Intrauterine growth restriction: perinatal assessment in predicting the offspring neurologic impairment. A 2 years prospective study

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Abstract

Objective. *We aimed to assess the correlation between some perinatal parameters in intrauterine growth restriction (IUGR) pregnancy and postnatal neurological impairment in the offspring. Those parameters were studied as predicting factors for the offspring's neurological outcomes at the age of 2.* ***Methods.*** *This was a prospective observational study including 81 pregnancies complicated by intrauterine growth restriction. By the perinatal surveillance parameters we studied the umbilical artery (UA), ductus venosus (DV) and middle cerebral artery, Doppler features, biophysical profile (BPP) score, antenatal Kanet neurologic score, Apgar score, birth acidemia, gestational age and birth weight. The neonates were monitored during the next 2 years from the point of view of neurological outcomes such as: motor anomalies, abnormal speech, abnormal hearing and vision, neurosensory abnormalities, cerebral palsy, global neurodevelopment delay. At the end of those two years we made the connections between the perinatal assessments and postnatal findings, describing the relationship of the perinatal parameters' disturbances with the specific postnatal neurologic outcomes.* ***Results.*** *Seventeen pregnancies (25%) had absent or reversed end-diastolic velocities (A/R-EDV) on UA, 25 (36.76%) abnormal DV Doppler features, 20 (29.41%) abnormal BPP, 21 (30.88%) and 6 (8.82%) had abnormal, respectively borderline Kanet scores. The gestational age was in the range 32-38 weeks and the birth weight between 1530-1730 g. After 2 years of follow up we found 14 (20.58%) cases of motor abnormalities, 6 (8.82%) cases of abnormal hearing, 17 children (25%) with speech abnormalities, 8 (11.76%) cases of neurosensory abnormalities and 12 (17.64%) cases of global neurodevelopment delay. There were no cases of visual abnormalities and only one case of cerebral palsy.* ***Conclusions.*** *In IUGR pregnancies the most important independent predictor factor for poor neurodevelopment remains UA R-EDV, even though DV abnormalities, BPP abnormal score as well as gestational age and birth weight play an important role in most of the offspring's neurologic impairments.*

Keywords: *intrauterine growth restriction, Doppler, neurodevelopment*

Introduction

Intrauterine growth restriction (IUGR) represents the second cause of perinatal mortality after prematurity, and when these two conditions are associated the mortality raises up to 6 to 10 times[1]. Perinatal morbidities are usually the consequences of the association IUGR-prematurity, which act synergistic, but it is well known that even delivered at term, the restricted fetus has high risk for neonatal axfisia, inefficient circulatory adaptation, short term decompensation, but also long term morbidities.

Fetal response to hypoxemia is different for the trunk organs than the brain. Vasoconstriction in peripheral arteries occurs with increasing the resistance in the trunk's vessels as evidenced by the elevated in the umbilical, thoracic and descending aorta Doppler resistance indices (the so called 'hind limb reflex') as a result of increased right ventricular afterload[2,3]. Vasodilatation occurs in the cerebral circulation in response to hypoxemia and it is reflected by in the decreased Doppler indices at this level (the so called 'brain sparing effect') with a reduction of left ventricular afterload[4]. This balance between left and right ventricular afterload decreases the cerebro-placental Doppler index ratio and redistributes the oxygenated blood to the heart and brain. The overall effect is an improved distribution of well-oxygenated blood to the vital organs with a preferential redirecting of the blood flow towards the placenta for re-oxygenation. In the organs considered as non vital the blood flow is decreased. All these version changes are reflected by the abnormal Doppler indices, corroborated with direct measurement of the fetal cardiac output, increases in umbilical venous volume flow and progressive decrease of the amniotic fluid[2,5,6].

The restricted fetuses with chronic hypoxemia will have a delay in the maturation of central nervous system accompanied by a global decline of fetal activity[7,8]. Because of the delayed integration of fetal heart rate control and the reduced fetal activity and hypoxemia the baseline heart rate will be higher, with low variability and reactivity[9,10]. Chronic, progressive hypoxemia gets to decrease the amniotic fluid volume with a gradual decline in fetal breathing, gross body movements, tone and fetal heart variability. These changes are in fact the consequences of hypoxemia and acidemia, independent of cardiovascular status[11]. The placental dysfunction results also in a delayed maturation of several fetal behaviors, such as coupling and cyclicity of behavior and integration of movement patterns into stable behavioral states[12,13].

Although initially it was thought that the fetus with IUGR, developing into a hostile, stressful environment will have greater ability to adapt to life outside the womb, current studies have

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shown the opposite. IUGR neither increase the survival rate, nor improve the neonatal respiratory or cardiovascular adaptability. Currently it is generally accepted that the fetus with IUGR does not adapt to extra uterine life better than the non-restricted fetus and it is accepted that premature fetuses and IUGR act synergistic in terms of complications[14,15].

Several studies have shown that chronic intrauterine hypoxia and protein restriction affects the fetus with IUGR with a negative impact on the number and size of cells in the brain which result in an overall decreased brain dimensions with lower deoxyribonucleic acid component and a reduced number of synapses[16,17].

Neurological assessment is a critical issue and it cannot be neglected for these children. Neurological development is influenced not only by birth weight, but also by premature fetuses as demonstrated by Baschat and contributors in a multicenter observational trial in which the biophysical and Doppler velocimetry score were also assessed[18]. In this study it was found that only the IUGR fetuses that were born at extremely premature stages had a significantly higher incidence of neurological abnormalities, the results obtained were the same as the one of Low and colleagues[19]. On long term, these children have also a delay in neurodevelopment. Other studies have noted a link between a small size of the fetal skull, severity intrauterine delay of growth (RCIU) and subsequent neurological performance[20,21]. Interestingly, some certain conditions that occur suddenly for a short period of time, such as intrapartum asphyxia has no long-term sequelae and does not correlate with impaired neurodevelopment, attention deficits or other behavioral abnormalities. Unlike these cases, the restricted infants are at high risk for neurodevelopment abnormalities and decreased cognitive performance.

While the relationship between antenatal or perinatal parameters and short term complication has been frequently studied, making more obvious these relationships, the implication of these parameters in late complications needs further documentation.

Most of prenatal evaluation methods of IUGR fetus (arterial and venous Doppler parameters and biophysical variables) are meant to diagnose the fetal distress and so the immediate perinatal outcomes. This study aimed to go further and establish a relationship between abnormal prenatal parameters and the postnatal neurological outcomes, to establish correlations between abnormal perinatal fetal parameters (Doppler measurements, biophysical profile (BPP) score) and the severity of neurological outcomes at these children at the age of 2. Once established these correlations, we will be able to elaborate with certainty the neurological antenatal prognostic factors in IUGR pregnancy.

Methods

The prospective observational study was performed in the Neonatology Department and the Obstetrics & Gynecology Clinic of Elias Universitary Emergency Hospital during 4 years, from september 2008 untill october 2012. The study had two phases:

a. The prenatal phase - the pregnant women were included in the study (according to the inclusion criteria), and than they have been followed up by the appropriate protocol, using obstetrical ultrasound. The inclusion criteria were: IUGR pregnancy more than 32 weeks of gestation (a first trimester ulltrasound was considered mandatory for a correct estimated age), singletone pregnancy, with normal morphology and karyotype, abdominal circumference less than the 5th percentile for the given gestational age, placental dysfunction documented by raised pulsatility index in umbilical artery, the last Doppler examination realized during the last 24 hours before delivery, pregnant women with perspective for the follow up visits. The exclusion criteria were: delivery before 32 weeks, multiple pregnancy, chorioamnionitis, maternal diabetes, evidence of fetal infection, abnormal fetal karyotype, fetal anomalies, unavailability of follow up.

All the pregnant women who consented to participate in the study were followed with a uniform monitoring protocol which included Doppler studies for umbilical artery (UA), ductus venosus (DV), middle cerebral artery (MCA), and BPP score, Kanet antenatal neurologic score. Each of these parameters was recorded as normal or abnormal, as it follows:

- The end-diastolic velocity in the umbilical artery was considered normal where it was present and abnormal to where it was absent or reversed (A/R-EDV).
- A decrease in the MCA of the pulstility index (PI) with more than 2 standard deviations (>2SD) was recorded as brain sparing effect.
- Increased PI of the DV with more than 2 spectrum disorders was recorded as abnormal
- BPP score was considered abnormal values 4, 2 or 0. Also a score of 6 in the presence oligohydramnios was considered abnormal.
- Antenatal Kanet neurological assessment score was considered normal in the range 14-20, borderline between 6 and 13 and abnormal in the range 0-5[22].

The testing frequency was determined by the rate and degree of Doppler abnormalities. Patients were delivered for maternal indications or an abnormal BPP. The last surveillance result before delivery was used in the final analysis. The time interval between the last surveillance examination and delivery was noted.

b. The postnatal phase

At birth we recorded: gestational age and the way of delivery, birth weight, Apgar score at 1 minute and 20 minutes, umbilical artery pH and complete evaluation of pediatric congenital, neurological and growth abnormalities.

A cord artery blood gas sample was obtained from an umbilical cord segment clamped immediately after birth: acidemia was defined when the pH <7.0 and/or base deficit <-12. The Apgar scores at 1 and 20 minutes were assigned by the attending neonatologist. The general assessment of the newborn included: assessment of the vital signs, estimation of gestational age by clinical criteria, reporting the actual weight to the weight curves corresponding to the gestational age and sex, examination of the head (cranial perimeter, squamous suture) and spine, identification of dysmorphic features suggestive for congenital anomalies.

The eventual neonatal neurological impairment was assessed by: the Apgar score at 10, 20 minutes, the acid-base fetal status, determination of arterial pH and base excess in

a segment umbilical cord clamped immediately at birth, the clinical neurological examination of the newborn (vital signs, level of alert, examining the skin, head and spine, motor functions, cranial nerves, reflexes, sensory examination and evaluation of behavior), Amiel-Tison neurological Score[23].

Following discharge, neonates underwent follow-up examinations with the occasion of each visit done at 3, 6, 9, 12, 18 and 24 months corrected age. At each visit there was performed neurological assessment and neurodevelopment assessment using Amiel-Tison neurological Score and Bayley Scale of Infant Development (BSID III, the recent version)[24].

At the corrected age of 2 we focused on the most frequent neurological impairments for these children resulted from IUGR pregnancies, looking for: motor abnormalities, hearing and visual disorders, speech abnormalities, global neurodevelopment delay, and neurosensory anomalies.

After diagnosing these conditions we studied a possible correlation to the changes in certain parameters evaluated and recorded in the perinatal time. The aim is to provide a comparative analysis of the prenatal diagnosis criteria and the postnatal evolution criteria. Thus for each category of neurological abnormalities seen in 2 years, we have studied the possible association with perinatal parameters change, implying here not only prenatal factors (normal/abnormal Doppler indices in the UA, MCA, DV, biophysical and Kanet score), but also a few postnatal parameters (Apgar score at birth and at 20 minutes, arterial pH measured in a segment of umbilical cord clamped immediately after birth).

The data were analyzed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) with XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and the IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA). The information obtained were stored in Microsoft Excel files and afterwards they have been statistically processed in order to analyze the relationship between clinical and laboratory data of patients. The proportional distribution of abnormal developmental testing was related to abnormal antenatal tests using Chi-square or Fisher's exact test as appropriate. For each perinatal test we calculated the specificity, sensibility, positive and negative likelihood ratio in relation to each neurologic abnormality.

Results

Out of the 81 pregnant women who consented to participate to the study, 68 completed the assessment. This was due to the withdrawn of 13 cases: 4 stillbirth, 1 neonatal death and 8 cases that did not complete the follow-up as required. Regarding the prenatal surveillance parameters we found seventeen pregnancies (25%) with A/R-EDV, 25 (36.76%) with abnormal DV Doppler features, 20 (29.41%) with abnormal BPP, 21 (30.88%) and 6 (8.82%) who had abnormal, respectively borderline Kanet scores. Eight neonates (11.76%) had birth acidemia and 22(32.35%) had Apgar score less than 8.

The neurologic outcomes found at the corrected age of 24 months are shown in Table 1. After 2 years of follow up we found 14 (20.58%) cases of motor abnormalities, 6 (8.82%) cases of abnormal hearing, 17 children (25%) with speech abnormalities, 8 (11.76%) cases of neurosensory abnormalities and 12 (17.64%) cases of global neurodevelopment delay. There were no cases of visual abnormalities and only one case of cerebral palsy.

Table 2 shows the associations between every specific 2-year outcome and the main perinatal parameters. Among perinatal findings, birth acidemia and 20 minutes Apgar score did not have a significant influence on neurodevelopment outcomes, unlike A/R-EDV on the umbilical artery and DV abnormalities who had the most important influence.

The gestational age was in the range 32-38 weeks and the birth weight between 1530-1730 g, most of the births (69.12%) occurred before 37 weeks and 57.39% had the birth weight under 2500 g. Figure 1 illustrates that most of the adverse outcomes were found to neonates delivered before 37 weeks and to the ones who had birth weight less than 2500 g, as illustrated in Figure 2. The cut-offs with the highest predictive accuracies are shown in Table 3. By these assessments it seems that in our study group delivery before 35 weeks of gestation and birth weight <2050 g were associated with most of the postnatal neurologic outcomes. These results we have obtained are higher than the ones cited in the literature, probably due to the fact that our study did not include cases of extreme prematurity or extremely low birth weight.

Discussion

This study evaluated the relationship between arterial and venous Doppler findings, BPP, perinatal variables and 2-year neurodevelopment in pregnancies complicated by IUGR secondary to placental dysfunction.

Though a normal end diastolic velocity on umbilical artery is associated with the absence of motor abnormalities, A/R-EDV is not a good predicting marker for these kinds of anomalies. Nevertheless, abnormal DV has a high sensitivity and specificity in predicting the motor abnormalities at the corrected age of 24 months and so it is highly recommended for this specific neurologic outcome. In our study neither the deteriorated BPP score nor the brain sparing effect showed any importance in determination the motor abnormalities. As for birth acidemia and low 1 minute Apgar score, though it has a high specificity for motor disturbances, it has a tendency to over diagnose.

Regarding the abnormal speech development, by the perinatal factors we followed, this outcome seems to be better predicted by the A/R-EDV on umbilical artery with a tendency to under diagnose and by the abnormal DV-PI which tends to over diagnose. Umbilical artery with A/R-EDV represents also the only feasible predicting factor for the hearing deficit.

Another important observation of this study is that the global neurodevelopment delay seen at 24 months seems to be determined mostly by the umbilical artery A/R-EDV with a small contribution of abnormal DV-PI or birth acidemia. These two last parameters cannot be thus used as individual predicting factors due to their good sensitivity with a low specificity. As for the neurosensory impairment, the brain sparing effect is not a recommended test for this type of neurologic outcome, unlike the umbilical artery A/R-EDV who proved it's utility once again and therefore it can be considered a good predicting factor. The abnormal DV-PI can be an acceptable method for neurosensory impairment's anticipation, but with a clear

Table 1 Neurologic outcomes at the corrected age of 24 months

Type of neurologic impairment	No of cases	Incidence
Motor abnormalities	14	20.58%
Hearing deficite	6	8.82%
Visual abnormalities	0	0
Abnormal speech development	17	25%
Cerebral Palsy	1	1.47%
Global neurodevelopment delay	12	17.64%
Neurosensory abnormalities	8	11.76%

Table 2 Associations between every neurologic outcome and the most significant perinatal parameters

Neurologic outcome	Perinatal parameter	Sensibility (%)	Specificity (%)	LR+	LR–	Accuracy (%)	p
Motor abnormailties	UA A/R-EDV	42.86	79.63	2.10	0.72	72.06	0.096 NS
	Abnormal DV-IP	85.71	75.93	3.56	0.19	77.94	3.995×10^{-5} HS
	Abnormal MCA-IP	78.57	57.41	1.84	0.37	61.76	0.033 S
	Abnormal BPP	57.14	77.78	2.57	0.55	73.53	0.019 S
	Birth acidemia	42.86	96.30	11.57	0.59	85.29	0.0006 HS
Abnormal speech development	UA A/R-EDV	64.71	88.24	5.50	0.40	82.35	5.29×10^{-5} HS
	Abnormal DV-IP	64.71%	72.55	2.36	0.49	70.59	0.008 S
	Abnormal MCA-IP	88.24	62.75	2.37	0.19	69.12	0.0004 HS
Hearing deficit	UA A/R-EDV	100.00	82.26	5.64	0.00	83.82	0.0001 HS
Global neurodevelopment delay	UA A/R-EDV	83.33	87.50	6.67	0.19	86.76	3.49×10^{-6} HS
	Abnormal DV-IP	83.33	73.21	3.11	0.23	75.00	0.0004 HS
	Abnormal MCA-IP	83.33	57.14	1.94	0.29	61.76	0.023 S
	Abnormal BPP	75.00	80.36	3.82	0.31	79.41	0.0004 HS
Neurosensory abnormalities	UA A/R-EDV	100.	85.00	6.67	0.00	86.76	3.28×10^{-6} HS
	Abnormal DV-IP	100.00	71.67	3.53	0.00	75.00	0.0001 HS
	Abnormal MCA-IP	100.00%	56.67%	2.31	0.00	61.76%	0.0049 S

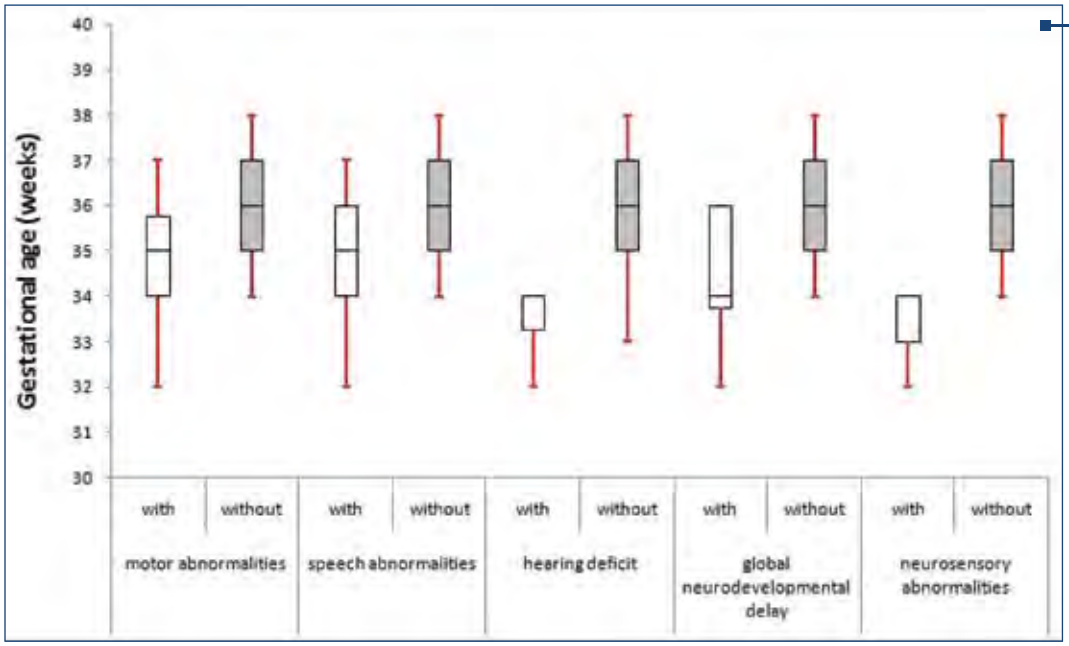

Figure 1. Gestational age at delivery and neurologic impairment. The median, interquartile range and range of gestational age at delivery for infants with or without neurologic outcomes

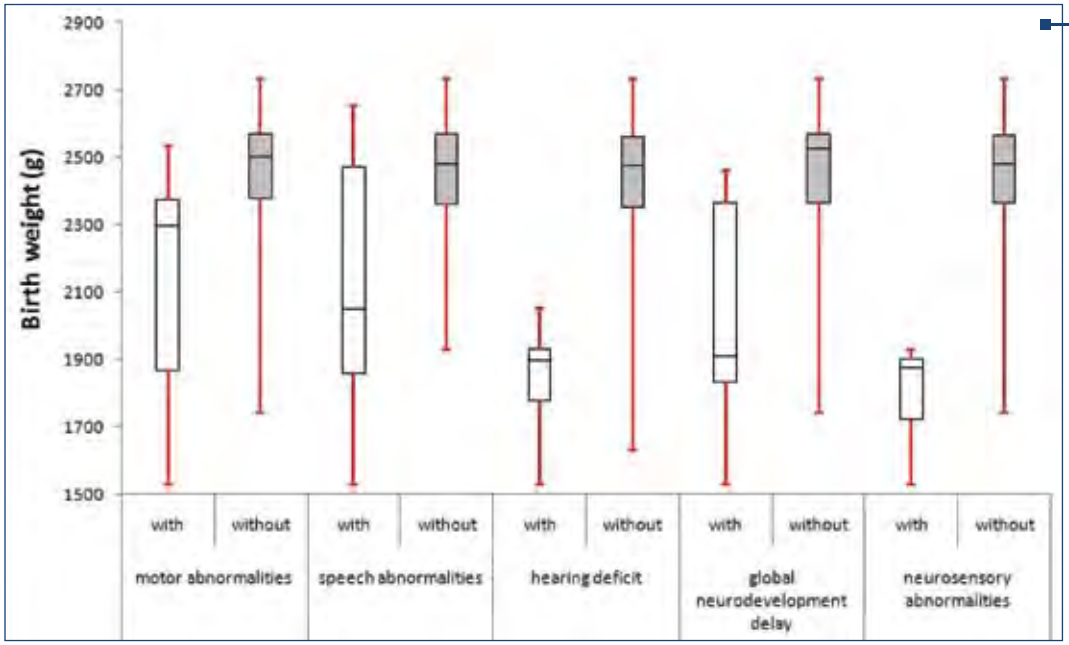

Figure 2. Birth weight and neurologic impairment. The median, interquartile range and range birth weight for infants with or without neurologic outcomes

tendency to overdiagnose, almost 2/3 of the IUGR pregnancies with DV Doppler deterioration did not have this outcome at the corrected age of 24 months.

We also studied the fetal behavior and clinical integration of the neurological antenatal score Kanet in attempt to make any correlation between abnormal values of the score and the studied neurologic outcomes. Although we found some highly significant association between abnormal or borderline scores and most of the studied neurological abnormalities, the nature of this association is unclear. Besides neurosensory disorders where we did not find any connection to the Kanet score, the rest of the neurologic outcomes (motor abnormalities, speech and hearing disorders, global neurodevelopment delay) seem to have a statistically significant association with abnormal Kanet score. Despite this association, the Kanet antenatal neurological score cannot be used as safe single criteria for anticipating most of the neurologic outcomes at the corrected age of 24 months. This is due to the numerous cases diagnosed with various neurological outcomes that showed normal or no more than borderline Kanet scores. Our findings regarding the Kanet score's significance in predicting neurological outcomes are limited by the small

Table 3 Predictive cut-offs for neurologic outcomes based on receiver-operating characteristics curve (ROC) statistics

Neurologic outcome	Perinatal variable	AUC (95%CI)	Cut-off	sensitivity	specificity	p
Motor abnormalities	Gestational age	0.789 (0.669-0.909)	<36 weeks	0.714	0.704	< 0.0001
	Birth weight	0.817 (0.705-0.929)	<2430 g	0.786	0.685	< 0.0001
Speech abnormalities	Gestational age	0.770 (0.667-0.873)	<35 weeks	0.471	0.980	< 0.0001
	Birth weight	0.747(0.895-0.600)	<2200 g	0.529	0.980	0.001
Hearing deficit	Gestational age	0.977 (0.929-1.000)	<35 weeks	1.000	0.952	< 0.0001
	Birth weight	0.957 (0.935-0.979)	<2200 g	1.000	0.935	< 0.0001
Global neurodevelopment delay	Gestational age	0.839 (0.772-0.905)	<35 weeks	0.667	0.982	< 0.0001
	Birth weight	0.879 (0.785-0.974)	<2050 g	0.667	0.982	< 0.0001
Neurosensory abnormalities	Gestational age	0.995 (0.950-1.000)	<35 weeks	1.000	0.983	< 0.0001
	Birth weight	0.988 (0.950-1.000)	<2050 g	1.000	0.983	< 0.0001

number of subjects and of course the subjectivism touch on ultrasound examination and calculating the Kanet.

In the study group, because we encountered only one case of cerebral palsy we could not make any correlations with perinatal parameters.

Conclusions

Gestational age and birth weight play a significant role in neurodevelopment outcomes, as shown by most of the clinical trials[25], but this role is not being reflected in our study because we did not include cases of extreme prematurity or extremely low birth weight.

Our study revealed that marked elevation in placental blood flow resistance are primary risk factors for global delay and poor neurosensory development. The brain sparing effect and abnormal venous Doppler parameters, birth acidemia and low Apgar scores did not have an independent impact. The potential impact of persistent biophysical deterioration was not studied because patients with an abnormal score were delivered promptly.

In IUGR pregnancies the most important independent predictor factor for poor neurodevelopment remains umbilical artery A/R-EDV, even when multiple perinatal factors are considered. ■

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