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Premature newborns: Actual problems of raising and prevention of adverse consequences

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The review summarizes the literature data on the perinatal pathology of premature infants, the frequency of their development in the following months and years of life of neuropsychiatric and somatic diseases. The results of experimental and clinical studies are presented, revealing the general pathogenetic mechanism – oxidative stress, underlying bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, periventricular leukomalacia, open ductus arteriosus and persistent pulmonary hypertension. The interrelation of the processes of inflammation and oxidative stress, which play a leading role in the brain damage of the fetus and newborn, is considered. The literature data on the possibility of preventing severe complications in the antenatal period of development with the timely use of surfactant, magnesium sulfate and acetylcysteine are presented, It is emphasized that the first hours of a premature baby's life are a critical period for an individual approach to resuscitation, the beginning and effectiveness of drug therapy aimed at suppressing oxidative stress and systemic inflammation, which is confirmed by modern trends in optimizing the care of premature babies using pentoxifylline, erythropoietin, cortexin and melatonin.

Keywords: oxidative stress; prematurity; magnesium sulfate; acetylcysteine; cortexin; melatonin.

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Недоношенные дети: актуальные проблемы выхаживания и профилактики неблагоприятных последствий

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В обзоре обобщены данные литературы о перинатальной патологии недоношенных детей, частоте развития у них в последующие месяцы и годы жизни нервно-психических и соматических заболеваний. Приведены результаты экспериментальных и клинических исследований, раскрывающие общий патогенетический механизм — оксидативный стресс, лежащий в основе бронхолегочной дисплазии, ретинопатии недоношенных, некротизирующего энтероколита, перивентрикулярной лейкомаляции, открытого артериального протока и персистирующей пульмональной гипертензии. Рассмотрена взаимосвязь процессов воспаления и оксидативного стресса, играющих ведущую роль в поражении мозга плода и новорожденного. Представлены данные о возможности профилактики тяжелых осложнений в антенатальном периоде развития при своевременном применении сурфактанта, сульфата магния и ацетилцистеина. Подчеркнуто, что первые часы жизни недоношенного ребенка — критический период для проведения реанимационных мероприятий, медикаментозной терапии, направленной на подавление окислительного стресса и системного воспаления, что подтверждают современные исследования по оптимизации выхаживания недоношенных детей с использованием пентоксифиллина, эритропоэтина, кортексина и мелатонина.

Ключевые слова: оксидативный стресс; недоношенность; сульфат магния; ацетилцистеин; кортексин; мелатонин.

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One of the most important public health problems worldwide is how to optimize care of infants born preterm, as they have a high risk of not only neonatal morbidity and mortality but also the development of somatic and neuropsychic pathologies in the short or long-term. The number of premature births worldwide exceeds 15 million per year, and prematurity is the leading cause of death in children aged 0–5 years and 35% of all deaths worldwide annually (3.1 million) [1]. The proportions of children weighing <1500 and 1500–2000 g account for 16% and 27% of all children born prematurely, respectively. In most countries, over the past 10 years, the number of infants born prematurely has increased, especially in the UK, USA, and Japan, while a downward trend has been observed in France, Finland, and China [2].

In Russia, as in other countries, infants born between the 22nd and 37th weeks of pregnancy (154–259 days from the first day of the last menstrual cycle) with a weight of 500–2500 g and a length of up to 45 cm are considered premature. Worldwide, the proportion of children with extremely low bodyweight (ELBW) is 0.4%–1.9% of the total number of live births, and they account for more than 45% of deaths in the perinatal period [3]. Over the past 20 years in many countries, the survival rate of children with a gestational age of <28 weeks ranges from 54% to 73%, with a higher rate observed in those born in perinatal centers [4]. With the introduction of new medical technologies in Moscow in 2001, the early neonatal mortality rate of infants born prematurely with ELBW was 45.1%, and the infant mortality rate ranged from 48.8% to 64.5%. The main causes of neonatal mortality were the pathology of the respiratory system (81.7%), nervous system (49.6%), and infectious diseases (43.4%) [5].

An increase in the survival rate of children with ELBW is observed in many developed countries due to the improvement of resuscitation methods, respiratory interventions, and drug therapies, and provision of adequate parenteral nutrition. Moreover, diseases such as respiratory distress syndrome (64%–83% of children), cerebral ventricular hemorrhages of grade III–IV (27%–37%), patent ductus arteriosus (34%), sepsis during the perinatal period caused by morphological and functional immaturity (30%–31%), necrotizing enterocolitis (8%), bronchopulmonary dysplasia (48%), and grade III–IV retinopathy (33%) cause a high incidence of neurological disorders and chronic diseases in subsequent years of life [6, 7]. Yangel et al. [8] analyzed the survival rate and neurological outcomes in 4274 children born in 11 perinatal centers at 22–24 weeks of gestation. Children were divided into three groups: the first, second, and third groups consisted of those born in 2000–2003, 2004–2007, and 2008–2011, respectively. The survival rate of children increased from 30% in the first group to 36% in the third group. Regarding the frequency of impaired psychomotor development, the same trend was observed (from 16% to 20%), but severe neurological consequences remained at the same level (16%).

Perinatal pathology due to severe immaturity leads to cerebral palsy (21%–28%), blindness (2%–8%), and hearing impairment (5%) [9]. A meta-analysis of long-term consequences in 4125 infants born prematurely with ELBW revealed mental retardation, speech impairment, and learning disabilities; the greater the severity of these diseases, the lower the gestational age at birth [10]. In Russia, children with ELBW have infantile cerebral palsy, mental retardation, convulsive states (40%), and damage to the organs of hearing (20%) and vision (25%) [11]. In addition, in adolescence, attention-deficit, aggressiveness, depressive, and mental disorders occur, leading to profound disability and seriously diminished quality of life [12, 13]. Infants born prematurely are also at risk of obesity, arterial hypertension, cardiovascular pathology, dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, and bronchial asthma [14].

Considering the significant contribution of prematurity to the formation of childhood diseases in the last decade, researchers aimed to elucidate the pathophysiological mechanisms that determine their development and substantiate new approaches to the prevention and treatment of adverse consequences. A general pathogenetic mechanism has been established – oxidative stress – which underlies dysfunctions of all organs of an infant born prematurely. Bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, periventricular leukomalacia, patent ductus arteriosus, and persistent pulmonary hypertension are classified as oxygen radical diseases of neonatology [15].

Reactive oxygen and nitric oxide radicals are formed during oxidative phosphorylation processes in the mitochondria, and they are controlled by various components of the antioxidant defense system (such as superoxide dismutase, glutathione peroxidase, catalase, and vitamin E) [16]. Under conditions of hypoxia, hyperoxia, inflammation, ischemia with insufficient production of antioxidants, excessive formation of free radicals, especially superoxide anions, hydroperoxides, and hydroxyl radicals, is highly toxic for the mitochondria, leading to their dysfunction, which in turn contributes to even greater oxidative stress and cell death [17].

Infants born prematurely are prone to oxidative stress. The antioxidant defense system in the fetus matures during the third trimester of pregnancy [18]; therefore, the transition from a relatively hypoxic fetal environment to an environment with high oxygen tension leads to oxidative stress and subsequently to oxidations of lipids, proteins, and polysaccharides, DNA damage, and other unfavorable consequences [19, 20]. Most of those born prematurely as a result of chronic intrauterine hypoxia due to maternal

diseases and impaired uteroplacental circulation are already in a state of oxidative stress before birth, which significantly increases during resuscitation and infection [21]. In addition, infants born prematurely have a high level of free iron, which also contributes to the excess production of toxic radicals [22]. Oxidative stress as a result of hyperoxia and mechanical ventilation causes alveolar epithelium damage, surfactant inactivation, and lung inflammation: the less mature the newborn, the more severe the damage accompanied with the development of bronchopulmonary dysplasia and more severe subsequent respiratory disorders [23]. Increased mitochondrial oxidative stress has been described in numerous animal models with persistent pulmonary hypertension, bronchopulmonary dysplasia, or necrotizing enterocolitis [24, 25]. Studies in neonates who received mechanical ventilation have demonstrated an increase in the oxidation of lipids and proteins in the lung tissue and a reduction in the antioxidation of biological fluids [26].

The brain of premature infants born in the critical period of intensive axonal and dendritic growth, glial differentiation, proliferation, myelination, and active vasculogenesis in the absence of autoregulation of cerebral circulation is sensitive to oxidative stress. The brain is susceptible to oxidative stress because of high oxygen consumption and increased levels of intracellular free iron and polyunsaturated fatty acids in neuronal membranes with a low content of enzymatic antioxidants [27]. Precisely at this time, owing to the need for intensive treatment with the use of mechanical ventilation in most infants born very premature, the risk of brain damage increases as a result of inflammatory reactions and hemodynamic instability [28, 29] caused by excessive stretching of the alveoli, compression of the pulmonary capillaries, an increase in pulmonary resistance, and a decrease in cardiac output [30]. In addition, many infants born prematurely experience inflammation when the mother has chorioamnionitis [31].

The inflammatory process is a source of excessive production of free radicals with subsequent damage to cellular components and the formation of endothelial dysfunction. Proinflammatory cytokines induce NO synthase expression, peroxynitrite formation, and apoptosis. The relationship between inflammation and oxidative stress plays a leading role in brain damage [32]. Experimentally, resuscitation using high oxygen concentrations in the cortex and subcortical structures led to excessive production of proinflammatory cytokines and reactive oxygen radicals [33]. In newborns with perinatal hypoxia/ischemia, the concentration of the proinflammatory cytokine interleukin-6 in the cerebrospinal fluid is increased and the activity of the antioxidant enzyme glutathione peroxidase is decreased, which confirms the importance of inflammation and oxidative stress in the pathogenesis of encephalopathy [34].

Excessive production of proinflammatory cytokines and reactive oxygen radicals, which cause the activation of microglial cells, excitatory amino acids, energy depletion, and apoptosis, leads to white matter damage in infants born prematurely and other adverse consequences such as impaired hearing, vision, and speech, periventricular leukomalacia, and cerebral palsy [10]. Oxidative stress in the brain persists months after birth and, with changes in the methylation of cytosine nucleotides in the DNA [35], affects gene expression, which is accompanied by deregulation in the differentiation and development of cells, and ultimately leads to a decreased number of cells and irreversible morphofunctional changes underlying disorders such as cognitive development, hyperexcitability, seizures, depression, and autism spectrum disorders [36–38].

The results of experimental studies and analysis of the clinical outcomes of perinatal pathology help develop specific biomarkers for the early diagnosis of oxidative stress, new approaches to therapy, and prevention of adverse long-term consequences from new perspectives [33, 39]. Researchers provided increased attention to the identification of risk factors for preterm birth, their prodromal signs for timely hospitalization of a pregnant woman in the perinatal center, and the provision of high-tech care to her and her newborn.

The use of glucocorticoids during pregnancy ≤34 weeks with the expected risk of childbirth in the next 7 days promotes fetal lung maturation [40] and reduces the risk of cerebral palsy by suppressing the effect of proinflammatory cytokines in the brain tissue [41]. The World Health Organization recommends prophylactic use of magnesium sulfate in mothers at risk of childbirth at ≤ 33 weeks [42]. Numerous experimental and clinical studies have revealed that magnesium sulfate found in fruits exerts an anti-inflammatory effect, helps reduce the production of free radicals, blocks calcium channels, prevents excitotoxicity and apoptosis of neurons, increases the production of neurotrophic factors involved in the restoration and development of neural networks, and consequently decreases the risk of cerebral palsy in children born before the 30th week of gestation [43–46].

Since chorioamnionitis in a pregnant woman is associated with oxidative stress and the development of hypoxic/ischemic brain damage in the fetus under the influence of proinflammatory cytokines, a randomized placebo-controlled pilot trial of the effectiveness of antenatal and postnatal use of acetylcysteine was carried out for neuroprotection (NCT00724594). Earlier experimental studies have shown that acetylcysteine easily penetrates the blood–brain barrier, suppresses the production of proinflammatory cytokines and oxidative stress in the fetal brain, restores intracellular glutathione levels and vascular reactivity, and stabilizes cerebral blood flow [47, 48]. Clinical trials have confirmed the safety and optimal efficacy of the drug [49, 50].

The time of the onset of oxidative stress in the fetus and the initiation of antioxidant therapy plays a major role in the genesis of adverse effects, especially in infants born prematurely, while the mode of birth does not significantly affect the immediate and long-term health parameters of children with ELBW [41]. After the premature birth of an infant, the earliest prevention of excessive oxidative stress is to maintain a temperature regimen and minimize tactile and painful effects of invasive procedures [51, 52]. Delayed clamping of the umbilical cord by 180 s for infants born prematurely who do not need resuscitation contributes to hemodynamic stability and a decrease in the incidence of acute cerebrovascular accidents [53]. Primary resuscitation measures in the delivery room are required in up to 20% of infants born prematurely, the majority of whom are those born with bodyweight <1500 g. The use of low oxygen concentrations and sparing individually selected ventilation modes prevents intraventricular hemorrhages and damage to the white matter of the brain [54].

In infants born prematurely who need mechanical ventilation, the optimal inspiratory pressure depends on the degree of morphological and functional maturity of the lungs. It is selected individually during primary resuscitation under controlled heart rate (HR) and oxygen saturation data (S_pO_2). The required peak pressure during the first mandatory breaths ranged from 20 to 40 cm H_2O. Recent studies have shown the effectiveness 5–10-second lung inflation in infants born prematurely as a starting point to create and maintain functional residual lung capacity. In children born before the end of the 28th week of gestation, it is recommended to start mechanical ventilation with 30% oxygen and in the rest with air and, only if ineffective, increase the oxygen concentration. The basis for an increase in oxygen concentration during mechanical ventilation is a reduced HR (60–100 beats/min) within 60 s from the beginning of ventilation. In cases of a moderate decrease in HR, a stepwise (by 10%–20% every minute) increase in oxygen concentration is necessary until the HR is at >100 beats/min. If mechanical ventilation is required in children with a HR of >100 beats/min, supplemental oxygen should be used if cyanosis (S_pO_2 <80%) persists for >5 min. It is necessary to maintain the pCO_2 level between 45 and 55 mmHg for the prevention of intra- and periventricular hemorrhages. The timely use of a surfactant reduces the severity of not only respiratory disorders but also periventricular brain lesions [55].

The first 72 h after a premature birth is a critical period for the initiation and effectiveness of drug therapy aimed at suppressing oxidative stress and systemic inflammation [56]. The results of numerous experimental studies have led to the elucidation of specific mechanisms for the restoration and development of damaged tissues and brain structures of newborns using pentoxifylline [57] and erythropoietin [58]. The latter has anti-inflammatory and antiapoptotic effects, stimulates the expression of vascular endothelial growth factor and nerve growth factor, and protects oligodendrocytes from damage [59]. Clinical trials have confirmed its safety and the possibility of using it as a neuroprotective agent in the neonatal period [58, 60]. In recent years, for the treatment of diseases of the central nervous system in children, the peptide bioregulator cortexin (Geropharm, St. Petersburg) has been successfully used, which has antioxidant activity, and the optimal ratio in its composition of a wide range of trace elements and vitamins potentiates the neuromodulating and neuroprotective effect [61]. To our knowledge, we have shown for the first time the effectiveness of monotherapy with cortexin at a dose of 0.5 mg/kg during the first 10 days of life in infants born prematurely whose intrauterine development proceeded under conditions of chronic hypoxia. After the treatment, the general condition of the studied infants improved due to a decrease in the severity of neurological disorders and the formation of tonic and reflex reactions, while they corresponded to the conceptual age in 59.1% of those born at 33–35 weeks of gestation [62].

Currently, multicenter, randomized placebo-controlled clinical trials (NCT00649961) of the efficacy of melatonin as a neuroprotector in neonates undergoing intrauterine chronic hypoxia and severe asphyxia at birth and in infants born very prematurely are underway (NCT00649961). Melatonin is considered the most promising drug for neuroprotection owing to its ability to absorb reactive oxygen radicals, block NO synthases (neuronal and inducible), suppress lipid peroxidation and excitotoxicity cascade, and modulate inflammation mechanisms, which has been convincingly proven by numerous experimental studies [65, 66]. In addition, a study revealed its safety and efficacy in the treatment of cerebral ischemia, sepsis, respiratory distress syndrome, and necrotizing enterocolitis in infants born prematurely [67]. The authors, analyzing the literature data on the inclusion of melatonin in the therapy of newborns with various pathologies, concluded that the use of melatonin for a short time is effective and safe even at high pharmacological doses and can reduce the incidence of complications [68]. Further large-scale placebo-controlled international clinical trials will determine the characteristics of pharmacokinetics, optimal doses and duration of melatonin use in newborns for its inclusion in treatment protocols for perinatal pathology, especially when caring for infants born very prematurely [69].

Thus, early detection of the onset of preterm labor or its prodromal signs, timely hospitalization of a pregnant woman in the perinatal center, and provision of high-tech care to her and her newborn will help reduce perinatal mortality and morbidity and optimize the quality of life of infants born prematurely.

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