Review

Detection of fetal hypoxia: a review of the literature

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ABSTRACT

Fetal hypoxia is a condition characterized by a reduced oxygen supply of fetal tissues. Although fetal hypoxia can be caused by many factors, it usually occurs due to progressive placental insufficiency and is associated with intrauterine growth restriction. In a state of fetal hypoxia, adaptation mechanisms are activated, and bloodstream centralization occurs, which is beneficial to the fetal brain (brain sparing effect), heart, and adrenal glands, while the periphery remains deprived of adequate amounts of oxygen. It is important to emphasize that diagnostic tools for measuring blood flow redistribution in favor of the fetal brain have been developed, and their bases are Doppler indices of the umbilical and middle cerebral arteries. Monitoring of the Doppler indices, particularly cerebroumbilical ratio, is the most important prenatal diagnostic tool for the prognosis of neurodevelopmental disorders. New findings are based on the fact that functional and structural brain damage occurs even in stable hemodynamic compensatory mechanisms, so the brain sparing effect is not considered to be an entirely physiological response. The consequences of fetal hypoxia and intrauterine growth restriction can be periventricular leukomalacia, intracranial bleeding, and a wide range of functional neurological damage. Therefore, research in modern perinatal medicine should be based on finding a new high-quality diagnostic tests or using a combination of the existing ones to allow early diagnosis of potentially endangered fetuses and define the time of delivery. This would prevent perinatal brain damage and its long-term effects on the health of children.

KEYWORDS: chronic hypoxia; doppler indices; intrauterine growth restriction; placental insufficiency

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INTRODUCTION

Fetal hypoxia is a condition characterized by low oxygenation of the fetus, which leads to functional disorder of organs, organic systems and cells. In a state of fetal hypoxia the most endangered organs are the one that consume the most oxygen – heart, adrenal glands and the brain (1).

CAUSES OF FETAL HYPOXIA

According to Hutter et al. (2), fetal hypoxia can be divided into three subtypes: preplacental, postplacental and uteroplacental.

The most common causes of preplacental hypoxia are hypoxic environment (e.g. high-altitude) or preexisting maternal diseases (e.g. cyanotic heart disease, heart decompensation, pulmonary hypertension). De novo hypoxia during the pregnancy is associated with anemia, infection and chronic inflammatory diseases, which limits not only the mother's oxygenation but the fetuses' as well.

In postplacental hypoxia only the fetus is hypoxic, which can be the result of reduced flow through umbilical arteries (e.g. because of thrombosis, mechanical compression, rupture) or

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reduced blood flow to the fetal tissues (ischemic hypoxia), progressive heart failure of the fetal heart (e.g. because of complete heart block, congenital heart malformations), low fetal hemoglobin concentration (anemic hypoxia) or wide range of genetic anomalies.

The most common causes of fetal hypoxia are the ones that affect placenta. In uteroplacental insufficiency there is a reduced placental perfusion with maternal blood and consequent decrease in fetal arterial blood oxygen content doe to low pO2, causing hypoxemic hypoxia (3). Uteroplacental hypoxia is associated with abnormal placentation early during pregnancy, and later with vascular abnormalities of the placenta. In pregnancies with intrauterine growth restriction (IUGR), gestational hypertension and preeclampsia, abnormal placenta is a frequent finding (2).

PATHOPHYSIOLOGY OF PLACENTA

The phases of placental dysfunction can be subdivided broadly into preclinical phase, clinical phase and deterioration.

In preclinical phase the changes in venous circulation occur. The increased flow through ductus venosus can result in redistribution of blood flow towards fetal heart, while the flow through the fetal liver decreases. Moreover, the endocrinological disorders can also develop (dysfunction of hypothalamic-pituitary-adrenal axis, hypothyroidism). In preclinical phase the changes in nutritional and endocrinological environment is dominant, without the fetal hypoxia (4). These changes precede the clinical manifestations, and the first one is deceleration in growth of abdomen.

In clinical phase the progress of placental insufficiency occurs and hypoxemic hypoxia develops. Fetus reaction to hypoxia is redistribution of arterial blood flow with centralization as main characteristic. The centralization of blood flow is a result of vasodilatation of cerebral, cardiac and adrenal blood vessels, and vasoconstriction of pulmonary, intestinal, renal, skeletal and skin blood vessels. The purpose of redistribution of blood flow is protection of vital organs, especially the brain that is the most sensitive to hypoxia. This phenomenon is called brain sparring effect (5). However, as the insufficiency progresses, fetal brain begins to use ketones and lactates as energy sources, and the head of the fetus is growing slowly. Hematological disorders also develop because of the extramedullary hematopoiesis stimulated by hypoxia. The red blood cell count and the tendency of thrombosis increases which leads to impairment of blood flow through the fetal side of the placenta. As the nutritional deficit continues, the growth rate of all fetal tissues slows down and the fetal weight drops below the 10th percentile (6).

Deterioration of placental insufficiency leads to arterial redistribution compensatory mechanism breakdown. The reactivity of blood vessels of the fetal brain is changing and vasomotor paralysis develops. Chronic hypoxia progresses to acidemia, and also circulatory and metabolic decompensation develops with functional disorder of vital organs (7).

CONSEQUENCES OF INSUFFICIENT PLACENTA

Decreased Nutritional Function

Decreased nutritional function leads to IUGR. IUGR is a decrease in fetal growth which growth potential is bigger than the one measured during pregnancy. This pathology can be fined in 3-10% of all pregnancies (8). Although the literature review can bring different criteria for distinguishing the normal from abnormal fetal growth, the most common used criteria in Croatia is 10th percentile of gestational age. However, if the fetal weight is lower than 10th percentile but the weight gain is optimal, it is probably case of constitutionally small fetus. Nevertheless, if the fetal weight is below 10th percentile or even above 10th percentile, but the weight gain is inadequate during the several consecutive measurements, it is probably case of the real IUGR. To conclude, the children with growth restriction are not necessarily low birth weight for gestation children, and within low birth weight for gestation children we can find healthy, genetic smaller children (9).

Clinical recognition of placental insufficiency depends on timing of insufficiency during pregnancy. If growth restriction occurs in early phase of pregnancy, during more intensive cell division, a large number of cells will be damaged and the basis for further development of the fetus will be reduced. That will result in a symmetric growth restriction because all organs will be reduced equally (1). Symmetric growth restriction is marked by significant fetal circulation disorder, with a decreased flow through umbilical arteries as an indicator of elevated resistance in placenta. Studies have shown that the risk of developing neurological abnormalities increases with the increased resistance in umbilical artery (10). However, because of the often associated morbidity due to immaturity, the independent influence of the indicators of insufficiency on motoric development is difficult to

predict (11). On the other hand, if growth restriction begins at later stage of pregnancy, vital organs, such as the heart, brain, and adrenal glands, will receive a larger amount of blood and their growth will be normal at the expense of other organs. Clinically, such newborns are recognized by large head in relation to the abdomen due to reduced liver and abdominal fat. In such cases, we are talking about the asymmetric type of fetal growth restriction (1). If the placental insufficiency is less severe, fetuses usually have reduced weight, and the growth in length and volume of the head does not change. Flow in umbilical arteries is normal or minimally changed, and the selective redistribution of the circulation within the fetal brain is a basic hemodynamic characteristic. Because of this, the disorder in the later stage of pregnancy often goes unnoticed and is missed by clinical evaluation (12).

Many adult developing diseases have their foundations in prenatal age. Hypertension, hyperlipidemia and glucose intolerance (so-called metabolic syndrome X), and obesity, type 2 diabetes, renal and pulmonary diseases, as well as neurocognitive difficulties can be associated with the prenatal fetal condition. It seems that a limited supply of nutrients and oxygen has a long-term effects on the development of many organs (8).

Fetal hypoxia is often found in fetuses with growth restriction and placental insufficiency, and it is one of the major causes of perinatal morbidity and mortality. The most important consequence of fetal hypoxia is perinatal brain damage. Fetus exposed to hypoxia is trying to protect vital organs (brain, adrenal glands, heart) by activating biophysical, endocrine and metabolic responses (13).

Decreased Respiratory Function

Fetal Movements and Biophysical Profile of the Fetus

During the expressed body and breathing movements, 15-30% of total available oxygen is consumed. Brain centers regulate fetal behavior and are sensitive to the amount of available oxygen, so in hypoxia the fetus sedates the motoric function to reduce the metabolic oxygen demand. The behaviors that are monitored during fetal development are body and breathing movements, and together with tonus, amniotic fluid volume and non-stress test (cardiotocography) represent the elements of biophysical profile (1). The fetal biophysical profile is used to evaluate fetal blood oxygenation. It is established because of the fact that implementation of several different parameters together are better in the evaluation of fetal status than individual ones (14). The principle of biophysical profile lies on the fact that hypoxia will depress the brain centers responsible for certain functions (15), and the studies have confirmed that the biophysical profile points correlate with values of gases from umbilical blood vessels (16,17). The maximum sum of points in the biophysical profile is 10. The sum of points between 8 and 10 indicate the normal state of the fetus, while 4 and less signalize the severe fetal condition and the necessity of urgent delivery (1).

Amniotic Fluid

Amniotic fluid is one of the indicators of cardiovascular status and depends on the flow through the fetal kidneys. Production of urine begins around the 11th week of pregnancy (15), and after the 15th week of pregnancy the urine becomes the mean source of amniotic fluid. During hypoxia and acidosis, chemoreceptors in the arch of aorta and carotid artery are stimulated, and bloodstream redistribution occurs in the organs crucial for fetal survival (18,19). Therefore, during the chronic hypoxia, a decrease in the volume of amniotic fluid is present, so the measurement of fluid can be used to evaluate the fetal status (20).

Fetal Circulation and Doppler Indices

Evaluation of fetal circulation is possible due to ultrasound. The development of ultrasonic technology has enabled blood flow and fetal oxygenation monitoring and it is the most important method for detecting endangered fetuses. The ultrasound can track the anatomic location, direction and velocity of the blood flow, and the shape of the pulse wave. Doppler indices are calculated during monitoring, and they consist of systolic/diastolic (S/D) ratio, pulsation index [PI, PI = (S-D)/A], and resistance index [RI, RI = (S-D)/S], where S stands for peak flow velocity in systole, D is the flow at the end of the diastole, and A mean velocity through one heart cycle (3,8).

Blood flow velocities and Doppler indices can be used to estimate fetal oxygenation. Thus, during the compromised uteroplacental circulation (i.e. increased resistance of the placenta) the impedance in umbilical artery (URI, umbilical artery resistance index) increases, and that, in severe cases, decreases or even reverses the flow at the end of the diastole (21). However, studies have demonstrated that increased impedance in the umbilical arteries becomes evident only when at least 60% of the placental vascular bed is obliterated (22). The risk of neurological abnormalities increases with degree of

deterioration of the blood flow through the umbilical artery (10). The importance of URI is also in the fact that it is a Doppler criteria for diagnosing IUGR (23). In addition, IURG with absent or reversed end-diastolic frequencies in the umbilical artery is associated with increased incidence of a permanent neurological damage (24).

In fetal hypoxemia there is an increase in the blood supply to the brain, myocardium, adrenal glands and spleen, and reduction in the perfusion of the kidneys, gastrointestinal tract and the lower extremities (3). For the detection of fetal hypoxia, the blood flow in the middle cerebral artery is used. The middle cerebral artery carries 80% of the total brain circulation, and the cerebral artery resistance index (CRI) can be used as indicator of centralization of the bloodstream. In normal pregnancies, the resistance in this artery is high until 34th week of gestation and drops afterwards. During hypoxia there is an increase in the velocity of flow at the end of the diastole in the middle cerebral artery, which can be seen as reduction of Doppler indices (25). It is caused by vasodilatation during brain sparring effect to ensure as much oxygen as possible (26). Increase in the flow through the cerebral arteries is also facilitated by increased umbilical artery resistance. This leads to a reversal of the flow through the aortic isthmus from the descending aorta toward the ascending aorta (27). pCO2 affects the cerebral blood flow too. When pCO2 is high, the velocity of flow during systole in middle cerebral artery increases (28).

Since there is a large biological reserve in the placental capacity, it is possible that there is no change in brain flow despite the increased impedance of umbilical artery. Only when fetal needs exceed the placental capacity, the impedance in middle cerebral artery decreases, and the result is a decrease in CRI (29). Progressive reduction in CRI is a sign of progression of hypoxia (19). Also, abnormal waveforms in the umbilical artery are an early sign of fetal impairment. According to Bekedam et al., abnormalities in the umbilical artery precede the occurrence of cardiotocographic signs of fetal hypoxemia in more than 90% of cases. The median time interval between absence of end-diastolic frequencies and the onset of late decelerations is 12 days (range 0-49 days) (30).

In early phases of fetal hypoxia, blood vessel reactivity is maintained, but later it disappears. Compensation through cerebral vasodilatation is limited and a plateau is reached at least 2 weeks before the development of the fetus is jeopardized. Then, due to the increased impedance in the brain blood vessels, a decrease in brain perfusion occurs and that is reflected in the increase in CRI. The loss of cerebrovascular reactivity occurs before the heart rhythm changes, and may be due to multiple mechanisms: maximum vasodilatation achievement, brain edema development, and autoregulation mechanisms. Therefore, elevation in CRI is a sign of decompensated hypoxia and fetal acidosis (29,31,32). Consequently, arterial vessels are unsuitable for longitudinal monitoring of growth restricted fetuses. Cardiac and venous velocity waveforms give more information regarding fetal well-being or compromise (3).

Cardiac flow is influenced by the modifications of arterial impedance. Increased placental and systemic resistance produce increased right ventricular afterload and cerebral vasodilatation produces a decrease in left ventricular afterload. Also, growth restricted fetuses show impaired ventricular filling and lower peak velocities in the aorta and pulmonary arteries (33-35). This leads to hemodynamic shift of cardiac output in favor of the left ventricle, leading to improved cerebral perfusion (3). However, with deterioration the cardiac output declines, suggesting a progressive worsening in cardiac function (36). There is a symmetrical decrease in ventricular ejection force in both ventricles, and it decreases in a short time interval (about 1 week). As a result, cardiac filling is also impaired (3).

Fetal hypoxia also causes changes in the blood flow through the ductus venosus and the flow increases due to vasodilatation. In experiments on the fetal sheep, the blood flow through the venous duct increased by up to 10%, and that allows bypass of the fetal liver and delivery of more oxygenated blood to systemic circulation (37,38). Due to vasodilatation of the ductus venosus, the pressure in the right atrium increases, and consequently, Doppler index of ducus venosus increases. Therefore, ductus venosus flow monitoring is used to reveal how compromised is the cardiovascular system in fetuses with growth restriction and placental pathology (8). In extreme conditions, umbilical blood may pass exclusively through the ductus venosus and this may lead to an impaired perfusion of the liver and cause metabolic changes. Studies on fetal sheep have also shown an increase of the amplitude of vena cava pulsations during hypoxemia and increased afterload (39). During systole, the flow waveforms of vena cava show an increase in peak forward flow and during atrial contraction retrograde flow occurs. Increased right ventricular afterload and thus increased ventricular end-diastolic pressure may result in highly pulsatile venous blood flow waveforms and umbilical venous pulsations due to transmission of arterial pressure

waves through the venous duct (40). In growth restricted fetuses, an increase of reverse flow in the inferior vena cava during atrial contraction occurs with progressive fetal deterioration (41,42). The next step is reversed a-wave in the ductus venosus, and finally, the high venous pressure indices a reduction of velocity at end-diastole in the umbilical vein, causing end-diastolic pulsations (43). Development of these pulsations is close to the onset of abnormal fetal heart rate patterns and is associated with fetal acidemia (44,45). Fetal venous Doppler is useful in monitoring growth restricted fetuses with redistribution. Hecher et al. compared fetal venous and arterial blood flow with biophysical assessment in 108 high-risk pregnancies after 23 weeks of gestation. The most interesting results were found in a group of 41 fetuses with arterial redistribution. There were no significant differences in arterial Doppler indices between fetuses with normal and abnormal biophysical assessment parameters, whereas venous pulsatility was significantly increased in compromised fetuses compared to the non-compromised group. Therefore, Doppler investigation of the fetal venous circulation may play an important role in monitoring the redistribution of blood flow in growth restricted fetuses and thereby may help to determine the optimal time for delivery (46). Evaluation of the fetal venous system in normal and abnormal conditions has drawn increasing interest in recent years. Whereas the assessment of the fetal heart and the arteries is standardized, the fetal venous system is still lacking a systemic approach (47).

However, Doppler indices are frequently used together as a ratio. Cerebroumbilical (C/U) ratio is the ratio of middle cerebral artery resistance index (CRI) and the umbilical artery resistance index (URI), and it is the most accurate indicator of redistribution of the blood flow in favor of the fetal brain (48). In normal pregnancies, the resistance index of cerebral artery is higher than placental resistance, so the C/U ratio is higher than 1. The reduction in C/U ratio is proportional to the reduction of fetal pO2, i.e., to the degree of hypoxia. As flow redistribution occurs, the C/U ratio decreases as the URI increases and CRI decreases. Therefore, the C/U ratio allows earlier placental insufficiency detection than CRI and URI separately, and its pathological values are associated with poor perinatal outcome and brain damage in children with IUGR (49,50).

However, the redistribution of the flow in favor of the fetal brain is a physiological adaptation in short period of hypoxia. Studies on animal models and human fetuses have shown that this redistribution phenomenon cannot prevent perinatal brain damage in case of severe or long-term hypoxia (51). It is therefore considered that the degree of hypoxia and its duration have a cumulative effect on the fetal brain. The introduction of the hypoxia index (HI, calculated as the sum of the daily values of C/U ratio expressed as percentages of the limit value 1), provides a more accurate estimation of the intensity of redistribution of the bloodstream. High specificity (96%) and sensitivity (88%) of this index in prediction of perinatal brain damage is proofed, but prognostic significance for the neurological outcome of the children with IUGR will have to be investigated yet (13).

To conclude, the application of different Doppler indices has not yet established the boundaries of physiological and pathophysiological mechanisms in IUGR with neurodevelopmental disorders. Studies have shown a significant correlation between the flow dysfunction in the umbilical artery and reduction of the C/U ratio with a poor neurodevelopmental outcome (7,52). New data mention certain neurological disorders even when cardiovascular compensation is missing or cannot be clinically proved (53,54).

NEUROLOGICAL EVALUATION

Due to development of imaging techniques, the clinical neurological evaluation of the newborn became less used. The trend of reliance on neuroscience methods has, however, proved insufficient in predicting neurological outcomes and updated the need for neurological tests at the early age (23).

In a paper written by Starcevic et al. (54), a neurological evaluation of the newborn by Amiel-Tison and ultrasound of the brain was used to evaluate functional and morphological brain damage in children who suffered late growth restriction. Neurological estimation by Amiel-Tison proved that 70% of children with late-onset growth restriction had functional impairments, while 53.37% had ultrasonically proven morphological lesions. A large part of these children had normal Doppler indices parameters (C/U ratio>1). In other words, functional and morphological changes of the brain in the fetus with late IUGR may also occur before activation of cardiovascular compensatory mechanisms (i.e. before Doppler indices can detect fetal hypoxia). Therefore, the brain sparring effect could be a sign of progression of neurological damage.

Apart from the mentioned, many other neurological tests have been developed (Gross,

BNBAS, Dubowitz, NACS, etc.) (8). However, all of the above tests are applied to a newborn child, and rare are those which would assess the condition of a fetus during intrauterine life. Therefore, an international team of scientists has developed a special test that monitors the behavior of the fetus and it is called KANET (Kurjak Antenatal Neurodevelopment Test). KANET is the first method that uses four-dimensional ultrasound to evaluate spontaneous fetal movements in the same way that neonatologists perform a neurological assessment in newborns, and the parameters are being followed up from the first trimester. Parameters that are followed in KANET are isolated head anteflexion, cranial sutures and head circumference, isolated eye blinking, facial alteration or mouth opening, isolated leg and hand movements or hand to face movements, fingers movements, and gestalt perception of general movements. Each parameter carries 0 to 2 points. The points are summed up and interpreted as abnormal (0-5), borderline (6-9) and normal (10-16). The first results proved that the perinatal neurologic findings estimated by KANET, are in correlation with postnatal outcome. Of course, more studies are required to draw safe conclusions and before the test could be recommended for wider clinical practice (55,56). A group of scientists even suggests combination of Doppler parameters and KANET to detect fetuses endangered with intrauterine hypoxia (57).

Despite all, there is still no powerful diagnostic tool that would definitely separate normal fetuses from the fetus with a risk of neurological damage. Although there are correlations between fetal acid-base status and neurological outcomes, there is no exact pH limit below which neurological disorders occur. Also, in late growth restriction, acid-base parameters are slightly disturbed, and therefore are weaker indicators of neurological outcome than Doppler indices. Doppler indices monitoring has prognostic significance for neurodevelopmental disorders, while C/U ratio has priority over CRI and URI parameters. However, according to recent findings, the risk of neurodevelopmental damage exists even if C/U ratio is higher than 1, moreover, the actual risk exists at ratio 1.13. In other words, the risk for neurological damage exists in the fetus with growth restriction and with hemodynamic compensatory mechanisms (54). Also, clinical neurological assessment is characterized by greater sensitivity and specificity than ultrasound in detecting neurological disorders in the newborns. Normal neurological development is possible in children with normal ultrasound and neurological findings, whereas in children with normal ultrasound and pathological neurological findings further monitoring is necessary (23).

Nowadays, high-quality evidence shows that giving magnesium sulfate to the mother before birth can help protect the preterm baby's brain (58). The general consensus is to achieve intravenous administration to the mother at least four hours prior to preterm delivery, but the optimal timing of administration in relation to delivery is still not known (59). To optimize fetal neuroprotection and prevent cerebral palsy, magnesium sulfate administration should target a maternal serum magnesium level between 3.7 and 4.4 mg/dL at delivery (60). Benefit is seen regardless of the reason for preterm birth. Widespread adoption of th1is relatively inexpensive treatment would lead to important health benefits for infants born preterm (61).

CONCLUSION

Fetal hypoxia is one of the biggest challenges for the fetus during intrauterine life, but also for scientists dealing with this problem. Although the fetus initiates defensive mechanisms in response to hypoxia, it is still unknown whether all compensatory mechanisms are physiological or pathological responses to already occurred impairment. Recent studies have already confirmed that the brain sparring effect is not a completely physiological response, and that certain structural and morphological disorders exist even before the redistribution of blood flow in favor of the fetal brain. The question remains how and to what extent fetal responses to hypoxia can be used to diagnose and prevent damage of the fetal organs, especially the brain as the most sensitive one. Therefore, the most important goal of modern perinatal medicine is to detect precise methods of fetal status estimation and in that way prevent perinatal brain damage, and to provide algorithms about the timing and way of delivery of high-risk fetuses.

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