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Biochemical factors of hypoxia and their role in assessing the functional state of the fetus

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The constant frequent incidents of fetal hypoxia during pregnancy and childbirth remain the leading unsolved problem in modern practical obstetrics. In some cases, the onset of a pathological process can be diagnosed earlier due to the on-time monitoring of functional disorders of the fetus. However, the existing diagnostic methods do not show the compensatory and adaptive capabilities of the fetus; do not lead to an in-depth understanding of the pathophysiology of this condition and do not contribute to the implementation of evidence-based therapy. This review summarizes current knowledge about the diagnosis of functional disorders of the fetus and discusses possible ways of assessing adaptive mechanisms in response to stress during pregnancy and childbirth. The article shows the development of biochemical methods for diagnosing functional disorders of the fetus. The putative biochemical markers for assessing the compensatory capabilities of the fetus during pregnancy and childbirth are presented.

Keywords: fetal hypoxia; fetal distress; brain-derived neurotrophic factor; glial cell-derived neurotrophic factor.

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Биохимические факторы гипоксии и их роль в оценке функционального состояния плода

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Неизменная частота случаев гипоксии плода во время беременности и родов остается ведущей нерешенной проблемой современного практического акушерства. Путем своевременного отслеживания нарушений функционального состояния плода в ряде случаев удается рано диагностировать патологический процесс. Однако существующие методы не позволяют выявлять компенсаторно-приспособительные возможности плода, не ведут к углубленному пониманию патофизиологических основ данного состояния и внедрению терапии. Целью обзора стали обобщение современных знаний о диагностике функционального состояния плода, анализ возможных способов оценки адаптационно-приспособительных механизмов плода в ответ на воздействие стресс-факторов при беременности и в родах. В статье показано развитие биохимических методов диагностики функционального состояния плода и представлены предполагаемые биохимические маркеры для оценки компенсаторных возможностей плода во время беременности и родов.

Ключевые слова: гипоксия плода; дистресс плода; нейротрофический фактор мозга; глиальный нейротрофический фактор.

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ЭКО•ВЕКТОР

Despite the existing methods for diagnosing the functional state of the fetus during childbirth, one of the global problems of modern obstetrics is, on the one hand, the constant incidence of newborns with impaired functional state, and on the other hand, an increasing number of surgical interventions during childbirth, which are sometimes unreasonable [1].

Childbirth is a physiological process, however, both the mother and the fetus experience stress on the verge of their compensatory and adaptive capabilities, and a favorable outcome for childbirth depends largely on the successful implementation of compensatory and adaptive mechanisms in both the fetus and the mother [2].

In the current stage of medicine development, objectively assessing the functional state of the fetus by one diagnostic method is not possible. To establish the diagnosis of an impaired functional state of the fetus, combinations of various groups of methods are used. However, the pathogenetic mechanisms of compensatory and adaptive reactions in the fetus have been little studied and are described mainly in experimental models.

In clinical practice, such methods for diagnosing the functional state of the fetus as auscultation of fetal heart tones, visual assessment of the nature of the amniotic fluid, electrocardiography, and cardiotocography of the fetus are used. They are well-studied and successfully used in clinical practice. However, the data on their use is controversial and contradictory [3]. Modern principles of providing qualified medical care imply a much more objective (careful) approach to pathological processes and the formation of clearer algorithms to reduce the level of perinatal complications. One of the possible ways is expanding the knowledge about the pathogenetic mechanisms of compensatory and adaptive reactions in the fetus and, consequently, to identify new markers that have diagnostic and prognostic value.

The earliest example of this approach was the introduction of the Saling test in 1962. However, the method has significant drawbacks (i.e., invasiveness and the inability to determine the nature of acidosis). Neonatal complications (e.g., impaired neurological development and end-organ damage) are associated with metabolic rather than respiratory acidosis [4, 5], which led to the study of lactate. Several authors found a positive correlation between the duration of stage 2 of labor, lactate level in the umbilical cord blood of a newborn, and perinatal outcome [6]. Other researchers concluded that the lactate level determination is more appropriate than the pH value in the blood of the fetal head [7]. However, some studies revealed that the combination of these two methods in clinical practice, despite the high sensitivity and specificity, is not recommended due to the increase in unreasonable surgical interventions [8]. Only a few works describe and correlate the labor stage and the fetus position concerning the planes of the small pelvis during the Saling test or lactate measurement [8–10].

The generally accepted upper limit of normal lactate levels is 4.8 mmol/L, which is supported by studies using the LactateProTM analyzer. The LactateProTM analyzer was initially developed for testing athletes. The indicators obtained using other portable devices may differ, and the reference values in the manuals are indicated without considering the lactate analyzer type [7, 11].

Most fetal lactate is formed during stage 2 of labor [7]. In the work by Wiberg et al. published in 2016, a new range of physiological lactate levels in the blood of the fetal head during stage 2 of labor [1.1 and 5.2 mmol/L (±2 SD)] using the Lactate ProTM analyzer was proposed [10]. In addition, the authors note the dependence of the lactate level of the fetal head blood on the parity of labor, regional methods of anesthesia, and uterotonic agents (oxytocin). In 2018, Wiberg et al. assessed the dependence of the lactate level in the blood of the fetal head, measured in stage 2 of labor, on the outcome in a child at 4 years old and revealed an increase in the number of cognitive dysfunctions and fine motor disorders with an increase in the lactate level at birth in these children [12].

The point-of-care testing and lactate test strip method has become attractive. However, the reference values given in various manuals should be noted to differ depending on the analyzer used. Moreover, Remneva et al. showed the feasibility of determining the lactate level in the amniotic fluid and the lactate–creatinine ratio to accurately determine the presence of the degree of fetal hypoxia [13]. In the work by Pogorelova et al., the proteomic composition of amniotic fluid was analyzed, which established that zinc-α_2-glycoprotein can be recommended as an informative marker of fetal growth retardation [14].

Loukovaara et al. found that erythropoietin and S100B obtained by sampling amniotic fluid can also be fetal hypoxia markers [15]. In subsequent studies, Summanen et al. concluded that S100B and erythropoietin in neonatal serum are not reliable birth asphyxia biomarkers. The authors studied the role of copeptin in neonatal cord blood serum and indicated its potential as a biomarker for acute birth asphyxia and neonatal distress. Thus, correlations of this parameter with excess base and pH of the umbilical artery were revealed. In addition, umbilical cord serum copeptin levels were significantly higher in children born vaginally and increased with labor duration [16].

Many authors point out that hypoxia induces ischemia and myocardial necrosis, and alteration markers of the target organ can then become biochemical hypoxia factors [17, 18]. One such marker is troponin. Stefanovic et al. revealed that elevated troponin level in the amniotic fluid is an independent predictor of fetal respiratory distress syndrome development [19]. The average cardiac troponin T

level in the venous blood of children 4 h after birth was later established to be significantly higher in the group of patients with asphyxia, and the method itself had high sensitivity (83.9%) and specificity (96.6%). In addition, the level of the marker correlated positively with an increase in the degree of hypoxic–ischemic encephalopathy [20]. However, other researchers note an increase in the troponin level in the umbilical cord arterial blood plasma in premature newborns with congenital malformations of the fetal heart without impairment of its function, which indicates the need to study the threshold values and the role of this protein as a fetal hypoxia marker in more detail [21].

In 2019, Wang et al. demonstrated the relationship between the levels of serum protein S 100β, C-reactive protein, and cystatin C, as well as troponin I (cTnI), cord blood creatine kinase MB, and CK MB isoforms with the neonatal hypoxic–ischemic encephalopathy development [22]. As a clinical example, the case of an increase in the cTnI level in the venous blood of a pregnant woman, described by Turrini et al., was presented. Extragenital diseases (pericarditis, myocarditis, pulmonary embolism, kidney disease, and so on) that cause an increase in the value of this indicator were ruled out, and an increase in the cTnI level was concluded to may be of intrauterine origin [23]. Fleming et al. established that the increase in cTnI level was due to myofibrillar damage caused by hypertension [24]. However, other authors did not register an increase in the cTnI level in venous blood plasma in patients with preeclampsia/eclampsia [25]. The authors of the described clinical case believe that the increase in the troponin level is associated with severe fetal hypoxia. In their report, the researchers mention that the conventional wisdom is that cTnI does not cross the placenta. However, in this case, the authors believe that deep damage to the placenta could be associated with the entry of fetal cTnI into the mother's blood. The argument supporting the intrauterine origin of the molecule was due to a decrease in the cTnI level during fetal death and its normalization after pregnancy termination.

Despite the advantages of the aforementioned studies, one of the main disadvantages of these methods is their injury rate (if blood is taken from the fetus during delivery) or their significance is only for retrospective assessment of the fetus state (in the case of cord blood sampling after the birth of the fetus).

In 2013, Whitehead et al. published works and revealed a hypoxia-induced microRNA, the level of which increased during labor in maternal blood during acute fetal hypoxia. Simultaneously, a correlation was demonstrated with the fetal acidemia level at birth, as well as hemodynamic disorders in the fetal vessels during Dopplerometry [22, 26]. In addition to the advantages related to the sensitivity and specificity of the method, an important role is played by the possibility of prospective diagnostics and relatively low invasiveness [27]. In 2015, Looney et al. reported a significant decrease in the microRNA (hsa-miR-374a) expression in cord blood in children with perinatal asphyxia and neonatal hypoxic–ischemic encephalopathy [28]. Other authors in a clinical study in newborns with hypoxic–ischemic encephalopathy studied the miRNA-21 and HIF-1α expressions. Their levels were higher in the blood serum of children with hypoxic–ischemic encephalopathy compared with the children in the control group [29]. In a clinical review of the role of miRNAs in the development of hypoxic–ischemic encephalopathy in newborns, Ponnusamy attempted to associate all known changes that occur at the cellular level, both in physiological and pathophysiological processes registered in hypoxic–ischemic encephalopathy in the developing brain of a newborn. The authors believe that further study of the issue may pave the way for improving the diagnostics of traumatic brain injury in newborns and the search for effective neuroprotectors [30].

In 2010, van Patot raised the subject of not only diagnosing fetal distress but also assessing compensatory capabilities. Comparing changes in the placenta in puerperas living at sea level and an altitude of 3,100 m above sea level, compensatory and adaptive mechanisms are concluded to be activated in the latter. In the placenta, the levels of polyunsaturated fatty acids, phosphocreatine, taurine, and inositol increase, and the levels of monounsaturated fatty acids and the ratio of adenosine triphosphate/adenosine diphosphate are lower compared to women living at the sea level [31].

In the context of damage to target organs, the tissue of the central nervous system should be mentioned, which is extremely sensitive to the effects of hypoxia. Compensatory and adaptive mechanisms in the human fetus are practically not studied, and attempts to study them are mainly experimental. Despite the introduction of new technologies that improve outcomes in newborns with high perinatal risk, the incidence of perinatal neurological complications in developed countries is not currently decreasing, and they constitute a significant part of the range of perinatal cerebral lesions and significantly affect early childhood morbidity, disability, and mortality [30, 32].

Hypoxia is one of the leading factors for brain cell damage during ischemia. A decrease in oxygen level impairs oxidative phosphorylation on the mitochondrial membrane, uncouples the components of the respiratory chain, the occurrence of energy deficiency and acidosis, releases glutamate, and disturbs Ca^{2+} accumulation, which leads to the activation of free radical processes and is one of the main causes of neuron death [32–35]. After successful resuscitation measures, oxygenation and perfusion of the brain of the newborn are restored, but then the so-called secondary or delayed damage to the central nervous system occurs without changing the intracellular pH value against the stable

work of the cardiovascular and respiratory systems, which is associated with reoxygenation [13, 32, 36].

A promising approach to increase the compensatory and adaptive capabilities of the nervous system is the activation of endogenous systems that contribute to the survival of nerve cells under the action of stress factors and the maintenance of their functional activity. The use of neurotrophins, such as glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and so on, is of great interest. Ostrova and Avrushchenko in experiments *in vivo* showed the ability to synthesize BDNF in the neuronal population of cerebellar Purkinje cells. The authors believe that this property is one of the most important factors that increase the resistance of neurons to death in the postresuscitation period. This factor may play a role in the compensatory and adaptive mechanisms of the fetus during hypoxic injury [37]. In 2016, Mitroshina et al. published the results of an experiment that studies the effect of GDNF on the resistance of animals to ischemic brain damage under conditions of global ischemia, a model of bilateral carotid artery occlusion. The authors concluded that GDNF contributes to the survival of animals in cerebral ischemia simulation and the neurological status normalization in the postischemic period [33].

In their experimental work, Morozov et al. found that the levels of BDNF, nerve growth factor NGF, and protein S-100 significantly decrease in rat brain structures (cortex, hippocampus, and cerebellum) in early ontogeny after prenatal hypoxia [39]. Subsequently, these authors showed the effect of prenatal hypoxia on the levels of BDNF and neurospecific enolase (NSE) in the hippocampus and blood serum of rats on days 5, 10, and 30 of life. Within the indicated periods, the BDNF and NSE levels in the hippocampus of rats in the group of animals exposed to hypoxia decreased. Simultaneously, the level of these factors in the blood of animals increased. The authors concluded that prenatal hypoxia interferes with the performance of the functions of these proteins, affect the formation of synaptic plasticity processes due to the lag in the development of synapses and disruption of the integrity of neurons, and fail in their development both in early ontogenesis and later in the life of animals [40]. In 2020, Shchelchkova et al. published a study where they showed that chronic hypobaric hypoxia in pregnant female mice in trimesters 1 and 3 led to a significant decrease in the level of neurotrophic factors BDNF and GDNF in blood plasma [41]. GDNF maintains the efficiency of the respiratory chain, the functional state of mitochondria, contributing to the adaptation of cells to the effects of ischemia. One of the mechanisms of the protective GDNF action can be a decrease in the number of free radicals formed during ischemia [42–44]. Several studies have found that mesenchymal stem cells exert a neuroprotective effect through complex mechanisms (e.g., secretion of neurotrophic factors, angiogenesis, apoptosis inhibition, and immune system modulation) [45–48].

An experimental study by Lee et al. was presented as an illustration [49]. The authors suggested that neurotrophic factors released into the medium by stem cells can confer regenerative abilities on hypoxia-damaged organotypic cultures of hippocampal slices. The hippocampus was revealed to be less damaged after growing in a conditioned medium than after growing in a Gwalior medium [consisting of 25% Hank's balanced salt solution (GibcoBRL/Life Technologies, Eugene, OR, USA), 25% heat-inactivated horse serum (Hyclone, Logan, UT, USA), 50% Eagle medium (BME, GibcoBRL/Life Technologies), 6.5 mg/mL glucose and 200 mM glutamax I (GibcoBRL/Life Technologies)]. Moreover, stem cells can express various neurotrophic and growth factors. The study authors state that NGF, GDNF, and the vascular growth factor VEGF act as neuroprotectors under hypoxic injury conditions [49].

Other studies have confirmed data on the mechanisms of the neuroprotective effect of mesenchymal stem cells (i.e., the secretion of neurotrophins, including brain and glial neurotrophic factors [50, 51]) as another way to reduce the pathogenic effect of hypoxic–ischemic damage, which was described by Sheng et al. in 2018 [52]. The results of an *in vitro* study demonstrated that prolonged hypoxia downregulates BDNF-TrkB signaling, leading to an increase in the TNFα level in the cerebral cortex, which induces neuroinflammation and neurotoxicity, while activation of the delta-opioid receptor regulates BDNF-TrkB signaling, reducing the TNFα level in the cerebral cortex. Upon activation of δ-opioid receptors, the expression of astrocytic BDNF, NGF, and GDNF increases, which leads to an increase in cell growth and improves their functioning and phenotypic development, which ultimately plays a decisive role in protecting the brain against hypoxic/ischemic encephalopathy [52].

In *in vitro* studies, the introduction of neurotrophic factors into the culture medium under conditions of ischemic damage promotes the preservation and restoration of the functional activity of neural networks [53, 54]. Recently, in an experimental study, the antihypoxic effect of GDNF was shown when administered intranasally under the influence of acute hypobaric hypoxia [55]. GDNF has pronounced neuroprotective properties. Its prophylactic use preserves cell viability, spontaneous bioelectrical activity, and morphological and functional structures of neural networks of primary hippocampal cultures after hypoxic damage. GDNF was also demonstrated to be involved in maintaining the level of AMPA receptors containing the GluR2 subunit, which may be the key mechanism of the neuroprotective GDNF action [56]. Ikeda et al. published the results of experiments simulating ischemic/hypoxic brain injury in 7-day-old rats. The extent of damage was significantly attenuated with intracerebral GDNF injection (2 or 4 μg) within 30 min after stroke. The authors note that higher GDNF expression and its mRNA in the developing

brain may be one of the factors responsible for the relative resistance to ischemia in the fetus and newborn in contrast to the adult brain [38].

Experimental studies have become the basis for studying the role of neurotrophic factors in clinical practice. In 2006, Golosnaya and Kotiy found that a decrease in the BDNF and VEGF levels in the blood serum of newborns to trace values in the first day of life and the first week of life, respectively, is prognostically unfavorable. An increase in the levels of these neurotrophins by 1.5–3 times indicates good adaptive capabilities of the nervous system. The study noted that a direct correlation was revealed, in preeclampsia, with a low VEGF level by the first day of a newborn's life, which indicates a high risk of perinatal hypoxic brain damage in this group of patients [58]. Shchelchkova et al. found no significant differences in the GDNF and NSE levels in the venous umbilical cord blood plasma of newborns during physiological labor and labor complicated by hypoxia. The authors attribute this to the activation of compensatory mechanisms during childbirth. However, a significant decrease in the BDNF level was registered in the group of newborns with complicated delivery. According to researchers, this indicates a low degree of brain protection against hypoxic damage, which can lead to the development of degenerative processes in the brain tissues of newborns [57]. According to Morozova et al., under conditions of chronic hypoxia in placental insufficiency, the genetic program for the development of all functional systems of the fetal body is disrupted, which complicates postnatal adaptation and programs the risk of adverse consequences, including the deep disturbances in brain homeostasis. The authors emphasize that determining not only the presence and degree of damage but also the possibility of compensatory mechanisms is important for a favorable perinatal prognosis. In 2019, results were published in which full-term newborns with intrauterine growth retardation of degrees 2–3 had an increased NSE level in the umbilical blood serum, while the BDNF level was low. The data obtained indicate brain damage combined with the lack of adequate compensatory capabilities. Under these conditions, the degree of damage to neuronal structures increases with an increase in the gestation period [59]. In the process of clinical follow-up, in 2020, Shchelchkova et al. found an increased expression of neurotrophic factors, BDNF and GDNF, in cord blood serum in groups with favorable birth outcomes for newborns, which is consistent with previous results and literature data. The authors believe that this can partially explain the compensatory capabilities of newborns even in the presence and implementation of stress factors during childbirth. Moreover, a low level of neurotrophic factors BDNF and GDNF in cord blood serum was recorded in a group of infants with a high risk of developing adverse consequences of hypoxic damage [41].

The aforementioned studies open up the possibility of searching for fundamentally new, pathogenetically substantiated ways of influencing brain dysfunction of hypoxic–ischemic etiology both in neurology and in several other specialties, for example, in neonatology with hypoxic–ischemic damage to the brain of a newborn, using synthetic analogs of neurotrophins [60].

Thus, a review of the literature shows that many methods currently exist for the functional assessment of the state of the fetus during childbirth.

Data on the sensitivity and specificity of routine diagnostic methods are still contradictory, and the issue of verification of fetal hypoxia has not been resolved. The compensatory and adaptive mechanisms of the fetus, which are implemented in childbirth, are underinvestigated. In recent years, great importance has been focused on the expression of mRNA proteins, which are markers of alteration of target organs. Great experimental and clinical significance in the mechanism of regulation of compensatory and adaptive capabilities is attached to neurotrophic factors, which are genetically determined. The search for the least invasive, more reliable, and cost-effective methods to assess the condition of the fetus in labor to improve perinatal outcomes remains an urgent problem and requires further study.

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