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Review Article

Duration of Fetal Immobility During Maternal Apnea Reflects its Resistance to Hypoxia

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Abstract

It has been established that fetal immobility is part of its reserves of adaptation to hypoxia, and the duration of fetal immobility during maternal apnea indicates their magnitude. Based on this, voluntary maternal apnea in the third trimester of pregnancy can be used to assess fetal resistance to hypoxia in order to predict the likelihood of newborn asphyxia. The fact is that during the normal course of pregnancy, the fetus remains motionless for at least 30 seconds from the moment of the onset of voluntary maternal apnea. In cases of symptoms of severe fetoplacental insufficiency, the fetus remains motionless for less than 10 seconds after the onset of apnea, after which convulsive contractions of the extremities occur in the fetus. It has been established that with good fetal resistance to hypoxia, there is a high probability that the fetus will be able to maintain its health until the end of pregnancy and natural childbirth. In the case of excessively low fetal resistance to hypoxia, continuation of pregnancy and natural delivery is contraindicated, since the probability of developing newborn asphyxia is high. Therefore, it is recommended to start urgent continuous hyperventilation of the mother's lungs with gaseous oxygen until she develops symptoms of mild oxygen poisoning and at the same time a Cesarean section.

Keywords: Pregnancy; Newborn Asphyxia; Intrauterine Hypoxia; Apnea; Oxygen; Immobility; Adaptation; Resistance; Encephalopathy

Abbreviations

ADP: Adenosine Diphosphoric Acid; FRH: Fetal Resistance to Hypoxia; PaO_2: Partial Pressure of Oxygen; PtO_2: Partial Tissue Pressure of Oxygen.

Introduction

The safe development of the fetus in the womb throughout pregnancy and the birth of a healthy baby remains the dream of every pregnant woman. Unfortunately, this dream is not realized for all women and not in every pregnancy: annually, 2.6 million pregnancies worldwide end in stillbirth [1]. In addition, perinatal encephalopathy is still not excluded as an unfortunate outcome of pregnancy and childbirth [2]. Although several risks of stillbirth and perinatal encephalopathy have been identified, the true causes of these complications are not fully known and reliable prevention measures have not been developed [1].

The intensity of research conducted worldwide to address these problems has increased significantly in the early 21st century. This has made it clear that the problem cannot be solved without

assessing fetal oxygen gas supply [3]. This was first pointed out by Josiah Barcroft 100 years ago, but the situation has not been clarified much. So we still have much to find out [4]. It has now been established that in the first half of pregnancy the fetus does not need oxygen very much. But from 33-34 weeks of gestation, the fetus becomes more and more in need of oxygen [5]. It has also been found that in the third trimester of pregnancy, it is the fetal brain that becomes more dependent on oxygen than any other part of the body [6].

At the same time, recent studies show that the fetus develops in the womb throughout gestation under hypoxic conditions [3,5]. At first glance, these data seem paradoxical and unbelievable. However, to date, no one has refuted them. Nevertheless, most researchers have difficulty accepting the scientific fact that the fetus develops in the womb under conditions of intrauterine hypoxia and that this is the norm [3,5].

Nevertheless, assessment of fetal oxygenation remains a key aspect of perinatal care worldwide. However, indirect assessment methods are used. These include auscultation of the fetal heart rate and/or cardiotocography. Unfortunately, the results obtained by commonly used diagnostic models incorporating these methods do not allow assessment of the magnitude of fetal brain reserves to hypoxia, but nevertheless allow diagnosis of unfortunate neonatal outcomes in real time [7].

In the absence of an accepted method for reliable and timely assessment of fetal brain viability in the womb under conditions of intrauterine hypoxia during the third trimester of pregnancy and during vaginal delivery, researchers and health care providers must consider any symptoms that increase the likelihood of predicting the outcome of pregnancy and childbirth. It has been reported that fetal growth retardation, or fetal intrauterine developmental delay, is the second most common cause of perinatal mortality. Therefore, immediate termination of pregnancy upon diagnosis of fetal growth retardation is considered justified as it minimizes perinatal mortality [8]. However, the study of fetal growth dynamics by definition does not reflect the viability of the fetal brain and its reserves for adaptation to hypoxia.

Placental pathology is recognized as an important risk factor for stillbirth and perinatal encephalopathy, the diagnosis of the structure and function of which is carried out everywhere using multiparametric methods of magnetic resonance imaging [8]. But the condition of the placenta also, by definition, does not reflect the viability of the fetal brain and the amount of reserves for its adaptation to hypoxia. Therefore, attempts to find the main cause of stillbirths and perinatal encephalopathy, based on the study of the function and structure of the placenta, are doomed to failure.

In recent years, the attention of researchers has been attracted by smoking and obesity of pregnant women as risk factors for sudden unexpected infant death. It is reported that due to the increasing rates of maternal obesity and smoking, studies conducted in these areas may reveal potential causal mechanisms of this link [9]. Indeed, these risk factors may reduce fetal oxygen levels, which may be critical for fetal brain viability, especially during the third trimester of pregnancy. Low fetal oxygen has been shown to play a critical role in fetal processes such as angiogenesis, trophoblast invasion and differentiation, and immune regulation [10].

Thus, there is no doubt that oxygen gas is vital for the all-round development of the fetus in the womb. The role of oxygen for fetal development increases with increasing gestational age and reaches its maximum values from 34 to 39 weeks of gestation until the birth of the infant. It is also evident that molecular oxygen is needed by the fetus primarily for the development of its brain. In general, the predominant role of oxygen and oxygen metabolism in the qualitative intrauterine development of the fetus and its brain is fully consistent with the generally recognized idea of the predominant role of oxygen gas in ensuring the qualitative life of the organism of its mother, as, indeed, of the organisms of all humans and many warm-blooded animals, as well as for the viability of their brain cells [11]. At the same time, a lack of clarity in the understanding of the following facts hinders the completion of discussions and the beginning of building a clear picture of the dependence of stillbirths and perinatal encephalopathies on fetal cerebral hypoxia. First, it has been established that in normal pregnancies, the amniotic fluid in which the fetus floats in the uterine cavity is formed from fetal urine, which is free of oxygen [12]. Second, it has been shown that in normal pregnancies, blood in the umbilical veins of fetuses throughout most of pregnancy has a partial pressure of oxygen (PaO_2) of approximately 20 to 25 mmHg [11]. In contrast, the normal PaO_2 in arterial blood in adults, including the pregnant woman, is 75 to 100 mm Hg at sea level [13]. Based on these data, researchers conclude that the fetus normally develops in the womb under hypoxic conditions [3,5].

Indeed, if we compare the oxygen content of the blood of a pregnant woman and the blood of her fetus, we see the following: the mother's blood contains more oxygen than the blood of her fetus. The results of this comparison lead us to conclude that the fetus is in a state of hypoxia. Nevertheless, common sense suggests that such a conclusion cannot be absolutely true. However, the opposite conclusion needs facts, not conjecture. Such facts are still insufficient, as there are very few studies on the oxygen content in the blood of pregnant women, as well as in various organs and tissues of her body and in the body of her fetus in norm and pathology [14]. Therefore, this article is devoted to a critical review of the available information on the significance of oxygen levels in different parts of the adult body, on the one hand, and the fetus and the intensity of oxygen metabolism in its brain cells in the womb, on the other hand, in the context of stillbirth and perinatal encephalopathy, with the aim of developing technologies to prevent them.

Dynamics of partial pressure of oxygen in blood and human body tissues

The human body consists of different parts of the body, different organs and tissues, which are differently supplied with arterial blood and oxygen according to their metabolic needs [15]. Therefore, the amount of dissolved oxygen in different parts of the body, organs, tissues and cells at each unit of time is different [13]. The oxygen content of tissues has been found to depend not only on the intensity of aerobic metabolism and arterial blood supply in them, but also on such factors as atmospheric pressure, temperature, physiological, pathological and metabolic conditions [16]. It has been reported that due to this principle of gas exchange, human lungs under normal conditions (at sea level) provide an almost equal partial pressure of oxygen (PaO_2) in alveoli and capillaries, which usually corresponds to 75-100 mm Hg [13,16]. From the moment the blood in the capillaries of the lungs is enriched with oxygen, it is called arterial blood, although such blood flows to the heart through pulmonary veins. The arterial blood is then released by the heart into the arterial bed, through which the oxygen-enriched blood travels to all the parts of the body through the arteries.

It has been reported that under normal conditions, the partial pressure of oxygen in the alveoli and in the pulmonary capillaries has the same value. The partial pressure of oxygen in the pulmonary shunt blood from the bronchial veins is then reduced to 40 mm Hg. This blood then mixes with blood from the lungs, so that blood in the pulmonary veins reaching the atria has PaO_2 of 95 mm Hg. This is known as the "pulmonary venous admixture" [13]. But the oxygen content of arterial blood does not remain at the same level throughout the arterial bed: it decreases as the blood moves to peripheral parts of the body. Within organs and tissues, partial tissue pressure of oxygen (PtO_2) has also been shown to be variable. In particular, the mean partial pressure of oxygen in the cytosol surrounding the cells of peripheral tissues of the human body is almost half the PtO_2 in pulmonary capillaries [17].

Why does this happen? First, because as the blood flows from the lungs to the peripheral parts of the body, the blood gradually gives up its oxygen to all aerobic cells and to organs and tissues it encounters along the way. In particular, part of the oxygen is consumed by the formational elements of the blood itself (e.g., leukocytes), as well as endothelial cells and myocytes of the vascular walls. In general, however, the partial pressure of oxygen in tissues is regulated not only by their distance from the heart, the rate of blood flow, but also by the availability of oxygen and the rate at which it flows from one area to another [18]. In addition, the partial pressure of oxygen in tissues also depends on the intensity of aerobic metabolism in the tissues, consistent with the Bohr effect, which explains why hemoglobin releases more oxygen to cells in tissues that have more intensive oxygen metabolism. Thus, brain neurons have the most intense aerobic metabolism in the body, so they are more dependent on the presence of oxygen than other cells in the body to maintain their viability [19]. In particular, skeletal muscle myocytes have a low aerobic metabolic rate, so they are less dependent on oxygen deprivation and are more resistant to hypoxia than brain neurons [17].

But this does not limit the "movement" of oxygen in the body. As soon as oxygen reaches the outer membrane of cells, it moves through it inside the cells, where it can be used in the process of aerobic metabolism. In this case, the availability of oxygen for intracellular metabolic processes is determined by the value of the oxygen partial pressure gradient between the extracellular and intracellular biological media. Moreover, the real participation of oxygen in aerobic metabolism inside each cell is determined by the value of the gradient between the partial pressure of oxygen outside the cell and in mitochondria, since these subcellular organelles are the oxygen energy "stations" of cells [20]. Inside mitochondria, a

series of enzyme-catalyzed chemical reactions occur that convert metabolites of anaerobic glycolysis into carbon dioxide and water using oxygen. At the same time, oxidation energy is released as heat and stored as high-energy phosphates [21]. Not surprisingly, the PaO_2 inside cells is the lowest, ranging from 1 to 10 mm Hg [22].

So, as soon as oxygen arrives with arterial blood to the cells of tissues of various organs, the cells immediately begin to carry out cellular gas exchange. In this case, through the outer membranes of cells, gases that are under higher partial pressure on one side of the membrane diffuse through it into tissues located on the opposite side of the membrane and have a lower partial pressure of the corresponding gases. This is how oxygen and carbon dioxide exchange occurs in both directions of cell membranes in all tissues [22].

Basically, the partial pressure of oxygen in tissues reflects the balance between its delivery to tissues and their consumption of oxygen. In other words, the partial pressure of oxygen in tissues reflects the balance between arterial blood flow and the rate of tissue oxygen consumption. Therefore, this index is not always an unambiguous indicator of the state of aerobic metabolism. For example, it has been shown that PtO_2 in the cerebral cortex of healthy adults at rest at sea level ranges from 20-25 mm Hg, while PtO_2 in the cerebral cortex increases to 48 mm Hg when they perform strenuous physical work or climb high in the mountains [23]. PtO_2 in the liver of adult humans has been shown to be between 50-55 mm Hg [24]. According to published data, in the skeletal muscles of adult humans, PtO_2 ranges between 7.5 and 31 mm Hg [25]. At the same time, PtO_2 in various layers of skin in adult humans ranges between 3.2 and 38 mm Hg. For completeness of the dynamics of partial pressure of oxygen in the blood of different parts of the body, it should be pointed out that the blood in the umbilical veins of fetuses in pregnant women in normal pregnancies contains oxygen in the range of 20 - 25 mm Hg [3]. Consequently, in a normal pregnancy, the value of partial pressure of oxygen in the blood flowing from the placenta to the fetus is approximately 5 times lower than in the blood of the pulmonary capillaries of the pregnant woman. This is not surprising, as there is a placental barrier that is an obstacle to the passage of many substances from the blood of a pregnant woman into the blood of her fetus [26].

Consequently, in healthy people, the blood in the peripheral arterial bloodstream, as well as in the tissues of peripheral organs, contains 2.5 - 15 times less oxygen than in the alveoli and pulmonary capillaries. At the same time, tissue oxygen demand varies over time. In particular, tissue oxygen demand increases with increased muscle activity. Therefore, the determination of oxygen partial pressure in peripheral blood vessels and tissues of peripheral organs, including the fetus in the womb, without assessing the oxygen demand of selected tissues, identifying the degree of oxygen deficiency and its significance for preserving the viability of the selected tissue during a certain period of oxygen insufficiency (tissue resistance to hypoxia) does not allow us to make an unambiguous conclusion about the sufficiency of oxygen supply of tissues, i.e. about normo-, hypo- or hyperoxia.

Temperature as a factor in oxygen metabolism and fetal intrauterine life in the context of hypoxic brain cell damage and stillbirth of partial pressure of oxygen in blood and human body tissues

The human body temperature is an important factor in human vital activity, since changes in the temperature of organs and tissues change the intensity of chemical processes occurring in them. The temperature dependence of the metabolic basis of vital activity is illustrated by the Arrhenius law, which states that an increase in the temperature of the interaction medium by 10 °C increases the rate of chemical reactions by an average of 2 times [27]. A healthy human is considered to have an average body temperature of 36.5 - 37.5 °C (97.7-99.5 °F). However, more accurate information about human body temperature is provided by the following correction: human body temperature changes cyclically throughout the day by an average of 1.0 °C, which is called the circadian rhythm. Consequently, in the human body, the rate of chemical, biochemical and biophysical processes, including the rate of oxygen metabolism, is also not constant and at least undergoes cyclic changes that are similar to the circadian rhythm of body temperature.

It has been shown that in a person aged about 40 years (assuming that he or she sleeps at night and is awake during the day), body temperature has its lowest value between 4 and 6 hours, after which it rises in the next 12 hours to its highest values, which are usually observed between 16 and 18 hours, and after that body temperature begins to gradually decrease [28]. In addition, body temperature can change due to internal factors, such as diseases accompanied by inflammation (which develops hyperthermia) or ischemia (which usually develops local hypothermia), as well as

due to external temperature influences. In particular, local warming (e.g., with a warm heating pad) and local cooling (e.g., with an ice bubble) have been used for medical purposes since ancient times. It should be added that total body temperature in humans decreases with increasing age. Therefore, the body temperature of elderly people is lower than that of young people [29]. It is reported that regardless of this, all other things being equal, the intensity of aerobic metabolism in the human body is on average 1.1 times higher in the evening than in the early morning. In this connection, oxygen consumption in tissues in the early morning is less than at other times of the day. Therefore, the outcome of commensurate episodes of acute hypoxia and/or cerebral ischemia that occurred in a person in the early morning may be less unfortunate than in the afternoon [30].

The protective role of local hypothermia in tissue ischemia is most widely used in the field of organ and tissue preservation and transplantation [31]. The protective role of local cooling of the patients' head during cerebral ischemia and hypoxia has also been confirmed in recent years [32]. The authors showed that local head cooling increases the brain resistance to oxygen deficiency. Under these conditions, local hypothermia was called therapeutic hypothermia, and a new direction in the therapy of diseases with the help of special local temperature effects was called targeted temperature management [33]. In this regard, new medical technologies for brain cooling are being developed. In particular, the possibility of cooling the adult brain through oxygen lavage of nasal cavities has been shown. In turn, clinical and experimental evidence is expanding on the ability of artificial localized therapeutic head hypothermia to increase the resistance of brain cells to hypoxic injury [34]. Local cooling of the brain of adult patients has been shown to increase brain viability not only in hypoxemia caused by cardiac arrest, but also in ischemia of brain tissue caused by mechanical head trauma and cerebral hemorrhage in stroke [35]. In parallel, there are reports of the use of therapeutic hypothermia in obstetrics to prevent perinatal encephalopathy. Fetal temperature is thought to be an important factor in perinatal encephalopathy because the intensity of oxygen metabolism in all fetal organs and tissues, including the brain, and the oxygen demand of the tissues is higher the higher their temperature. On this basis, it is concluded that hypothermia of the fetal and/or neonatal head increases the resistance of brain cells to hypoxia [28,36]. Therefore, it has been proposed to monitor the dynamics of the local temperature of the fetal head during vaginal delivery and of the newborn's head using infrared video recording [37].

At the same time, it has been pointed out that fetal head temperature and fetal brain oxygen demand are directly related to maternal body temperature [38]. Because the diurnal rhythm of maternal body temperature precludes a stable value of maternal body temperature throughout the day and night, fetal brain oxygen demand and resistance to hypoxia change daily according to the dynamics of maternal body temperature because of the circadian rhythm of temperature [28]. It has been shown that, when assessing the dynamics of fetal resistance to hypoxia, it is reasonable to assume that the body temperature of the mother and her fetus may be about 36.1 °C (97 °F) in the early morning and about 37.2 °C (99 °F) in the evening. Based on these data, it is concluded that a cyclic increase in fetal body temperature of 1.1°C in the evening compared to the morning temperature causes the same cyclic increase in fetal brain oxygen metabolism in the fetal brain, with a concomitant decrease in fetal resistance to cerebral hypoxia in the evening by a factor of 1.11 compared to the morning period of the day. Therefore, the same reserve of fetal adaptation to hypoxia may have different significance for preserving its health and life during vaginal delivery at different body temperatures of the mother and her fetus. The fact is that vaginal delivery may be accompanied by periods of placental and fetal ischemia [6]. It is most likely that such a difference in temperature can be observed in vaginal deliveries developing in the early morning or evening [39]. The use of a thermal imager is recommended to record the local temperature dynamics of different body regions of the mother and her newborn infant. It has been reported that the temperature of the mother and her fetus in vaginal deliveries occurring at different times of the day is an important factor for the development of perinatal encephalopathy. Therefore, it is very important to use early therapeutic hypothermia of their head to prevent hypoxic damage to fetal and neonatal brain cells [28,40].

Therapeutic hypothermia of the head (or brain) has been reported to be analogous to hibernation, a physiological phenomenon of decreasing body temperature along with head temperature in warm-blooded animals hibernating in winter [30]. It has been shown that during winter hibernation in warm-

blooded animals, brain temperature decreases and its resistance to hypoxia (ischemic/hypoxic damage) increases [41]. It has been found out that cooling of organs and tissues, including the brain, during natural hibernation and artificial hypothermia reduces the intensity of their metabolism, including aerobic metabolism occurring in their mitochondria. Due to the fact that cooling of the brain reduces the intensity of its aerobic metabolism, the brain's resistance to oxygen deficiency increases. It has been shown that hypothermia increases brain resistance not only to hypoxia, but also to many other damaging factors [36,42].

Consequently, one of the most important indicators of tissue resistance to hypoxic/ischemic damage is the duration of tissue viability (tissue survival time) under conditions of oxygen deficiency (hypoxia) and/or arterial blood supply (ischemia). Also, very important is the finding that inhibition of oxygen metabolism of tissues by cooling them increases the duration of the period of preservation of their viability under conditions of ischemia and hypoxia [30]. In other words, cooling (hypothermia) increases and heating (hyperthermia) decreases tissue resistance to hypoxia and ischemia.

On this basis, it follows that the cause of hypoxic damage to brain cells is a discrepancy between the intensity of their aerobic metabolism on the one hand and the intensity of their oxygen supply on the other hand over an excessively long period of time. In other words, aerobic metabolism occurring in brain cells with an intensity exceeding the intensity of oxygen delivery to them begins to damage these cells not immediately, but after a certain period of time [38,40]. In this regard, brain cells can be protected from hypoxic damage by timely increasing oxygen delivery to the brain (e.g., by increasing its blood supply) and/or decreasing the intensity of oxygen metabolism of brain cells (e.g., by head cooling) [43].

Time and temperature as 4th and 5th dimensions and factors of hypoxic brain cell damage

Time has long been recognized as the fourth dimension. We all move through time in only one direction with a (relatively) constant velocity. The definition of time in the exact sciences is considered in terms of the fundamental interactions between atomic and subatomic particles at a temperature of absolute zero. This is important because the behavior of atoms accelerates at higher temperature, since temperature is a measure of the average kinetic motion of particles. The life activity of modern biological objects takes place in an environment that has been significantly altered by human activity and is different from that for which all biological objects were originally created by nature and in which life has evolved over millennia. It is therefore legitimate to conclude that humans were not designed to live in urban environments, to work in factories and mills, to sit at desks and tables while attending school and university, or to receive information for many hours from television, computer and/or smartphone screens in office spaces. At the same time, it has been found that a significant change in the environment can change the lives of living beings very quickly. A clear demonstration of the claimed is the fact that female fruit flies (Drosophila) turn egg production on and off almost instantaneously in response to changes in their food supply [44].

Time, together with temperature, has a significant influence on the organization, origin, maintenance, and improvement of all life on Earth (evolution). However, time and temperature are often neglected in biomedical research [45]. Circadian rhythms have been shown to be important for all aspects of biology because the functional activity of all organs and systems of biological objects vary with the time of day and their lifespan. The authors analyzed 1000 articles published in 2015 in 10 major areas of biological sciences. Only 6.1% of the articles contained information about the time of day at which experimental measurements and manipulations were performed. It should be added that regardless of circadian rhythms, excessively long life span (old age) of an organism is characterized by deterioration of its health status and functional activity of organs and systems [46].

Thus, biological clocks and time are inseparable from the circadian rhythm of temperature of biological objects. Circadian rhythms are a defining feature of biological systems; therefore, knowledge of what part of a biological object's life and what part of the day these systems are evaluated in is fundamentally important information [45]. The time factor is especially important when conducting experiments on cold-blooded animals, as well as on those warm-blooded experimental animals that lead a nocturnal lifestyle. The fact is that the body temperature of cold-blooded animals changes over time under the influence of changes in the temperature of the external environment, and the dynamics of body temperature of small warm-blooded experimental animals

during the day and night differs radically from the dynamics of body temperature of humans. In addition, the intensity of metabolism and life expectancy of small experimental animals is 10-30 times shorter than the average life expectancy of humans [43]. Therefore, a full-fledged account of time and temperature as factors of regulation of chemical, physical, physicochemical, biochemical, biophysical processes (reactions) and functional activity of biological objects in general gives hope for rethinking the relationship between life and death and can contribute to the progress of philosophy not only about life and death, but also about life after death, i.e. about immortality of the living [47].

Consequently, time, known as the fourth dimension, is a relative measure for living things. The fact is that their body temperature is variable, and biological clocks can change their course depending on the temperature. Moreover, freezing a biological object or a carrier of "vital" information can stop the biological clock for an indefinite period of time! It has been reported that freezing "properly" molecules and/or other forms of "vital" information ensures that the biological clocks of the corresponding life forms are stopped [47].

It follows that time is a relative (moreover -variable) quantity for life and death of biological objects, including a human being's brain cells.

At the same time, temperature is also of relative importance to "life". The fact is that "life" is very happy at "comfortable" temperature, sad at higher temperature, dies at excessively high temperature, but with proper freezing "freezes", losing metabolism (canned), for an infinitely long time [47]. To this we should add that temperature affects more than just time (fourth dimension). Temperature has been shown to change the aggregate state of substances and materials as well as length, width and height, i.e. the first three dimensions. It has been found that increasing temperature (heating) increases the length, width and height of objects, the value of their volume, absolute and specific gravity and many other physical and chemical properties [48].

In this regard, it was proposed in 2021 to consider temperature as a fifth dimension [47].

So, time and temperature as factors of life and biological death of people and animals have relative importance for them, are unstable values, but remain interconnected with each other in all circumstances. At the same time, both time and temperature are important factors of oxygen metabolism. In particular, time is a component of the rate of the oxygen energy process occurring in mitochondria and consisting of oxidative phosphorylation of adenosine diphosphoric acid (ADP) and electron transport along the respiratory chain. In recent years, it has been shown that the rate of these processes (it is not separable from time) is an important factor in the "health" and "disease" of mitochondria [49]. It has been reported that hypoxic damage of myocardial mitochondria under conditions of oxygen deficiency is accompanied by excessively strong dissociation of respiration and oxidative phosphorylation of ADP with simultaneous increase in the rate of oxidation of Krebs cycle substrates. It has been established that the culprit of rapid oxygen consumption by mitochondria and pathological dissociation of respiration and oxidative phosphorylation in them is calcium (Ca^{2+}), which is intensively and unrestrainedly taken up by mitochondria at the transition of ischemic/hypoxic damage of mitochondria from the stage of reversible change to the stage of irreversible damage due to the energy of electron transport along the respiratory chain [50,51]. It has been shown that at the same time Ca^{2+} destroys mitochondria.

Thus, time is an important factor in oxygen metabolism in the human body, because with the prolongation of life a person ages and comes closer and closer to biological death, which is caused by hypoxic damage to brain cells. Prolonged lack of oxygen in the brain causes dissociation of respiration and oxidative phosphorylation of ADP in mitochondria of brain cells and unrestrained capture of calcium cations by mitochondria. In this case, calcium capture by these subcellular organelles causes hypoxic damage to the mitochondrial structure the faster and more tragic, the more intensively mitochondria oxidize substrates of the Krebs cycle and the greater the speed at which electrons fly along their respiratory chain.

Hypoxemia in pregnant women with apnea and vaginal delivery and low fetal resistance to intrauterine hypoxia as factors of stillbirth

Unfortunately, there is still no consensus among researchers as to what is the main cause of stillbirths. There is also no consensus on the importance of risk factors for stillbirths. Therefore, the search for the causes of stillbirths continues. In doing so, researchers rely on established facts. In particular, it has been established that

stillbirths occur predominantly at 38-40 weeks of gestation and that the oxygen demand of the fetal brain increases during this period [52-54]. It is therefore suggested that our understanding of the mechanism of fetal death during this period of gestation should be updated [55,56]. It has been reported that one of such updates may be a turn to hypoxic brain cell damage as a single cause of biological death in humans and warm-blooded animals regardless of age and health status [57-60]. It has been shown that hypoxic damage of brain cells develops not so much due to oxygen deficiency as due to excessively long duration of the brain hypoxia period exceeding the maximum period of preservation of its viability (its survivability) under hypoxia conditions limited by the available reserves of adaptation to hypoxia [6,30,36,60].

The maximum possible duration of safe intrauterine fetal hypoxia has been proposed to be assessed by ultrasound by the duration of fetal immobility during voluntary apnea of the mother. The essence of the above ultrasound examination as a functional test for fetal resistance to hypoxia was first detailed in the description of the invention "Method for assessment of foetus resistance to hypoxia by MY Gausnekht" (RU 2432118, 27.10.2011) [61]. It was shown that a peculiarity of intrauterine development of the fetus is that the fetus has sufficient reserves of adaptation to the physiologic period of hypoxia. However, these reserves are limited, and the fetus is unable to stop aerobic metabolism in the brain after complete depletion of oxygen reserves in the body. Therefore, if the duration of hypoxia is too long, hypoxic damage develops in fetal brain cells and the cells die [37,62-66]. At the same time, the duration of the hypoxia period successfully experienced by the fetus is the longer, the more oxygen reserves and other reserves of adaptation to hypoxia the fetus has. In other words, the longer the period of hypoxia successfully experienced by the fetus, the greater the fetal resistance to hypoxia. Therefore, at the end of pregnancy, the duration of the period of intrauterine hypoxia that develops during breath-holding in the pregnant woman and the fetal resistance to a prolonged period of hypoxia are important factors in stillbirth [37,57-60,62-65,67-69].

It has been established that the process of urgent fetal adaptation to hypoxia has a universal character and is a combination of urgent redistribution of arterial blood (oxygen-rich blood) in favor of the brain (to the detriment of peripheral organs and body parts) with simultaneous cessation of fetal motor activity [70,71]. This adaptation to hypoxemia is manifested in the same way not only in the fetus, but also in newborns and adults. In the latter cases, it is manifested by pallor and even lividity of the skin of the peripheral areas of the body, which is known as "acrocyanosis" [62]. Acrocyanosis is manifested not only by a change in skin color, but also by local cooling of bluish areas of the fingertips and/or toes under conditions when the ambient temperature is lower than the human body temperature. Foci of local hypothermia are well detected by infrared thermography [72-76]. However, the described adaptive reorganization of the circulation to hypoxia has not been widely used to assess fetal resistance to hypoxia.

Another is the assessment of fetal resistance to hypoxia, based on the diagnosis of the duration of the period of immobility of the fetus during maternal apnea (using the modified Stange test) [61,77]. It has been found that in a normal pregnancy and when the fetus has large reserves of adaptation to hypoxia, the fetus in the third trimester of pregnancy is immobile for the duration of the pregnant woman's voluntary respiratory arrest (apnea period) [30,36]. When a pregnant woman has signs of severe fetoplacental insufficiency, the fetus remains immobile for only a few seconds after the pregnant woman begins to hold her breath. It has been shown that after exhaustion of fetal adaptation reserves to hypoxia, the fetus actively extends its arms and legs, "kicks" and "knocks" limbs into the uterine wall, maximally extends (straightens) the fingers of both hands and makes sudden periodic respiratory movements of the chest. With this violent movement and "knocking" of its limbs in the uterine wall, the fetus sends a distress signal, requiring an urgent increase in oxygenation to preserve its health and life [38,40] (Figure 1).

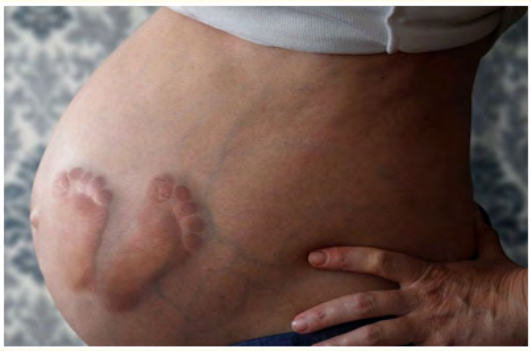

Figure 1: The drowning fetus is signaling distress that it has run out of hypoxia adaptation reserves and that without urgent oxygenation it may drown in the amniotic fluid.

Monitoring fetal biomechanics in voluntary maternal apnea has formed the basis of several invented methods of prenatal screening of fetal resistance to hypoxia, which are proposed to be performed in women's clinics and maternity hospitals using standard ultrasound examination of pregnant women (RU 2432118, 27.10.2011; RU 2511084, 10.04.2014; RU 2529377, 27.09.2014). It is shown that in normal maternal apnea, the fetus is immobile for more than 30 seconds. The appearance of fetal respiratory chest movements less than 10 seconds after the onset of maternal apnea indicates low fetal resistance to hypoxia. It has come to the attention of researchers that low fetal resistance to hypoxia can be considered a relative contraindication to vaginal delivery and an absolute indication for urgent Cesarean delivery [36,40,77,78].

In addition, inventions have been developed that make it possible to assess fetal resistance to hypoxia directly by each pregnant woman independently under any conditions without the use of ultrasound. For this purpose, a pregnant woman voluntarily holds her breath on a deep breath for the maximum possible period of time and measures the duration of immobility of her fetus with the help of a stopwatch and fingers of her hands, or with the help of sensitive sensors placed in special devices for individual use by pregnant women for this purpose (RU 2749637, 16.06.2021; RU 2780137, 19.09.2022; RU 2780274, 21.09.2022) (Figure 2).

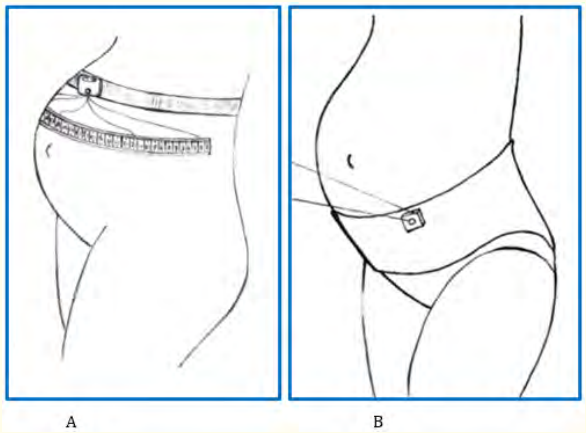

Figure 2: Schematic representation of placement of devices with sensitive sensors on the body of a pregnant woman. A - centimeter tape with sensors and adhesive tape, B - bandage with sensitive sensors.

Therefore, delayed caesarean section may be one of the risk factors for severe asphyxia of newborns and neonatal mortality. Therefore, in order to reduce the risk of severe asphyxia of newborns and neonatal mortality, urgent intrauterine fetal resuscitation was proposed by hyperventilating the mother's lungs with oxygen gas until she develops symptoms of oxygen poisoning compatible with life [79].

In recent years, there have been reports that lowering the body temperature of the fetus, fetal head, adult human, and aquarium fish (therapeutic hypothermia) reduces the risk of hypoxic-ischemic brain damage and increases the survival rate of biological objects under hypoxia [6,38,39,43]. At the same time, the therapeutic effect of hypothermia is explained by slowing down the intensity of metabolism, including aerobic metabolism, and reducing the oxygen demand of cooled tissues, which prolongs their viability under hypoxia conditions [64,80-90].

It has been reported that the head temperature of the fetus of a pregnant woman is completely dependent on the body temperature of his mother because the fetus is unable to regulate its own temperature. At the same time, the body temperature of a pregnant woman is variable. A very important factor in the fluctuation of body temperature of a pregnant woman is the time of day, because there is a circadian rhythm [28]. It has been shown that the body temperature of a mother and her fetus can be about 36.1 °C (97 °F) between 4 and 6 hours in the morning and about 37.2 °C (99 °F) between 4 and 6 hours in the afternoon [91]. Consequently, the temperature of a mother and her fetus cyclically change by an average of 1.1 °C each day.

Since, according to Arrhenius' law, a 10 °C increase in temperature increases the rate of chemical reactions by a factor of 2 (and vice versa), a 1.1 °C increase in fetal body temperature increases its metabolic rate by an average of 1.11 times (and vice versa). On this basis, it was concluded that a period of physiologic hypothermia develops in the body of a pregnant woman and her fetus in the early morning every day. It is because of this that during the period of morning physiologic hypothermia the fetal brain has on average 1.11 times lower intensity of aerobic metabolism, and accordingly 1.11 times higher resistance to hypoxia [39].

Therefore, the same reserve of fetal adaptation to hypoxia may be of different importance for the preservation of fetal health and

life during equally long periods of intrauterine hypoxia that develop at different times of the day. In particular, apnea of the pregnant woman and uterine contractions during vaginal delivery are likely causes of the development of periods of intrauterine hypoxia [6,92-99]. In this regard, the cyclic rhythm of the daily temperature of the mother and her fetus is an important factor in stillbirth and neonatal encephalopathy, the causes of which may be (in special cases) apnea and/or vaginal delivery. It is the increased resistance of the brain to hypoxia during morning physiologic hypothermia that explains why warm-blooded animals and humans give birth to their cubs mostly early in the morning, usually before sunrise. There is no doubt that early morning vaginal delivery is the best solution for successful continuation of the human race [39]. The early morning decrease in body temperature of the pregnant woman lowers the body temperature of her fetus. Morning physiologic hypothermia of the fetus increases the resistance of its brain to intrauterine hypoxia, which can develop periodically when the uterus contracts as strongly as possible during vaginal delivery, reduces the likelihood of stillbirth, and increases the likelihood of high mental capacity in the children born!

The regularity of this phenomenon is confirmed not only by Arrhenius' law, but also by the biblical description of the place and time of day when the virgin Mary gave birth to the prophet Isa: the prophet was born in the cold "Cave of the manger" in the early morning, even before the rising of the Bethlehem star and the Sun (Figure 3).

Figure 3: Scene of the virgin Mary giving birth to Jesus in the cave of the manger.

In this regard, it was recommended to use the period of physiologic hypothermia in the body of a pregnant woman as the optimal time of day for the safe resolution of labor especially in the case of low fetal resistance to hypoxia. At the same time, the formation of temperature obstetrics was started [28,36-39]. Moreover, temperature obstetrics as a new direction in obstetrics and gynecology began to form in Russia, and above all, it began with the development of inventions (RU 2502485C2, 27.12.2013; RU 2622594C1, 16.06.2017; RU 2626302C1, 25.07.2017; RU 2749637, 16.06.2021).

A list of the inventions used in this article is presented in Table 1.

Number in order	Authors, title, invention patent number, date of publication
Ultrasound assessment of fetal resistance to hypoxia using the modified Stange test	
1	Urakov AL, Urakova NA, Sokolova NV, Sokolov NV, Gausknekht MJ, Gausknekht AJ. Method for assessment of foetus resistance to hypoxia by MY Gausnekht. RU Patent No. 2432118C1, 27.10.2011.
2	Urakov AL, Urakova NA, Urakova TV., *et al*. Method for labor by N.V. Sokolova RU 2441592C1, 10.02.2012
3	Radzinskij VE, Urakov AL, Urakova NA. Method of protecting fetus from hypoxic damage in labour. RU 2503414C2, 0.09.2013
4	Urakov AL,Urakova NA, Radzinskij VE, Sokolova NV, Gausknekht MJu. Method for assessing foetus resistance to obstetric hypoxia. RU 2511084C2, 10.04.2014
5	Urakov AL, Urakova NA, Kasatkin. NA Urakova's method for antenatal assessment of foetal adaptation to repeated hypoxia. RU 2529377C1, 27.09.2014
Use of fingertips or sensitive stnsors and a stopwatch to assess fetal resistance to hypoxia using a modified Stange test	
6	Urakov AL, Urakva NA. Method for choosing the type of delivery RU 2749637C1, 16.06.2021

7	Urakova NA, Urakov AL, Stolyarenko AP. Diagnostic bandage for a pregnant woman. RU 2780137C1, 19.09.2022
8	Urakova NA, Urakov AL, Stolyarenko AP. Tag with sensors and sticky tape for measuring the duration of the immobile state of the fetus during diagnostic apnea RU 2780274C1, 21.09.2022
Temperature obstetrics	
9	Radzinskij VE, Urakov AL, Urakova NA. Method of obstetric assistance in travails. RU 2502485C2, 27.12.2013
10	Urakova NA, Urakov AL. Infrared diagnostic technique for neonatal fetal hypoxia RU 2622594C1, 16.06.2017
11	Urakova NA, Urakov AL, Kasatkin AA. Method for time of day determination for caesarean section. RU 2626302C1, 25.07.2017

Table 1: List of patents for inventions that have been developed to assess the fetal resistance of a pregnant woman to hypoxia to prevent stillbirth and encephalopathy.

Conclusion

It was found that inside the womb of a pregnant woman, her fetus does not require more oxygen for its development than the peripheral organs and tissues of the woman's body itself. It was found that the values of the partial pressure of oxygen in the blood, which supplies oxygen to both the fetus and the peripheral tissues of a woman, do not differ significantly from each other. It has been reported that with apnea in a pregnant woman, especially during 38-40 weeks of pregnancy, as well as during periods of maximum uterine contractions during vaginal delivery, periods of oxygen deficiency in the fetus may occur. In this case, the fetus immediately assumes a stationary state and, with continued lack of oxygen, remains stationary until the reserves of adaptation to hypoxia are exhausted, after which the fetus develops rapid motor activity of the limbs and respiratory movements of the chest.

It has been shown that continuous oxygen supply to the fetus is one of the main conditions for preserving its life and health in the second half of pregnancy and during vaginal delivery. It has been established that fetal oxygenation is most important for the life support of the brain, since the brain is the leader in the intensity of aerobic energy metabolism among all its organs and tissues. It has been found that continuous adequate oxygen supply to the fetal brain becomes most important at the end of gestation and during vaginal delivery. The fact is that it is during these periods that the oxygen demand of the fetal brain reaches maximum values, and the oxygen supply to the fetus may be reduced due to sudden respiratory arrest in the mother, or due to detachment and/or ischemia of the placenta due to excessive myometrial contractions.

It has been established that the most important condition for preserving brain viability is the continuity of biochemical and biophysical processes that form the basis of metabolism of brain tissue cells. Therefore, in order to preserve its viability, the brain needs continuous supply of molecular oxygen with such a debit of oxygen at which the amount of oxygen delivered to the brain per unit of time would correspond to the amount of oxygen metabolized by it per unit of time. When the intensity of the oxygen supply to the brain (debit of oxygen) is suddenly reduced below the level required for normal metabolic "utilization" of oxygen by brain tissue, the fetus immediately "turns on" the system of adaptation to the lack of oxygen. This adaptation has been shown to involve an economy of oxygen utilization in all organs and tissues except the brain. One of the mechanisms of adaptation of the fetus to oxygen deficiency is its assumption of immobility for the entire period of oxygen deficiency in the presence of sufficient reserves to hypoxia.

It has been found that the fetus normally remains motionless for more than 30 seconds during maternal apnea. In low fetal resistance to hypoxia, the duration of fetal immobility approaches zero, followed by rapid limb movement and respiratory chest movements. It has been reported that excessively low fetal resistance to hypoxia and/or excessively prolonged oxygen deficiency can cause hypoxic damage to brain cells. Moreover, in some cases, hypoxic damage to fetal brain cells can cause stillbirth and/or encephalopathy within seconds of the onset of apnea in the pregnant woman and/or uterine contractions during vaginal delivery. Therefore, to prevent stillbirths and encephalopathy, it

is suggested that fetal resistance to hypoxia should be assessed in a timely manner using the modified Stange test and, in case of excessively low fetal resistance to hypoxia, labor should be immediately terminated by cesarean section.

In this regard, monitoring fetal motor dynamics during maternal apnea may become a method of prenatal screening in the future.

Author Contributions

NU and AU contributed equally. All authors contributed to drafting the first manuscript, and read, and approved the final manuscript.

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Conflict of Interest

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