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FETAL CEREBROVASCULAR RESPONSE TO CHRONIC HYPOXIA – IMPLICATIONS FOR THE PREVENTION OF BRAIN DAMAGE

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Abstract

Fetal hypoxia is one of the leading causes of perinatal morbidity and mortality. One of the most severe sequels of fetal hypoxic insult is the development of perinatal brain lesions resulting in a spectrum of neurological disabilities, from minor cerebral disorder to cerebral palsy. One of the most important fetal adaptive responses to hypoxia is redistribution of blood flow towards the fetal brain, known as the "brain sparing effect". The fetal blood flow redistribution in favor of the fetal brain can be detected and quantified by the Doppler cerebral/umbilical ratio (C/U ratio = cerebral resistance index (CRI) / umbilical resistance index (URI)). Our studies on animal models and human fetuses have demonstrated clearly that this phenomenon can not prevent the development of perinatal brain lesions in the case of severe or prolonged hypoxia. Fetal deterioration in chronic and severe hypoxia is characterized by the disappearance of the physiological cerebral vascular variability (vasoconstriction and vasodilatation), followed by an increase in cerebral vascular resistance. However, our latest study on growth restricted and hypoxic human fetuses has shown that perinatal brain lesions can develop even before the loss of cerebrovascular variability. The fetal exposure to hypoxia can be quantified by using a new vascular score, the hypoxia index. This parameter, which takes into account the degree as well as duration of fetal hypoxia, can be calculated by summing the daily % C / U ratio reduction from the cut-off value 1 over the period of observation. According to our results, the use of this parameter, which calculates the cumulative, relative oxygen deficit, could allow for the first time the sensitive and reliable prediction and even prevention of adverse neurological outcome in pregnancies complicated by fetal hypoxia.

Key words: fetal hypoxia, IUGR, cerebrovascular response, hypoxia index

Introduction

The efficient delivery of oxygen via the placenta is essential for normal fetal growth and development. Placental insufficiency, with consequent reduction in fetal nutritive and oxygen supply is one of the most important causes of intrauterine growth restriction (IUGR) and fetal hypoxia. There is evidence that prenatal adaptation to a reduced nutritive supply does not only result in IUGR but may also lead to long-term metabolic consequences, such as increased susceptibility to some of the current most common diseases, hypertension or diabetes mellitus. Furthermore, fetal hypoxia is one of the main causes of perinatal mortality and morbidity (1). Episodes of acute and chronic fetal hypoxia can result in brain lesions, which may leave long-term neurological sequels such as auditory and visual impairment, mental retardation and seizure disorders, or the most severe sequel, cerebral palsy (2). Moreover, minimal brain alterations, such as a reduction in learning capabilities, dyslexia, and attention-deficit/hyperactivity disorder (ADHD) could originate from the prenatal and/or perinatal exposure to hypoxia (3, 4). For these reasons some of the major goals of modern obstetric screening procedures are the identification of growth-restricted fetuses among the small for gestational age (SGA) fetuses, early detection of fetal hypoxia in high-risk pregnancies, intensive surveillance of hypoxic fetuses, and timely termination of high-risk pregnancies in order to prevent the development of hypoxic brain injury, but also to minimize the risks of prematurity.

Nowadays, the management of IUGR includes the combination of serial morphological ultrasound examinations to assess fetal growth and amniotic fluid quantity, combined with functional testing such as biophysical profile, fetal heart rate testing, and Doppler examinations of fetal hemodynamics. Unfortunately, even if hypoxia is detected, none of the presently available tests can define what amount of hypoxia the fetus can endure without

developing hypoxic brain lesions and for what duration (5). Only the answer to these questions would enable the definition of the optimal timing of delivery in the case of chronic fetal hypoxia and prevention of perinatal brain damage; although in this situation the delay of the delivery might cause the prolongation of fetal exposure to hypoxia, which could affect brain development and cause the brain damage, early delivery carries the risk of prematurity and associated risk of neurological disorders. A recent multicenter study has shown that infants at risk of hypoxia are being delivered at the correct time to minimize mortality, but could be being delivered too early to minimize brain damage associated with prematurity; this resulted in an increased number of neurologically disabled children after the two-year follow-up period (5). These results indicate that the border between the physiological adaptation and pathophysiological processes is extremely fragile and needs to be determined precisely in order to prevent neurological damage.

During the past decade, our investigations have been focused on the fetal cardiovascular responses to hypoxia. These responses, which include redistribution of the cardiac output towards the vital organs, are considered the most important adaptive reactions responsible for maintaining fetal homeostasis (6, 7). The redistribution of blood flow towards the fetal brain is known as the "brain sparing effect" (6- 8). Although the brain sparing effect attempts to compensate for the reduced oxygen delivery to the fetal brain, our studies on animal and human fetuses have shown that this phenomenon cannot prevent the development of brain lesions (9-11). In order to obtain a more precise assessment of fetal exposure to hypoxia, Arbeille et al. have introduced a new vascular parameter, the hypoxia index (HI), which takes into account the degree and duration of cerebral blood flow redistribution and calculates the cumulative, relative oxygen deficit during the chronic hypoxia (12). The hypoxia index was found to be a good predictor of fetal distress at the delivery in pregnancies complicated by malaria or maternal hypertension and chronic fetal hypoxia (12-14). Finally, our latest study

has shown that this parameter has great value in the prediction of morphological, ultrasonically detected brain lesions in chronically hypoxic fetuses (15). The overview of fetal cardiovascular responses to acute and chronic hypoxia with the emphasis on fetal cerebral circulation will be described in this review. Furthermore, we will discuss the possibilities of prevention of perinatal brain lesions in chronically hypoxic fetuses by using the new vascular score, the hypoxia index.

Doppler assessment of fetal hemodynamic responses to hypoxia

Placental insufficiency, which is the main cause of IUGR and fetal hypoxia is characterized by serious abnormalities of the placental vascular system and a consequential increase in the placental vascular resistance, which can be easily detected and quantified by Doppler indices, such as the umbilical artery resistance index (UA RI) (16). Arabin and co-workers found that only 7% of placentas with absent end-diastolic umbilical flow were normal (17). In 74% of placentas, they noted evidence of chronic placental insufficiency, manifested by small placental villi, fibrosis and microfibrinous deposits. The remaining 19% showed a reduced perfusion capacity. This increase of impedance to flow in the umbilical artery is associated with hypoxia and a poor perinatal outcome (17). Other studies have confirmed that Doppler examination of umbilico-placental vessels can identify fetuses that need intensive surveillance among small for gestational age (SGA) fetuses, and the clinical usefulness of umbilical artery velocimetry in high-risk pregnancies has been clearly demonstrated (18). However, umbilical artery Doppler velocimetry could not identify the fetuses that developed distress at delivery or were delivered by cesarean section (18). This should not come as a surprise because umbilical artery velocimetry can reveal local placental modifications, probably responsible for IUGR

and fetal hypoxia, but it does not provide a direct insight into the fetal response to hypoxia and fetal wellbeing.

Fetal hypoxia activates a range of biophysical, cardiovascular, endocrine, and metabolic responses. Fetal cardiovascular responses to hypoxia include modifications of heart rate, increase in arterial blood pressure, and redistribution of cardiac output towards the brain, heart, and adrenals (7). Decreased pO_2 dilates the cerebral and myocardial vessels in order to maintain the constant delivery of oxygen and metabolic substrates (1). The reduction of cerebrovascular resistance can be determined by using the standard Doppler indices measured on the main cerebral arteries and one of the widely used indices is the middle cerebral artery resistance index (MCA RI). The blood flow redistribution between the brain and the placenta can be detected and quantified by use of the cerebral/umbilical (C/U) ratio (6-8, 19). This ratio takes into account the placental insufficiency responsible for IUGR and hypoxia, and the cerebral response to hypoxia. Values of the C/U ratio lower than 1 correspond to a redistribution of the fetal blood flow towards the brain, in response to a reduction in fetal pO_2 (6-8, 19). Although both cerebral and umbilical vascular resistances decrease as pregnancy progresses, the vascular resistance in cerebral arteries always remains higher then in umbilical arteries and the C/U ratio remains greater than 1 (8). A decrease in the C/U ratio below the cut-off limit of 1-1.1 indicates that blood flow redistribution in favor of the brain has occurred (7, 8). Moreover, the C/U ratio is not heart rate-dependent as are the resistance indices because it is calculated from indices measured on the same fetus at the same heart rate.

The experiments on animal models have shown that the C/U ratio can precisely detect fetal blood flow redistribution (7, 20). During acute hypoxia, induced on fetal lambs by umbilical cord compression or maternal aortal compression, good correlation was found between the absolute values of the C/U ratio and corresponding values of fetal pO_2. Furthermore, the correlation between absolute values of the C/U ratio and corresponding values of fetal pO_2

was significantly higher then the correlation between the absolute values of the cerebral resistance index and fetal pO_2 (7).

Many studies (19, 21-24) have confirmed that this parameter has a high sensitivity and specificity in detection of fetal blood flow redistribution and prediction of fetal hypoxia in growth-restricted human fetuses. It has been shown that the sensitivity of the C/U ratio in the prediction of perinatal outcome exceeds the sensitivity of cerebral resistance or UA RI alone, even in pregnancies complicated by only moderate hypoxia (21, 22). However, despite the ability to detect blood flow redistribution and predict fetal distress at delivery, a decreased in the C/U ratio (or increase in the umbilical-cerebral ratio, the U/C ratio) seems unreliable in predicting the consequences of the exposure to hypoxia on the fetal brain. Scherjon et al. (24) calculated the ratio between umbilical and cerebral pulsatility indices (the U/C ratio, which is pathological when greater than 1) on 117 high-risk fetuses. The antenatally raised value of the U/C ratio was associated with adverse obstetric outcome, but no association was found between this parameter and the occurrence of perinatal brain tissue lesions. This should not surprise, as a single Doppler measurement is not sufficient for identifying the real hemodynamic stage induced by hypoxia. Although the C/U ratio (or the U/C ratio) accurately indicates that hypoxia has occurred, the one single measurement can provide no information about the duration of the hypoxic episode or about the amount of fetal pO_2 reduction during the hypoxic episode. Several research groups have examined the temporal sequence of fetal hemodynamic changes in IUGR and hypoxia, aiming to determine the indicators of fetal deterioration (25-29). Expectedly, the decrease in C/U ratio and decrease in middle cerebral artery resistance (MCA) were the earliest notable changes in fetal hemodynamics (27). During blood flow redistribution and the existence of the brain sparing effect, precordial venous flows were initially normal, whereas the internal jugular and cerebral transverse sinus blood flow were enhanced suggesting an increased cerebral venous return (28, 29). Later on the

progressive elevation in fetal venous resistance indices, such as ductus venosus resistance index, occurred, followed by spontaneous late heart rate decelerations and an occurrence of pulsatile umbilical flow, indicating the deterioration of fetal cardiovascular function and a decreased cardiac output (30, 31). The deterioration of cardiac function and the decline of cardiac output were attributed to the hypoxemic/ischemic myocardial dysfunction. The MCA resistance remained constantly decreased as the venous flows deteriorated, although the terminal increase of MCA resistance, prior to delivery or fetal death was noted in some fetuses (27, 28, 31). Therefore, it has been suggested that venous Doppler changes can facilitate the detection of fetal compromise (27, 28, 31). However, one should bear in mind that the alterations in venous circulation reveal myocardial dysfunction, while offering no information about the effects of hypoxia on fetal brain structure and functions. Furthermore, this sequential deterioration can rarely be observed beyond 32-34 weeks of gestation. After this period, the fetal growth asymmetry and the brain sparing effect can be the only evidence of placental insufficiency and fetal hypoxia (32- 34), which implies that the hemodynamic indicators of fetal distress should be searched for in the fetal cerebral circulation.

Fetal hypoxia and cerebrovascular autoregulation

The middle cerebral artery and other cerebral arteries are capable of undergoing autoregulation to preserve cerebral metabolism and function in the presence of hypoxia. This autoregulation permits vasoconstriction or vasodilatation to maintain constant perfusion of the cerebral tissues and is controlled by metabolic, neural, and chemical mediators. Experiments on fetal lambs have shown that even acute, short-term hypoxia can affect cerebral autoregulation. Oxygen saturation at 50% lasting longer than 10 minutes has been shown in a global abolition of cerebrovascular autoregulation for several hours (35, 36). Furthermore,

impaired oxygen transfer across the placenta (e. g. in placental abruption) is one of the common causes of the loss of cerebral autoregulation in neonates, and autoregulation seems to be more vulnerable than other regulatory mechanisms for the cerebral circulation (37).

The loss of cerebrovascular autoregulation is known to contribute to the development of intraventricular hemorrhage and periventricular leukomalacia in neonates (38, 39). In chronically hypoxic human and animal fetuses, the impairment of cerebrovascular autoregulation has been demonstrated by the oxygen inhalation test (40-42). In fetuses with the brain sparing effect that did not develop fetal distress, maternal inhalation of oxygen caused an increase in the cerebral vascular resistance. However, fetuses that later developed fetal distress, did not respond to the oxygen test. The absence of vascular responses to oxygen indicated either impaired placental transfer or the loss of cerebrovascular reactivity. Another investigation has shown that the middle cerebral artery pulsatility index decreases week by week in hypoxic human fetuses without fetal distress, but remains relatively stable (although decreased) during the same period in acidemic fetuses (43).

An abnormal cerebrovascular response to the CO_2 inhalation test was found in chronically hypoxic fetal lambs, where hypoxia was induced by daily administration of nicotine equivalent to 20 cigarettes to pregnant ewes (44). During the nicotine treatment and prior to the inhalation test, a decrease in cerebral and umbilical vascular resistances, which can be observed in normal pregnancies, was absent. The reduced capability of brain vessels to adapt by vasodilatation could be attributed to the vasoconstrictive effect of nicotine but could also be due to its deleterious effect on the growth and maturation of brain structures (44).

In another study, fetal hypoxia was induced by daily administration of 1- or 2-mg/kg cocaine to pregnant ewes, from midgestation onwards (9). The mean birth weight was significantly lower in the cocaine-treated fetuses than in the control group and values of fetal pO_2 confirmed moderate but significant hypoxia in these animals. During the cocaine treatment,

blood flow redistribution was detected in treated fetuses and the decrease in the C/U ratio was proportional to the decrease in fetal pO_2 (9). However, during acute hypoxic tests (umbilical cord compression and maternal aortal compression), the cerebral resistance index and the C/U ratio decreased to a much lesser extent in the cocaine-treated groups that in the control group, indicating the reduced ability of the cerebral vessels of cocaine-treated fetuses to vasodilate in response to acute hypoxia superimposed to chronic hypoxia. Later, a postmortem examination of the fetal brains revealed hypoxic-ischemic lesions such as selective neuronal loss in the parasagittal cortex, striatum, hippocampus and Purkinje cells, accompanied by diffuse perivascular edema and occasional focal perivascular hemorrhage (11), despite the maintained cerebrovascular reactivity.

Consecutive Doppler monitoring of the cerebral and umbilical hemodynamic changes in a growth-retarded and hypoxic human fetus showed the existence of several phases in the evolution of fetal hemodynamic changes (10). At the beginning of the surveillance period, the C/U ratio was lower then 1 and close to 0.7 (30% decrease from the normal limit). During the first six days, the MCA RI and the C/U ratio decreased, but not uniformly, indicating that cerebrovascular reactivity was still efficient. In the following eight days, these two indices remained stable, indicating an absence of cerebral vascular variability, and afterwards they increased progressively, reaching the highest values two days prior to delivery and fetal death. At this stage, the breakdown of compensatory mechanisms has occurred and acidosis has developed. A postmortem examination of the fetal brain revealed cerebral lesions of the hypoxic type, such as pathological gliosis in the germinal matrix, centrum semiovale, and the cerebellum, as well as a marked vasodilatation of the main cerebral arteries. Similar evolution of fetal hemodynamics with the loss of cerebrovascular variability was later registered in five growth-restricted and hypoxic fetuses (45). The loss of cerebrovascular variability was observed in all fetuses, whereas in two fetuses it was followed by an increase in

cerebrovascular resistance (45). The progress of fetal deterioration during the two weeks of surveillance is shown in Figure 1. It is important to point out that the loss of cerebrovascular variability occurred in all five fetuses during the development of fetal hypoxia remarkably earlier than the changes in the fetal heart rate, and was in all cases associated with adverse fetal outcome. The disappearance of physiological cerebral vascular variability (vasoconstriction and vasodilatation) might be the result of several events. First, the cerebral vessels may reach their maximal level of vasodilatation. Furthermore, the prolonged brain hyperperfusion (brain sparing effect) and the hypoxia may induce the formation of brain edema, which limits the dilatation of the vessels. Finally, the autonomous cerebral flow regulation may be impaired, due to lesions of the cerebral tissue, induced by a prolonged hypoxia (45). The sequence of hemodynamic changes observed in these studies (10, 45) might explain the lack of association between the last value of the U/C ratio and structural brain lesions (24). One single finding of a decreased C/U ratio (or increased U/C ratio) does not allow a distinction between the brain sparing effect with maintained vascular reactivity or the loss of cerebral vascular variability induced by chronic hypoxia. Only repeated measurements (every 1-3 days) of the fetal cerebral and umbilical Doppler indices during the period of several days can provide a more realistic evaluation of the exposure to hypoxia and its consequences on brain development.

Hypoxia index – a new parameter for prediction of perinatal brain lesions

The above-described results have confirmed that fetal cerebral hyperperfusion cannot prevent the development of brain lesions during chronic hypoxia (9-11, 45). Even in the presence of the brain sparing effect, fetal neurological outcome depends on the degree of oxygen deprivation as well as on the duration of fetal exposure to hypoxia. Aiming to quantify the

cumulative, relative oxygen deficit in fetuses exposed to hypoxia, Arbeille et al. have introduced a new vascular score, the hypoxia index (HI). This parameter can be calculated by summing the daily C/U ratio reduction (in % from the cut-off value 1 or 1.1) over the period of observation (14). The decrease in the C/U ratio from the cut-off value expressed as a percentage of this limit is proportional to the reduction in pO_2 from the lower limit of the normal range (pO_2 relative deficit) (14). By adding the decrease in the C/U ratio below the cut-off value over the period of observation, the cumulative relative deficit in pO_2 to which the fetus was exposed during this period is measured. The authors tested this new hemodynamic score for its sensitivity in the prediction of fetal distress at the delivery in pregnancies complicated by moderate and transient hypoxia due to malaria crises (12, 13). During a long malaria crisis (more than 10 days), fetal Doppler showed a greater decrease in C/U ratio over a longer period of time than in the case of a short crisis (<10 days). Thus, abnormal fetal heart rate at delivery, several weeks after the crisis, was more frequently recorded in fetuses exposed to more significant and prolonged hypoxia (long crisis). A hypoxia index higher than 150 was strongly associated with the development of abnormal fetal heart rate patterns; hence it was proposed that HI value of 150 might represent the greatest amount of oxygen deprivation the fetus can tolerate without developing heart rate abnormalities or other signs of acute distress. According to their results, a fetus whose pO_2 was 20% lower than the normal values (C/U ratio 0.8) could tolerate hypoxia without developing heart rate abnormalities for about one week (7.5 days) (12). Similar results were obtained when HI was tested as a predictor of fetal functional disturbances (abnormal fetal heart rate) at delivery in pregnancies complicated with maternal hypertension and fetal hypoxia (14).

However, although these studies indicated that HI is superior to other Doppler parameters in the prediction of fetal distress at delivery in pregnancies complicated by hypoxia, they did not

evaluate its ability to predict the development of brain tissue lesions in chronically hypoxic fetuses. In order to explore the relation between chronic fetal hypoxia and cerebral hyperperfusion and neonatal brain tissue lesions, as well as to determine the value of HI in the prediction of such lesions, we performed a prospective study on 29 growth-restricted fetuses, followed at least two weeks prior to delivery, and delivered between 30 and 40 weeks of gestation (15). The umbilical and middle cerebral artery velocity waveforms were recorded and the MCA RI, UA RI, C/U ratio and HI were calculated at 48 hours intervals for the duration of at least two weeks prior to delivery. After birth, obstetric parameters (gestational age and weight, five minute Apgar score, umbilical arterial and venous blood gas values) and neonatal brain sonography were used as outcome parameters.

During the period of surveillance, hypoxia was detected in 22 fetuses and neonatal brain lesions were later found in 13 of these infants. None of the seven fetuses that had a normal C/U ratio during the whole period of observation developed brain lesions. The evolution of fetal hemodynamics in one of these seven fetuses without hypoxia is shown in Figure 2. As can be seen in this case, the C/U ratio remained higher than 1 and cerebrovascular variability was constantly present. After delivery, neonatal neurosonography revealed normal results. At the beginning of the period of observation, a similar variability in the MCA RI and the C/U ratio was also observed in all 22 hypoxic fetuses. In 17 of these fetuses, this variability remained present until delivery, although the MCA RI and C/U ratio were decreased. The evolution of fetal hemodynamic in one of these fetuses is shown in Figure 3. In this fetus, the HI, calculated on the basis of the C/U ratio values, was 110. Pregnancy was terminated by cesarean section due to progressive olygohydramnios. However, despite the brain sparing effect (decreased MCA RI and C/U ratio) and the maintained cerebrovascular variability, the neonatal neurological ultrasound detected intracerebral hemorrhage. The neonatal brain lesions were detected in seven other fetuses from this group.

Nevertheless, in five hypoxic fetuses (C/U ratio < 1), cerebrovascular variability was lost for a minimum period of six days and brain lesions were later detected in all of them. In three of these five fetuses, in which the C/U ratio was below the physiological limit by 30-35%, the MCA RI and C/U ratio finally increased and reached their highest values. Prior to delivery, severe abnormalities of fetal heart rate occurred, and were followed by neonatal death in one case. Figure 4 shows the evolution of fetal hemodynamics in one of these fetuses. It can be seen that umbilical end-diastolic blood flow was absent until two days before the termination of pregnancy; therefore the MCA RI and C/U ratio were equal. The disappearance of cerebrovascular variability was observed between days 208 and 214, and was followed by an increase in MCA resistance and C/U ratio. In this fetus the HI was 416; pregnancy was terminated by emergency cesarean section due to severe fetal heart rate abnormalities and neonatal ultrasound examination revealed severe intracranial hemorrhage.

The HI was calculated as previously suggested (14) but instead of using HI 150 as the cut-off values, we tested the absolute values of HI, last C/U ratio, last cardiotocography as well as the perinatal outcome parameters, as potential predictors of perinatal brain lesions using the C.45 decision tree algorithm (46, 47), based on data mining methodology. The decision tree is a useful prediction algorithm that has been used in many areas of bioinformatics, such as gene finding, tumor classification, etc. An advantage of the tree based classification algorithms is its relative ease of interpretation, which can help the user to understand and improve the classification rules. An extensive description of the method has been given elsewhere (15, 46, 47). Here we can emphasize that its advantage in comparison with the classical statistics comes from the fact that it generates models from historical data that are later used for prediction. In data mining techniques, the greatest chance of success comes from combining the expert's knowledge of the data with advanced analysis techniques in which the computer itself identifies the underlying relationships and features in the data. The decision tree learner

selected only HI, with a cut-off value 74 for its resulting decision tree (Figure 5). This indicated that only HI out of all variables used in designing the decision tree emerged as having a prognostic value for prediction of brain lesions. All neonates with HI values equal to or lower than 74 were identified as having normal neurosonographic findings. On the other hand, neonates with HI higher than 74 were found to have neurosonographically detected brain lesions. According to this classifier, 13 hypoxic fetuses who developed brain lesions were identified correctly, whereas in the group of fetuses without brain lesions (n=16) one fetus was classified as having brain lesions. The stability of the classifier was then tested by the 29 fold leave-one-out cross validation test, and the sensitivity of the resulting classifier was 100% whereas specificity was 93.6%. Furthermore, although the last value of the C/U ratio correlated well with umbilical arterial and venous pO_2 and pH (Table 1), the HI showed a significantly stronger correlation with umbilical arterial and venous pO_2, pCO_2 and pH (Table 2).

We have to emphasize that the cut-off value of the C/U ratio used in this study for prediction of brain tissue lesions (C/U <1) was different than the cut-off used in the previous studies for the prediction of fetal heart rate abnormalities (C/U< 1.1), which together with the different target populations and different statistical methods, makes these studies difficult to compare (12-14). However, the lower cut-off value of the HI obtained in this study might indicate that brain tissue lesions could develop far earlier than the functional signs of fetal deterioration, such as the heart rate abnormalities. This finding is supported by the latest MRI study, which has detected structural changes in the brains of neonates born from pregnancies with placental insufficiency and IUGR, without detectable intrauterine hypoxia or any other pathological condition. These changes were related to alterations of the brain caused by the neuroendocrine consequences of IUGR (48). The chronic nutrient deficit due to placental insufficiency and

consequently high levels of fetal cortisol, might also increase the vulnerability of the rapidly developing fetal brain to hypoxic insults.

Although our results need to be evaluated on a larger number of fetuses as well as on the fetuses below 30 weeks of gestation with early onset IUGR, they allow the conclusion that this parameter could be superior to any other parameter in the evaluation of fetal wellbeing and prediction of neurological sequels.

Conclusion

Prevention of perinatal hypoxic/ischemic brain lesions remains one of the most challenging areas in modern perinatology. The process of making a decision to terminate a pregnancy complicated with IUGR and fetal hypoxia requires a constant balancing between two potential threats – exposure to hypoxia and development of hypoxic brain lesions in the case of a delay versus the risk of damages related to prematurity. Although the fetus is able to adapt to hypoxia by increasing cerebral perfusion, the blood flow redistribution (C/U ratio <1) can be considered as a beneficial physiological adaptation for a short period of time, which depends on the pO_2 reduction as well as on the duration of exposure to hypoxia. The loss of cerebrovascular variability, notable in some of the chronically hypoxic fetuses, could be considered as a sign of progressed fetal deterioration. Furthermore, our latest results have indicated that brain tissue lesions can develop even before the loss of cerebrovascular variability, although its contribution to the worsening of the brain damage cannot be excluded. The new vascular score, HI, which takes into account both the duration and the intensity of fetal flow redistribution and calculates the cumulative relative oxygen deficit, represents a promising tool for the prediction of poor neurological outcome of hypoxic fetuses. Although this parameter requires extensive testing to confirm its potential, our results indicate that it

might be useful in the evaluation of the consequences of fetal exposure to hypoxia. The use of this parameter might allow not only the identification of fetuses at risk for the adverse outcome, but could also represent a significant advance in the prevention of the most severe sequels of the chronic intrauterine hypoxia, perinatal brain damage.

References

1. Brace RA. Regulation of blood volume in utero. In: Hanson MA, Spencer JAD, Rodeck CH (eds) Fetus and neonate. Physiology and clinical applications, vol 1: The circulation. Cambridge: Cambridge University Press; 1993. pp 73-79.

2. Johnston MV, Trescher WH, Ishida A, Nakajima W. Neurobiology of hypoxic-ischemic injury in the developing brain. Pediatr Res 2001; 49(6):735-41.

3. Schreuder AM, McDonnell M, Gaffney G, Johnson A, Hope PL. Outcome at school age following antenatal detection of absent or reversed end diastolic flow in the umbilical artery. Arch Dis Child Fetal Neonatal Ed 2002; 86:108-14.

4. Barker DJ. Fetal growth and adult disease. Br J Obstet Gynaecol 1992; 99: 275-276.

5. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M. GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet 2004; 364:513-20.

6. Di Renzo GC, Luzi G. Management of intrauterine growth retardation. In: Kurjak A, Chervanek F (eds). Fetus as a patient. New York, London: Partenon Publishing Group 1996. pp 527-539.

7. Arbeille P, Maulik D, Fignon A, Stale H, Berson M, Bodard S, Locatelli A. Assessment of the fetal pO2 changes by cerebral and umbilical Doppler on lamb fetuses during acute hypoxia. Ultrasound Med Biol 1995; 21: 861-70.

8. Arbeille P, Roncin A, Berson M, Patat F, Pourcelot L. Exploration of the fetal cerebral blood flow by duplex Doppler linear array system in normal and pathological pregnancies. Ultrasound Med Biol 1987; 13: 329-337

9. Arbeille P, Maulik D, Salihagic A, Locatelli A, Lansac J, Platt LD 1997 Effect of long term cocaine administration to pregnant ewes on fetal hemodynamics, oxygenation and growth. Obstet Gynecol 1997; 90: 795-802.

10. Fignon A, Salihagić A, Akoka S, Moraine C, Lansac L, Laurini R, Arbeille P. Twenty-day cerebral and umbilical Doppler monitoring on a growth retarded and hypoxic fetus. Eur J Obstet Gynecol Reprod Biol 1996; 66: 83-86.

11. Laurini RN, Arbeille B, Gemberg C, Akoka S, Locatelli A, Lansac J, Arbeille P. Brain damage and hypoxia in an ovine fetal chronic cocaine model. Eur J Obstet Gynecol Reprod Biol 1999; 86:15.

12. Arbeille P, Carles G, Bousquet F, Body G, Lansac J. Fetal vascular changes during pregnancy complicated by malaria. J Ultrasound Med 1998; 17: 223-9

13. Arbeille P, Carles G, Tobal N, Herault S, Georgescus M, Bousquet F, Perrotin F. Fetal flow redistribution to the brain in response to malaria infection. J Ultrasound Med 2002; 21: 739-46.

14. Arbeille P, Perrotin F, Salihagic A, Hakan S, Lansac J, Platt LD. Fetal Doppler hypoxic index in the prediction of abnormal fetal heart rate at delivery in chronic fetal distress. Eur J Obstet Gynecol Reprod Biol 2005; 121(2): 171-7.

15. Jugovic D, Tumbri J, Medic M, Kusan M, Kurjak A, Arbeille P, Salihagic-Kadic A. New Doppler parameter for prediction of perinatal brain lesions in chronically hypoxic fetuses. Ultrasound Obstet Gynecol 2005 (submitted)

16. Wladimiroff JW, van den Wijngaard JA, Degani S, Noordam MJ, van Eyck J, Tonge HM. Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies. Obstet Gynecol 1987; 69: 705-709.

17. Arabin B, Jimenez E, Wogel M, Weitzel HK. Relationship of utero and fetoplacental flow velocity waveforms with pathomorphological placental findings. Fetal Diagn Ther 1992; 7(3-4): 173-179.

18. Neilson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high risk pregnancies. Cochrane Database Syst Rev. 2000; (2):CD000073.

19. Bonnin P, Guyot O, Bailliart O, Benard C, Blot P, Martineaud JP. Relationship between umbilical and fetal cerebral flow velocity waveforms and umbilical venous blood gases. Ultrasound Obstet Gynecol 1992; 2:18-22.

20. Arbeille P, Berson M, Maulik D, Locatelli A, Bodard S. New implanted Doppler sensors for the assessment of the main fetal hemodynamics. Ultrasound Med Biol 1992; 18:97-103.

21. Gramellini D, Folli MC, Raboni S. Cerebral-umbilical Doppler ratio as predictor of adverse outcome. Obstet Gynecol 1992; 79: 416-420.

22. Arbeille P, Maulik D, Stree JL, Fignon A, Amyel C, Deufel M. Fetal cerebral and renal Doppler in small for gestational age fetuses in hypertensive pregnancies. Eur J Obstet Gynecol Reprod Biol 1994; 56(2):111-116.

23. Arbeille P, Leguyader P. Cerebral, renal and umbilical Doppler in the evaluation of IUGR and fetal well being on hypertensive pregnancies. J Ultrasound Med 1992; 22: 31.

24. Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The "brain-sparing" effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. Am J Obstet Gynecol 1993; 169: 169-75

25. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol. 2001; 18: 571-577.

26. Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, Battaglia FC, Galan HL. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely-growth restricted fetus. Ultrasound Obstet Gynecol 2002; 19: 140-46.

27. Senat MV, Schwarzler P, Alcais A, Ville Y. Longitudinal changes in the ductus venosus, cerebral transverse sinus and cardiotocogram in fetal growth restriction. Ultrasound Obstet Gynecol 2000; 16:19-24.

28. Baschat AA, Gembruch U, Reiss I, Gortner L, Weiner CP, Harman CR. Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 2000; 16:407-413.

29. Harrington K, Thompson MO, Carpenter RG, Nguyen M, Campbell S. Doppler fetal circulation in pregnancies complicated by pre-eclampsia or delivery of a small for gestational age baby: 2. Longitudinal analysis. Br J Obstet Gynaecol 1999; 106:453-466.

30. Severi FM, Rizzo G, Bocchi C, D'Anton D, Verzuri MS, Arduini D. Intrauterine growth retardation and fetal cardiac function. Fetal Diagn Ther 2000; 15:8-19.

31. Baschat AA, Gembruch U, Gortner L, Reiss I, Weiner CP, Harman CR. Coronary artery blood flow visualisation signifies hemodynamic deterioration in growth restricted fetuses. Ultrasound Obstet Gynecol 2000; 16:425-431.

32. Hershkovitz R, Kingdom JC, Geary M, Rodeck CH. Fetal cerebral blood flow redistribution in late gestation: Identification of compromise in small fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol 2000; 15: 209-212.

33. Baschat AA, Harman CR. Antenatal assessment of the growth restricted fetus. Curr Opin Obstet Gynecol 2001; 13: 161-168.

34. Severi FM, Bocchi C, Visentin A, Falco P, Cobellis L, Florio P, Zagonari S, Pilu G. Uterine and cerebral fetal Doppler predict the outcome at third trimester small-for-gestational age fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol 2002; 19: 225-228.

35. Tweed A, Cote J, Lou H, Gregory G, Wade J. Impairment of cerebral blood flow autoregulation in the newborn lamb by hypoxia. Pediatr Res. 1986; 20:516-519.

36. Tweed WA, Cote J, Pash M, Lou H. Arterial oxygenation determines autoregulation of cerebral blood flow in the fetal lamb. Pediatr Res 1983; 17:246-249.

37. Paulson OB, Waldemar G, Schmidt JF, Strandgaard S. Cerebral circulation under normal and pathologic conditions. Am J Cardiol 1989; 63:2C-5C.

38. Volpe JJ. Brain injury in the premature infant: Overview of clinical aspects, neuropathology, and pathogenesis. Semin Pediatr Neurol 1998; 5:135-151.

39. Funato M, Tamai H, Noma K, Kurita T, Kajimoto Y, Yoshioka Y, Shimada S. Clinical events in association with timing of intraventricular hemorrhage in preterm infants. J Pediatr. 1992; 12:614-619.

40. Arduini D, Rizzo G, Romanini C, Mancuso C. Hemodynamic changes in growth retarded fetuses during maternal oxygen administration as predictors of fetal outcome. J Ultrasound Med 1989; 8:193-196.

41. Edelstone DI, Peticca BB, Goldblum LJ. Effects of maternal oxygen administration on fetal oxygenation during reductions in umbilical blood flow in fetal lambs. Am J Obstet Gynecol 1985; 152:351-358.

42. Nicolaides KH, Campbell S, Bradley RJ, Bilardo CM, Soothill PW, Gibb D. Maternal oxygen therapy for intrauterine growth retardation. Lancet. 1987; 1:942-945.

43. Mori A, Iwashita M, Nakabayashi M, Takeda Y. Effect of maternal oxygen inhalation on fetal hemodynamics in chronic hypoxia with IUGR. J Matern Fetal Invest 1992; 2: 93-99.

44. Arbeille P, Bosc M, Vaillant M, Tranquart F. Nicotine-induced changes in the cerebral circulation in ovine fetus. Am J Perinatol 1992; 4:270-274.

45. Salihagic A, Georgescus M, Perrotin F, Laurini R, Arbeille B, Fignon A, Zudenigo D, Kurjak A, Arbeille P. Daily Doppler assessment of the fetal hemodynamic response to chronic hypoxia: A five case report. Prenat Neonat Med 2000; 5: 35.

46. Quinlan J.R. C4.5: Programs for Machine Learning. San Mateo:Morgan Kaufmann; 1993. pp 3-41.

47. Witten IH, Frank E, Data Mining. San Francisco:Morgan Kaufmann; 2000. pp 169-170.

48. Tolsa CB, Zimine S, Warfield SK, Freschi M, Sancho Rossignol A, Lazeyras F, Hanquinet S, Pfizenmaier M, Huppi PS. Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. Pediatr Res 2004; 56:132-138.
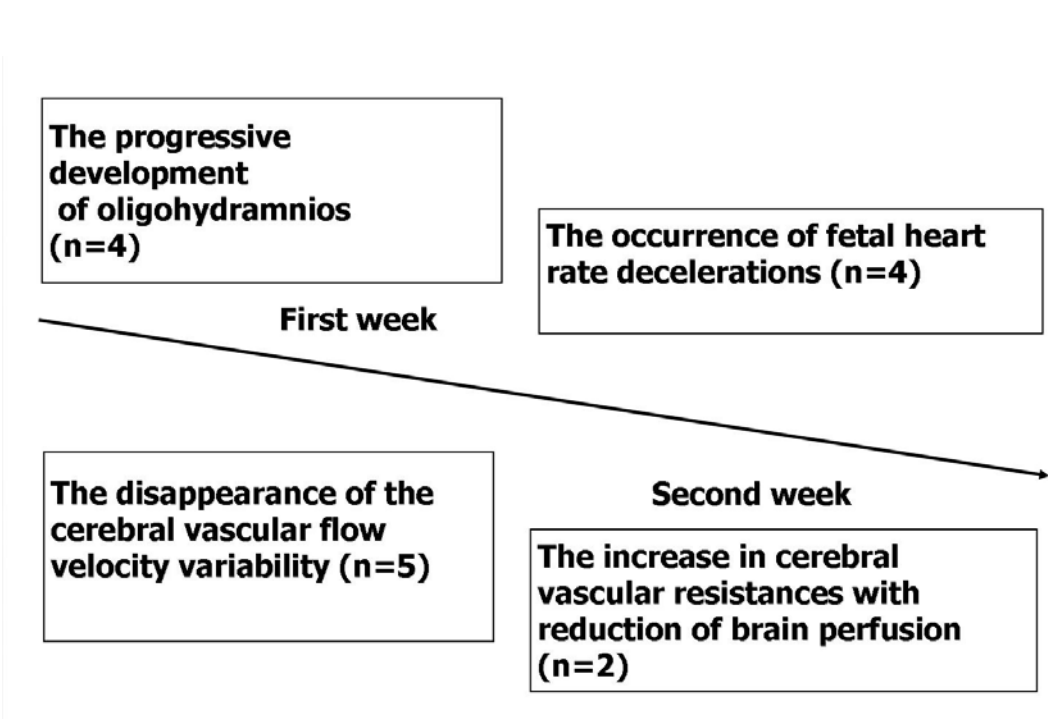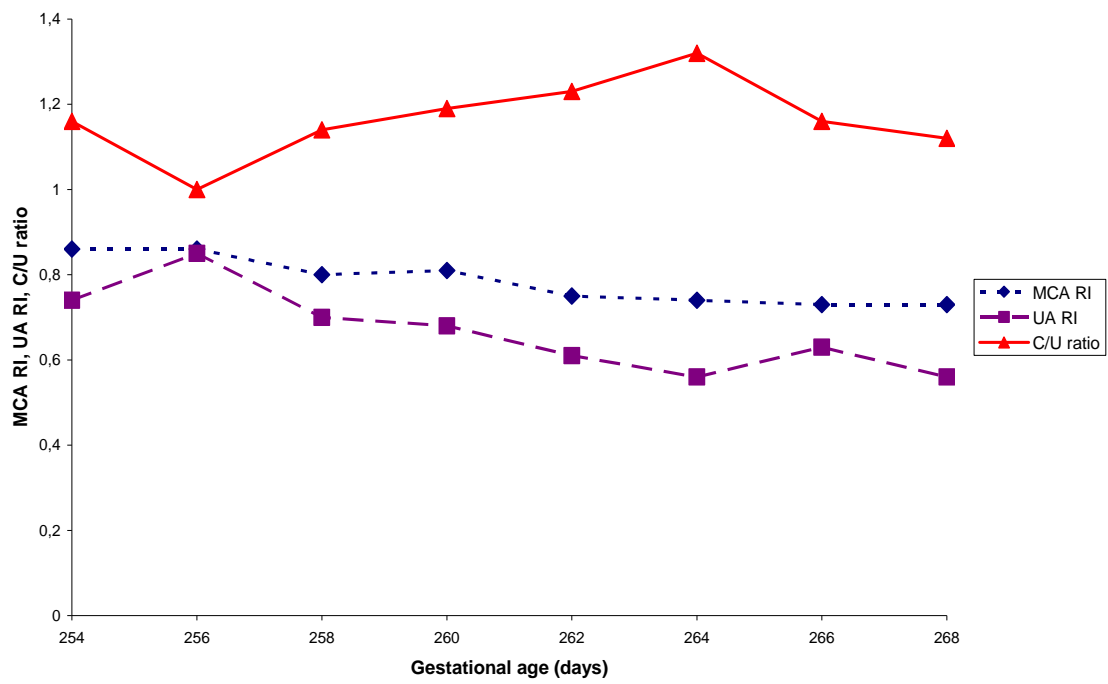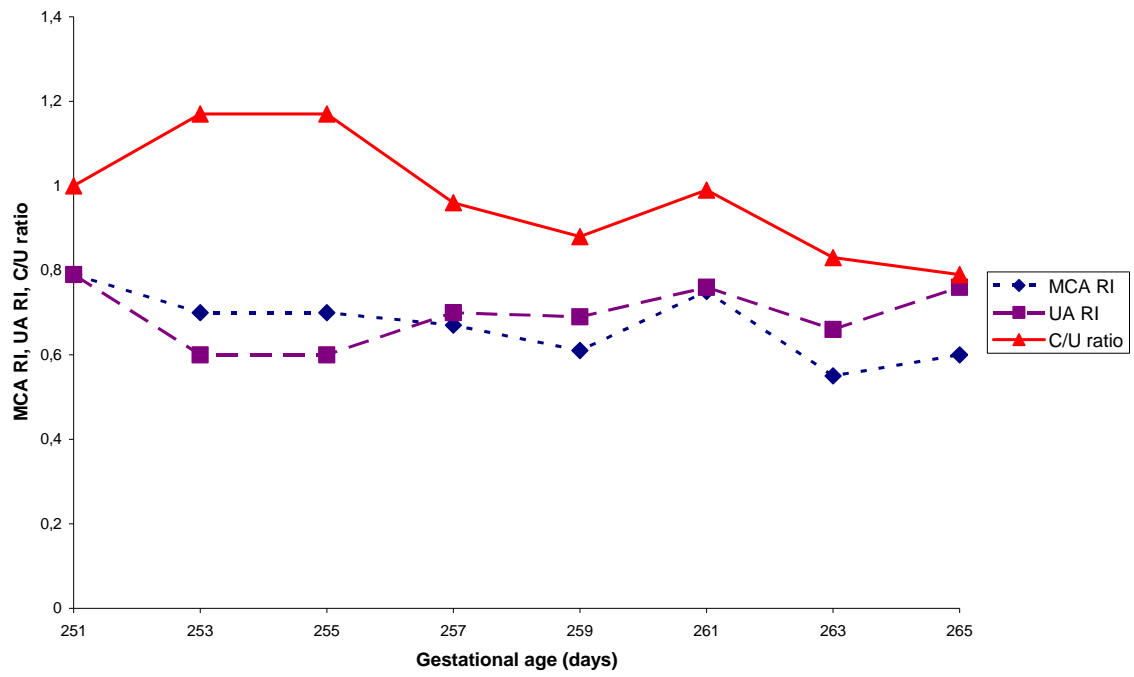
FIGURES AND TABLES

The progressive development of oligohydramnios (n=4)	The occurrence of fetal heart rate decelerations (n=4)

First week

The disappearance of the cerebral vascular flow velocity variability (n=5)	Second week
	The increase in cerebral vascular resistances with reduction of brain perfusion (n=2)

Figure 1

Figure 2

Figure 3
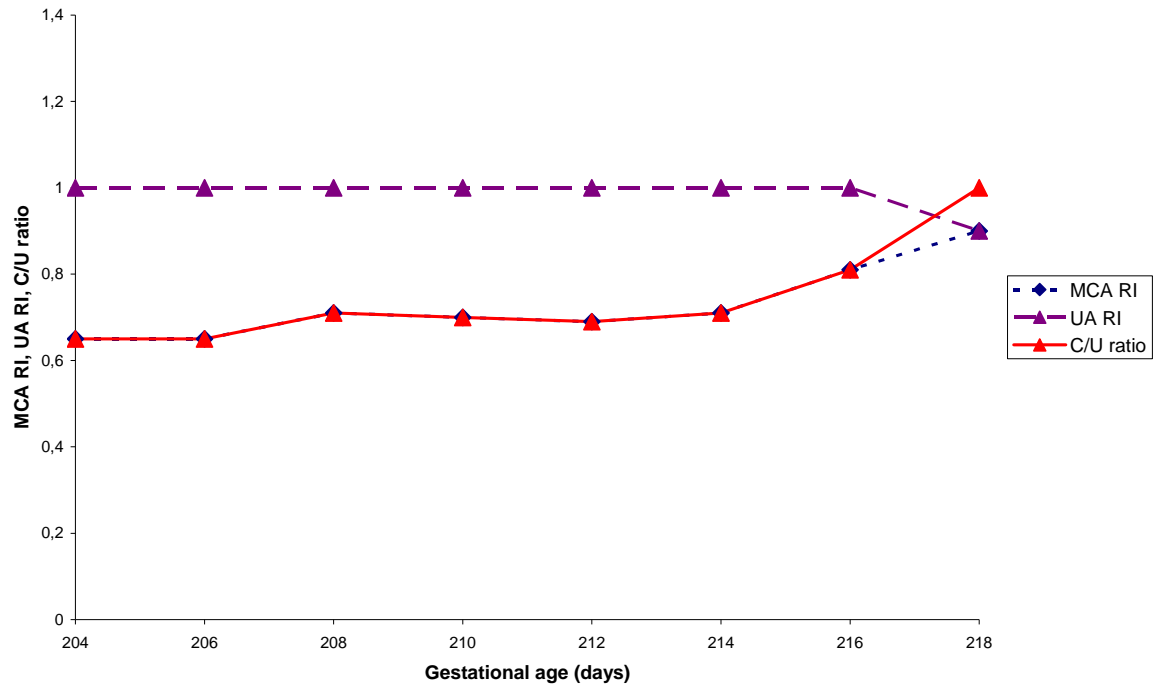
Figure 4
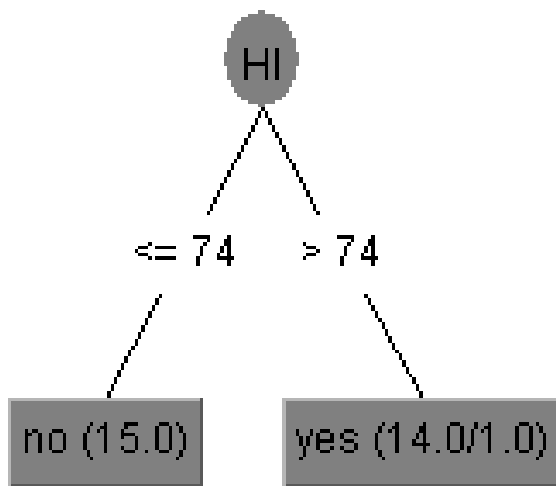
Figure 5

Umbilical blood parameters	C/U ratio		
	Rs	95% CI	P
pO_{2a}	-0,528	0,7614 - -0,1737	<0,005
pCO_{2a}	0,1206	-0,2898 - 0,4878	0,55
pO_{2v}	-0,5128	-0,7524 - -0,1532	<0,01
pCO_{2v}	0,3036	-0,0982 - 0,6206	0,1
pH_a	-0,6044	-0,8048 - -0,2804	<0,001
pH_v	-0,494	-0,7413 - -1287	<0,01

Table 1

Umbilical blood parameters	Rs	95% CI	p
		HI	
pO_{2a}	-0,6997	-0.8562 to -0.4258	<0.0001
pCO_{2a}	0,6505	0.3489 to 0.8300	<0,0005
pO_{2v}	-0,6038	-0.8044 to -0.2794	<0,001
pCO_{2v}	0,7653	0.5348 to 0.8898	<0.0001
pH_a	-0,701	-0.8568 to -0.4279	<0.0001
pH_v	-0,6617	-0.8361 to -0.3661	<0,0005

Table 2

FIGURE AND TABLE LEGENDS

Figure 1. The progress of fetal deterioration in five growth-restricted and hypoxic fetuses during the two-week observation period.

Figure 2. Evolution of the umbilical artery resistance index (UA RI), middle cerebral artery resistance index (MCA RI), and C/U ratio in a growth-restricted fetus during the two-week Doppler surveillance period, characterized by a normal C/U ratio and a maintained MCA RI and C/U ratio variability.

Figure 3. Evolution of the umbilical artery resistance index (UA RI), middle cerebral artery resistance index (MCA CRI), and the C/U ratio in a growth-restricted and hypoxic fetus during the two-week Doppler surveillance period, characterized by a decrease in the C/U ratio (indicating hypoxia) and a maintained MCA RI and C/U ratio variability.

Figure 4. Evolution of the umbilical artery resistance index (UA RI), middle cerebral artery resistance index (MCA RI), and C/U ratio in a growth-restricted and hypoxic fetus during the two-week Doppler surveillance period, characterized by a decreased C/U ratio (indicating hypoxia), followed by a loss of MCA RI and C/U ratio variability and a terminal increase in these parameters.

Figure 5. Classification pruned tree, constructed by C 4.5 algorithm. The starting node specifies the test, hypoxia index (HI), which should be implemented on the samples. The possible results of the test (>74 or ≤74) are shown on the branches. Leaves designate the classes: no-neonates without brain lesions; yes – neonates with brain lesions.

Table 1. Spearman rank order correlation of the cerebral-umbilical ratio (C/U ratio) and biochemical parameters from umbilical blood.

a:arterial; v:venous; Rs:Spearman rank order correlation; CI:confidence interval; p: probability.

Table 2. Spearman rank order correlation of the hypoxia index (HI) and biochemical parameter from umbilical blood.

a:arterial; v:venous; Rs:Spearman rank order correlation; CI:confidence interval; p: probability.