Medicinski podmladak

Medical Youth

Mini review article

NEURODEVELOPMENTAL OUTCOME IN PRETERM NEONATES

NEURORAZVOJNI ISHOD PRETERMINSKE NOVOROĐENČADI

Ilija Palić[1,2], Ružica Kravljanac[1,3]

[1] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[2] Institut za neonatologiju, Beograd, Srbija
[3] Institut za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić“, Beograd, Srbija

Correspondence: palicilija152@gmail.com

Abstract

Preterm birth is the leading cause of neonate mortality and the second cause of death for children under 5 years of age in the world. The neonates born with very low birth weight (< 1500 g) and extremely low birth weight (< 1000 g), as well as neonates born very preterm and extremely preterm are at high risk for neurodevelopmental disabilities. Three common and frequent forms of brain injury in preterm neonates are intraventricular hemorrhage, white and gray brain matter injury. Motor developmental delay is early identified in premature neonates, especially during the first three years of life. The major motor deficit is cerebral palsy, but in school age, minor motor dysfunctions are diagnosed and named developmental coordination disorder. The second domain in which developmental delays are identified is cognitive development. Children born prematurely have lower intelligence quotient and a high risk of speech and language disabilities. The low gestational age and low birth weight are the risk factors for emotional disorders, attention deficit/hyperactivity disorders and autism spectrum disorders. The frequency of visual impairment and hearing loss decreased with enlarging gestational age at birth. Intracranial hemorrhage and neonatal seizures are identified as prominent risk factors for later-onset epilepsy. A key strategy to reduce neurodevelopmental disability is the prevention of preterm delivery. Transport of pregnant women with a risk of preterm delivery and delivery in tertiary centers, prenatal administration of glucocorticoids and magnesium sulfate decreases the risk of preterm brain injury and improves neurodevelopmental outcomes. Also, the program “Neonatal Individualized Developmental Care and Assessment Program” and the application of the “skin-to-skin contact” method (Kangaroo Mother Care) have favorable effects on the neurodevelopmental outcome in premature neonates. Future research should make new recommendations for neuroprotection of the preterm neonates.

Keywords:
prematurity,
brain injury,
neurodevelopmental disabilities

doi:10.5937/mp75-41666
Editorial board: podmladak.med.bg@gmail.com
e-ISSN: 2466-5525

Sažetak

Prevremeno rođenje je vodeći uzrok smrtnosti novorođenčadi i drugi uzrok smrtnosti dece mlađe od 5 godina u svetu. Novorođenčad rođena sa vrlo malom (< 1500 g) i ekstremno malom telesnom masom (< 1000 g), kao i ona koja su rođena kao vrlo preterminska (28 - 32 nedelje gestacije) i ekstremno preterminska (< 28 nedelje gestacije) u visokom je riziku za neurorazvojne smetnje. Tri uobičajena i česta oblika oštećenja mozga prematurusa su intraventrikularno krvarenje, oštećenje bele i sive moždane mase. Zastoj u motornom razvoju kod preterminske novorođenčadi identifikuje se rano, posebno tokom prve tri godine života. Najveći motorni deficit je cerebralna paraliza, ali se u školskom uzrastu dijagnostikuje manja motorna disfunkcija, označena kao poremećaj razvojne koordinacije. Drugi domen u kome se identifikuje razvojno kašnjenje je kognitivni razvoj. Prevremeno rođena deca imaju niži koeficijent inteligencije i visok rizik od kašnjenja u razvoju govora i jezika. Niska gestacijska starost i niska telesna masa na rođenju faktori su rizika za emocionalne poremećaje, poremećaj pažnje i hiperaktivnost i poremećaje iz autističnog spektra. Incidencija oštećenja vida i gubitka sluha opada sa porastom gestacijske starosti na rođenju. Intrakranijalna hemoragija i neonatalne konvulzije identifikovane su kao istaknuti faktori rizika za kasniju pojavu epilepsije. Ključna strategija za smanjenje neurorazvojnog kašnjenja je prevencija prevremenog porođaja. Transport žena sa rizikom od prevremenog porođaja i porođaj u tercijarnom centru, prenatalna primena glukokortikoida i magnezijum sulfata smanjuju rizik od oštećenja mozga kod prematurusa i poboljšavaju neurorazvojni ishod. Takođe, program „Neonatalna individualizovana razvojna nega i program procene" i metoda „kontakt koža-na-kožu" (engl. *Kangaroo Mother Care*) imaju povoljan efekat na neurorazvojni ishod preterminske novorođenčadi. Buduća istraživanja trebalo bi da donesu nove preporuke za neuroprotekciju preterminske novorođenčadi.

Ključne reči:
prematuritet,
oštećenje mozga,
neurorazvojne
smetnje

Introduction

Preterm delivery (PD) means delivery before 37 weeks of gestational age (GA). The World Health Organization (WHO) defines subcategories of preterm neonates: extremely preterm (EPT) (< 28 weeks GA), very preterm (VPT) (28 - 31 + 6/7 weeks GA), moderate preterm (MPT) (32 - 33 + 6/7 weeks GA) and late preterm (LPT) (34 - 36 + 6/7 weeks GA). About 15 million children are born before term every year, i.e. 1 out of 10 neonates. Approximately one million children die each year due to complications of PD. Also, preterm birth is the leading cause of neonate mortality and the second cause of death for children under 5 years of age in the world (1).

Over the past several decades, medical scientific and technological advances, including the use of mechanical ventilation (MV), exogenous surfactants, and antenatal glucocorticoid therapy, have contributed to the enlargement in survival of preterm neonates. With enlarged survival of these neonates increases the risk of neurodevelopmental disorders. The preterm neonates have several risk factors, which can affect all aspects of neurologic development (2, 3). The neonates born with very low birth weight (VLBW) (< 1500 g) and extremely low birth weight (ELBW) (< 1000 g), as well as neonates born VPT and EPT are at high risk for neurodevelopmental disabilities (4, 5).

This review article focuses on the recent research into the neurologic consequences of prematurity. The aim of our study is to summarize neurologic disorders in preterm neonates, risk factors, neurologic development, as well as interventions that can improve the development of children born before term.

Preterm brain injury

Preterm brain injury (PBI) occurs as a result of the influence of a large number of factors, including hypoxia and ischemia, inflammation, infection, MV, and exposure to glucocorticoids, sedatives or drugs of abuse. Three common forms of PBI are: intraventricular hemorrhage (IVH), white matter injury (WMI) and gray matter injury (GMI) (6, 7).

Intraventricular hemorrhage originates from small blood vessels in the subependymal germinal matrix. The frequency and severity of IVH enlarge with decreasing GA and occurred in 40 - 60% of VLBW neonates. According to Papile's grading system, there are four grades of severity of IVH (**table 1**). Long-term neurodevelopmental delay is associated with a greater degree of IVH, especially with degree III of IVH with posthemorrhagic ventriculomegaly and degree IV of IVH with intraparenchymal hemorrhage (7-9).

Table 1. Papile's grading system of intraventricular hemorrhage (8).

Grades	Finding
Grade 1	Germinal matrix hemorrhage
Grade 2	Intraventricular hemorrhage without ventricular dilatation
Grade 3	Intraventricular hemorrhage with ventricular dilatation
Grade 4	Intraventricular hemorrhage with ventricular dilatation and parenchymal hemorrhage

In immature brains of preterm neonates, WHI occurs as a periventricular leukomalacia (PVL) and diffuse WHI. Periventricular leukomalacia implies focal necrosis that is localized periventricularly and is associated with diffuse reactive gliosis and activation of microglia in the white matter of the brain. These necroses can be large, easily visualized by transfontanellar ultrasound, known as "cystic PVL" and observed in less than 5% of VLBW neonates. Much more often, white matter necrosis is small and leads to glial scarring that is not easily seen by neuroimaging, and this form is termed "non-cystic PVL". (10, 11).

The pathophysiology of the WHI includes toxicity of glutamate, free radical, and/or cytokine to oligodendrocyte precursors, GABAergic interneurons, subplate neurons and axonal damage. All these processes result in changes in the development of the cerebral cortex. Dysmyelination is one of the main features of chronic WMI. The cystic form of WMI is commonly associated with neurodevelopmental disabilities (7, 11, 12).

Several studies indicate changes in gray matter are a substantial contributor to neurodevelopmental delay. A significant reduction in the growth of the gray matter structures of the brain, including the thalamus, globus pallidus, hippocampus and cerebral dentate nucleus, have determined by various neuroimaging techniques. The histopathological signs of GMI are loss of neurons and/or gliosis (7, 11, 13).

The association between WMI/PVL and neuronal/axonal deficits is termed "encephalopathy of prematurity" introduced by Dr Joseph Volpe in 2005 (11, 14).

Motor development

Premature neonates are at risk for motor development disabilities. The major motor deficit in premature neonates is often categorized as cerebral palsy (CP), disorder of motor development and posture. Cerebral palsy occurs as a result of congenital brain anomalies or injury to the developing brain. Spastic diplegia is the most frequent subtype of CP in children born prematurely (2, 4, 15, 16).

The incidence of CP decreases in children born VPT (17). Arnaud et al. (16) found that about two-thirds had a spastic form of CP. In children born 32 - 36 weeks GA, the prevalence of CP significantly decreased with an average reduction of 4% per year. The conclusion of the study was that the prevalence of CP in preterm neonates continues to decline, except in EPT neonates. The results of EPIPAGE prospective cohort study were that at two years of age, prevalence of CP decreased with increasing GA, 20% at 27 weeks GA, 12% at 27 to 28 weeks GA, 8% at 29 to 30 weeks GA, 7% at 31 weeks GA, and 4% at 32 weeks GA (18).

The diagnosis of CP is difficult to establish before 18 to 24 months of age, especially if the neurologic signs are mild (19). It is very important to identify children with risk factors for the occurrence of CP, which include low GA, low birth weight (LBW), multiple gestation, low arterial pH of umbilical cord blood, low Apgar score (AS), intrauterine infection, neonatal sepsis, prolonged MV, placental abruption, PD, prolonged rupture of membranes, postnatal corticosteroid therapy, retinopathy of prematurity (ROP) and male gender. The risk of occurrence CP is enlarged in preterm neonates with cerebral lesions, such as cystic PVL or intraparenchymal hemorrhage (2, 4, 18, 20).

Also, preterm neonates, especially born VPT, are at risk of a minor motor dysfunction classified as developmental coordination disorder (DCD). The diagnosis of DCD is often made only when the child starts school. The disorder includes delayed motor milestones, balance abnormalities, deficit in gross and fine motor control and visual motor integration (2, 17, 19). The prevalence of DCD estimates ranges from 2% to 20% of children (20). The EPIPAGE-2 is a prospective cohort study that evaluated children born between 22 and 34 weeks GA in 25 French regions in 2011. The results of this study were that at 5½ years of age prevalence of CP was the highest in children born 24 - 26 weeks GA, 12.4%, compared with 5.9% in children born 27 - 31 weeks GA and 2.4% in children born 32 - 34 weeks GA. Similar results were found for DCD; 18.8% in children born 24 - 26 weeks GA had DCD compared with 5.0% in children born 32 - 34 weeks GA (22).

Developmental coordination disorder affects activities of daily living and also have effects on academic attainment and mental health (20). Uusitalo K. et al. (17) conducted a prospective follow-up study and evaluated children born VPT in Finland between 2001 and 2006. This study found that children born VPT with DCD had more cognitive disabilities than children born VPT without motor deficits. Also, children born VPT with DCD reported lower health-related quality of life than children born VPT without DCD.

Cognitive and language development

Cognitive outcomes after PD are heterogeneous. The frequency of severe cognitive disabilities is higher in populations of neonates born VPT and EPT (23, 24). Pascal A. et al. (25) in a systematic review reported a prevalence of cognitive disabilities in VPT and VLBW neonates was estimated at 16.9%. The prevalence of mild cognitive disabilities was higher (14.3%) than moderate-to-severe cognitive disabilities (8.2%). Also, these authors reported that the estimated pooled prevalence of cognitive disabilities was higher in neonates born EPT and VPT, 29.4% and 14.3%, respectively.

Children born prematurely have lower intelligence quotient (IQ), lower executive functioning and lower processing speed than FT children (2). In addition to low GA and LBW, other risk factors are small for GA (SGA), cerebral lesions (IVH and cystic PVL), presence of seizures, low AS, metabolic acidosis, male gender, bronchopulmonary dysplasia, low socio-economic status of parents and lack of breastfeeding (2, 3, 24, 26).

Children born EPT are at high risk for comorbid intellectual and learning disabilities. This fact was

confirmed by the study of Johnson S. et al.; at 11 years old, children born EPT (47%) have a higher prevalence of intellectual and learning disabilities than children born at term (4.6%). Also, these children have three times increased risk for special educational needs. Difficulties with mathematics are especially common (27, 28).

Preterm neonates are at an increased risk of speech and language disabilities (19). Language impairments in preterm neonates include mild to moderate disabilities in the development of vocabulary and grammar, as well as language comprehension (29, 30). Cohen-Foster et al. found that at 4 years old, children born VPT had significantly lower receptive and expressive language ability than full-term (FT) children. The main predictors of children's overall language development were the social status of a family, the severity of WMI and mental health of parents (29). Asztalos et al. reported to exist positive association between primary caregiver education and cognitive and language development at 18 to 21 months of corrected age in neonates born EPT (31).

Mental health

Several studies have shown PD as a significant risk factor for psychiatric disorders, and emotional and behavioral problems, especially infant born VPT and EPT (32 - 34). As well as other neurologic consequences of prematurity, low GA and LBW are the main risk factors for specific psychiatric disorders, including emotional disorders (anxiety, depression), attention deficit/hyperactivity disorders (ADHD), and autism spectrum disorders (ASD). This pattern of behavioral and emotional disabilities is named the "preterm behavioral phenotype" (32).

Leviton A. et al. (35) identified prenatal, perinatal and postnatal risk factors for ADHD. The risk factors associated with diagnosed ADHD were: low maternal age at delivery, obesity before pregnancy, and smoking during pregnancy. Other identified risk factors for ADHD include magnesium for seizure prophylaxis, male gender, birth of only one child, administration of drugs (sedative or antibiotic), ventriculomegaly, ROP, recovery of *Mycoplasma spp.* from the placenta parenchyma, MV on postnatal day 7 and "surgical" necrotizing enterocolitis (NEC).

The results of a national cohort study by Crump C. and al. (36) showed that neonates born EPT and VPT have an increased risk of ASD, 6.1% for EPT (22 - 27 weeks), and 2.6% for VPT to MPT (28 - 33 weeks) than 1.6% for early FT (37 - 38 weeks), and 1.4% for late FT (39 - 41 weeks). The overall prevalence of ASD in preterm neonates was 2.1%.

These emotional and psychiatric disorders can affect academic achievement and social integration (37, 38). Also, a study by Davies C. et al. (39) reported that several prenatal and perinatal factors, including PD, LBW and SGA, are associated with the later onset of psychosis, such as schizophrenia.

Vision and auditory development

Children born prematurely have an enlarged risk of various visual impairments, such as strabismus, refractive errors, reduced visual acuity and deficits in cortical visual processing. The ROP is a proliferative vascular disease of the retina and the main risk factor for visual impairment in premature neonates which can cause blindness. (24, 40, 41). Numerous visual impairments may be consequences of abnormal brain development or cerebral injury. Development of the cerebral visual system is susceptible to injury through the last trimester of pregnancy (2, 40).

Preterm neonates admitted to the neonatal intensive care unit (NICU) are at higher risk of deafness. Also, neonates born VPT and VLBW neonates, exposures to ototoxic drugs (gentamicin, furosemide) have been reported as risk factors for hearing impairment. Common conditions, such as hyperbilirubinemia or hypoglycemia, are also risk factors for hearing impairment in neonates admitted to NICU (24, 42, 43).

The study of Hirvonen M. et al. (44) found that the frequency of visual and hearing impairments enlarged with decreasing GA at birth. The identified risk factors for these impairments were maternal smoking during pregnancy, AS < 4 at the first minute of age, NICU admission, SGA, MV, intracranial hemorrhage (ICH) and neonatal seizures. Also, neonates born VPT and LPT were associated with an enlarged risk of deafness, and neonates born VPT had an enlarged risk of visual impairment.

Epilepsy and prematurity

Preterm neonates are susceptible to seizures in the first weeks of life. The reported incidence of seizures in this population varies from 4% to 48%. Seizures during the neonatal period, especially in preterm neonates, are more often to contribute to poor neurodevelopmental outcomes (45-47).

Hirvoven M. et al. (47) reported that the incidence of epilepsy was 2.53% in the neonates born VPT, then 0.51% in the FT neonates. This study reported that ICH and neonatal seizures were identified as prominent risk factors for later-onset epilepsy. The overall incidence of epilepsy was 0.54% and it decreased with increasing GA up until 41 weeks. A similar result was reported in the study of Chou IC et al. (48); the overall incidence of epilepsy in preterm neonates was 2.96%. In groups of preterm neonates with ICH, hypoxia-ischemia and cerebral congenital anomalies, the overall incidence of epilepsy was 15.9%, 6.92% and 14.3%, respectively.

Neuroprotective interventions

A key preventive and treatment strategy to reduce PBI focuses on different adverse factors that these neonates can be exposed to before, during or after delivery. First of all, the most important is the prevention

of PD. Primary prevention includes weight optimization, healthy nutrition, vitamin and mineral supplementation, and smoking cessation. Secondary prevention efforts are directed at women who are at higher risk of PD. These forms of prevention include administration of progesterone, cervical cerclage and treatment of infections (12, 49).

Tocolytic therapy is used to extend the pregnancy and the most often used are calcium channel blockers, such as nifedipine. These drugs can prolong pregnancy by 48 hours and reduce the frequency of IVH in preterm neonates (8, 50).

Transport of preterm neonates (≤ 32 weeks GA) in the first 48 hours of life between hospitals is a risk factor for developing acute PBI, especially severe IVH. The increased risk of acute PBI born outside tertiary centers may relate to medical staff who may lack specific training and expertise for resuscitation of preterm neonates. The best way to transport premature neonates is transport in the womb (transport *in utero*) to ensure that optimal obstetric and neonatal care is received (50-52). The impact of mode and timing of birth on IVH incidence is unclear. There is no proof that routine cesarean section (CS) has decreased the risk for mortality and IVH, than vaginal delivery. The studies suggest that emergency delivery has a higher risk for PBI than delivery mode. Routine CS is recommended only if the fetus is in the breech position. The pregnant woman and her gynecologist make the final decision on how to end the delivery (8, 51).

According to the American College of Obstetricians and Gynecologists (ACOG), a single dose of betamethasone or dexamethasone is recommended to all women who are at risk for PD before 35 weeks GA, within 7 days. Antenatal corticosteroids were shown to reducing the incidence of IVH, severe IVH and WMI (12, 51-53). A Cochrane systemic review in 2016 evaluated 30 studies and showed that treatment with antenatal glucocorticoids is associated an overall reduction neurologic consequence of prematurity, including: death in perinatal and neonatal period, respiratory disorders, IVH, NEC, need for MV and sepsis in the first 48 hours of life (54). A single dose of glucocorticoids in neonates born before 34 weeks GA has a beneficial effect on neurodevelopmental outcome (55).

Several studies found that the administration of magnesium sulfate ($MgSO_4$) to pregnant women in PD was associated with a significant reduction the risk motor disabilities in early childhood (56-58). The use of $MgSO_4$ for women at risk of imminent PD before 32 weeks GA is recommended by WHO and ACOG with the Society for Maternal Fetal Medicine (59, 60).

According to American Academy of Pediatrics (APP) and ACOG, delayed cord clamping (DCC) is recommended for 30 to 60 seconds in term and preterm neonates who has good muscle tone, active breathing efforts and heart rate more than 100. Several studies reported that DCC decreases the incidence of all degrees of IVH, but not with severe IVH specifically. Also, DCC appears to protect against motor impairment later during life (8, 51, 61, 62).

It is very important to prevent hypothermia in premature neonates in the delivery room, because it has been associated with enlarged risk for acute PBI (8, 51). Hypercapnia, defined as the partial pressure of carbon dioxide blood levels of more than 60 mmHg, is a risk factor for acute brain injury in neonates born EPT. Volume-targeted ventilation is recommended to be used in premature neonates in the first 72 hours after birth, since this mode of ventilation has been shown to reduce the incidence of severe IVH (63, 64). Caffeine is used to treat apnea of prematurity. Several clinical trials have reported that caffeine has a favorable effect on the brain in premature neonates. The effects of caffeine depend on the dose, but also on the length of administration (51, 52, 62, 65, 66). Also, midline position and elevation of the infant's head have been reported as protective factors for developing IVH (8, 51). Several studies have reported favorable effects of breastfeeding on the neurological development of the preterm infant (52, 62).

A special intervention program "Neonatal Individualized Developmental Care and Assessment Program" (NIDCAP) was developed to improve the neurodevelopmental outcome of premature neonates. The implementation of the NIDCAP program includes adequate positioning and handling, minimizing pain and stress, introducing the mode "day-night", noise reduction, skin protection, nutrition and family involvement in treatment and care. The presence of parents is important for reducing stress in premature neonates, especially skin to skin contact between mother or father and infant (Kangaroo Mother Care) (62, 67, 68).

Despite the challenges associated with PBI and intervention that can improve neurodevelopmental outcomes, there are a large number of other agents with potential neuroprotective effects currently in various stages of trials. Future research should make new recommendations for reducing PBI and improving neurodevelopmental outcomes.

Conslusion

Prematurity is associated with a high risk of neurodevelopmental and lifelong disability. Prevention is extremely important. Numerous preventive strategies are aimed at PD, but also at factors that can have a harmful effect on premature neonates. Applying all these preventive measures reduces PBI, which decreases the risk of developing neurodevelopmental disabilities.

References

1. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Eds CP Howson, MV Kinney, Je Lawn. World Health Organization. Geneva, 2012.
2. Ream MA, Lehwald L. Neurologic Consequences of Preterm Birth. Curr Neurol Neurosci Rep. 2018; 18(8):48.
3. Hass JV, Panceri C, Procianoy RS, Silveira RC, Valentini NC. Risk Factors for cognitive, motor and language development of preterm children in the first year of life. Rev Paul Pediatr. 2022;

41:e2021165.
4. Chung EH, Chou J, Brown KA. Neurodevelopmental outcomes of preterm infants: a recent literature review. Transl Pediatr. 2020; 9(1):S3-S8.
5. Neil JJ, Volpe JJ. Encephalopathy of Prematurity: Clinical-Neurological Features, Diagnosis, Imaging, Prognosis, Therapy. In: Volpe JJ, Inder TE, Darras TB, de Vries LS, du Plessis AJ, Neil JJ, et al., editors. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier Science; 2018. p. 425-57.
6. Yates N, Gunn AJ, Bennet L, Dhillon SK, Davidson JO. Preventing Brain Injury in the Preterm Infant-Current Controversies and Potential Therapies. Int J Mol Sci. 2021; 22(4):1671.
7. Back SA, Miller SP. Brain injury in the Preterm Infant. In: Gleason CA, Juul SE, editors. Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier Science; 2018. p. 879-96.
8. Lim J, Hagen E. Reducing Germinal Matrix-Intraventricular Hemorrhage: Perinatal and Delivery Room Factors. Neoreviews. 2019; 20(8):e452-e63.
9. Tan AP, Svrckova P, Cowan F, Chong WK, Mankad K. Intracranial hemorrhage in neonates: A review of etiologies, patterns and predicted clinical outcomes. Eur J Paediatr Neurol. 2018; 22(4):690-717.
10. Lee YA. White Matter Injury of Prematurity: Its Mechanisms and Clinical Features. J Pathol Transl Med. 2017; 51(5):449-55.
11. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009; 8(1):110-24.
12. Yates N, Gunn AJ, Bennet L, Dhillon SK, Davidson JO. Preventing Brain Injury in the Preterm Infant-Current Controversies and Potential Therapies. Int J Mol Sci. 2021; 22(4):1671.
13. Fleiss B, Gressens P, Stolp HB. Cortical Gray Matter Injury in Encephalopathy of Prematurity: Link to Neurodevelopmental Disorders. Front Neurol. 2020; 11:575.
14. Kinney HC. The encephalopathy of prematurity: one pediatric neuropathologist's perspective. Semin Pediatr Neurol. 2009; 16(4):179-90.
15. Fuentefria RDN, Silveira RC, Procianoy RS. Motor development of preterm infants assessed by the Alberta Infant Motor Scale: systematic review article. J Pediatr (Rio J). 2017; 93(4):328-42.
16. Arnaud C, Ehlinger V, Delobel-Ayoub M, Klapouszczak D, Perra O, Hensey O, et al. Trends in Prevalence and Severity of Pre/Perinatal Cerebral Palsy Among Children Born Preterm From 2004 to 2010: A SCPE Collaboration Study. Front Neurol. 2021; 12:624884.
17. Uusitalo K, Haataja L, Nyman A, Ripatti L, Huhtala M, Rautava P, et al. Preterm children's developmental coordination disorder, cognition and quality of life: a prospective cohort study. BMJ Paediatrics Open. 2020; 4(1):e000633.
18. Ancel PY, Livinec F, Larroque B, Marret S, Arnaud C, Pierrat V, et al. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE cohort study. Pediatrics. 2006; 117(3):828–35.
19. McGowan EC, Vohr BR. Neurodevelopmental Follow-up of Preterm Infants: What Is New? Pediatr Clin North Am. 2019; 66(2):509-23.
20. Spittle AJ, Orton J. Cerebral palsy and developmental coordination disorder in children born preterm. Semin Fetal Neonatal Med. 2014; 19(2):84-9.
21. Blank R, Barnett AL, Cairney J, Green D, Kirby A, Polatajko H, et al. International clinical practice recommendations on the definition, diagnosis, assessment, intervention, and psychosocial aspects of developmental coordination disorder. Dev Med Child Neurol. 2019; 61(3):242-85.
22. Pierrat V, Marchand-Martin L, Marret S, Arnaud C, Benhammou V, Cambonie G, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. BMJ. 2021; 373:n741.
23. Stålnacke SR, Tessma M, Böhm B, Herlenius E. Cognitive Development Trajectories in Preterm Children With Very Low Birth Weight Longitudinally Followed Until 11 Years of Age. Front Physiol. 2019; 10:307.
24. Jois RS. Understanding long-term neurodevelopmental outcomes of very and extremely preterm infants: A clinical review. Aust J Gen Pract. 2019; 48(1-2):26-32.
25. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. Dev Med Child Neurol. 2018; 60(4):342-55.
26. Beaino G, Khoshnood B, Kaminski M, Marret S, Pierrat V, Vieux R, et al. Predictors of the risk of cognitive deficiency in very preterm infants: the EPIPAGE prospective cohort. Acta Paediatr. 201; 100(3):370-8.
27. Johnson S, Strauss V, Gilmore C, Jaekel J, Marlow N, Wolke D. Learning disabilities among extremely preterm children without neurosensory impairment: Comorbidity, neuropsychological profiles and scholastic outcomes. Early Hum Dev. 2016; 103:69-75.
28. Simms V, Cragg L, Gilmore C, Marlow N, Johnson S. Mathematics difficulties in children born very preterm: current research and future directions. Arch Dis Child Fetal Neonatal Ed. 2013; 98(5):F457-63.
29. Foster-Cohen SH, Friesen MD, Champion PR, Woodward LJ. High prevalence/low severity language delay in preschool children born very preterm. J Dev Behav Pediatr. 2010; 31(8):658-67.
30. Sansavini A, Guarini A, Alessandroni R, Faldella G, Giovanelli G, Salvioli G. Are early grammatical and phonological working memory abilities affected by preterm birth? J Commun Disord. 2007; 40(3):239-56.
31. Asztalos EV, Church PT, Riley P, Fajardo C, Shah PS. Canadian Neonatal Network and Canadian Neonatal Follow-up Network Investigators. Association between Primary Caregiver Education and Cognitive and Language Development of Preterm Neonates. Am J Perinatol. 2017; 34(4):364-71.
32. Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. Pediatr Res. 201; 69(5 Pt 2):11-8.
33. Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC, et al. Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. Pediatrics. 2018; 141(1):e20171645.
34. Hornman J, de Winter AF, Kerstjens JM, Bos AF, Reijneveld SA. Emotional and Behavioral Problems of Preterm and Full-Term Children at School Entry. Pediatrics. 2016; 137(5):e20152255.
35. Leviton A, Hooper SR, Hunter SJ, Scott MN, Allred EN, Joseph RM, et al. Antecedents of Screening Positive for Attention Deficit Hyperactivity Disorder in Ten-Year-Old Children Born Extremely Preterm. Pediatr Neurol. 2018; 81:25-30.
36. Crump C, Sundquist J, Sundquist K. Preterm or Early Term Birth and Risk of Autism. Pediatrics. 2021; 148(3):e2020032300.
37. Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelsson P, Gissler M, et al. Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/ Hyperactivity Disorder. Pediatrics. 2015; 136(3):e599-608.
38. Scott MN, Hunter SJ, Joseph RM, O'Shea TM, Hooper SR, Allred EN, et al. Neurocognitive Correlates of Attention-Deficit Hyperactivity Disorder Symptoms in Children Born at Extremely Low Gestational Age. J Dev Behav Pediatr. 2017; 38(4):249-59.
39. Davies C, Segre G, Estradé A, Radua J, De Micheli A, Provenzani U, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. Lancet Psychiatry. 2020; 7(5):399-410.
40. Leung MP, Thompson B, Black J, Dai S, Alsweiler JM. The effects of preterm birth on visual development. Clin Exp Optom. 2018; 101(1):4-12.
41. Song CM, Ahn JH, Hwang JK, Kim CR, Kim MJ, Lee KM, et al. Retinopathy of Prematurity and Hearing Impairment in Infants Born with Very-Low-Birth-Weight: Analysis of a Korean Neonatal Network Database. J Clin Med. 2021; 10(20):4781.
42. Wroblewska-Seniuk K, Greczka G, Dabrowski P, Szyfter-Harris J, Mazela J. Hearing impairment in premature newborns-analysis based on the national hearing screening database in Poland. PLoS One. 2017; 12(9):e0184359.
43. Garinis AC, Kemph A, Tharpe AM, Weitkamp JH, McEvoy C,

Steyger PS. Monitoring neonates for ototoxicity. Int J Audiol. 2018; 57(sup4):S41-S48.
44. Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, et al. Visual and Hearing Impairments After Preterm Birth. Pediatrics. 2018; 142(2):e20173888.
45. Jacobs J, Spelbrink EM. Seizures in Preterm Infants. J Clin Neurophysiol. 2016; 33(5):382-93.
46. Lekha R, Charles M. Seizures in the Preterm Neonate. Neoreviews. 2017; 18(1):e52–e59.
47. Hirvonen M, Ojala R, Korhonen P, Haataja P, Eriksson K, Gissler M, et al. The incidence and risk factors of epilepsy in children born preterm: A nationwide register study. Epilepsy Res. 2017; 138:32-8.
48. Chou IC, Sung FC, Hong SY. Incidence of epilepsy in children born prematurely and small for gestational age at term gestation: A population-based cohort study. J Paediatr Child Health. 2020; 56(2):324-9.
49. Flood K, Malone FD. Prevention of preterm birth. Semin Fetal Neonatal Med. 2012; 17(1):58-63.
50. Stanojević M. Prevencija prijevremenog poroda: gledište neonatologa. Paediatr Croat. 2016; 60(1):137-45.
51. Ryan M, Lacaze-Masmonteil T, Mohammad K. Neuroprotection from acute brain injury in preterm infants. Paediatr Child Health. 2019; 24(4):276-90.
52. Sammut A, Austin T. Neuroprotection of the preterm infant. Obstet Gynaecol Reprod Med. 2019; 29(2):56-7.
53. Committee on Obstetric Practice. Committee Opinion No. 713: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2017; 130(2):e102–e9.
54. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017 3(3):CD004454.
55. Sotiriadis A, Tsiami A, Papatheodorou S, Baschat AA, Sarafidis K, Makrydimas G. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. Obstet Gynecol. 2015; 125(6):1385-96.
56. Doyle L, Crowther C, Middleton P, Marret S. Antenatal Magnesium Sulfate and Neurologic Outcome in Preterm Infants: A Systematic Review. Obstet Gynecol. 2009; 113(6):1327–33.
57. Conde-Agudelo A, Romero R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: A systematic review and metaanalysis. Am J Obstet Gynecol. 2009; 200(6):595–609.
58. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev. 2009; (1):CD004661.
59. WHO Reproductive Health Library. WHO recommendation on the use of magnesium sulfate for fetal protection from neurological complications. Geneva: World Health Organization, 2015.
60. American College of O, Gynecologists Committee on Obstetric P, Society for Maternal-Fetal M.: Committee opinion no. 455: Magnesium sulfate before anticipated preterm birth for neuroprotection. Obstet Gynecol. 2010; 115(3):669-71.
61. American Academy of Pediatrics Statement of Endorsement. Delayed umbilical cord clamping after birth. Pediatrics. 2017; 139(6):e20170957.
62. Parikh P, Juul SE. Neuroprotection Strategies in Preterm Encephalopathy. Semin Pediatr Neurol. 2019; 32:100772.
63. Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. Pediatr Res. 2005; 58(5):931–5.
64. Klingenberg C, Wheeler KI, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in neonates. Cochrane Database Syst Rev 2017; (10):CD003666.
65. Yang L, Yu X, Zhang Y, Liu N, Xue X, Fu J. Encephalopathy in Preterm Infants: Advances in Neuroprotection With Caffeine. Front Pediatr. 2021; 9:724161.
66. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012; 307(3):275–82.
67. Moody C, Callahan TJ, Aldrich H, Gance-Cleveland B, Sables-Baus S. Early Initiation of Newborn Individualized Developmental Care and Assessment Program (NIDCAP) Reduces Length of Stay: A Quality Improvement Project. J Pediatr Nurs. 2017; 32:59-63.
68. Westrup B. Family-centered developmentally supportive care: the Swedish example. Arch Pediatr. 2015; 22(10):1086-91.