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ABSTRACT

of the dissertation work for the degree of Doctor of Philosophy

CLINICAL SIGNIFICANCE OF VASOREGULATORY FACTORS IN CENTRAL NERVOUS SYSTEM LESIONS IN PREMATURE INFANTS

Specialty: 3220.01-Pediatry

Field of science: Medicine

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GENERAL CHARACTERISTCS OF THE SCIENTIFIC RESEARCH WORK

Relevance of the topic: The perinatal hypoxic lesions of the central nervous system (CNS) occupy a significant place in the structure of pathology of newborns, especially premature ones and consist 60-80% of all cases. It is proven that, hypoxic brain injury is complex process, including cerebral hypoperfusion with the development of circulatory and hemichypoxia. These processes occur on the background of metabolic, neurocirculatory, rheological disorders[1,2,3]. Hypoxic-ischemic encephalopathy takes the fifth place among causes of death among children under the five years of age. In case of hypoxic-ischemic encephalopathy (HIE) lethality reaches 50%. Most of death cases occur in the first week of life of infants and are mainly associated with multiple organ failure.

According to WHO data hypoxic ischemic CNS injury is the main cause of consequent development of disability in children depending on the severity. HIE ranges from 50-80% among reasons of diasbility in children[4,5]

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About 80% of children have serious neurological problems after severe HIE[6.] Hypertensive, hydrocephalic syndromes in 46.1% of cases with delayed motor or movement development in 57.5% of cases; psychoverbal development; occlusive hydrocephalus in 8.3% of cases, cerebral palsy in 5.5%; epilepsy, which is symptomatic in 4.6% of cases, respectively are observed most of all among the serious neurological consequences in premature newborns who have experienced severe form of HIE[6,7] .

The problem of determining the pathogenetic mechanisms of hypoxic-ischemic brain damage and the search for vasoregulatory markers that adequately reflect these verity of damage to the nervous system remains relevant today. It is known that, nitric oxide is a compound produced by endothelial eNOS, the neuronal nitric oxide synthase nNOS1, which is present in endothelial, neuronal brain cells[8,9]. Processes associated with vasoregulatory functions, which are occurring in the body of a premature infant are not sufficiently studied. The information about the nature of changes in vasoregulatory systems in premature infants with CNS injuries is practically absent, besides it questions of their influence on one or another system of vital activity of the body of infant, is not studied.

Thus, studying of the complex of vasoregulatory mechanisms in the central nervous system injuries in premature infants depending on gestational age is relevant and has scientific and practical interest.[10]

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The object and subject of the study:

The objects of the study were premature newborns with CNS injury. Studying of vasoregulatory mechanisms (nitric oxide synthetases) in the formation of CNS pathology was the subject of observation.

The purpose of the study: study the role of vasoregulatory mechanisms in damage of the central nervous system in premature infants.

Objectives of the study:

1. To analyze ante- and prenatal risk factors of formation of hypoxic-ischemic encephalopathy in premature infants.
2. To study the features of nitric oxide synthase systems (eNOS and nNOS) depending on gestation age of premature infants.
3. To determine the connection between severity of HEI in premature infants and the level of NO synthase (eNOS and nNOS).
4. To detect the effect of neuronal and endothelial nitric oxide synthase (eNOS and nNOS) on the nature of the CNS lesion (ICH, PVL).
5. To develop an evaluation and prognostic table on complex of clinical-anamnestic and laboratory-instrumental methods for detecting of comparative risk factors of development of ischemic or hemorrhagic lesions of the central nervous system.

Methods of the study: The conventional clinical studies of functional state of organs and systems (postnatal assessment of gestational age, DubowitsL. scale, G.M. Dementieva and E.V. Korotkova scale, Ballard scale) have been conducted, the parameters of morphological-functional immaturity are detected according to the scale Hoepffnes W., Rauntenbach M. The severity of encephalopathy was assessed using the SarnatH.B scale.

There were carried out general laboratory(hematological, biochemical tests: blood gases, sodium, potassium, calcium, magnesium, albumin); Markers of vasoregulatory factors, in particular nitric oxide synthase - eNOS, NO, nNOS, were studied by the immunoenzyme method. Instrumental research methods: X-ray

diagnostics (RH) of the chest organs, NSG, Doppler studies of the vascular system, Echo CG, ECG according to indications were carried out. The neurological status was assessed.

The main provisions to be defended:

- obstetric and gynecological history burdened depending on women's health status , helps for formation of antenatal and intranatal risk factors for the development of hypoxic-ischemic encephalopathy in premature infants.

- morbidity frequency and severity rate of clinical course and progression of hypoxic-ischemic encephalopathy in premature infants directly depends on gestational age, intrauterine hypoxia and ischemia.

- activation of the nitric oxide synthase system (eNOS, nNOS) and NO depending on gestation age and severity rate of cerebral ischemia, indicate a violation of vasoregulatory mechanisms in HIE in premature infants.

- activation of eNOS, nNOSand NO in blood serum, indicates the damage of endothelium of the vascular bed, impaired neurogenesis, leading to damage to the central nervous system, the occurrence of ICH and PVL.

Scientific innovation of the study:

- Ante- and intranatal risk factors of formation of HIE in premature infants are analyzed and specified. It is approved that, maternal reproductive health plays a leading role in formation of CNS pathologies in premature infants. It was affirmed that the maternal reproductive health status plays a key role in the formation of central nervous system pathology in infants.
- The clinical and laboratory studies data of premature infants depending on gestational age taking into account the severity of damage to the central nervous system are presented.
- A relationship between the severity of hypoxic-ischemic encephalopathy in premature infants and the level of NO synthases has been identified.
- The features of the nitric oxide synthase system (eNOS, nNOS и NO) in premature infants, depending on gestational age are studied

for the first time. The role of endothelial, neuronal synthase and nitric oxide in development of CNS lesions in infants is shown. Vasoregulatory factors in CNS lesions in infants have been studied.

- Algorithm for identifying relative risk factors for the development of CNS lesions and evaluative and prognostictable of clinical and anamnestic, laboratory and instrumental research methods for identifying the relative risk factors for the development of ischemic or hemorrhagic lesions of the central nervous system are developed.

Practical significance of the study:

- Failure of the vasoregulatory system, which is expressed in the active expression of endothelial, neuronal nitric oxide synthases, occurs in case of damaging of the central nervous system.
- Activation of eNOS and nNOS leads to the activation of NO in blood serum, which creates the need to determine these markers, which indicate damage to the endothelium of the vascular bed, impaired neurogenesis.
- eNOS, nNOS, NO markers can be accepted as diagnostic criteria for assessing the severity of cerebral ischemia, which will help determine the role of vasoregulatory factors in damage to the central nervous system in premature newborns.
- The evaluative-prognostic table and an algorithm is developed and complex of clinical-anamnestic and laboratory-instrumental research methods to identify relative risk factors for ischemic and hemorrhagic lesions of the central nervous system is presented.

Approbation of the scientific research work:

The main provisions of the dissertation have been reported in the International Scientific-Practical Conference "Questions of education and science" (Tambov, Russia 2021), in Scientific-Practical Conference devoted to A.M.Aliyev (Baku, 2021). The first discussion of the scientific work was held at the interdepartmental session (Departments of Pediatrics, Anesthesiology and Resuscitation, Neurology and Clinical Neurophysiology) 05.07. 2023 year, protocol №2 and approbation of the dissertation work was

conducted at the Approbation Seminar of the Dissertation Council ED 2.27 (05.04.2024 year, protocol №7)of the Azerbaijan Medical University.

Implementation of results: The obtained results were implemented in the practical work of the Department of Neonatology and the educational process of the Department of Pediatrics of the Azerbaijan State Advanced Training Institute named after A. Aliyev.

Published materials: The main results of the research work were published in 6 journal articles, including 2 articles abroad (journals indexed in Scopus, Web of Science and other international indexing systems), and 4 articles in Azerbaijan. The articles were published in journals recommended by the Higher Attestation Commission. 4 theses were published on the topic of the dissertation.

Name of the organization where the dissertation work was conducted: The dissertation work was condycted at the Department of Pediatrics of the Azerbaijan State Advanced Training Institute named after A. Aliyev, in the departments of premature babies, resuscitation and intensive care of the Research Institute of Pediatrics named after K.Y. Farajeva of the Republic of Azerbaijan, in the maternity hospital of the Research Institute of Obstetrics and Gynecology.

The structure and volume of the dissertation work:

The dissertation work is written on 171 pages, illustrated with 10 tables, 22 pictures, 2 schemes, consists of introduction (9423 symbols), literature review (46911 symbols), materials and methods (9783 symbols), results of own researches (Chapter III - 47591 symbols and Chapter IV– 27869 symbols), discussion of achieved results (33298 symbols), conclusion (1658 symbols), practical recommendations (1141 symbols). The bibliographic index includes 171 foreign and 10 domestic literature sources. Total quantity of symbols (not including spaces, tables, figures, charts and references) is 177673.

MATERIALS AND METHODS OF THE STUDY

The research work was conducted in the departments of premature babies, resuscitation and intensive care of the Research Institute of Pediatrics named after. K.Y. Farajeva of the Azerbaijan Republic and in the maternity hospital of the Research Institute of Obstetrics and Gynecology in 2017-2022. Totally 102 premature infants of different gestational ages (g/a) with perinatal lesions (PL) of CNS were examined. Premature babies born by mothers with burdened obstetric anamnesis were the objects of examination. Infants were divided into 2 main groups: group I n=56 premature infants of gestation age 35-37 weeks with HIE; group II consists of n=46 premature infants of gestation age 28-34 weeks and less with HIE. n=30 conditionally healthy premature infants were included to the control group III (CG). The clinical, laboratory diagnostic and instrumental methods of examination of infants have been conducted. Clinical methods included postnatal assessment of gestationalage (Dubowits L. scale, Dementieva G.M. and Korotkova E.V. scale, Ballardscale), parameters of morphofunctional immaturity (Hoepffnes W., Rauntenbach M. scale), the functional state of organs and systems was analyzed. The severity of neonatal encephalopathy was detected based on results of assessment by Sarnat H.B. scale during first 24 hours of life of the infant. Laboratory research methods included hematological (hemogram, hemostasis), biochemical tests (KOS, Na, K, Ca, Mg, protein, albumin, glucose, CRP).

Instrumental research methods included RN-diagnostics of thechest, NSG, Doppler studies of the vascular system, Echo CG, ECG. The diagnosis of PL of CNS was based on data about antenatal history, clinical symptoms of the disease complex in the first 2-3 weeks of a child's life, detection of pathognomonic symptoms of CNS damage. Premature infants were examined by neuropathologist, ophthalmologist, according to indications - cardiologist, otolaryngologist, surgeon. Studying of vasoregulatory mechanisms was carried out using determination of endothelial nitric

oxide synthase (eNOS); nitric oxide (NO) and neuronal nitric oxide synthase (nNOS) was determined by ELISA using the Human nNOS Immunoassay R&D System reagent kit (ZAO BioKhimMak, Moscow). The biometric method (statistical processing) was carried out by means of the "STATISTICA-10" software package; the graphs were built using "ORIGN-7"). At $p<0.05$ and ($p<0.01$, $p<0.001$), the differences between the data were considered significant, what meets the requirements of biomedical research.

RESULTS AND DISCUSSION

102 premature infants with different gestation ages were covered by our research work. These children were divided into two main groups. (Group I n=56; Group II n=46 premature infants with HIE). Premature infants of the first degree accounted for 49 (48.1%) cases with a gestational age of 36-37 weeks (body weight 2290±185 g, height 43.5±1.5 cm). Premature babies of the second degree - 32 (31.4%), gestational age 34-35 weeks, body weight 1625±125 g, height 42.7±1.8 cm. Premature babies of the third degree - 19 (18.6%), gestational age 30-33 weeks, body weight 1350±150 g, height 41.3±1.9 cm. Premature babies of the fourth degree - 2 (1.9%), gestational age 28 weeks, body weight 1020±105 g, height 7.4±1.2 cm. 72 babies (70.6%) were born by mothers under 35 years of age; over 35 years - 30 (29.4%). The largest percentage was made up by multiparous women - 65(63,7%) cases; and primiparous women- 37(36.7%) cases. The quantity of male premature babies was 53(52%); female premature babies consisted 49(48%) cases. The chronic intrauterine hypoxia was seen in 41premature infants (40.2% of all cases). 20 premature infants (19.6%) were born with asphyxia, entanglement of the umbilical cord was noted in 11 (10.8%) infants.

For correct assessment of health status of infants we studied the health status of mothers. According to anamnesis the most common extragenital pathologies among women were: anemia in 19 (18.6%) cases; diseases of the genitourinary organs in 11 (10.8%); endocrine diseases in 5 (4.9%); preeclampsia in 5 (4.9%) cases, varicose veins

of the lower extremities - in 3 (2.9%); acute viral infections in 15 (14.7%); neurosis in 5 (4.9%) cases, respectively. Gynecological diseases such as followings also were observed among these women: ovarian dysfunction in 11 (10.8%) women; chronic inflammatory diseases of the appendages - in 4 (0.4%) cases; ovarian endometriosis - 3 (2.9%); erosion of the cervix - 8 (7.8%); endometritis - 3 (2.9%) cases. Spontaneous miscarriages were noted in anamnesis in 8 (7.8%) cases and pregnancy after in vitro fertilization (IVF) -in 1(0.9%) case. Preterm birth was registered in 5 (4.9%) women. The birth of children with various malformations was noted in 2 (1.96%) cases. In 5 (4.9%) women, babies from a previous pregnancy were born with intrauterine growth retardation (IUGR).Birth of children with malformations was noted in anamnesis of 2(1.96%) women and medical abortion anamnesis of 19(41.3%) women. Preeclampsia was registered in 46 (45%) cases, fetoplacental insufficiency (FPI) in 29 (28.4%) cases. Premature abruption of the placenta was also observed in 5 (4.9%) cases, the threat of termination of this pregnancy was registered in 14 (12.7%) women.

Thus, antenatal and intranatal factors from the fetus have the crucial importance in the occurrence of HIE. From the point of view of the mother, a burdened obstetric and gynecological history, the course of pregnancy and childbirth, the peculiarities of the fetoplacental circulation, etc., what makes it possible to attribute the above factors to the risk group for the development of pathology of the central nervous system in an infant, play a dominant role.

Analyzing anamnesis of infants depending on gestation age, it should be noted that, 49(48%) of babies were infants with gestation age 36-37 weeks, 25(24.5%) – with g/a 33-34 weeks; 19(18.7%) – with g/a 32-33 weeks. The smallest percentage consisted infants with g/a 34-35 weeks – 7(6.9%); <28 weeks – 2(4.3%) cases. The body mass of children in the group I was – 2112.5±362.5 g.; in group II – 1207.5±292.5 g. Assessment of the condition of infants according to the Apgar scale at birth at the 1st minute: 4.37±0.06 points in group I; 3.58±0.07 points in group II; respectively, at the 5th minute:

6.04±0.1 - in group I; 5.45±0.07 points in group II. 27 (26.5%) infants were on CPAP; on IVL-17 (16.7%); on parenteral nutrition 28 (27.4%).

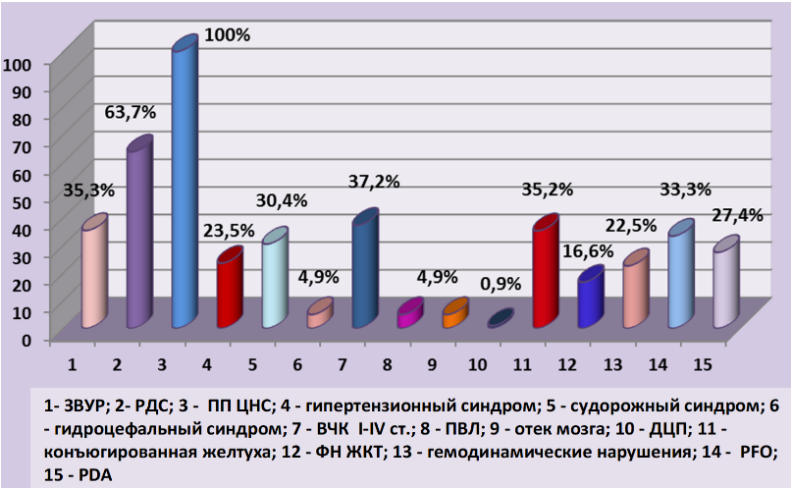
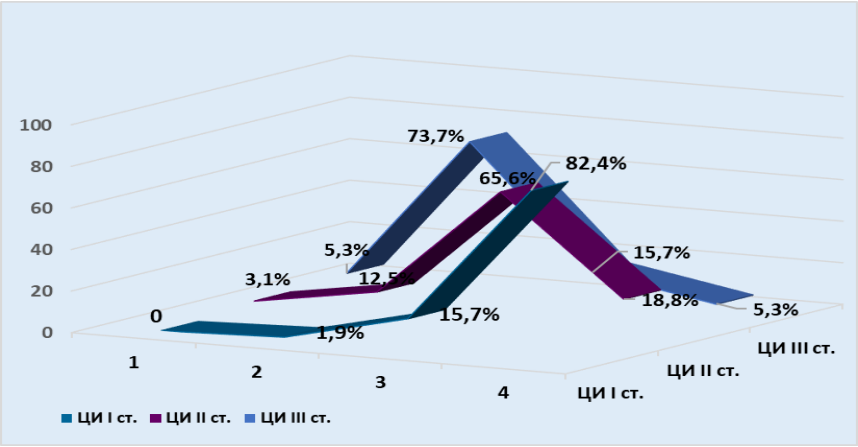


Fig. 1 Diagram of the frequency of occurrence of clinical syndromes and manifestations in premature infants

Figure 1 shows a diagram of the frequency of occurrence of clinical symptoms and syndromes in premature infants. It should be noted that PL of CNS was diagnosed in 100% of cases. Among the clinical manifestations and syndromes in these infants the followings were observed: RDS – 65(63.7%) cases; IUGR – 36(35.3%) cases; hypertension syndrome - 24 (23.5%) cases; convulsive syndrome - 31 (30.4%) cases; intracranial hemorrhage of level I-IV – 38 (37.2%) cases (Fig. 2). It should be noted that respiratory lesions in infants proceeded in the form of РДС from the first days of life, confirmed by the RH study.

The followings are almost equally diagnosed: PVL – 5(4,9%) cases: cerebral edema – 5(4,9%); CCP was observed in 1 case (0.9%). Conjugated jaundice - in 36 (35.2%) cases, hemodynamic disorders were noted in 23 (22.5%) cases also were observed; hemodynamic disturbances were noted in 23 (22.5%) cases; open

foramen oval (ductus oval) PFO - in 34 (33.3%) cases; open aortic duct (PDA) - in 28 (27.4%) cases. Functional disorders of the gastrointestinal tract were registered in 17(16.6%) babies. The following manifestations were observed in the clinical picture of CNS lesions in infants: anxiety (28.2%) cases; hyperesthesia (11.2%); depression syndrome (53.4%); tremor of hands and chin (33.7%); foot clonus (8.3%) cases; changes in muscle tone and reflexes: dystonia - 38.2% of cases, hypertonicity 13.5%, hypotension - 11.2%; spontaneous reflexes of Moro, Babinski are enhanced in 48.3% of cases, unstable - in 19.2%, weakened reflexes of oral automatism (ROA) in 34% of cases, severe eye symptoms (exophthalmos - in 37.2%; "+" symptom of Graefe 19%; transient strabismus - 8.6% of cases; horizontal nystagmus in 7.9% of cases, respectively. Also the followings were noted in the clinical picture: weakness, depression of consciousness, painful monotonous cry, clonic convulsions. Neurosonographic studies showed: increased pulsation of cerebral vessels, symmetrical dilatation of the lateral ventricles, increased echogenicity of the periventricular area, dilation of the lateral ventricles, ICH in the periventricular area. It should be noted that the neurological symptoms were observed on first days of life of children. The doppler studies of children with hydrocephalus showed an increase in the resistance index (IR) of blood vessels, an increase in the speed of blood flow through the cerebral vessels, which is explained by ventricular dilatation, which leads to stretching of the arteries and a decrease in their lumen. In case of ICH of infants, according the results of doppler studies slowing of blood flow in the anterior cerebral artery was observed in 13.7% cases.



Pic.2 Diagram of distribution of premature babies with cerebral ischemia (CI)

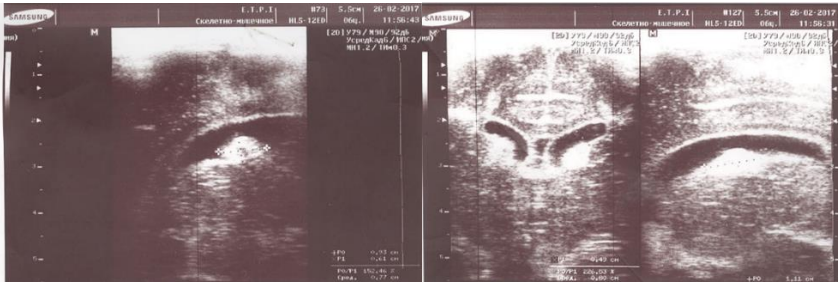
The comparative diagram of the distribution of premature infants with cerebral ischemia depending on the gestational age is given on picture 2. We separately analyzed the health status of infants born with extremely low (ELBM) and low body mass (LBM). RDS in these children proceeded with symptoms of respiratory failure of varying severity. Hypothermia, shortness of breath, hypoxemia, decrease in blood PaO2 <40 mm Hg, secondary apnea, perioral and acrocyanosis were observed in 100% of cases. Auscultatory against the background of weakened breathing, crepitant rales were heard in the lungs. RH picture showed reduction of pneumatization to "white lungs". Respiratory support included: CPAP, mechanical ventilation, surfactant therapy.

Thus, mild CI (stage I) in premature infants with a gestational age of <28-30 weeks was not detected in any case. Stage III of cerebral ischemia in most cases was observed in newborns of 28-30 weeks of gestation (5.3%) and 30-33 weeks of gestation (73.7%), largest proportion of stage II ischemia was found in infants, born at 34-35 weeks of gestation, and in premature infants 36-37 weeks of gestation, I stage of cerebral ischemia was noted in 82.4% of cases.

PL of the CNS of a hypoxic-ischemic nature depended on the severity of the transferred hypoxia, on the severity of cerebral ischemia (CI) of the brain, on the maturity of the infant. According to the classification, mild form of CI (stage I) was registered in 51(50%) cases, moderate form of CI (stage II) – in 32(31.4%) cases, severe form of CI (stage III) - in 19(18.6%) cases. According to the classification of Sarnat H.B. hypertensive syndrome, moderate hypercapnia, hypoxemia, acidosis were noted in the clinical picture of mild form of CI. The dopplerographic picture showed an increase in the velocity of blood flow through the main vessels of the brain of a compensatory nature. There were noted increased intracranial pressure, convulsions, hypertension, apnea, CNS depression syndrome in this category of infants in case of moderate form of CI. The dopplerographic picture showed increased diastolic velocity, signs of hypoperfusion of the anterior cerebral artery, decreased RI. Convulsions, a syndrome of depression, a violation of the rhythm of breathing, ocular neurological symptoms, and cerebral edema were observed in the clinical picture in severe PP CNS, CI stage III. Infants with stage III CI had intrauterine growth retardation (IUGR).

In the doppler picture, there were: persistent cerebral hypoperfusion, decreased diastolic velocity, increased RI. Hypoxic-hemorrhagic lesions of the central nervous system, manifested by ICH were the most frequent and serious problem for infants. It should be stressed that in infants with gestation age в 24-25 weeks ICH was detected in 6.8% of cases, with g/a 26-29 weeks – in 5.9% cases, with g/a 28-29 weeks – in 4.9%, with g/a 30 weeks – in 2.9% cases. Periventricular hemorrhages (PVH) with subepidemic hemorrhage on stage I was registered in 9 (8,8%) cases, PVH on stage II - in 5 (4,9%) cases, PVH on stage III – in 3 (2,9%) cases. It is necessary to note that, as the lower the gestational age of infants, as the more pronounced the course of HIE is observed. Characterizing the NSG data, we should say that in 4,9% of cases an increase in echogenic density in the periventricular zones, expansion

of the ventricles, wrinkling of the white matter of the brain around the ventricles were visualized.



Pic. 3. (a; b) Neurosonographic study.

Thrombus are seen in the subependymal zone on the left 9x6 mm and on the right 11x6.5 mm. Signs of immature brain. Intracranial hemorrhage stage I. Periventricular leukomalacia. Premature III stage. (own observation)

A picture of NSG in a premature infant with extremely low body weight is shown in pic.3.

Convulsions were observed in the first week of life of babies. Convulsions of tonic character were registered in 11,2% of cases. Clonic convulsions have occurred in preterm infants at 34-36 weeks of age. Hemodynamic disorders were expressed by violation of microcirculation, peripheral and central cyanosis, cardiac arrhythmia, edematous syndrome, marbling of the skin, the duration of the "white spot" for more than 3 seconds. In all observed infants hemodynamic disorders were assessed as secondary, caused by damage of the lungs and central nervous system.

It is possible that, functional failure of pathogenetic mechanisms plays a key role in the formation of the pathology of the perinatal period, a key role in the development of hypoxic and ischemic processes. Undoubtedly, these questions are related with pathogenetic aspects of vasoregulatory markers that perform endothelial, neuronal functions. The nitric oxide system plays an important, decisive role in the pathogenesis of hypoxic-ischemic

processes leading to the development of CNS pathology in premature infants. In connection with that we have studied nitric oxide synthesis in 71 premature infants taking into consideration their gestation age. 3 groups were divided: group I consisted of 20 premature infants with CI on stage I. The II group included 32 premature infants with CI on stage II and the group III consisted of 19 premature infants with CI on stage III. 20 conditionally healthy babies were in the group IV. During conducting the study, the increased eNOS level was observed in infants with 30-33 weeks gestation age. Particularly, during the first 3 days of infant's life the eNOS level indicator was 8,6 IU/ml in comparison with data of children in the group IV - 2,11±0,004 IU/ml. Despite, the eNOS level was slightly less than during first 5 days and was 7,5 IU/ml, on the 5-7th day, this indicator was 5 times higher than those in group IV – 1,98±0,01 IU/ml($p<0,05$). Activation of eNOS level was noted also in infants with 34-35 weeks gestation age: 8.92±0.12 IU/ml and 7.77±0.11 IU/ml (in 1-3rd and 5-7th days) in relation to CG, respectively ($p<0.05$).

For children in the group I with 36-37 weeks gestation age eNOS was detected within the interval of 9.79±0.14 IU/ml and 6,36±0,09 IU/ml (in 1-3rd and 5-7th days), respectively. In CG this indicator is registered within the interval of 2.11±0.004 IU/ml and 1.98±0.01 IU/ml ($p<0,05$) (1-3; 5-7 days). The comparative analysis showed that eNOS synthase levels in infants of the group II changed in well-defined intervals. So, in premature newborns 28-30 weeks of gestation, eNOS was 5.82 IU/ml and 5.42 IU/ml on 1-3rd and 5-7th days, respectively ($p<0,05$). In the group IV this indicator changed between 2.11±0,004 IU/ml and 1.98±0.01 IU/ml ($p<0.05$). Some increasing of eNOS was seen in infants with 30-33 weeks of gestation age in the group I: 6.52±0.18 IU/ml and 6.08±0.15 IU/ml during the first three and 5-7 days. In the group IV, the given indicator changed between 2.11±0.004 IU/ml on 1-3rd days and 1.98±0.01 IU/ml on 5-7th days ($p<0,05$) respectively. In infants with gestation age 34-35 weeks the active expression of eNOS was registered, the values of which were twice the levels in the CG and

were 6.68±0.009 IU/ml on 1-3rd days and 6.08±0.15 IU/ml on 5-7th days in comparison with group IV ($p<0.05$), respectively. For children with gestation age 36-37 weeks values of eNOS were registered during the first 3 days within the interval of 6.28±0.12 IU/ml, and 4.93±0.05 IU/ml on the 5-7th days of life, these values exceeded values in the group IV for 2-3 times, respectively ($p<0.05$).

Increase in the level of eNOS in a comparative aspect with the values in group IV is characteristic for the children of the group III with severe form of HIE. Especially, in infants with gestation age 28-30 weeks the value of given indicator was 6.76 IU/ml in the first three days of the life and on the 5-7th days it was 5.90 IU/ml ($p<0.05$). Also for infants with gestation age 30-33 weeks on the 1-3rd days of the life eNOS was detected between 7.12±0.03 IU/ml, and this value was more than the respective value in the group IV for two times. On the 5-7th days level of eNOS slightly decreased till 5.12±0.03 IU/ml, but in comparative aspect was more than the same indicator in CG : 1.98±0.01 IU/ml ($p<0,05$) respectively.

Thus, the comparative analysis, based on gestational age, revealed a statistically significant increase in the level of neuronal synthase. Endothelial synthase levels were higher both in the first three days of life and at 5-7 days in premature infants with severe hypoxic-ischemic encephalopathy in comparison with the control group. The level of neuronal synthase in this group was 33.6±0.2 nkmol/l compared to the control group - respectively 14,09±0,14 nkmol/l ($p<0,05$) on 5-7th day. Increase in nNOS level in infants of group II was detected. Increase in the concentration of neuronal synthase compared to the control group is characteristic for infants with gestation age 30-33 weeks. In the first three days of life, the nNOS level in these infants ranged from 43.3±0.85 nkmol/l and 39.35±0.53 nkmol/l, respectively, compared to 17.22±0.10 nkmol/l in the control group ($p<0.05$). On 5th -7th days in infants with the indicated gestational ages, there is a slight decrease in the level of neuronal synthase to 38.2±0.44 nkmol/l and 32.83±0.41 nkmol/l, compared to the control group with the 14,09±0,14 nkmol/l, ($p<0,05$).

During the first 3 days of life of infants with gestation age 34-35 weeks the level of neuronal synthase was increased till 37.7±0.20 nkmol/l in comparison with values of the control group which was 0.17±0.001 nkmol/l ($p<0.05$). Also in group III, compared to the control group there was noted an increase in the level of neuronal synthase in infants with a gestation of 30-33 weeks in the first three days: the nNOS level was 46.04±0.4 nkmol/l, and on the fifth to seventh day of life this indicator varied in the range of 38.2±0.4 nkmol/l, in comparison with the control group, where nNOS values were 17.22 ±0.10 nkmol/l and 14.09±0.14 nkmol/l (1-3; 5-7 days) ($p <0.05$), respectively. In newborns with a gestation of 34-35 weeks, the level of neuronal synthase in the first three days was 43.5±0.4 nkmol/l, and on the fifth-seventh day - 41.65±0.3 nkmol/l. For children with a gestation of 28-30 and 36-37 weeks, nNOS levels in the first three days fluctuated in the range of 46.9 nkmol/l and 43.4 nkmol/l, and on the fifth to seventh days - 38.6 nkmol/l and 40 .3nmol/l. Thus, it is worth noting that an increase in the level of the indicator in question was characteristic of all the infants examined.

Deviations of the level of nitric oxide (NO) in the peripheral blood in infants with different gestational age upwards regarding to the compared CG also were revealed. Comparative statistical analysis among infants of the group I showed some increasing of NO level, especially: in the group I, in children with g/a 30-33 weeks, the level of NO was registered in the range of 36.1 mmol / l (1-3 days) and 29.7 mmol / l (5-7 days) compared to CG: 23 .3±0.4 mmol/l (1-3 days) and 20.3±0.3 mmol/l (5-7 days) ($p<0.05$), respectively. With almost the same frequency, fluctuations in the level of this indicator in the peripheral blood were detected in infants with g/a 34-35 weeks and 36 - 37 weeks. So, in infants with g/a 34-35 weeks NO level changed within the interval of 27.1±0.17 mmol/l (1-3 days) and 26.8±0.2 mmol/l (5-7 days); in children with g/a 36-37 weeks NO level was 27.7±0.11 mmol/l (1-3 days) and 26.9±0.13 mmol/l (5-7 days), while in the CG this indicator was slightly reduced and registered in the range of 23.3±0.4 mmol/l (1-3 days) and 20.3±0.3 mmol/l (5-7 days) ($p<0.05$). When characterizing infants with a

moderate form of HIE (group II), it should be noted that in infants with gestation age <28-30 weeks; 30-33 weeks and 36-37 weeks in the first 1-3 days of their life excess of NO value compared to CG was detected. In particular: 49.2 mmol/l (< 28-30 weeks); 40.1±0.7 mmol/l (30-33 weeks); 33.1±0.5 mmol/l (34-35 weeks); 36.1±1.08 mmol/l (36-37 weeks) on days 1-3, while in the CG the NO level was reduced - 23.3±0.4 mmol/l ($p<0.05$), respectively. On the fifth and seventh days of the life of infants NO level was In particular: 49.2 mmol/l (< 28-30 weeks); 40.1±0.7 mmol/l (30-33 weeks); 33.1±0.5 mmol/l (34-35 weeks); 36.1±1.08 mmol/l (36-37 weeks) on days 1-3, while in the CG the NO level was reduced - 23.3±0.4 mmol/l ($p<0.05$), respectively.

It is necessary to note that levels of NO which are characteristic for infants with severe HIE (group III) were more than two times than in CG depending on gestation age. In particular, elevated NO 62.9 mmol/l (<28-30 weeks); 55.01±0.5 mmol/l (30-33 weeks); 50.6±1.3 mmol/l (34-35 weeks); 46.7 mmol/l (36-37 weeks) on days 1-3, while in the CG the NO level was 23.3±0.4 mmol/l ($p<0.05$), respectively. On the fifth and seventh days of life NO levels were respectively: 58.6 mmol/l (< 28-30 weeks); 52.3±0.3 mmol/l (30-33 weeks); 46.8±0.5 mmol/l (34-35 weeks); 41.2 mmol/l (36-37 weeks). In the CG this indicator was 23.3±0.4 mmol/l in the first three days of life and 20.3±0.3 mmol/l in 5^{th}-7^{th} days of life, respectively ($p<0,05$).

Based on the study materials, we have developed an algorithm of CNS PP development in newborn infants, which demonstrates key risk factors, features of the clinical course and informative laboratory and instrumental research methods (Scheme 1). This diagram illustrates an impact of hypoxic ischemic encephalopathy biochemical processes, which can be conditionally divided into three stages. At the first stage the attention is concentrated on burdensome obstetric and gynecological history of the mother, the course of pregnancy and childbirth, also on intrauterine or intranatal hypoxia, or asphyxia during childbirth. These factors contribute to the development of hypoxia and ischemia of different severity. It causes disruption of

biochemical processes, loss of ATP and blocking of ATP-dependent ion transport pumps. Penetration of Ca2+ ions into the cell occurs. Blocking of ATP-dependent ion transport pumps leads to a delay in the release of Ca2+ ions from the cell. As a result, neurotransmitters are released that activate N-methyl-D-aspartate NMDA, the release of glutamate, which provokes excitotoxicity of cells with the release of free radicals. Ultimately, the vasoregulatory mechanisms of the nitric oxide synthase system (NOS) are activated. The vasoregulatory mechanisms of the nitric oxide synthase (NOS) system are activated eventually. The conducted studies showed that, brain cells receive a limited amount of O2 as a result of hypoxemia, caused by insufficient oxygen in the blood, and ischemia, which develops because of the reduced blood supply to the brain, what leads to tissue hypoxia of the brain. Impact of hypoxia and ischemia promotes activation of expression of endothelial, neuronal synthases. The processes occurring in endothelial and neuronal cells of the brain lead to increasing of NO expression. Cerebral blood flow is disrupted as a result of these processes. As a result, the cerebral ischemia develops and the risk of serious neurological consequences in premature infants as higher as the course of the ischemic process is more severe.

Therefore, the trigger mechanisms for cerebrovascular accidents are hypoxia, cerebral ischemia, the regulation mechanism of which is directly depends on the processes of vascular, nervous and autoregulatory interaction. These two processes are closely interconnected via signaling pathway, which is regulated by nitric oxide synthase and can be changed or blocked as a result of occurred hypoxia and ischemia. Unfavorable pregnancy and childbirth, fetoplacental insufficiency, pregnancy complications, socio-biological and obstetric-gynecological factors, as well as extragenital and somatic pathologies may have impact on fetoplacental circulation of the fetus. These factors lead to disruption of oxygen metabolism of the fetus, what ultimately leads to the development of hypotension and the occurrence of acidosis, with metabolic or respiratory nature. It should be noticed that currently there is no specific methods of prophylactics hypoxic-ischemic encephalopathy. Therefore, the depletion of

compensatory mechanisms as more pronounced as longer the ischemic process lasts.

As a result, develops the hypotension, which not only contributes to a decrease in cerebral perfusion and blood circulation, but also leads to ischemic brain damage. The energy deficiency occurs in brain cells as a result of these processes. Also it should be noticed that either metabolic acidosis or respiratory or mixed acidosis (pH <7.0) is detected in premature infants with intrapartum asphyxia.

Low Apgar score for the infant's general condition, the presence of neurological symptoms such as seizures, depression syndrome, agitation, ocular neurological symptoms, muscle hypotonia, as well as respiratory distress syndrome, heart failure and other manifestations let us to combine them under the general name hypoxic-ischemic encephalopathy. Thus, more pronounced above-described changes, taking into account the morphofunctional immaturity of premature infants leads to more severe hypoxic-ischemic encephalopathy.

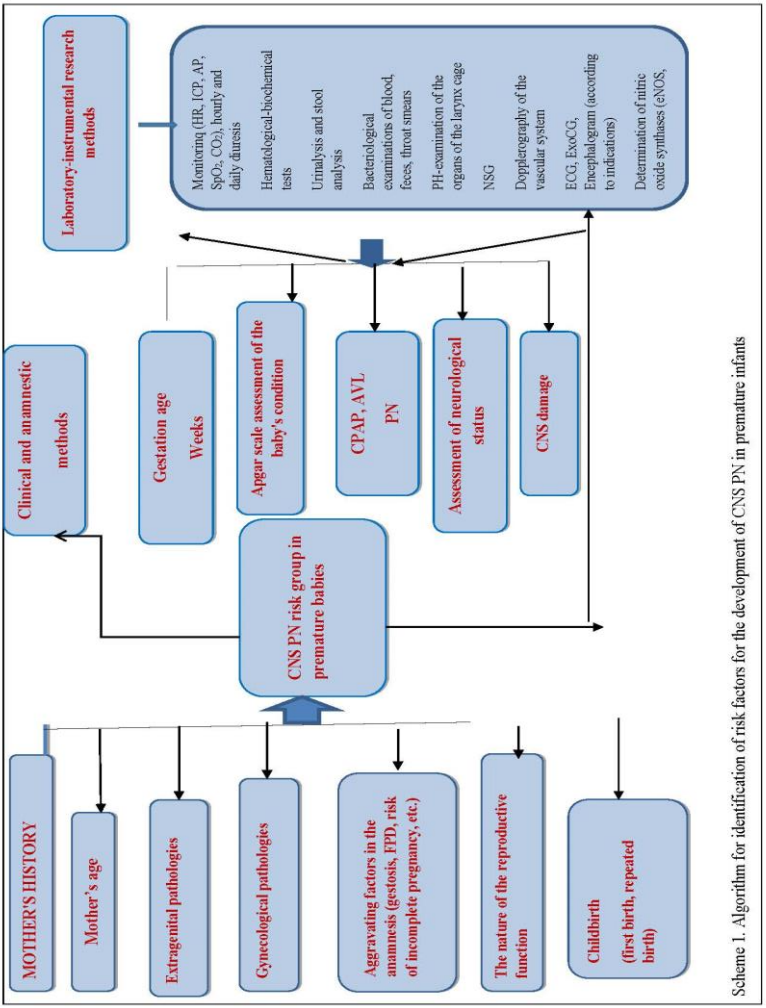
Thus, the conducted studies affirmed that the vasoregulatory processes associated with the nitric oxide system play leading role in the pathogenesis of the development of pathologies of the central nervous system. The activation of the expression of endothelial, neuronal synthase happens as a results of effects of hypoxia, ischemia. The processes occurring in endothelial and neuronal cells of the brain, enhance NO expression. Cerebrovascular accident occurs because of these processes. As a result, cerebral ischemia develops, and the more severe the course of the ischemic process leads to the higher risk of serious neurological consequences in infants. Consequently, hypoxia, cerebral ischemia, the mechanism of regulation of which is directly dependent on the processes of vascular, nervous and auto-regulatory interactions have the trigger mechanism for violation of cerebral circulation. These two processes are closely interconnected through the signaling pathway, which is regulated by NO and can change or block as a result of hypoxia and ischemia.

In accordance with the set tasks we present the assessment and prognostic table containing a set of clinical-anamnestic and

laboratory-instrumental research methods for identifying the relative risk factors leading to the development of ischemic or hemorrhagic lesions of the central nervous system in premature infants of different gestational ages. The presented table will be useful for the further research aimed at developing strategies, allowing to establish in real time reference values of both clinical and vasoregulatory parameters, taking into account central hemodynamics.

The parameters given on the table allow consider them as predictors of the possible development of pathology of the nervous system. It will make possible to conduct long-term research in this area with the aim of predicting and improving health outcomes in preterm infants.

The studies which we have conducted showed that, endothelial and neuronal dysfunction can be expressed as non-specific reaction of cerebral vessels and neurons of the brain, manifested by an imbalance in the formation of both vasoconstrictor and vasodilator substances, leading to a violation of the processes of regulation of the tone of cerebral vessels, homeostasis, as well as a change in the functional state of neurons and neuronal communication. As a result, both structural and functional changes in the endothelium of the cerebral vessels occur due to the formation of nitric oxide synthases and the development of an inadequate response to the state of the brain. So, increased expression of nitric oxide synthases leads to violation of central hemodynamics, and the effect of hypoxia and ischemia on the brain serves as a trigger, triggering a cascade of vasoregulatory processes that activate the NO synthase system. These aspects of pathogenesis, affirm that HIE is based on cerebrovascular dysfunction and mechanisms of vascular dystrophy that occur against the background of oxygen starvation of cells and tissue as a whole, due to hypoxia and ischemia of the brain.



Scheme 1. Algorithm for identifying risk factors for the development of CNS PP in premature infants

Estimation and forecast table for identifying of relative risk factors for the development of ischemic or hemorrhagic damage to CNS according the results of a complex of clinical, anamnestic and laboratory and instrumental research methods

№	Risk factors	Frequency, %
I	**Anamnestic content**	
	Extragenital diseases in mothers	
	anemia	18,6%
	severe viral infections	14,7%
	diseases of the urinary system	10,8%
	Preeclampsia	4,9%
	neurosis	4,9%
	endocrine diseases	4,9%
	Varicose veins	2,9%
	Gynecological diseases in mothers	
	chronic inflammatory diseases of the appendages	0,4%
	ovarian dysfunction	10,8%
	colpitis	12,7%
	cervical erosion	7,8%
	cervical endometritis	2,9%
	Endometriosis, ovarian cysts	2,9%
Reproductive function of mothers		
	history of spontaneous miscarriages	7,8%
	history of medical abortions	41,3%
	history of premature birth	4,9%
	pregnancy after IVF	0,9%
	birth of children with IUGR from a previous pregnancy	4,9%
	The course of this pregnancy in mothers	
	hypertensive disorders	45%
	fetoplacental insufficiency	28,4%
	threat of miscarriage	13,7%
	oligohydramnios/polyhydramnios	12,7%

	premature rupture of amniotic fluid	4,9%
II	**Laboratory and instrumental research content**	
	Research methods	parameters, indicators, markers
	Monitoring	HR, RR, AH, SpO_2, pCO_2
	hourly and daily diuresis	all premature babies
	laboratory and instrumental research methods	frequency, %
	hemogram	General blood test
№	**Risk factors**	**Frequency, %**
	biochemical tests	Acid-base composition of blood, sodium, potassium, calcium, magnesium, albumin, protein C-reactive protein, etc.
	urine and stool examinations	All premature infants
	Bacteriological examinations of blood, feces, throat swabs	-
	Neurological status assessment	-
	RN diagnostics of chest organs	-
	NSG	-
	Doppler studies of the vascular system,	-
	ECG, EchoCG	-
	Encephalogram	according to indications
III	Enzyme immunoassay (ELISA)	
	endothelial synthase	eNOS
	neuronal synthase	nNOS
	Nitric oxide	NO
I V	Risk factors for the development of ischemic and hemorrhagic damage to CNS	
	Clinical and anamnestic content of examination of premature infants with HIE depending on gestational age	
	gestational age 36 weeks	48%
	gestational age 34 weeks	6,9%
	gestational age 33 weeks	24,5%

	gestational age 32 weeks		18,7%	
№	**Risk factors**		**Frequency, %**	
	gestational age <28 weeks		1,96%	
V	Risk factors for the development of ischemic and hemorrhagic damage to CNS			
	Gestational age (weeks)		35-37 weeks n=56	< 28 till 34 weeks n=46
			35,5±1,5	30,5±3,5
	Apgar score	For 1 min	4,37±0,06	3,58±0,07
		For 5 min.	6,04±0,1	5,45±0,07
	pH		7.27±0,005	7,15±0,01
	CPAP		25%	28,2%
	AVL		4,3%	19,6%
	intrauterine hypoxia		41,2%	
	Asphyxia		19,6%	
	umbilical cord entanglement around the neck		10,8%	
	IUGR		35,3%	
№	**Risk factors**		**Frequency, %**	
	RDS		63,7%	
	Oppression syndrome		53,4%	
	Patent foramen ovale (botal duct) (PFO)		33,3%	
	Patent aortic duct (PDA)		27,4%	
	Hypertension syndrome		23,5%	
	Hemodynamic disorders		22,5%	
	Gestational age	CI stage I.	CI stage II	CI stage III
	<28 weeks - 30 weeks	0	3,1%	5,3%
	30-33 weeks	1,9%	12,5%	73,7%
	34-35 weeks	15,7%	65,6%	15,7%

Identified pathophysiological mechanisms of infant brain damage in HIE let us significantly prevent or reduce poor long-term prognosis - development of disabling psychoneurological pathologies.

Thus, the hypoxic status of the fetus and asphyxia in childbirth, leading to the occurrence of perinatal lesions of the nervous system in a premature infant, are serious complication of pregnancy and childbirth. HIE has significant clinical importance, as the occurrence of adverse consequences significantly affects the quality of life, forming disability, which determines the serious social significance of this problem. In connection with it, compliance with preconception preparation of a woman, timely identification of risk factors, pathologies either before, or after pregnancy, implementation of preventive measures and effective treatment let significantly decrease the percentage of neurological disorders, disability and mortality among preterm infants.

Thus, CNS injuries of hypoxic-ischemic nature in premature infants has an important social significance, as serious consequences allow us to consider it as an urgent problem of modern society, adversely affecting the quality of life.

CONCLUSION

1. Antenatal and intrapartum risk factors (extragenital pathology - 76.5%; complications of pregnancy and childbirth: hypertensive disorders- 45%; uteroplacental circulation disorders - 28.4%; threat of abortion - 13.7%; fetal hypoxia - 40.2%; asphyxia - 19.6%) play leading role in formation of hypoxic-ischemic encephalopathy.
2. The active expression of endothelial (2.5 times), neuronal nitric oxide synthase (2 times) in premature infants with gestation age 36-37; 34-35; 30-33 weeks is an indicator of damaging of the endothelium of cerebral vessels and neurogenesis, leads to impaired cerebral circulation, the occurrence of cerebral ischemia of varying severity ($p<0,05$) [7;8].

3. Severity of HIE in premature infants is connected with activation of the nitric oxide systems: endothelial, endothelial (eNOS), neuronal (nNOS) dysfunction, what helps to increase expression of nitric oxide (NO) leading to vasoconstriction and vasodilation of cerebral vessels ($p<0,05$) [6;7].

4. Activation of eNOS, nNOS and NO in babies with HIE leads to damaging of endothelium of the vascular bed, impaired cerebral blood flow, leading to serious consequences in premature infants with extremely low body weight and low body mass [4:6:7;8].

5. Evaluation and prognostic table for a complex of clinical, anamnestic and laboratory and instrumental research methods is an informative and reflects relative risk factors, what serves as a predictor of the development of ischemic and hemorrhagic damage to the central nervous system in premature infants.

PRACTICAL RECOMMENDATIONS

1. Antenatal and intranatal risk factors (social and biological factors, obstetric and gynecological factors, extragenital, somatic pathology, course and complications of pregnancy and childbirth, state of fetoplacental circulation) in women make strengthening the preconception examination in order to eliminate the identified violations in the state of their health extremely important, what will significantly decrease or eliminate complication risks of pregnancy, childbirth, postpartum and perinatal periods.

2. Endothelial (eNOS), nuronal (nNOS) nitric oxide synthases and nitric oxide(NO) can be used as diagnostic criteria for assessment of severity rate of cerebral ischemia, what will let significantly decrease or eliminate long-term negative prognosis for HIE in premature infants - development of a disabling neuropsychiatric pathology.

3. The presented evaluative-prognostic table for a complex of clinical-anamnestic and laboratory-instrumental research methods for detection of relative risk factors can be used as additional, non-

invasive, informative content for early prognosing of development of ischemic or hemorrhagic damage of CNS in premature infants.

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LIST OF ABBREVIATIONS

ABBREVİATİON

IVH	–	intraventricular hemorrhage
HIE	–	hypoxic ischemic encephalopathy
g\a	–	gestational age
CP	–	cerebral palsy
IUGR	–	intrauterine growth retardation
AVL	–	artificial ventilation of the lungs
CT	–	computed tomography
MRT	–	magnetic resonance imaging
NSG	–	neurosonography
PVH	–	periventricular hemorrhage
PVL	–	periventricular leukomalacia
PN	–	parenteral nutrition
RDS	–	respiratory distress syndrome
CNS	–	central nervous system
ELBW	–	extremely low body weight
CPAP	–	Constant Positive Airway Pressure
NO	–	nitric oxide
NOS	–	nitric oxide synthase
eNOS	–	endothelial form of nitric oxide
nNOS	–	neuronal form of nitric oxide
$PaCO_2$	–	partial pressure of carbon dioxide
PaO_2	–	partial pressure of oxygen in arterial blood
pH	–	pH value, reflects the degree of acidity or alkalinity of the environment
σ	–	dispersion
X_M	–	average value
p	–	reliability coefficient
P_K	–	polydispersity coefficient

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