

CHRONIC HYPOXEMIA AND FETAL HEMODYNAMICS

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REZUMAT

Hipoxemia fetală este rezultatul unor procese fiziopatologice feto-materne ce determină modificări hemodinamice fetale variate. Pentru evaluarea fetală sunt importante atât calitatea cât și cronologia acestor modificări. De regulă hipoxia fetală este determinată de insuficiența vasculară placentară. Este important de precizat faptul că acidemia hipoxică este o etapă terminală a procesului evolutiv ce începe cu modificări placentare funcționale și structurale, trecând prin faza de restricție de creștere intrauterină (RCIU) și conducând în situații necontrolate la decesul fetal in utero. Ecografia și în special ecografia Doppler pot ajuta medicul obstetrician în evaluarea stării fetale prin studierea adaptărilor hemodinamice fetale la diverse situații fiziopatologice materne și fetale, acestea fiind corelate cu gradul de hipoxemie. Este cunoscut faptul că există o corelație strânsă între gradul de hipoxemie sau acidoza fetală și velocimetria Doppler.

Cuvinte cheie: hipoxemie fetală, velocimetrie Doppler, modificări hemodinamice fetale, restricția de creștere intrauterină (RCIU)

ABSTRACT

Fetal hypoxemia may be the result of different feto-maternal pathophysiological processes which can produce completely different fetal hemodynamic modifications, not only in relation to the quality but particularly in relation to the chronology of the hemodynamic events. However, fetal hypoxia is mostly due to placental vascular insufficiency and it is important to point-out that fetal hypoxemia-acidemia is part of the terminal pathway starting from placental functional and structural alterations, through fetal IUGR, leading to intrauterine fetal death. Sonography and, particularly, Doppler ultrasound technologies can help the obstetrician in the evaluation of the fetal well-being studying the fetal hemodynamic adaptations to different maternal and fetal pathophysiological conditions, which are correlated particularly to hypoxemia. A close correlation between the grade of fetal hypoxemia or fetal acidemia-hypocarboxemia and the pattern Doppler-velocimetry is proved.

Key Words: Fetal hypoxemia, Doppler velocimetry, fetal hemodynamic modification, Intrauterine Growth Restriction (IUGR)

INTRODUCTION

Fetal hypoxemia may be the result of different feto-maternal pathophysiological processes which can produce completely different fetal hemodynamic modifications, not only in relation to the quality but particularly in relation to the chronology of the hemodynamic events. However, fetal hypoxia is mostly due to placental vascular insufficiency and it is important to point-out that fetal hypoxemia-acidemia is part of the terminal pathway starting from placental functional and structural alterations, through fetal IUGR, leading to intrauterine fetal death. Sonography and, particularly, Doppler ultrasound technologies can help the obstetrician in the evaluation of the fetal well-

being studying the fetal hemodynamic adaptations to different maternal and fetal pathophysiological conditions, which are correlated particularly to hypoxemia.

A close correlation between the grade of fetal hypoxemia or fetal acidemia-hypocarboxemia and the pattern Doppler-velocimetry is proved.

PATHOPHYSIOLOGICAL BASIS

Several mechanisms are involved in the beginning of the process which leads the fetus to the hemodynamic changes, from the adaptation to the decompensation, during hypoxemia: feto-maternal immunologic tolerance alterations, failure of the endothelial vasodilator tone control (possibly alterations of the NO system), reduction of maternal plasmatic expansion, increased maternal blood viscosity at low shear rate, inappropriate trophoblastic invasions with histological, morphological and functional placental alterations and others. All these processes induces an increased impedance to flow in the uterine-placental district and in the umbilical arteries.¹⁻⁷(Fig. 1)

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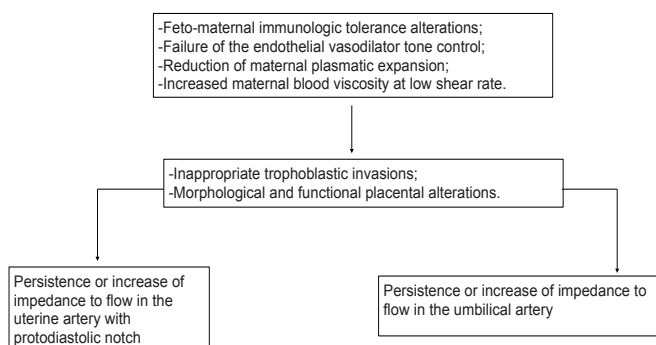
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When the structural and functional placental alterations appear and/or increase, the fetus adapts himself to this situation with a decreased growth, alterations in the behavior (i.e., decrease of the episodes of body movements) and hemodynamic changes in order to maintain the supply of oxygen and substrates for tissues with active metabolism such as brain, heart and adrenals.⁸

Only when the obstruction of placental vessels is over 60 % there is a detectable and clear alteration in the umbilical artery velocity waveform profile.⁷ Thus, when a particular level of pO₂ is reached there is a redistribution of the fetal blood flow. These hemodynamic modifications that are known as the “brain sparing effect”, which produce a “fetal hemodynamic centralization” are thought to be protective against hypoxic insult and consist of a vasodilation with an increase of blood flow in the fetal structures which are most sensitive to hypoxemia (such as the brain, adrenals and coronary arteries) and a decrease of blood supply in the peripheral vascular districts such as pulmonary, intestinal, cutaneous, renal and skeletal vessels.⁸⁻¹⁶ These changes in arterial perfusion are mediated by neuronal stimulation, either directly through stimulation of the vagal centre or through chemoreceptors in the aorta and in the carotid arteries.

If the utero-placental vascular bed alterations persist, this produces a further increase of the impedance to flow in the umbilical artery and in the fetal aorta and, mainly as a result of the hypoxemia, in the renal artery. Moreover, these factors cause a further increase of the hypoxemic fetal status balanced by a more pronounced fetal blood flow redistribution with lowest impedance to flow values in the cerebral vessels. The “centralization of blood flow” influences cardiac hemodynamics with a decreased left ventricle afterload due to the cerebral vasodilation and an increased right ventricle afterload due to the systemic vasoconstriction. This phase is characterized by the extreme response of the fetus to hypoxemia which leads, after a different time, to the decompensatory phase.

Figure 1. Mechanism involved into utero-placental vascular alterations and related hemodynamic changes:



The last phase is characterized by the impairment of fetal cardiac function which is unable in balancing all factors above mentioned. Due to the persistent severe hypoxemia and to the consequent polycythemia and increased blood viscosity, there is an impairment of fetal cardiac contractility which is the most important factor leading to the terminal decompensatory phase. The impairment of the cardiac function causes the decrease of the cardiac afterload and the increase of the cardiac preload leading to the increase of the atrio-ventricular gradient, abnormal ventricular filling with increase of venous pressure beyond the inferior vena cava, hepatic and ductus venosus circulation throughout the umbilical vein blood flow. Moreover, during this stage the reduced cardiac output and the high blood viscosity cause also a reduction in the cerebral perfusion leading to the disappearance of the so called “brain sparing”. The disappearance of the latter may be also induced by a mechanical mechanism induced by the edema produced by the brain damage of the hypoxic insult.¹¹

FETAL HEMODYNAMIC ADAPTATION AND ITS CHRONOLOGY

There is a close correlation between hemodynamic fetal pattern, analyzed with Doppler-velocimetry, and all the pathophysiological events just reported .

a. Stage of the utero-placental hemodynamic alterations

Fetal hypoxemia, as a consequence of utero-placental alteration, is generally due to a process that develop in a long period of time and probably begins in the first weeks of pregnancy and these placental alterations seem to begin long before both any possible evidence of significant hemodynamic changes in fetal vessels or any clinical fetal symptoms.

This early stage is characterized by the alteration of the utero-placental hemodynamics with protodiastolic notch and high impedance to flow values. Considering the processes which lead to the conclamate utero-placental vascular insufficiency, fetal hemodynamic profile might remain “normal” for an even long period of time: the umbilical artery velocity waveform shows a positive blood-flow pattern throughout the whole cardiac cycle and the impedance to flow values expressed as pulsatility index (PI) is normal with a not significant light increase. The Doppler velocimetry of the remaining main fetal vessels and districts (particularly aorta, renal artery, femoral artery, cerebral vessels, etc.) are also in the range of the normality with not significant alterations. Under these “normal” conditions the mean PI of the middle cerebral arteries

(MCA) is found to be higher than that of either the internal carotid (ICA) or the anterior cerebral arteries (ACA), while that of the posterior cerebral artery (PCA) is usually found to be lower than that of MCA and ACA, and it is higher than that of the umbilical artery (UA). The MCA, because of its relatively great dimension and the simplicity of its sampling, has been one of the most investigated cerebral vessels and it appears to be one of the most sensitive to initial hypoxemia; particularly, it seems that its sub-cortical segment (M2) answers earlier than the proximal part of the vessel (M1).⁹ Besides, the ratio between the flow indices of the two parts of the vessels (M2/M1) became lower than two standard deviations in the presence of an initial fetal hypoxemic status.¹⁰ In conclusion, the alteration in the utero-placental vascular bed and the alterations in the placental metabolites and gas exchange, in this initial stage, produces only light and not significant fetal hemodynamic modifications (light increase of the impedance to flow in umbilical artery and in the fetal peripheral vessels and a light decrease in the cerebral vessels) and the main hemodynamic change which is possible to detect with Doppler technology is the decrease in the impedance to flow values characterizing the sub-cortical segment of the middle cerebral artery (MCA-M2), but this main hemodynamic event is of doubtful clinical application.

However recent studies show that an evaluation of the proximal segment of MCA should be far more reliable; this part of cerebral fetal circulation in fact seems to be only slightly influenced by fetal behavioral state.^{17,18}

b. Early stage of fetal blood flow redistribution

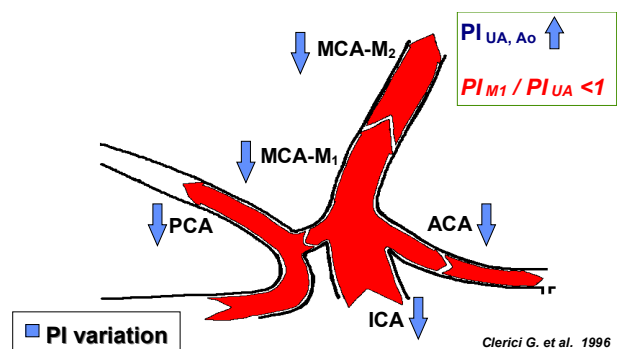
Fetal Doppler velocimetry shows an increase in the impedance to flow values as pulsatility index of the umbilical artery but also of the aorta, the renal artery and of many other arterial peripheral vessels which can be analysed. The increase of the vascular resistance of the aorta is probably related to different factors such as result of the increase in vascular impedance in the umbilico-placental vessels and arterial vasoconstriction of peripheral vessels due to progressive hypoxemia.

During this phase it is possible to observe some hemodynamic modifications which involve the whole fetal organism. These modifications are related to the substantial redistribution of the cardiac output that goes in the direction of the tissues which are important for fetal life. The inversion of cerebro-placental ratio, called “brain sparing effect”, is the most evident hemodynamic effect. In this stage it can be noticed a statistically significant increase of the blood flow and a decrease of the resistance in all the cerebral vessels examined, while, due to the hemodynamic

redistribution, it can be observed a decrease of the peripheral flow in the umbilical artery, abdominal aorta, renal artery, femoral artery and other vessels, with high impedance to flow values.⁸⁻¹⁴

The ratio between the PI of the middle cerebral artery and the PI of umbilical artery, the so called “cerebro-placental ratio” (C/P), can be considered as the Doppler flow expression of the “brain sparing effect”; the decrease of this ratio below two standard deviations is a sign of the incipient severe hypoxemia and in its presence it is possible to observe anomalies of the fetal biophysical profile, reduction of the FHR variability and reduction of amniotic fluid volume.¹² (Fig. 2)

Figure 2. Fetal blood flow redistribution during hypoxemia due to utero-placental vascular insufficiency – “brain sparing”¹⁷



(PI = pulsatility index; UA = umbilical artery; Ao = fetal aorta; MCA M1 – M2 = different segments of the middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; ICA = internal carotid artery).

During this stage, the pulsatility index of the umbilical artery and of the fetal aorta is elevated but Doppler velocimetry frequency values continue to be positive throughout the whole cardiac cycle, even in the end-diastolic phase. On the other hand and at the same time, it is possible to find high velocity frequencies during diastole in all cerebral vessels suggesting an increase of the fetal cerebral blood flow.

c. Advanced stage of fetal hemodynamic redistribution

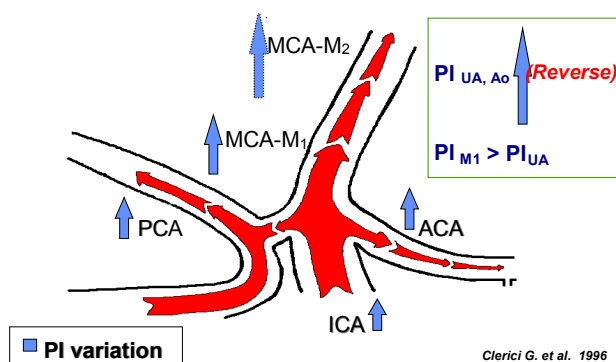
This phase is essentially characterized by a further increase in the impedance to flow in the umbilical artery and in the fetal aorta and, in the renal artery. Looking at umbilical artery flow velocity profile, a decrease of the diastolic frequencies is observed moving progressively to the absence of the diastolic flow: end-diastolic frequency disappears first, but subsequently the lack of blood flow is evident on the whole diastolic phase. This occurs, usually, when 80% of villi arterioles are occluded.⁸ Aortic velocity waveforms also exhibit a similar pattern with absence

of diastolic frequencies, usually preceding those observed in umbilical artery. At the same time the impedance to flow values in the cerebral vessels shows a further decrease leading to the lowest pulsatility index values in this district as a result of concurrent maximal vasodilatation of cerebral vessels.¹¹ Moreover, during this phase it is possible to find a relative decrease of the right cardiac output and an increased left cardiac output characterized by increased time to peak velocity in the aorta and by a decrease of the same parameter in the pulmonary arteries suggesting a preferential shift of cardiac output in favor of the left ventricle, leading to improved perfusion to the brain.

d. Decompensatory phase

During this phase, the cardiac output and the peak velocity of the main arterial trunks gradually decline and, as a consequence, the cardiac filling is impaired, suggesting a progressive deterioration of cardiac function. Therefore, these factors cause changes that induce hemodynamic alterations in all cardio-vascular districts (intracardiac, arterial and venous districts). The incipient heart failure produces a decreased cardiac output which causes the decrease in the peak velocity of the outflow tracts leading to the reverse flow in the aorta, in the umbilical artery and lately, as a terminal sign, in many other arterial vessels such as the cerebral vessels.^{15,19} However, during this phase, the increased viscosity of the fetal blood, the decrease of the cardiac output and, probably the cerebral edema, produce a decrease of brain perfusion, shown by the decrease of blood velocity especially during diastole and, thus, the disappearance of the “brain sparing effect”.^{11,15}(Fig.3)

Figure 3. Fetal cerebral artery velocity waveforms profiles during “decompensatory phase”.¹⁷



(PI = pulsatility index; UA = umbilical artery; Ao = fetal aorta; MCA M1 – M2 = different segments of the middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; ICA = internal carotid artery)

At the same time, the impairment of the cardiac contractility causes an increased atrio-ventricular gradient, abnormal ventricular filling underlined

by a decrease of the E/A ratio (E: pick due to ventricular diastole; A: pick due to atrial systole) of the atrio-ventricular blood flow velocity waveforms. The increased pressure gradient in the right atrium leads, during atrial contractions, to the evidence of the reverse flow in the ductus venosus and to an high percentage of abnormal reverse flow in inferior vena cava.^{16,20} The next step is the extension of the abnormal reversal blood flow from the inferior vena cava beyond the ductus venosus and the hepatic circulation into the umbilical vein, causing typical end-diastolic pulsations in this vessel. It has been observed that this hemodynamic pattern is associated with the onset of the severe fetal heart rate anomalies and with severe acidemia at birth.¹²

CONCLUSIONS

Fetal chronic hypoxemia induces a marked redistribution of blood supply in fetal circulation, preserving supplies for vital tissues as brain, heart and adrenals as long as possible; however, when compensation mechanisms become ineffective, a fast deterioration of fetal status is unavoidable. A correct clinical management may be hard to plan when a periodic evaluation with eco-doppler imaging is missing: variations of PI in fetal arteries or an inversion of cerebro-umbilical ratio should require a close follow-up, in order to determinate the hemodynamical adaptation status of the fetus.¹⁸ Evidences such as the absence of the end-diastolic flow in umbilical artery or aorta with normal venous velocimetric profile can encourage the obstetrician to continue the pregnancy if necessary (in relation to the gestational age and the risks linked to prematurity). On the other side, an inverted diastolic-flow in umbilical artery and/or in the aorta, associated with abnormal venous doppler-patterns (in particular in the ductus venosus, inferior vena cava and umbilical vein), suggests a severe deterioration of fetal status, and it is an indication to deliver the baby.²⁰⁻²²

A major problem in the management of fetal chronic hypoxemia is the detection of the true moment when fetal status change from a “compensation” stage to a critical one: the difficulties of this evaluation is that it requires a center with a high grade of specialization, with both technical and human resources able to manage these pathologies.

REFERENCES

1. Jauniaux E, Jurkovic D, Campbell S, et al. Doppler ultrasonographic features of the developing placental circulation: correlation with anatomic findings. *Am J Obstet Gynecol* 1992;166:585-7.
2. Warwick BG, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity

- waveforms and placental resistance: pathological correlation. *Br J Obstet Gynaecol* 1985;92:31-38.
3. Nordenvall M, Ullberg U, Laurin J, et al. Placental morphology in relation to umbilical artery blood velocity waveforms. *Eur J Obstet Gynecol Rep Biol* 1991; 40:179-90.
 4. Trudinger BJ, Warwick BG, Colleen MC. Utero-placental blood flow velocity-time waveforms in normal and complicated pregnancy. *Br J Obstet Gynaecol* 1985;92:39-45.
 5. Trudinger BJ, Warwick BG, Colleen MC. Flow velocity waveforms in maternal utero placental and fetal umbilical placental circulations. *Am J Obstet Gynecol* 1985; 152:155-63.
 6. Trudinger BJ, Warwick BG, Colleen MC, et al. Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol* 1985;92:23-30.
 7. Trudinger BJ, Stevens D, Connelly A, et al. Umbilical artery flow velocity waveforms and placental resistance: the effects of the embolization of the umbilical circulation. *Am J Obstet Gynecol* 1987;157:1443-8.
 8. Mari G, Deter RL. Middle cerebral artery flow velocity waveforms in normal and small-for-gestational-age fetuses. *Am J Obstet Gynecol* 1992;166:1262-70.
 9. Veille JC, Penry M. Effect of maternal administration of 3% carbon dioxide on umbilical artery and fetal renal and middle cerebral artery Doppler waveforms. *Am J Obstet Gynecol* 1992;167:1668-71.
 10. Luzzi G, Coata G, Caserta G, et al. Doppler velocimetry of different section of the fetal umbilical artery in relation to perinatal outcome. *J Perinat Med* 1996;24:327-34.
 11. Clerici G, Luzzi G, Di Renzo GC. Cerebral circulation from healthy to IUGR and distressed fetus: what happens and how we can explain it. In Kurjak A., Di Renzo G.C. *Modern methods of the assessment of fetal and neonatal brain* CIC Int eds. 1996: 36-50.
 12. Bilardo CM, Sniijders RM, Campbell S, et al. Doppler study of fetal circulation during long-term maternal hyperoxygenation for severe early onset intrauterine growth retardation. *Ultrasound Obstet Gynecol* 1991;1:250-7.
 13. Scherjon SA, Smolders-DeHaas H, Kok JH, et al. 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.
 14. Weiner Z, Farmakides G, Schulman H, et al. Central peripheral hemodynamic changes in fetuses with absent end-diastolic velocity in umbilical artery: Correlation with computerized fetal heart rate pattern. *Am J Obstet Gynecol* 1994;170: 509-15.
 15. Van Den Wijngaard, Groenenberg IAL, Wladimiroff JW, et al. Cerebral Doppler ultrasound of the human fetus. *Br J Obstet Gynaecol* 1989;96:845-9.
 16. Cheema R, Dubiel M, Gudmundsson S. Fetal brain sparing is strongly related to the degree of increased placental vascular impedance. *J Perinatal Med.* 2006;34(4):318-22
 17. Clerici G, Luzi G, Cutuli A, et al. Cerebral hemodynamics and behavioral states. *Ultrasound Obstet Gynecol* 2002;19:340-343.
 18. Richardson BS, Bocking AD. Metabolic and circulatory adaptations to chronic hypoxia in the fetus. *Comp Biochem Physiol.*1998; 119A(3):717-23.
 19. Sepulveda W, Shennan AH, Peek MJ. Reverse end-diastolic flow in the middle cerebral artery: an agonal pattern in the human fetus. *Am J Obstet Gynecol* 1996;174: 1645-7.
 20. Gudmundsson S. Importance of venous flow assessment for clinical decision-making. *Eur J Obstet Gynecol Reprod Biol.* 1999;84:173-78.
 21. Rizzo G, Capponi A, Talone PE, et al. Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. *Ultrasound Obstet Gynecol.* 1996;7:401-10.
 22. Kiserud Torvid. Hemodynamics of the ductus venosus. *Eur J Obstet Gynecol Reprod Biol.* 1999; 84:139-47.