PriMera Scientific
Medicine and Public Health
Volume 1 Issue 1 August 2022
https://doi.org/10.56831/PSMPH-01-002
ISSN: 2833-5627

*Research Article*

# Hypoxic-Ischemic Family Brain Injury: Forecasting and Prevention

**Citation:** CP Posokhova., et al. "Hypoxic-Ischemic Family Brain Injury: Forecasting and Prevention". PriMera Scientific Medicine and Public Health 1.1 (2022): 03-10.

**Received:** July 20, 2022

**Published:** August 08, 2022



**CP Posokhova* and O Yu Kucherenko**

*Odessa National Medical University, Odesa, Ukraine*

***Corresponding Author:** CP Posokhova, Odessa National Medical University, Odesa, Ukraine.

## Summary

***The aim of the study*** - to investigate the influence of risk factors in the mother and morbidity in the neonatal period on the development of hypoxic-ischemic encephalopathy of newborns, depending on their gestational age, as well as to determine the effect of neuroprotection on the development of hypoxic brain lesions in premature infants.

***Materials and Methods*** At the first stage, a retrospective analysis of the course of pregnancy, child birth and the condition of newborns was carried out in 150 women whose children had suffered from hypoxic-ischemic brain damage. Group I (I G) consisted of 62 women who gave birth to full-term babies, Group II (II G) - 88 women who gave birth prematurely at 26+6 - 33+6 weeks of gestation. At the second stage, the level of neurospecific markers of nerve tissue damage (NSE and S100) was prospectively investigated in 60 preterm infants at gestational terms up to 32 weeks, which were divided in to two groups. The main group (MG) consisted of 30 preterm infants whose mothers were injected with magnesium sulfate for the purpose of neuroprotection, the comparison group (CG) - 30 preterm infants whose mothers did not receive neuroprotection for various reasons.

***Results and Discussion*** The risk factors for the birth of children with HIE include extra genital pathology in the mother (OR 1090.818, 95% CI 64.501-18447.401), urogenital infections-chlamydia (OR 21.87, 95% CI 1.264 - 378.397), prematurity, low weight bodies at birth, PROM, chorionamnionitis (OR 17.6, 95% CI 2.288 - 135.407), Apgar score <7 points, morbidity in the neonatal period. Neurospecific enolase (NSE) was significantly higher in children with gestational age up to 32 weeks and an Apgar score of <6 points. The lower concentration of protein S 100 in newborns of the main group can be explained by the protective effect of magnesium sulfate on the central nervous system of a premature new born.

***Conclusions*** Risk factors for neurological disorders in newborns include extragenital pathology, urogenital infections of the mother, prematurity, premature rupture of the membranes, the development of chorionamnionitis, and fetal growth retardation. Conducting neuroprotection with magnesium sulfate before delivery is an important measure to prevent hypoxic-ischemic brain damage to the fetus and premature newborn.

***Keywords:*** hypoxic-ischemic encephalopathy; prematurity; preterm labor; chorionamnionitis; neuroprotection

## Introduction

An alarming trend has been noted over the last two decades: while the number of healthy children in Ukraine is decreasing, the number of children with disabilities is increasing annually, on average by 16,000 children, or with an annual increase of 0.5% [1-3]. Disability of the child population is one of the most urgent problems, as it is a medical, social, psychological, economic problem and has national significance. Society's concern for disabled children has been going on for many years. Congenital anomalies, deformations and chromosomal disorders remain in the 1st place, mental and behavioral disorders are in the 2nd place, and in the 3rd place are diseases of the central nervous system, the rate of which is 61.64 per 1000 births, and the rate of children's cerebral paralysis (cerebral palsy) - 0.13 [4-6].

According to statistics, 65% of cases of damage to the central nervous system in newborns are due to hypoxic-ischemic disorders, and only 15% are due to various postnatal and genetic factors [6]. Lesions of the nervous system lead to child disability in 20.6% of cases, while in 70-80% of cases they are due to perinatal factors [7, 8].

At the current stage, a number of risk factors for HIE (hypoxic-ischemic encephalopathy) have been identified, which can be grouped into the following categories: socio-demographic factors, maternal health, pregnancy course and complications, fetoplacental complex condition, fetal condition, childbirth course and complications, newborn condition, the quality of medical care in health care institutions [9, 10].

One of the most severe perinatal consequences of HIE is the development of cerebral palsy. The overall prevalence of cerebral palsy is approximately 2 per 1,000 live births. The prevalence of cerebral palsy is much higher in preterm compared to full-term children and increases with decreasing gestational age and body weight (BW) at birth [11-14].

The frequency of cerebral palsy depends on the gestational age (GA): GA<28 weeks - 82 per 1000 live births, GA from 28 to 31 weeks - 43 per 1000 live births, GA from 32 to 36 weeks - 6.8 per 1000 live births, GA> 36 weeks - 1.4 per 1000 live births.

The frequency of cerebral palsy depends on the body weight at birth: <1500 g - 59.2 per 1000 live births, 1500 to 2499 g - 10.2 per 1000 live births, > 2500 g - 1.33 per 1000 live births. In large epidemiologic studies of children with cerebral palsy, approximately 25% were very preterm (GA<32 weeks), 10-20% were moderately preterm or late preterm (GA 32-36 weeks), and 60% were born at term (GA> 36 weeks) [15, 16].

A meta-analysis of 26 observational studies showed that both clinical and histological chorionamnionitis were associated with an increased risk of cerebral palsy (relative risk [RR] 1.9, 95% CI 1.5-2.5) [17]. Another case-control study found that any maternal infection during pregnancy was associated with an increased risk of cerebral palsy (OR 2.9, 95% CI 1.7-4.8) and that neonatal infection was strongly an independent predictor of cerebral palsy (OR 14.7, 95% CI 1.7-126.5) [18].

Thus, prematurity, intrauterine and intranatal hypoxia of the fetus has a multifactorial etiology, which leads to neonatal hypoxic-ischemic encephalopathy with adverse consequences.

## The purpose of the study

Is to study the influence of maternal risk factors and morbidity in the neonatal period on the development of hypoxic-ischemic encephalopathy in newborns depending on their gestational age, as well as to investigate the influence of neuroprotection on the development of hypoxic brain lesions in premature newborns.

## Research Materials and Methods

We conducted a retrospective analysis of the course of pregnancy, childbirth and the condition of newborns in 150 women whose children suffered hypoxic-ischemic brain damage during pregnancy and childbirth, as a result of which is a delay in mental and physical development, neurological diseases and cerebral palsy. Depending on the date of delivery, we distinguished two groups: the first

group (II G) consisted of 62 (42.3%) women who gave birth to full-term children, the second group (II G) consisted of 88 (58.7%) women who gave birth prematurely in in the period from 26+6 to 33+6 weeks of gestation.

The average age of women in both groups did not differ and was 28.9±2.6 years. Harmful habits, such as smoking, were more than 30% of women in both groups. Odds ratio (OR) in case of harmful habits in pregnant women such as smoking/alcohol was 4.128 (95% CI 1.129 - 15.094).

According to our data, pregnant women with II G who gave birth prematurely, compared to women with I G, had such extragenital diseases as exacerbation of chronic pyelonephritis (15.8%), acute respiratory infections during pregnancy (18.2%)), respiratory diseases (15.9%), pulmonary tuberculosis (4.5%), HIV infection (9.1%) and surgical intervention (appendectomy) in 2.2% of women. The infectious factor in II G women could be the trigger for premature births and the birth of premature babies.

The odds ratio (OR) in pregnant women with extragenital pathology whose children have cerebral palsy was large (OR 1090.818, 95% CI 64.501-18447.401), which indicates an unfavorable prognosis for children whose mothers have extragenital pathology.

One of the causes of miscarriage and premature birth is urogenital infection in pregnant women.

The presence of such genital infections as chronic candidiasis (29.5 %), trichomoniasis (15.9 %), syphilis (9.1 %), bacterial vaginosis (10.2 %), HIV infection contributed to premature birth in pregnant women (9.1%). In total, almost 70% of pregnant women with II G had urogenital infections during pregnancy. These infections were not treated in almost 50% of pregnant women during pregnancy.

| ***Urogenital infections*** | ***The first group Urgent childbirth n=62*** | | ***ThesecondgroupPrematurebirth n=88*** | |
|---|---|---|---|---|
| | ***Abs.*** | ***%*** | ***Abs.*** | ***%*** |
| Bacterialvaginosis | 4 | 6,4 | 9 | 10,2 |
| Chlamydia | 3 | 4,8 | 10 | 11,3* |
| Trichomoniasis | 4 | 6,4 | 14 | 15,9* |
| Chroniccandidiasis | 8 | 12,9 | 26 | 29,5* |
| Syphilis | 2 | 3,2 | 8 | 9,1* |
| Genitalherpes | 1 | 1,6 | 3 | 3,4 |
| Total | 22 | 35,4** | 61 | 69,3** |

*Note.* Significance relative to group Γ I * p<0.05.

***Table 1:*** Urogenital infection in examined women of both groups.

In the case of genital infections in pregnant women of both groups, the odds ratio was as follows: chronic candidiasis (OR 2.352, 95% CI 0.973 - 5.686), trichomoniasis (OR 4.809, 95% CI 0.228 - 101.408), chlamydia (OR 21.87, 95% CI 1.264 - 378.397), HIV infection (OR 2.858, 95% CI 0.115 - 70.978).

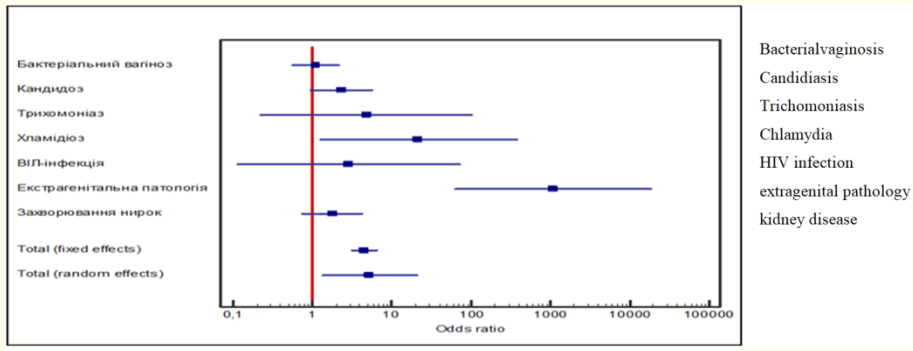


***Figure 1:*** The risk of giving birth to children with HIE in examined pregnant women.

Childbirth in both groups of our observation proceeded with complications. Thus, premature rupture of the membranes occurred in 73 (48.6%) pregnant women in both groups, which is 4 times more than in the 1st CG. A waterless interval of more than 48 hours and chorionamnionitis were present in almost a third of women with II WG, which contributed to intrauterine infection and hypoxic brain damage. 6 (6.8%) pregnant women with II WG had a prolonged waterless period of more than 168 hours.

Thus, the risk factor for cerebral palsy with a water-free period of more than 24 hours was 6,255 (95% CI 1,363 - 28,701), in the case of the development of chorionamnionitis, the risk factor was 17.6 (95% CI 2,288 - 135,407). The above data confirm the role of an infectious factor in the development of hypoxic-ischemic encephalopathy.

| ***The course of childbirth*** | I ***G*** ***n=62*** | | II ***G*** ***n=88*** | |
|---|---|---|---|---|
| | ***Abs.*** | ***%*** | ***Abs.*** | ***%*** |
| Premature rupture of fetus membrane PRFM (24-48 hours) | 12 | 19,3** | 12 | 13,5** |
| PRFM (48 -168 hours) | 4 | 6,5 | 20 | 22,7* |
| PRFM (>168 hours) | 0 | 0 | 6 | 6,8 |
| Chorionamnionitis | 2 | 3,2 | 26 | 29,5* |
| Pelvicpresentation | 4 | 6,5 | 9 | 10,2 |
| Prematuredetachmentof a normallylocatedplacenta | 8 | 12,9 | 12 | 13,6 |
| Placentaprevia, bleeding | 2 | 3,2 | 2 | 2,3 |
| Tightentanglementoftheumbilicalcordaroundtheneck | 3 | 4,8 | 7 | 7,9 |
| Procreation/procreation | 8 | 12,9** | 22 | 25,0** |
| Weaknessoflaboractivity | 6 | 9,6 | 10 | 11,3 |
| Rapidchildbirth | 2 | 3,2 | 8 | 9,1* |
| Fetaldistress | 38 | 45,2** | 41 | 46,5** |
| Cesareansection (planned) | 4 | 6,4 | 7 | 7,9 |
| Urgentcaesareansection | 17 | 27,4** | 23 | 26,1** |
| Obstetricforceps | 6 | 9,7 | 0 | 0 |
| Vacuumextractionofthefetus | 4 | 6,4 | 2 | 2,2 |

*Note.* Significance relative to group Г I * p<0.05.

***Table 2:*** Course of childbirth in examined pregnant women.

The period of gestation is important for the development of HIE in newborns. The immature brain of the fetus is particularly sensitive to all factors that may arise during pregnancy and childbirth. Based on our data, pregnant women from group II gave birth to 24 (27.3%) children with extremely low body weight in the gestation period of 27-30 weeks of pregnancy, who had hypoxic-ischemic brain damage.

Apgar score is a prognostic factor of HIE in newborns. Thus, among 150 children of both groups, the Apgar score at 1 and 5 minutes was 2-3 points - 12-8%, 4-5 points - 38-25.4%, 6 points - 58-38.6%, 7 and above - 42-28%. That is, 72% of children had severe fetal distress at birth.

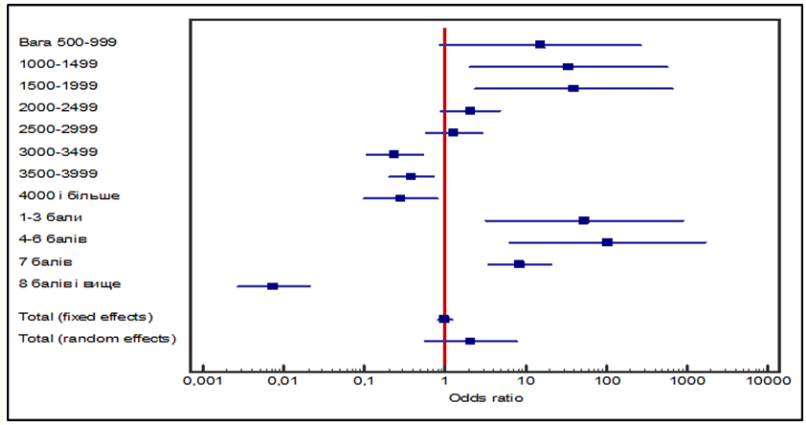


***Figure 2:*** Risk of developing GIE depending on birth weight and Apgar score.

Newborns had a large number of severe diseases in the neonatal period, and premature newborns had 2.3 times more. The most severe diseases in the neonatal period, which indicate severe hypoxic-ischemic damage to the brain, were intraventricular hemorrhage (IVH) in 27.3% of premature newborns, HIE in 59 (39.3%) children in both groups, cerebral edema in 12 (8%) of children in both groups, coma in 5 (5.7%) premature newborns. Brain damage was evidenced by the development of excitement syndrome in every fourth child, depression syndrome in 37.5% of premature children, and convulsions. Congenital infection contributes to brain damage, which was present in 31.8% of premature newborns. Unfavorable risk factors are the development of type I and II RDS, which 40-26.7% of children in both groups had. Necrotic enterocolitis complicated the condition of newborns in 28-41.8% of premature newborns. Thus, our data show that children who had hypoxic-ischemic brain damage were in serious condition and needed intensive treatment.

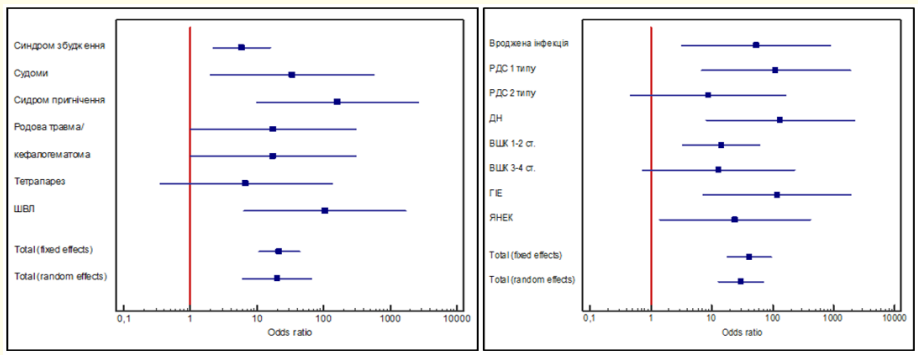


***Figure 3:*** The ratio of the chances of diseases to hypoxic-ischemic damage of the brain in newborns.

Thus, newborns with congenital infection, 3-4 stage IVH, HIE, convulsions, suppression syndrome, birth trauma, tetraparesis, and ventilator treatment have the greatest chance of brain damage. The above-mentioned diseases were probably more frequent in women born to women from the second group, who were not timely hospitalized with complications of pregnancy and childbirth without preventive measures for future children. 3 children from the comparison group died in the first 7 days. The causes of early neonatal mortality were 4th-stage coronary artery disease, birth trauma, and congenital infection. There were no perinatal losses in the first group of cases.

At the next stage of our research, in the event of a threat of premature birth, neuroprotection was performed on all pregnant women in order to determine markers of damage to the fetal brain. We divided all premature babies into two groups: the main group consisted of 30 premature babies who underwent neoprotection up to 32 weeks of gestation. The comparison group also included 30 premature babies, born at term up to 32 weeks, who for various reasons did not undergo neuroprotection.

In May 2011, the Canadian Society of Obstetricians and Gynecologists (SOGC) published a clinical guideline entitled "Magnesium Sulphate for Fetal Neuroprotection". The basis for the creation of this manual was the "problem associated with success". Magnesium sulfate for fetal neuroprotection is used according to the scheme: a loading dose of 4 g intravenously for 30 minutes followed by a maintenance infusion of 1 g/h. until the birth of the child. Magnesium has several intracellular actions, including anti-inflammatory effects and inhibiting calcium influx into cells [19, 20]. One Cochrane review and a meta-analysis of five randomized controlled trials (RCTs) [21] demonstrated that magnesium sulfate was effective in reducing the risk of HIE (RR 0.69, 95% CI 0.55-0.88) and the composite outcome of death or cerebral palsy (RR 0.86, 95% CI 0.75 to 0.99).

There is growing evidence that polyunsaturated fatty acids are important for normal brain development, promote larger birth weight, and reduce the risk of preterm birth. The results of preclinical and clinical studies indicate that the intake of arachidonic and docosahexaenoic acids during pregnancy is important for neurodevelopment and neuroprotection for premature infants [22].

One of the markers of nerve tissue damage is neuron-specific enolase (neuron-specificenolase -NSE) and S100B protein [23, 24]. Neuron-specific enolase (NSE) is a glycolytic enzyme that consists of dimers and is found in high concentrations in neurons and neuroendocrine cells, which catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Elevation of NSE in hypoxic fetal brain injury predicts neurological deficits. A high level of NSE is associated with adverse outcomes in newborns [25].

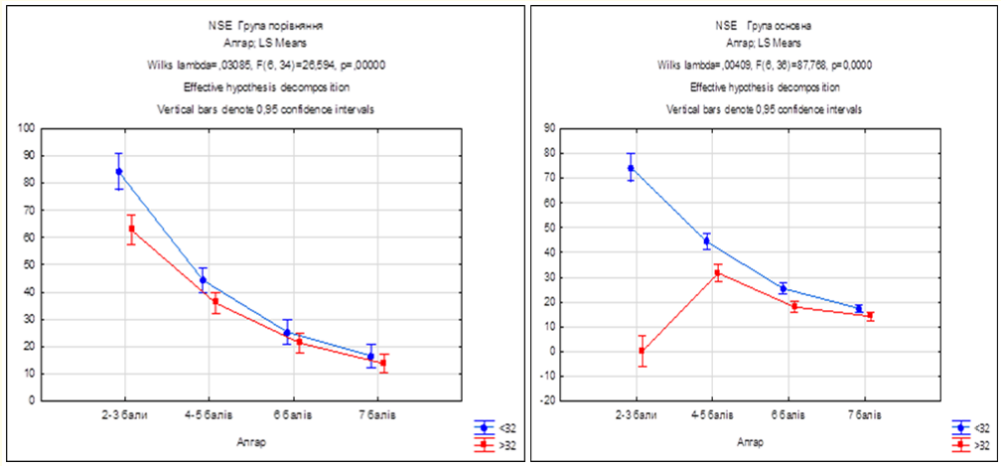


***Figure 4:*** The amount of neuron-specific enolase (ng/ml) in premature newborns depending on the gestational age and Apgar score.

Thus, the value of NSE was probably higher in children with a gestational age of up to 32 weeks and an Apgar score of less than 6 points.

Determining the concentration of S100 protein in biological fluids provides the necessary information about perinatal brain damage after perinatal asphyxia, HIE and IBS, physiological development of the central nervous system in healthy newborns, and the effectiveness of drug therapy in pregnant women and newborns [23, 25].

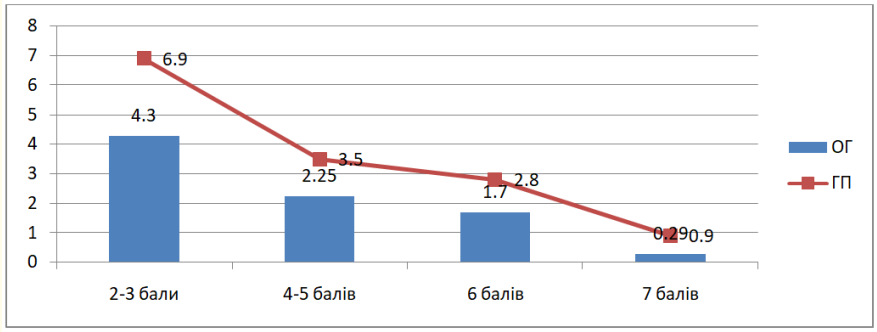


***Figure 5:*** Level of protein S 100 in premature newborns (μg/l).

The highest concentration of protein S 100 was found in profoundly premature babies with a gestational age of up to 32 weeks and an Apgar score of 2-3 points. The lower concentration of protein S 100 in the newborns of the main group can be explained by the neuroprotection of these children with magnesium sulfate before delivery, which has a protective effect on hypoxic brain damage. The concentration of protein S 100 reached almost normal values in newborns with an Apgar score of 7 points.

Thus, neurospecific markers such as NSE and S100 protein can predict the degree of hypoxic brain damage in newborns.

## Conclusions

1. Risk factors for neurological disorders in newborns are the presence of extragenital pathology, urogenital diseases in the mother, prematurity, pregnancy complications such as premature rupture of the fetal membranes, development of chorionamnionitis, fetal growth retardation.
2. Children with hypoxic-ischemic brain damage had a low Apgar score, were in a critical condition after birth, and required intensive treatment. Premature newborns had a 2.3 times higher percentage of severe diseases in the neonatal period.
3. Qualified antenatal care, prevention of premature birth and birth of children with low body weight, timely diagnosis of fetal hypoxia and neuroprotection with magnesium sulfate before delivery are important measures to prevent hypoxic-ischemic damage to the brain of the fetus and newborn.

## References

1. Antipkin Yu G., et al. The state of health and population of the country (chastyna 2) [Child health status – the future of the country (part 2)]. Health care - Child health, [in Ukrainian] 13.2 (2018): 142-152.
2. Slabkiy GO, Shafranskiy VV and Dudina OO. Disability of Children as a Public Health Problem: Prevention and Ensuring Effective Rehabilitation". Herald of social hygiene and health care organization of Ukraine [in Ukrainian] 3.69 (2016): 4-9.
3. State of health of children aged 0-17 years, including schoolchildren, for 2018 (analytical and statistical reference) [Child health status 0-17 years including for 2018 (analytical and statistical reference book)]. Kyiv: Ukrainian Medical and Statistical Center [in Ukrainian] (2019).

4. Dudina OO., et al. I will receive health care for those displaced [To the child health status]. Ukraine. Healthcare – Ukraine. The health of the nation, [in Ukrainian] 3 (2015): 10-11.
5. Moiseienko RO and Martyniuk VYu. Concepts and social and pediatrics (complex and medical and social rehabilitation of children from the environment) [The concept of social pediatrics (complex medical and social rehabilitation of children with disabilities)]. Rehabilitation tapaliatyvna medicine – Rehabilitation and palliative medicine, [in Ukrainian] 1.1 (2015): 118-121.
6. Palchik AB and Shabalov NP. Hypoxic-ischemic encephalopathy of the newborn [Finger AB Hypoxic-ischemic encephalopathy of newborns]. 4th ed., rev. and add. Moscow: MED press-inform [in Russian] (2013).
7. Gopagondanahalli KR., et al. "Preterm hypoxic-ischemic encephalopathy". Front. Pediatr 4 (2016): 114.
8. LaRosa DA., et al. "Understanding the full spectrum of organ injury following intrapartum asphyxia". Front. Pediatr 5 (2017): 16.
9. Lundgren C., et al. "Ante- and intrapartum risk factors for neonatal hypoxic ischemic encephalopathy". J. Matern. Fetal. Neonatal. Med 31.12 (2018): 1595-1601.
10. Munoz D., et al. "Risk factors for perinatal arterial ischemic stroke: a case-control study". Cell. Med (2018): 10.
11. Hirvonen M., et al. "Cerebral palsy among children born moderately and late preterm". Pediatrics 134.6 (2014): e1584-93.
12. Lees CC., et al. "2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial". Lancet 385.9983 (2015): 2162-2172.
13. Linsell L., et al. "Prognostic factors for cerebral palsy and motor impairment in children born very preterm or very low birthweight: a systematic review". Dev. Med. Child. Neurol 58.6 (2016): 554-569.
14. Oskoui M., et al. "An update on the prevalence of cerebral palsy: a systematic review and meta-analysis". Dev. Med. Child. Neurol 55.6 (2013): 509-519.
15. Stavsky M., et al. "Cerebral palsy-trends in epidemology and recent development in prenatal mechanism of disease, treatment and prevention". Front. Pediatr 5 (2017): 21.
16. Sellier E., et al. "Decreasing prevalence in cerebral palsy: a multi-site European population based-study 1980 to 2003". Dev. Med. Child. Neurol 58.1 (2016): 85-92.
17. Blume NK., et al. "Intrapartum fever and chorioamnionitis as risk forencephalopathy in term newborns: a case-control study". Dev. Med. Child. Neurol 50.1 (2008): 19-24.
18. Galinsky R., et al. "Complex interactions between hypoxia-ischemia and inflammation in preterm -brain injury". Dev. Med. Child. Neurol 60.2 (2018): 126-133.
19. WHO Reproductive Health Library. WHO recommendation on the use of magnesium sulfate for fetal protection from neurological complications (November 2015). The WHO Reproductive Health Library; Geneva: World Health Organization.
20. Magee L., et al. "SOGC clinical practical guideline. Magnesium sulfate for fetal neuroprotection". J. Obstet. Gynaecol. Can 41.4 (2019): 516-529.
21. "Committee Opinion No 455: Magnesium sulfate before anticipated preterm birth for neuroprotection". J. Obset. Gynecol 115.3 (2010): 669-671.
22. Klevebro S, Juu SE and Wood T. "A More Comprehensive Approach to the Neuroprotective Potential of Long-Chain Polyunsaturated Fatty Acids in Preterm Infants Is Needed-Should We Consider Maternal Diet and the n-6:n-3 Fatty Acid Ratio?". Front. Pediatr 7 (2020): 533.
23. Prikhodko AM., et al. "Biomarker of brain damage in newborns". Neonatology: news, opinions, training– Neonatology: nevs, opinions, training, [in Russian] 7.1 (2018): 70-76.
24. Amer-Wahlin I., et al. "Brain-specific NSE and S-100 proteins in umbilical blood after normal delivery". Clin. Chim. Acta 304.1-2 (2001): 57-63.
25. Roka A., et al. "Serum S100B and neuron-specific enolase levels in normothermic and hypothermic infants after perinatal asphyxia". Acta. Paediatr 101.3 (2012): 319-23.