfortable stimuli, especially for sensitive newborns. Early exposure to stressful and unpleasant situations affects the regulatory response stage of the developmental process and subsequently influences temperament and behavior in young children. Cassiano et al. showed that preterm infants had less temperamental control and higher activity levels than term infants, and also, less attention than age-matched infants. Temperament determines the control processes of self-development. It is characterized in early childhood by strong negative emotions, intrusiveness, and reduced control over effort [11].

The EXPRESS study included 399 preterm babies born before 27 weeks of gestation and 366 term infants. They assessed them at age 2.5 years using the 3rd edition Bailey Scale, and scores were recorded for cognitive development, receptive and expressive communication, and fine and gross motor skills. The prevalence of developmental delay in the preterm group was calculated based on the mean values of the control group. The analysis showed that this group had poorer results than the control group. The incidence of moderate-severe cognitive abnormalities was 10.8%, 14.9% for receptive communication, 14.5% for expressive communication, 12.4% for fine motor function, and 7% for gross motor [13].

Temperaments characterized by increased negative affectivity and decreased effortful control were associated with difficulties with generalizing, internalizing, and externalizing behaviors [14].

Behavioral concerns in school-aged preterm newborns are well-known, but research on this topic among early children (0-3 years) and preschoolers is limited (3-6 years). A meta-analysis revised fourteen cohort studies published between 2000 and 2012 in PubMed and PsycINFO that assessed risk factors for behavioral problems in preterm-born children aged 0 to 5 years. Even after correcting for prenatal and social risk factors, extremely and moderately preterm newborns, as well as very low birth weight infants, exhibited more behavioral problems and cognitive performance than term infants of equal ages (0-2 years and 3 to 5 years). The most common behavioral concerns are social and interpersonal skills, ineffective emotional self-regulation, and poor focus [15]. Additionally, preterm infants may exhibit less empathy and have trouble reading facial emotions and body language [16]. Early childhood behavioral disorders are symptomatic of future problems and should be addressed in follow-up programs [15].

Advanced imaging techniques, longitudinal monitoring in adulthood of people born at extreme prematurity, and a better understanding of the risk factors associated with neurological deficits have contributed to many current discoveries. Sensory impairment is frequently related to cognitive and social problems and is a target for therapy [4].

Electroencephalography (EEG) has the potential to provide a more precise prediction of the neurodevelopmental outcome of very premature newborns. Lloyd et al. showed that all newborns whose EEG remained normal or was initially abnormal but normalized throughout EEG recordings had a normal result at two years. This research showed a more significant positive predictive value (63%) than a study evaluating moderate/severe MRI white matter abnormalities at term comparable age (21%) [17]. Other studies evaluated the predictive utility of early EEG in later life; thus, children with negative results at ages 10–12 years had significantly lower total absolute band performance on days 1, 2, and 3 than children with typical cognitive test results (p 0.05) [18].

Van Gils et al., analyzed the combined predictive significance of neurological examination, head circumference, and cranial ultrasonography at term age for neurodevelopmental delay determined at 24 months corrected age of gestation in a prospective follow-up study. At 24 months of age, 26.5 % of infants had neurodevelopmental delays. Microcephaly (RR, 3.2; 95% CI, 1.6–6.7) and substantial ultrasonography abnormalities (RR, 2.7; 95% CI, 1.3–5.7) were linked with neurodevelopmental delay. The combination of the two tests demonstrated the highest positive predictive value (100%; 95% CI, 51%–100%), whereas the combination of a normal neurological examination, no major ultrasound findings, and a normal head size at term demonstrated the highest negative predictive value (89%; 95% CI, 79%–95%) [19].

According to Beunders et al., motor and cognitive outcomes were favorably associated with corpus callosum length at two months. Their work showed that the addition of corpus callosum length dramatically improved the prediction of neurodevelopmental outcomes based on risk variables in neonates [20].

Behavioral problems such as ADHD have a higher prevalence in premature newborns throughout early childhood. These impact significantly school performance and social integration and increase the risk of academic failure [21]. The main maternal risk factors include young age at conception, obesity before pregnancy, and smoking while pregnant. In addition, male sex, single fetal pregnancies, administration of sedatives and antibiotics, necrotic enterocolitis, ventriculomegaly, retinopathy of prematurity, and mechanical ventilation on the seventh postnatal day have been identified as fetal risk factors [22].

In conclusion, premature babies should be followed up to 2 years of corrected age in order to identify potential neurodevelopmental problems. Extremely preterm infants (< 28 weeks of gestation) have the highest rates of neurological complications, such as cognitive impairment, hearing loss, and retinopathy of prematurity [7].

The variety of adverse events that preterm infants can be exposed to before, during, and after birth poses significant obstacles to developing therapeutic interventions to prevent brain damage, including developmental vulnerability to injury during a particular gestational age. In addition, several procedures required for neonatal critical care, reduce mortality but increase the risk of brain injury. To date, interventions in preterm infants have been generally ineffective in improving long-term neurological outcomes, with very modest increases over time. However, promising treatments are being investigated in preclinical and clinical trials to reduce the burden of brain injury in preterm infants [9].

The general practitioner has to be aware and understand the complex pathology of prematurity, as he/she is responsible for integrating the multidisciplinary team of professionals implicated in the future care of a premature baby after discharge from the NICU. Moreover, by carefully monitoring the pregnancy together with obstetricians and perinatologists, the family doctor has a pivotal role in preventing some of the most important risk factors that can lead to preterm delivery.

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