

ДОДИПЛОМНА ТА ПІСЛЯДИПЛОМНА МЕДИЧНА ОСВІТА В УКРАЇНІ

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SCIENTIFIC TRENDS IN PERINATAL
MEDICINE AND NEONATOLOGY
AT BUKOVINIAN STATE MEDICAL
UNIVERSITY: ADVANCES
AND PROSPECTS

Summary

Bukovinian State Medical University (BSMU) of the Ministry of Health of Ukraine (Chernivtsi, Ukraine), according to the ranking criteria of the SciVerse Scopus database in 2023, is among the 10 best higher state educational institutions in Ukraine. In 2023, BSMU was ranked 2nd according to the Webometrics system. BSMU supports the implementation of the main provisions of Open Science in Ukraine, which is a priority for European research policy. BSMU started filling information data on the areas of open science in the National Electronic Research and Information System of Ukraine "URIS", which is commissioned by the Ministry of Education and Science of Ukraine and the Ministry of Digital Transformation of Ukraine in accordance with the main provisions of the unified national program "On the Implementation of the National Action Plan for Open Science in Ukraine".

Unfortunately, unfavorable demographic trends have recently persisted in Ukraine with a projected decline in the birth rate, an increase in mortality and forced migration as a result of military operations, aggression and genocide of the Ukrainian people. One of the key research areas is maternity and childhood, which has been the basis of scientific research at the Department of Paediatrics, Neonatology and Perinatal Medicine for many years. The aim of this research area is to improve the efficiency of medical care for newborns, including full-term and premature infants born with various forms of perinatal pathology and intrauterine developmental disorders, by improving algorithms for predicting, diagnosing and treating organ system disorders under conditions of birth stress.

Key words: Perinatal Medicine; Neonatology; Newborns; Perinatal Pathology.

Bukovinian State Medical University (BSMU) of the Ministry of Health of Ukraine (Chernivtsi, Ukraine), according to the ranking criteria of the SciVerse Scopus database in 2023, is among the 10 best higher state medical educational institutions in Ukraine. In 2023, BSMU was ranked 2nd according to the Webometrics system. In the ranking of institutions with the highest inventive output based on the results of utility model patents, the university took a creditable 3rd place.

The scientific area is led by the BSMU Scientific Department under the supervision of the Vice-Rector for Scientific Work. The BSMU Coordination Council for the representation of scientific achievements in the international scientific and information space is active. Currently, 35 research topics are being carried out at BSMU. Since January 2023, 2 research projects have been carried out at the expense of the State Budget of Ukraine. At present, 6 dissertations for the degree of Doctor of Science and 76 for the degree of Doctor of Philosophy are being completed. The bases for research work are the specialized departments and medical and preventive care institutions that are the clinical bases of the university.

In order to comprehensively promote research work, inventive and creative activities of scientists, ensure a systematic approach to the training of high-quality scientific and pedagogical staff, preserve and develop intellectual potential, the University has formed scientific schools whose findings address many medical problems, including diagnosis, treatment and prevention of diseases of the cardiovascular system, malignant tumours, tuberculosis, endocrine and immune systems, digestive and respiratory organs in children and adults. The University focuses on the exchange of scientific information and testing of scientific research.

For the successful implementation of scientific research, BSMU has an Educational and Research Laboratory, a Clinical Research Centre, 4 cross-departmental laboratories (biochemical, microbiological, morphological, immunological), as well as 17 departmental laboratories. The Clinical Trials Centre provides scientific and organizational support, accounting and management of the financial component, consulting support for inspections of sites by regulatory authorities, preliminary analysis of requests for trials and search for new research, and monitoring of the legal framework.

Every year, the university holds scientific forums registered in the State Register of Scientific Events of Ukraine, in which BSMU acts as an event organizer. Scientific meetings are covered using the Web Class video conferencing service of the URAN scientific and educational telecommunication network.

The University publishes 7 professional scientific and practical periodicals: "Bukovinian Medical Bulletin", "Clinical and Experimental Pathology", "Neonatology, Surgery and Perinatal Medicine", "International Endocrinological Journal", "Forensic Medicine", "Clinical Anatomy and Operative Surgery", "Topical Issues of Social Sciences and History of Medicine" (Ukrainian-Romanian). The journals are included in national and international databases of scientific information, catalogues and search systems. Scientific and practical journals "Neonatology, Surgery and Perinatal Medicine" and "International Endocrinological Journal" are included in the Scopus international database. Journal sites are presented on the OJS (Open Journal System) platform.

The number of scientific papers issued by BSMU staff remains stable and high. The quality and relevance of the research publications is confirmed by the large number of

articles published in leading scientific journals in Ukraine and abroad. The BSMU repository has more than 18720 electronic records, where not only university staff but also researchers from other higher education institutions in Ukraine and abroad can get acquainted with scientific works. On 1 October 2022, BSMU became one of the first 17 members of the ORCID Ukraine Consortium. All university employees are registered and have an individual ORCID researcher profile, and profiles are updated and corrected on an ongoing basis. A significant number of BSMU scientists have their own individual profiles in the international databases Scopus and Web of Science. Since 2023, general profiles of the university in Scopus and Web of Science have also been available.

The staff of BSMU supports the implementation of the main provisions of Open Science in Ukraine, which is a priority for European research policy. Open Science is a relevant, fundamentally new approach to the organization and implementation of the scientific process in different countries of the world. We believe that this philosophy of scientific research, based on high standards of transparency, cooperation and communication based on joint work, will provide additional opportunities for the dissemination and exchange of scientific information through the use of modern digital gadgets and technologies. In addition, open science involves providing open access to research results, explaining and promoting scientific knowledge to the public, etc. In general, the implementation of open science principles is expected to ensure greater transparency and integrity of scientific research, and in the long run, improve the quality of science and education in general. In 2023, the university started filling information data on the areas of open science in the National Electronic Research and Information System of Ukraine "URIS" (Ukrainian Research Information System), which is commissioned by the Ministry of Education and Science of Ukraine and the Ministry of Digital Transformation of Ukraine in accordance with the main provisions of the unified national program "On the Implementation of the National Action Plan for Open Science in Ukraine". The Regulations on the National Electronic Scientific and Information System "URIS" (Ukrainian Research Information System), and the List of Priority Information Resources of the System were approved by the Resolution of the Cabinet of Ministers of Ukraine on 27 September 2022.

One of the key research areas is maternity and childhood, which has been the basis of scientific research at the Department of Paediatrics, Neonatology and Perinatal Medicine of BSMU for many years. The aim of this research area is to improve the quality and efficiency of medical care for newborns, including full-term and premature infants born with various forms of perinatal pathology and intrauterine developmental disorders, by improving algorithms for predicting, diagnosing and treating organ system disorders under conditions of birth stress. These categories of newborns need intensive care for an effective start in life and long-term costly treatment involving a multidisciplinary team of specialists. In the future, they are at high risk of developing functional and chronic pathology, psycho-physical developmental disorders and disability, which significantly reduces the

quality of their future life and causes disruptions in the overall social adaptation of families.

The most vulnerable category is considered to be children born before the physiological gestation period (before reaching the full 37 weeks and/or weighing less than 2500 grams). In EU countries in 2018, one in 15 children among all newborns (6.6%) had a birth weight of less than 2500 grams. Between 2010 and 2018, some countries, such as Austria and the Czech Republic, recorded a significant decrease in the proportion of low birth weight babies, while this proportion remained unchanged in most other countries [1]. Respiratory pathology (respiratory distress syndrome, bronchopulmonary dysplasia, congenital pneumonia, persistent pulmonary hypertension, congenital malformations, etc.) takes the leading place in the structure of morbidity and mortality of preterm infants.

The scientific direction of the basic provisions of perinatal care, nursing and treatment of children from birth is extremely important for Ukraine, as recently unfavorable demographic indicators have persisted with a projected decline in fertility, an increase in mortality and forced migration as a result of military aggression and genocide of the Ukrainian people. Even in the pre-war period, in 2019, the country's perinatal mortality rate was 9.3 per 100,000, which was significantly higher than the average for Europe (7.38 per 100,000) and the EU (6.57 per 100,000). In 2018, the infant mortality rate (children under 1 year of age) was 7.18%, which was also significantly higher than the 4.0% target set by the UN Millennium Development Goals Program. The preterm birth rate in Ukraine in recent years has been around 5.8%, but only 80% of children weighing less than 1500 g and 40% of children weighing less than 1000 g survive to the end of 1 year, which is significantly lower than the corresponding figures for the vast majority of European countries.

The early diagnosis and treatment of critical conditions are of great importance for their short-term outcome and lifetime prognosis. To assess the severity of the disease in newborns, various scoring systems have been developed, such as the Score for Neonatal Acute Physiology II (SNAP II) and its perinatal extension (SNAP-Perinatal Extension, SNAPPE, SNAPPE-II), as well as the Clinical Risk Index for Babies II (CRIB II) [2]. The presented scales are aimed at early detection of sick newborns with an increased risk of morbidity and mortality and can contribute to improved patient care. Previous studies have shown that the modified NEOMOD (Neonatal Multiple Organ Dysfunction Scoring System) is a safe and accurate tool for determining the level of mortality and dysfunction of many organ systems, which affects the mortality of preterm infants [3].

Multiple organ dysfunction (MOD) is characterized by a progressive impairment of the physiological functions of two or more organ systems and is the main cause of morbidity and mortality in intensive care unit patients [3]. Gupta S. and Donn S. W. (2020) point out that ICU physicians must understand the pathophysiology of a patient's haemodynamic problems in order to objectively select therapy according to the cause, rather than being guided by traditional treatment approaches using volume, inotropes, and vasopressors. This requires an understanding of the physiological concepts of haemodynamics and the

pharmacodynamic properties of the pharmaceuticals used for treatment [4].

In establishing the prognosis of the severity of perinatal pathology and its consequences in a child in the later years of life, an important role is played by the analysis of the implementation of risk factors during pregnancy and childbirth in the mother. The peculiarities of the formation of short-term and long-term adaptation of the child's body after birth are of great importance.

Hypoxia is a universal factor in damaging the body of the fetus and newborn, in the presence of maternal problems during the gestation period and childbirth. Under conditions of hypoxia, children have a high probability of developing disabilities in the subsequent life years. In particular, according to the literature, in 5-10% of cases, there is a persistent motor deficit, in 20-50% – sensory or cognitive impairment that persists until adolescence [5].

Hypoxic-ischemic encephalopathy (HIE)/neonatal encephalopathy (NE) is a consequence of hypoxic exposure to the body of newborns, which accounts for a significant proportion of the pathology of this age group of children, in particular, in developed countries the incidence of NE is approximately 1.5 cases per 1000 live births. In low- and middle-income countries, the rates are much higher and reach 10-20 per 1000 live births [6]. Despite the advances in perinatal medicine in recent years, NE remains a significant cause of mortality, neurological disorders during the acute period, and the formation of psycho-neurological disorders and childhood disability in the future [7].

The brain of a newborn has a genetically determined set of reactions to hypoxia. It is not only an increase in cerebral blood flow, its redistribution between brain structures, but also typical changes in intracellular metabolism, in particular mitochondrial dysfunction, resulting in energy metabolism disorders, insufficiency of the body's antioxidant defense system, glutamatergic excitotoxicity and the development of apoptosis [6]. Therefore, the clinical and molecular aspects of the formation of NE [1, 8] are extensively discussed in the modern scientific literature to form the concept of pharmacological correction in the acute period of diseases and complex treatment in the period of recovery.

Our findings confirm the results of the latest years published in scientific sources. Mitochondria are a key part of the body's cellular energy system. Progressive mitochondrial dysfunction can lead to cellular energy deficiency, disruption of many important metabolic processes, cellular damage and cell death in hypoxic conditions. The analysis of energy metabolism in newborns with hypoxic damage showed a significantly reduced level of glycerol-3-phosphate dehydrogenase (GPDH) in umbilical cord blood against the background of increased lactate levels; succinate dehydrogenase (SDH) and NADH dehydrogenase (NADH), a significant decrease in the aerobic respiration rate (AR) and electron transport chain ratio (ETR) compared to the control group. Significantly reduced, compared to full-term infants, were the indicators in preterm infants. The obtained data confirm the concept of the presence of mitochondrial respiration disorders in newborns, which requires much attention to the need for multicenter studies to determine the possibilities of therapeutic correction of mitochondrial dysfunction in the treatment of hypoxic damage in newborns

in the acute period of disease and prevention of severe neurological and somatic dysfunction with the development of functional and chronic pathology.

Disturbances in energy metabolism in mitochondria trigger the activation of free radical oxidation (FRO). The phenomenon of ischaemia-reperfusion occurring in perinatal asphyxia causes an increase in the production of reactive oxygen species (ROS), activation of lipid peroxidation (LPO), oxidative modification of proteins (OMP), and stimulation of apoptosis or necrosis mechanisms, in particular of nerve cells [9]. An increase in ROS levels is detected in newborns almost immediately after asphyxia (up to 30 minutes) and can last for several days. Poorly developed innate mechanisms of antioxidant defense (AOD) make the central nervous system (CNS) of the newborn highly vulnerable to the adverse effects of oxidative stress [10]. Neuroinflammation and oxidative damage have a harmful interaction. ROS trigger microglial activation and the release of proinflammatory cytokines, followed by FRO activation. The control of early mechanisms of brain damage, considering possible areas of neuroprotective therapy, is also discussed in the current scientific literature [11, 12].

According to our findings, in newborns with clinical signs of impaired adaptation under perinatal pathology, compared with healthy children, there was a significant increase in the activity of free radical oxidation (FRO), in particular, the levels of malondialdehyde (MDA) and oxidative modification of proteins (OMP) with a decrease in ceruloplasmin (CP) and catalase (CAT), which confirms the insufficiency of the production of these enzymes of the body's antioxidant defense system under conditions of birth oxidative stress (OS). Also, the level of HS-groups of blood plasma was significantly reduced, and the levels of glucose-6-phosphate dehydrogenase (G6PD), glutathione S-transferase (GST), glutathione peroxidase (GP) of erythrocytes, as well as gamma-glutamyltransferase (GGT) and glutathione reductase (GR) of blood plasma were increased. These parameters were significantly more pronounced in the examination of preterm infants.

According to the literature, at the beginning of brain damage, due to a lack of oxygen supply to cells and tissues, there is a decrease in ATP production, excitotoxicity, massive Ca^{2+} influx into cells and lactacidosis – primary energy deficiency, as well as hypovolaemia and circulatory disorders occur [13, 14]. Subsequently, the level of high-energy phosphate is rapidly restored (latent phase), and 6-48 hours after hypoxia/ischemia, the secondary phase occurs, in which various pathophysiological mechanisms (oxidative and nitrosative stress, inflammation, etc.) result in cell death by apoptosis or necrosis. Gradually, the tertiary phase occurs, characterised by further deepening of brain damage in the months and years after the hypoxic injury [15].

The care of critically ill neonates can be improved and more targeted with new diagnostic criteria for multiorgan dysfunction within a critical time window. For example, modern echocardiographic assessment of cardiac function includes 2D, spectral Doppler, M-mode, tissue Doppler, and more recently, speckle tracking for strain analysis. These techniques can be used to assess systolic and diastolic cardiac function, left and right ventricular output, left

ventricular contractility, ejection fraction, and segmental myocardial motility. It also helps to assess proper heart pressure and function, as well as evidence of pulmonary hypertension, which is commonly associated with RDS, hypoxemia, and poor cardiac function in infants [4]. A previous study by Bokinić R. et al. (2016) demonstrated that the Myocardial Performance Index (MPI) is important for both full-term and preterm infants [16].

Dopplerography is a valuable tool for monitoring changes in blood flow velocities, assessing changes in cerebrovascular resistance, and determining the lower limits of cerebral blood flow autoregulation [17].

Splanchnic and renal perfusion in newborns is associated with other haemodynamic mechanisms, as well as the functioning of the cardiovascular, central nervous and endocrine systems, in particular. The use of pulsed-wave Doppler of the mesenteric and renal arteries in neonatology is associated with a number of technical difficulties: small size of organs, low blood flow intensity, inability to fix the child in one position and assess blood flow over several cardiac cycles, etc. However, the study of hemodynamic features of splanchnic and renal blood flow in NICU patients allows timely diagnosis of intestinal and renal dysfunction, correction of pharmacotherapy and prevention of severe irreversible intestinal and renal damage, such as necrotising enterocolitis (NEC) and acute kidney injury (AKI) [4]. Guang Y. et al. (2019) studied the correlation between superior mesenteric artery blood flow in the first 12 hours of life and the risk of NEC in preterm infants. In particular, the authors demonstrated the promising value of Doppler ultrasound for the prediction of NEC and pointed out the need for further research [18].

Lung sonography (lung ultrasound) is a modern instrumental method for diagnosing lung pathology. Systematic reviews, meta-analyses and clinical trial results show a high level of evidence for the sensitivity and specificity of this diagnostic method in neonatal practice [19]. Ultrasonography of the lungs in newborns has a number of significant advantages, namely: 1) performed at the patient's bedside; 2) no need for conventional anaesthesia; 3) no need for a sharp change in body position; 4) no risk of hypothermia in the child (provided the gel is preheated); 5) no ionizing radiation; 6) the ability to perform real-time scanning to determine not only structural changes but also to assess dynamic parameters [20]. Lung ultrasound has recently been added to the list of point-of-care ultrasound for use in paediatric and neonatal intensive care; evidence-based recommendations have recently been published [21]. Ultrasound examination of the lungs in newborns with respiratory failure is performed according to a protocol that is uniform for all participating medical institutions and is based on the recommendations of De Martino L, Yousef N, Ben-Ammar R et al. (2018) [22, 23].

Echocardiography is one of the most important methods of newborn examination. A 12 MHz sectoral transducer is used for morphological and functional assessment of the heart in accordance with the 2010 recommendations of the American Society of Echocardiography (ASE) [23]. As a non-invasive way to measure the overall systolic and diastolic myocardial function, the myocardial performance index (MPI) of the left and right ventricles (LVMPI,

RVMPI) is measured, introduced in the mid-90s by Tei et al. [24]. MPI is calculated by the formula $(ICT + IRT)/ET$ (ICT is isovolumetric contraction time, IRT is isovolumetric relaxation time, ET is ejection time) and is easily calculated as $(a-b)/b$ according to the Hernandez-Andrade et al. modification [25]. Doppler echo (clicks) of the opening and closing of the aortic valve (AV) and mitral valve (MV) are used as reference points to estimate the time of the ejection period. For neonatal transcranial, renal and abdominal ultrasound, a 5 MHz convection transducer is used. Color Doppler and pulsed-wave Doppler are performed to examine the blood flow curve of the anterior and middle cerebral arteries (MCA), superior mesenteric artery (SMA), right renal arteries (RRA), and left renal arteries (LRA). The following parameters are determined: FVI (flow-vascularization index), PI (pulsatility index), RI (restriction index), PV (peak velocity) (cm/s), EDV (end-diastolic velocity) (cm/s), V_{mn} (mean velocity) (cm/s), SV/SD (systolic velocity/diastolic velocity).

Chest radiography (CR) is the "gold standard" for detecting RDS in newborns, but it involves exposure to ionizing radiation. Newborns, due to their small size and close proximity to radiosensitive tissues and organs, are at greater risk of latent side effects of radiography compared to other age groups. Due to the fact that newborns undergo numerous radiographic examinations during their stay in the neonatal intensive care unit (NICU), efforts have been made to develop an alternative diagnostic test [26].

According to the analysis of antenatal and perinatal risk factors, clinical signs of diseases, results of biochemical and ultrasonographic methods of research, it is expected to develop criteria for multiorgan dysfunction in newborns, considering a set of laboratory parameters and organ haemodynamics disorders (cerebral, cardiac, abdominal, renal), which will improve the directions of medical care during intensive care for perinatal pathology resulting from hypoxic organ damage.

To create a comprehensive mathematical model for the prognosis of multiple organ dysfunction (MOD), it is reasonable to conduct a linear discriminant analysis of the main perinatal risk factors and indexed clinical and paraclinical markers. A multi-factor analysis of statistically significant clinical, biochemical and ultrasonographic criteria will be used to develop a complex mathematical model for the diagnosis of MOD. It is planned to create a graphical scheme for the prognosis, diagnosis and treatment of critically ill newborns, depending on the type of haemodynamic disorders (normo-, hypo-, hyperkinetic).

The results of the research effort will allow for further adjustments to clinical guidelines and protocols for newborn care. The research area requires an integrated approach to conducting multicenter studies, their reproducibility and effectiveness of practical output, with due regard for the evaluation of the following:

- The ability to timely prevent the development of multiple organ dysfunction in critically ill newborns, considering perinatal risk factors, clinical signs and the results of laboratory and instrumental examinations.
- Probabilities of accelerating the diagnosis of multiple organ dysfunction with the determination of the type of central haemodynamic disorders.

- Evaluation of the effectiveness of correction of treatment measures in the severe condition of newborns (parameters of non-invasive and invasive lung ventilation, prescription and dosage of inotropic drugs, volemic load, metabolic therapy, etc.)

Implementation of the research results into everyday neonatal practice will help reduce the incidence of MOD, acute kidney injury (AKI), nonspecific enterocolitis (NEC); the duration of artificial lung ventilation (ALV) and total parenteral nutrition (TPN); the frequency of inotropic therapy and mortality of preterm infants with respiratory distress syndrome (RDS) in the first month of life, and to reduce the length of stay in the neonatal intensive care unit (NICU).

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НАУКОВІ НАПРЯМКИ ПЕРИНАТАЛЬНОЇ МЕДИЦИНИ ТА НЕОНАТОЛОГІЇ НА БАЗІ БУКОВИНСЬКОГО ДЕРЖАВНОГО МЕДИЧНОГО УНІВЕРСИТЕТУ: ДОСЯГНЕННЯ ТА ПЕРСПЕКТИВИ

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Резюме.

Буковинський державний медичний університет (БДМУ) МОЗ України (м. Чернівці, Україна) за критеріями рейтингу бази даних SciVerse Scopus у 2023 році входить до 10 найкращих вищих державних навчальних закладів України. У 2023 році БДМУ посів 2 місце за системою Webometrics. БДМУ підтримує впровадження основних положень відкритої науки в Україні, яка є пріоритетом європейської дослідницької політики. БДМУ розпочав наповнення інформаційних даних за напрямками відкритої науки в Національній електронній науково-інформаційній системі України «URIS», яка створюється на замовлення МОН України та Міністерства цифрової трансформації України згідно з основними положеннями єдиної національної програми «Про реалізацію Національного плану дій щодо відкритої науки в Україні».

На жаль, останнім часом в Україні зберігаються несприятливі демографічні тенденції з прогнозованим зниженням народжуваності, зростанням смертності та вимушеною міграцією внаслідок військових дій, агресії та геноциду українського народу. Одним із ключових наукових напрямів є материнство та дитинство, яке протягом багатьох років є основою наукових досліджень кафедри педіатрії, неонатології та перинатальної медицини. Метою даного наукового напряму є підвищення ефективності надання медичної допомоги новонародженим, у тому числі доношеним та передчасно анродженим дітям, народженим з різними формами перинатальної патології та порушеннями внутрішньоутробного розвитку шляхом удосконалення алгоритмів прогнозування, діагностики та лікування ураження систем органів за умов пологового стресу.

Ключові слова: перинатальна медицина; неонатологія; новонароджені; перинатальна патологія.

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