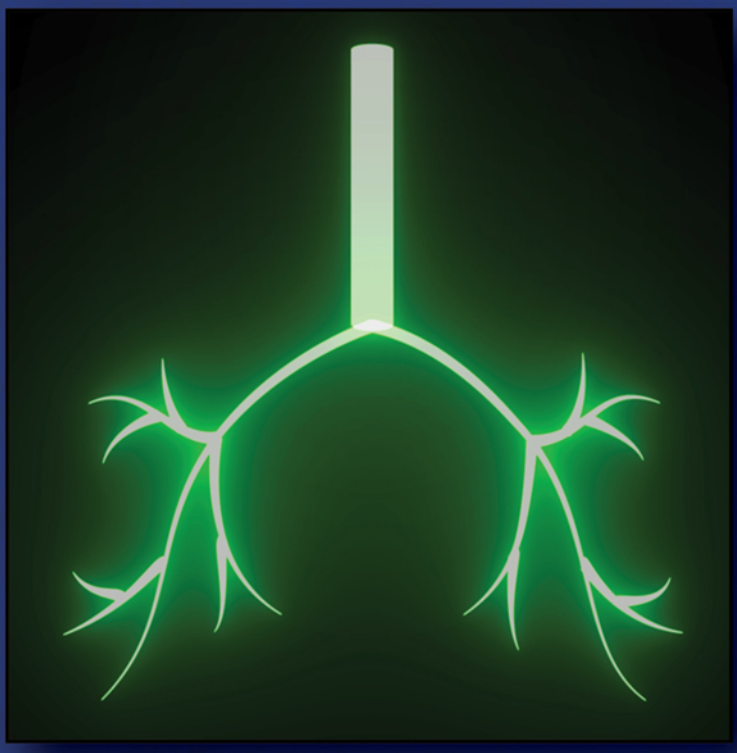
ASPHYXIA IN NEONATES



MILJANA Z. JOVANDARIC

with contributions by
Stefan Dugalic and Sandra Babic

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Asphyxia in Neonates

In severe asphyxia, lipid peroxidation occurs. Neonatal lipid concentration may indicate the severity of asphyxia and be a reason for needing cooling therapy. This book describes the results of research into the impact of oxygen deficits in neonates. The physiological consequences of asphyxiated newborn infants include changes in the pH of plasma and in lipid concentrations. These changes can result in apoptosis, loss of cell membrane integrity, and damage to the brain.

Key Features

- Reviews pathophysiology of asphyxia
- Describes the influence of asphyxia on lipid concentrations
- Summarizes the weight distribution of neonates with asphyxia based on lipid concentration
- Illustrates the use of lipids as an indicator of prognosis following asphyxia
- Provides guidance for lipid parameters in cooling therapy

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About the Author

Miljana Z. Jovandaric, MD, PhD, was born in Serbia. She graduated from the Faculty of Medicine, University of Belgrade, and completed her pediatric specialization in 1999 at the University Children's Hospital, Belgrade. Dr. Jovandaric completed her specialization in neonatology in 2003. She defended her master's thesis, "Analysis of lipid infants in women suffering from gestational diabetes mellitus (GDM)," in 2006 and doctoral dissertation, "Effect of hypoxia on electrolyte and lipid levels in term newborns," in 2018 as part of the medical faculty at University of Belgrade, Serbia. Dr. Jovandaric has been a research associate since 2020 as part of the medical faculty of the University of Belgrade, Serbia. Author and coauthor of 106 scientific papers presented at national and international conferences and journals, she's head of the Department of Sick Newborns at the Clinic for Gynecology and Obstetrics, Department of Neonatology, University Clinical Center of Serbia, Belgrade. Dr. Jovandaric has edited and/or contributed to the following books: *Childbirth: Placenta Abruption and Delivery Method*; *Selected Topics in Myasthenia Gravis: Maternal and Neonatal Outcome of Pregnancies with Autoimmune Myasthenia Gravis*; *Apoliproteins, Triglicerides and Cholesterol: Significance of Lipid and Lipoprotein in Organism*; and *Veganism: A Fashion Trend or Food as a Medicine – Veganism: A New Approach to Health*.

About the Contributors

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Sandra Babic, MD, was born in Belgrade, Serbia, and graduated from the Medical Faculty of the University of Belgrade. At the same faculty in 2015/2016, she enrolled and completed the specialist academic studies program in the field of human reproduction. She completed her study as a specialist in gynecology and obstetrics in 2020. She has been with the Clinic for Gynecology and Obstetrics UKCS since 2013, first as a volunteer and now as a clinical doctor. Dr. Babic has published several works in foreign and domestic professional journals.

Preface

Asphyxia in Neonates is a product of my long-term work with asphyctic newborns. This topic was the inspiration for my master's thesis, as well as doctoral studies and papers published in numerous journals. During the perinatal period, asphyxia is defined as a state of disturbed gas exchange, which is accompanied by an increase in lactate, carbon dioxide, and other waste products, as well as a significant decrease in the concentration of oxygen in the blood that leads to lipid peroxidation, damage and permeability of capillaries, and complex metabolic processes, and causing subsequent damage to the heart, brain, kidneys, and other organs. For years, different treatment modalities have been applied, as well as parameters for sending patients to therapeutic hypothermia. Lipid peroxidation and determining the concentration of lipids in the serum of asphyctic children proved to be a good predictive indicator of the severity of asphyxia.

Miljana Z. Jovandaric, MD, PhD

Chapter 1

Perinatal Asphyxia, Hypoxia, Ischemia, and the Newborn

Miljana Z. Jovandaric

1.1 Introduction

Perinatal asphyxia is a complex clinical problem that is most often defined as a disorder of respiratory gas exchange in the placenta of the fetus during delivery or in the lungs of the newborn after birth (1). Although the word "asphyxia" itself means "without a pulse" (Greek: *a* – no; *sphygmos* – beating pulse, suffocation, apparent death), asphyxia in the clinical sense means the condition of a newborn after birth, accompanied by cessation of breathing (apnea) with preserved or weakened pulse. The term *asphyxia* in medical terminology represents a state of neonatal respiratory distress with short-term and long-term effects on the body. Asphyxia can also be defined as a state of impaired gas exchange, accompanied by an increase in lactate, carbon dioxide, and other waste

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products, as well as a significant decrease in the concentration of oxygen in the blood (2).

While the term *asphyxia* is reserved for the combined state of hypoxia, hypercapnia, and acidosis, hypoxia (Greek *hypo* + Latin *oxygen* + Greek *haima* – blood) refers to states of oxygen deficiency without accompanying acidosis. Hypoxia means reduced tissue oxygen supply and is a consequence of reduced oxygen pressure in the blood (hypoxemic hypoxia), reduced blood flow (ischemic hypoxia), or reduced capacity of the blood to supply oxygen (anemic hypoxia). Ischemia is a decrease in blood flow, with a consequent decrease in oxygen and glucose in the required amounts, which leads to organ damage (3).

Hypoxia as a physiological-pathophysiological event has an important meaning during normal and pathological childbirth. During the initial dilation of the cervix, the pH of the fetal blood drops from 7.37 to 7.27 at full dilation. A certain degree of hypoxia and acidosis is present during normal labor. The variability of gases in the arterial blood is mild and reversible, so it is believed that this "transient asphyxia" has a physiological role in preparing the fetus for the beginning of normal breathing (4).

Most children (more than 95%) overcome this condition without major problems. Only a small number require active assistance during the first breath and the beginning of alveolar ventilation (which is actually a condition for survival). If the initiation of breathing is unsuccessful, respiratory stimulation will quickly prevent pathological inversion of blood gases in the newborn and establish extracellular and intracellular homeostasis. Thus, primary resuscitation by shortening the period of hypoxia, hypercapnia, and acidosis will prevent perinatal hypoxic tissue damage, the most severe of which is brain damage. Because of all this, asphyxia should be understood as a medical term for a clinical manifestation (the child is not breathing!), which is a consequence of varying degrees of hypoxia (5).

Although the pathophysiological mechanisms of severe asphyxia, hypoxia, or ischemia (focal or global) can be specifically simulated and investigated in research on animal models, in clinical reality it is almost impossible to separate these conditions, so they are labeled as hypoxic-ischemic damage. In human newborns, it is often very difficult to determine the duration of hypoxia and its intensity during the birth itself. There is also an attempt to measure the effect of anoxia (hypoxia) by the degree of asphyxia in a newborn whose potential is only partially known (e.g., gestational age) and whose resistance or sensitivity to different degrees of hypoxia are different from other neonates (6). The complexity of the definition of asphyxia/hypoxia/ischemia is best reflected in the recommendations of numerous authors for the more precise diagnosis of asphyxia/hypoxia by connecting clinical signs to biochemical parameters. The previous term *hypoxic-ischemic encephalopathy* has become insufficiently precise. Since it is not only about hypoxia and ischemia, a more adequate term based on current knowledge is *hypoxic-ischemic-reperfusion-reoxygenation brain lesion* (7).

1.2 Perinatal Asphyxia and the Newborn

There is a lack of data on the incidence of perinatal asphyxia/hypoxia. In developed countries with well-organized perinatal services, the incidence is 1–6/1,000 term newborns (8). The assessment of the incidence of asphyxia varies due to uneven attitudes, depending on whether only full-term, premature, or all children with signs of asphyxia are taken into account. In countries with a low level of development, the incidence ranges up to 26/1,000 live births. It is estimated that 30% of children have hypoxia/ischemia in developed countries, and 60% in developing countries have some evidence of intrapartum hypoxia/ischemia (9).

One of the most common causes of asphyxia is premature birth, with all the consequences that accompany this group of newborns. Premature birth is defined as any birth at a gestation period of less than 37 weeks of gestation. Extremely preterm is less than 28 weeks (10).

Premature birth is the most common cause of infant death worldwide. About 15 million babies are born prematurely each year (5% to 18% of all births). Late preterm birth accounts for 75% of all preterm births. This rate varies between countries. In the United Kingdom, 7.9% of babies are born preterm, and in the United States, 12.3% of all births are before 37 weeks of gestation (11). About 0.5% of births are extremely early births (20–25 weeks of gestation), and they account for the majority of deaths. In many countries, the rate of preterm birth increased between the 1990s and 2010s. Complications from premature birth led to 810,000 deaths in 2015 worldwide, compared to 1.57 million in 1990 (12).

The chance of survival at 22 weeks is about 6%, while at 23 weeks it is 26%, at 24 weeks 55%, and at 25 weeks about 72%. Chances of survival without long-term difficulties are less. Prematurity has increased in prevalence over the past few decades in almost all countries with reliable data on the trend. In 2014, preterm birth had a worldwide prevalence of 10.6%, affecting nearly 15 million births annually. Due to advances in treatment introduced during the 1970s and 1980s, the survival of preterm infants has also improved dramatically (13). Over 95% of preterm infants and most of those born extremely preterm (<28 weeks) who receive modern neonatal and pediatric care now survive (14).

Premature birth is one of the biggest public health problems of recent decades. The increased percentage of survival represents a great challenge for perinatal medicine to understand and prevent the neurodevelopmental consequences in a premature child. The first neonatal intensive care unit was established in the United States in 1965 at the Yale University

School of Medicine. Exogenous surfactant was used for the first time in the treatment of respiratory distress syndrome in 1980 (15). The next advance in perinatal medicine is the antenatal use of steroids, after the New York Declaration of 1994, formalized in the National Institute of Health consensus statement in 1994 and recognized by the American College of Obstetricians and Gynecologists soon after. The use of surfactants and antenatal corticosteroids are revolutionary therapies that have increased the survival of premature birth in children, but the long-term neurodevelopmental consequences are still being explored (16).

The application of new knowledge in clinical practice as well as the development of technology in the form of the use of ventilators with different modes of ventilatory support, adequate resuscitation in the first minutes of life, combined with the knowledge of the nutritional needs of newborns in the last 50 years, have significantly improved the outcomes and consequences for children who were born prematurely. Complications caused by incomplete growth and development of organs can be mitigated by adequate therapy in intensive care units. Adequate therapy and care in the first minutes, hours, days, and weeks as well as a multidisciplinary approach by a team of experts from various specialties are key factors for a favorable outcome and further progress of premature children. During the long-term follow-up of prematurely born children, various complications can be observed that can affect the quality of life. Prematurely born children often faces increased risks of psychological, neurological, and physical diseases. Adequate recognition of problems in primary and secondary health care institutions can prevent or stop the progression of the disease (17).

Extensive clinical and research data support the fact that being born prematurely is associated with an increased risk of long-term health and neurodevelopmental problems. Many factors have been studied that could have an impact, primarily

neurodevelopment. Environmental factors have an impact on brain maturation in the first days of life. The benefit of mother's milk and early breastfeeding is important in order to prevent necrotic enterocolitis, but the benefit for neurodevelopment has not been clearly proven. It has been established that noise, pain, and the environment of neonatal intensive care can negatively affect the neurodevelopment of newborns. Isolated intensive care rooms have no advantage over open rooms. The positive effects of the presence of parents with newborns (rooming-in) on shaping the long-term neurodevelopment of high-risk premature babies have been proven (18).

1.3 Division of Asphyxia (Hypoxia) According to Duration

1.3.1 Acute Asphyxia

The condition of acute asphyxia has been well studied in animal models. After a few superficial breathing movements in which there is no gas exchange, newborn animals stop breathing, which is called primary apnea and can last up to 10 minutes. However, most animals start gasping, increasing the frequency and power of breathing, which then gradually decrease until the last breath. This period of gasping is followed again by apnea, but this time it is terminal apnea (19).

Heart rate drops rapidly after birth, increases in primary apnea and early gasping, and then slows. Heart activity continues for 10 minutes or more after the last breath. The period from the last breath to the cessation of cardiac activity is called secondary or terminal apnea. At the end of terminal apnea, severe metabolic or mixed acidosis develops: pCO_2 exceeds 100 mmHg, pH < 6.5, and pO_2 is unmeasurable. Hyperkalemia develops with $K^+ > 15$ mmol/L. Newborn primates can survive a complete lack of oxygen for 20

minutes. This is made possible by large reserves of glycogen in the brain, liver, and myocardium, which can produce energy anaerobically, as well as the ability of neonatal tissues to metabolize lactates and ketones (20).

The animal's reaction to asphyxia depends on the stage of asphyxia. If the animal receives oxygen or air after terminal apnea, it no longer initiates spontaneous breathing. If only asphyxia is observed in the human newborn, the response depends on the pH of the blood at the time of birth. If its value is higher than 7.25 (primary apnea, mild acidosis), it starts breathing spontaneously. If its value is 7.00–7.10 (moderate acidosis), it can still breathe spontaneously but requires monitoring in the postpartum period. In very severe intrapartum asphyxia (pH < 7.00 [severe acidosis]), the child is usually lethargic, with bradycardia and terminal apnea. Reanimation of the newborn is required. After resuscitation, a certain number of newborns make a quick and complete recovery. In the majority, however, morphological and functional damage to numerous organ systems occurs, known as "post-asphyxia syndrome" (21).

1.3.2 Chronic Asphyxia

In chronic asphyxia, the fetus suffers from occasional repeated episodes of asphyxia (uncoordinated uterine contractions or occasional episodes of pressure on the umbilical cord), with a period of short-term recovery between them. During these episodes, blood pressure increases in the fetus, there is bradycardia, and fetal pO_2 (partial arterial oxygen pressure) is lowered. The process of glycolysis involves the breakdown of glucose via pyruvate to lactate under anaerobic conditions. pCO_2 (partial pressure of carbon dioxide) increases, and usually as a result, mixed respiratory and metabolic acidosis occurs. If such a child is born immediately, their breathing is suppressed, but they recover very quickly after resuscitation

with no significant consequences (that is, if there are no neonatal complications). However, if these episodes last longer, the fetus fails to recover between individual interruptions in oxygen supply. Hemodynamic compensatory possibilities are gradually exhausted, and hypotension and deeper acidosis occur. After delivery and despite rapid resuscitation, such a child will have early and late signs of post-asphyxia (22).

1.3.3 Division of Asphyxia (Hypoxia) Based on Apgar Score

Apgar represents a summary assessment of the vital parameters of a newborn. It is named after Virginia Apgar, an American anesthesiologist, who in 1953 introduced this simple, systematic examination of newborns, which includes five parameters: skin color, respiration, heart rate, muscle tone, and response to stimulation. Each of the parameters is evaluated with a score of 0, 1, or 2. The total score is the Apgar score (AS). A favorable Apgar is 8–10, moderate depression is indicated by AS 4–7, and severe depression by AS 0–3. Apgar is evaluated in the first (vitality) and fifth (adaptation) minutes after birth (23).

A low Apgar (<7) indicates the need for resuscitation, and the assessment can be performed further, thus monitoring the success of resuscitation. Apgar cannot be used to assess long-term prognosis. For some time, neonatology associations have been talking about the possibility of introducing a new, more precise AS. Specifically, skin color is an unreliable clinical parameter of vitality, especially in the first minute when the expected oxygen saturation is only 60–70%. At this saturation, the skin cannot be clearly pink, for which a score of 2 is given, but is slightly cyanotic (with a bluish tinge), resulting in a lower score. Oxygen saturation reaches a value of around 90% only around the fifth minute, which is when the skin becomes really pink (24–26).