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Abnormal antenatal Doppler velocimetry and cognitive outcome in very-low-birth-weight infants at 2 years of age

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KEYWORDS: cognitive outcome; Doppler; fetal and placental blood flow; MRI; VLBW

ABSTRACT

Objective *To study neurodevelopmental outcome at 2 years of corrected age in very-low-birth-weight (VLBW) (≤ 1500 g) preterm infants with abnormal fetoplacental flow.*

Methods *A total of 258 VLBW infants were born at Turku University Hospital between 2001 and 2006. Of these, 99 had undergone, within 1 week of delivery, antenatal Doppler assessment of blood flow in the umbilical artery (UA), fetal middle cerebral artery (MCA), descending aorta (DAo), aortic isthmus and ductus venosus and were eligible for inclusion in the study. Postnatally brain pathology was assessed by serial ultrasound and magnetic resonance imaging in 86 of the neonates and brain volume was measured in 80. Cognitive development was evaluated at 2 years of corrected age in 83 infants using the Bayley Scales of Infant Development-II. Motor development was assessed using the Hammersmith Infant Neurological Examination.*

Results *On univariate analysis, abnormal pulsatility index (PI) in the UA and an abnormal UA-PI/MCA-PI ratio (*$P = 0.04$ *and* $P = 0.003$*, respectively) as well as increases in both the DAo-PI and in the DAo-PI/MCA-PI ratio (*$P = 0.03$ *and* $P = 0.02$*, respectively), were associated with adverse cognitive outcome at 2 years of age. However, when controlling for cerebral volume using multivariate analysis, the association between abnormal antenatal Doppler characteristics and cognitive outcome became statistically non-significant, which indicated the determinant role of the volume reduction. Motor development was not associated with antenatal Doppler indices.*

Conclusion *Abnormal antenatal Doppler indices are associated with adverse cognitive outcome at 2 years in VLBW infants. Our findings suggest that this association may be mediated through brain volume. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

A subset of very-low-birth-weight (VLBW) infants suffer from placental dysfunction while *in utero*, and this factor could independently impact on neurodevelopment. One challenge in the context of abnormal fetoplacental flow is to balance the risks associated with prematurity[1–3] and intrauterine compromise[4,5].

Previous studies have demonstrated an association between absent or reversed flow (AREDF) in the umbilical artery (UA), and both increased perinatal mortality[1,6–8] and morbidity[1,5,6,9,10]. Furthermore, AREDF in the UA has been associated with cerebral palsy, hearing deficit and global developmental delay at 2 years of age in infants with intrauterine growth restriction (IUGR)[11]. AREDF of the UA is a sign of significant placental compromise, often preceded by the redistribution of fetal blood circulation. An abnormal ratio of the pulsatility index (PI) of the UA to that of the fetal middle cerebral artery (MCA) (UA-PI/MCA-PI) has also been found to be associated with perinatal mortality[12] and poor neonatal outcome, especially in IUGR infants[8,13–16]. Although the long-term consequences are unclear, an association has been reported between AREDF in the UA and impaired cognitive outcome at 8 years of age[17].

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Despite the fact that Scherjon *et al.*[18] reported no association between a raised UA-PI/MCA-PI ratio and neurodevelopmental delay at 3 years of age, the same cohort did have poor cognitive outcome at 5 years of age[19]. Baschat *et al.*[11] found no association between decreased impedance in the MCA and developmental outcome at 2 years of corrected age. Accordingly, the significance of brain sparing for long-term outcome is still unclear and its effect on the developing brain remains unexplained.

In previous work we found that a raised UA-PI/MCA-PI ratio was associated with decreased total brain and cerebral volume but not with brain lesions at term[20]. In other studies, however, the reduced total[21] and regional brain volumes[21–26] correlated with compromised neurodevelopment in very preterm infants up to 2 years of corrected age. The mechanism that mediates the association between abnormal placental blood flow velocity waveforms and adverse neurodevelopment has not been sufficiently elucidated.

We hypothesized that pathological antenatal Doppler blood flow waveforms would be associated with adverse cognitive and motor development and that this relationship is mediated by decreased brain volume or neonatal brain pathology.

This study aimed to determine whether there is an association between abnormal antenatal Doppler blood flow velocimetry and adverse neurodevelopmental outcome at 2 years of corrected age in a prospective cohort of VLBW preterm infants.

METHODS

This prospective study was part of a multidisciplinary project (the PIPARI Study) of VLBW infants born between 2001 and 2006 at Turku University Hospital. The study follows developmental and functional outcomes up to school age. A total of 258 VLBW infants were born and lived in the hospital catchment area during this period.

The PIPARI Study protocol was approved in December 2000 by the ethics review committee of the hospital district of South-West Finland. All participating parents received written and verbal information about the study and provided their informed consent.

Subjects

All pregnancies anticipated to result in preterm delivery before 32 weeks' gestation or with estimated birth weight of below 1500 g were examined by antenatal Doppler ultrasound velocimetry. The following inclusion criteria were used: Doppler measurements within 1 week before delivery performed by one of two experienced perinatologists (E.E. or P.P.), birth weight < 1501 g, serial brain ultrasound examinations and brain magnetic resonance imaging (MRI) at term, a Hammersmith Infant Neurological examination at 2 years of corrected age and a psychological assessment in Finnish or Swedish using the Bayley Scales of Infant Development at 2 years of corrected age (Figure 1).

Outcome variables

Bayley Scales of Infant Development-II

Cognitive development was assessed using the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development (2nd edition) (BSID-II) at 2 years of corrected age (from -1 week to $+1$ month)[27]. The MDI scale assesses memory, habituation, problem solving, early number concepts, generalization, classification, vocalization, language and social skills[27]. The MDI scale, which has a mean value of 100 (1 SD = 15)[27], was translated for the purposes of the present study as described earlier[28].

Hammersmith Infant Neurological Examination

The Hammersmith Infant Neurological Examination (HINE) assesses the neurological status of infants between 2 and 24 months of age[29]. It has been standardized in term infants at age points of 12 and 18 months[29] and the method has also been applied in preterm infants[30]. The examination assesses cranial nerve function, posture, movements, tone and reflexes, development of motor functions and behavior. The global score, a sum of all the individual item scores, is used to quantify the results. Scores below 74 are regarded as suboptimal at 18 months in a low-risk population of term infants[29]. Normal references are not available for preterm infants, so the global scores were used as continuous variables in statistical analyses. The neurological examinations were performed either by a physician (Jo.M.) or by a physiotherapist. Clinical diagnosis of cerebral palsy was assessed by pediatric neurologists.

Explanatory variable

The explanatory variable for cognitive and motor performance was an abnormal antenatal Doppler ultrasound velocimetry study, performed using a 3.5–5-MHz convex transducer (Acuson Sequoia, Mountain View, CA, USA). Blood flow velocity waveforms from the UA, the MCA, the descending aorta (DAo), the aortic isthmus and the ductus venosus were assessed. PI was calculated for the UA, the MCA and the DAo flow as described by Gosling and King[31] (PI = (systolic velocity − diastolic velocity)/mean velocity) from the mean of three consecutive waveforms. Ratios between the UA- and MCA-PIs and the DAo- and MCA-PIs were calculated and were used as continuous variables. The direction of the net blood flow of the aortic isthmus and end-diastolic flow of the ductus venosus was determined to be either antegrade, retrograde or absent, and the blood flow of each vessel was classified as normal or abnormal. Abnormal blood flow was defined as a UA-PI value and UA-PI/MCA-PI ratio above the 95th percentile, according to Arduini and Rizzo[32], for the appropriate gestational age. A UA-PI/MCA-PI ratio above the 95th percentile was considered to be brain sparing. AREDF of the UA and the ductus venosus, and absent

or retrograde net blood flow of the aortic isthmus were classified as abnormal. The managing clinicians were not blinded to Doppler velocity measurements.

Mediating factors

Brain ultrasound examination

A cranial ultrasound scan was performed by the attending neonatologist for all infants at 3–5 days, 7–10 days, 1 month of age and monthly thereafter until discharge from hospital[33]. Ultrasound examination was used to look for intraventricular hemorrhage (IVH)[34] and cystic periventricular leukomalacia. The cranial ultrasound scan was performed at term by a pediatric radiologist (H.R.) who was blinded to the clinical data, in order to assess the ventricular/brain ratio, the widths of the ventricular horns[35], and brain lesions. A 7.5-MHz vector transducer (Aloka SSD 2000, Aloka Co, Ltd, Tokyo, Japan) was used from January 2001 to August 2002 and an 8-MHz vector transducer (GE Logic 9, GE Medical Systems, Waukesha, WI, USA) was used from September 2002 to March 2007.

Brain magnetic resonance imaging

A brain MRI examination was performed at term. The imaging took place during postprandial sleep without pharmacological sedation or anesthesia[33]. For the first 60 investigations (70%), the MRI equipment was an open 0.23-Tesla Outlook GP (Philips Medical Inc., Vantaa, Finland), and the remaining 26 investigations (30%) were conducted using a 1.5-Tesla Philips Gyroscan Intera (Philips Medical Systems, Best, The Netherlands). The MRI images were analyzed by a neuroradiologist (R.P.) who was blinded to both the clinical information and the ultrasound examination results.

Categorization of brain imaging

The infants were categorized into three groups according to the most pathological brain findings, either on ultrasound or MRI[33,36]. The normal group consisted of infants with normal brain anatomy and extracerebral space ≤ 4 mm in width. The intermediate group consisted of infants with IVH Grades 1 to 2, dilation of no more than one of the four horns of the lateral ventricles, or caudothalamic cysts in any cranial ultrasound examination and extracerebral space of 5 mm in width or caudothalamic cysts or IVH Grades 1 to 2 on MRI. The infants included in the major pathology group were those with IVH Grades 3 to 4, white matter cysts or ventriculomegaly with 2–4 horns dilated, abnormal T1 or T2 signals in cortex, basal ganglia, thalamus, cerebellum or internal capsule, abnormal corpus callosum, increased width of extracerebral space (> 5 mm), ventriculitis, or a ventricular/brain ratio > 0.35.

Brain volume measurement

The volume measurement was performed on a GE workstation (GE AW1.0, GE Medical Systems) and the coronal T1-weighted images were analyzed with Functool 1.0 postprocessing software (GE Medical Systems). The volume measurement was performed manually[37]. Cerebral volume was used in this study because abnormal antenatal Doppler flow was associated with reduced cerebral volume in a subgroup of these infants[20]. The intraclass correlation coefficient (2,1)[38] for cerebral volume was calculated to describe reliability.

Confounding factors

The potential confounding factors were neonatal morbidity (one or several of the following: chronic lung disease, sepsis, meningitis, and necrotizing enterocolitis requiring surgery), gestational age at birth, gender, the use of antenatal corticosteroids and maternal education (classified as < 9 years, ≥ 9 and < 12 years, and ≥ 12 years). Preliminary analysis indicated that small-for-gestational age (SGA) status was not a significant predictor of MDI in the data. SGA was defined as birth weight below two standard deviations from the mean[39].

Statistical analysis

The associations between the antenatal Doppler ultrasound blood flow velocity waveforms and the outcome variables (MDI and HINE scores) were studied using regression analysis. Each Doppler parameter was considered separately in all analyses. Univariate associations were first studied using a simple linear regression model, before adjusted analysis was performed by adding potential confounding factors to the multiple regression model. Finally, brain pathology and cerebral volume were added to the regression model one at a time. Regression analysis was used to study the associations between Doppler measurements and cerebral volume controlling for gestational age.

Gestational age was controlled for when the associations between ordinal dependent variable, brain pathology and Doppler measurements were studied using cumulative logit models. Using an independent-samples *t*-test, continuous variables were compared between the study infants, and excluded infants who had not had an antenatal Doppler scan. In all statistical analyses, $P < 0.05$ was considered to be statistically significant. The data analysis was performed using SAS for Windows version 9.2 (SAS Institute, Cary, NC, USA). Continuous variables were described using mean, SD and range. The results of the regression analysis are presented using estimated regression coefficient (b) and standard error (SE).

Drop-out analysis

A drop-out analysis was conducted for those excluded infants ($n = 159$) who had not had antenatal Doppler

ultrasound velocimetry performed by E.E. or P.P. The drop-out infants did not differ statistically from the study infants in terms of gestational age, birth weight and the main outcome measures (MDI and HINE).

RESULTS

Ninety-nine VLBW infants who had been examined by antenatal Doppler ultrasound velocimetry were eligible for enrollment in the follow-up (Figure 1). In this group there were 11 deaths (11%): two intrapartum deaths (born at 24 + 6 and 25 + 6 weeks), eight neonatal deaths and one infant born at 26 weeks' gestation, weighing 580 g, who lived for 3 months and whose death was classified as after estimated term. There were no intrauterine deaths. Four infants (4%) were lost to follow-up and neonatal follow-up was refused in one case. The final study population consisted of 83 VLBW infants (Figure 1, Table 1). In the 99 infants eligible for inclusion, brain pathology was assessed in 86 (87%) and brain volume in 80 (81%). The intraclass correlation coefficient for the cerebral volume measurements was 0.99.

Considering the final study population of 83 VLBW infants, flow in the UA was abnormal in 17 fetuses (20%), AREDF was recorded in seven (8%), and abnormal MCA-PI was recorded in 18 cases (22%). An abnormal UA-PI/MCA-PI ratio was found in 16 fetuses (19%). Two fetuses (2%) had retrograde net blood flow in the aortic isthmus and three (4%) had AREDF in the ductus venosus. Doppler parameters for all vessels could not be measured in all cases.

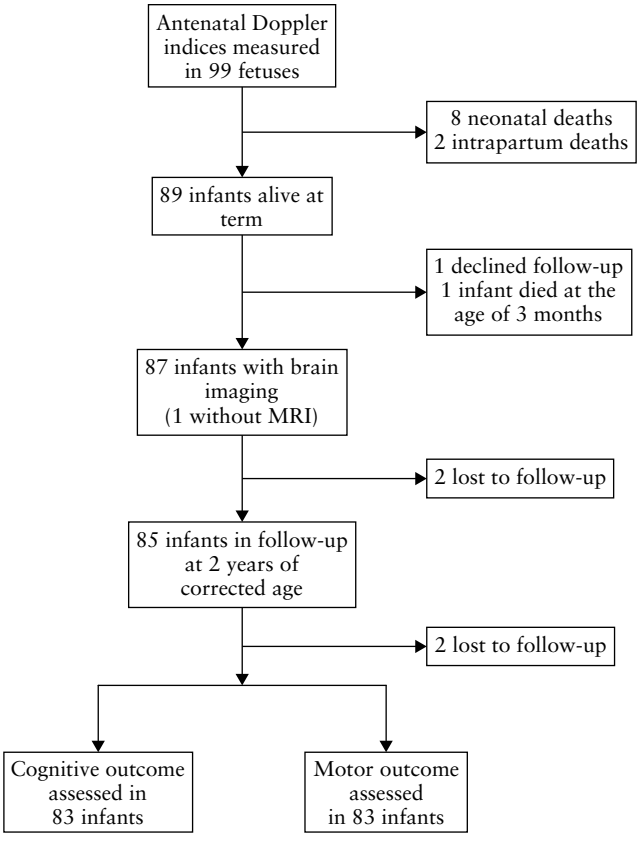

Figure 1 Flow chart showing the enrollment of infants in the study and subsequent loss to follow-up.

Those infants with abnormal UA-PI had reduced cerebral volume (mean 334 (SD 40.6) mL) compared to those with normal UA-PI (mean 367 (SD 51.0) mL). In addition, an abnormal UA-PI/MCA-PI ratio was associated with lower cerebral volume (mean 330 (SD 40.4) mL) than those infants with a normal UA-PI/MCA-PI ratio (mean 371 (SD 50.2) mL). When gestational age was taken into consideration, the difference in cerebral volume between normal and abnormal UA-PI infants was 33.5 (SE 13.6) mL ($P = 0.02$), and between normal and abnormal UA-PI/MCA-PI ratio infants it was 42.9 (SE 14.1) mL ($P = 0.003$).

The remaining antenatal Doppler ultrasound blood-flow velocity waveforms were not associated with cerebral volume. High UA-PI ($P = 0.04$, odds ratio (OR) = 3.08 (95% CI, 1.07–8.86)), UA-PI/MCA-PI ratio ($P = 0.03$, OR = 3.42 (95% CI, 1.10–10.69)) and DAo-PI/MCA-PI ratio ($P = 0.04$, OR = 3.17 (95% CI, 1.04–9.64)) were related to an increased incidence of brain pathology when controlled for gestational age. As expected, pathological flow in the UA and abnormal UA-PI/MCA-PI ratio were found more often in SGA infants (Table 2).

The mean value of MDI using BSID-II was 102 (SD 14). Ten infants (12%) had an MDI below 85 and one (1%) had an MDI below 70. The mean HINE score was 74 (SD 4). The HINE score was not associated with Doppler flow. Cerebral palsy was clinically diagnosed in five infants (6%).

Abnormal UA-PI and UA-PI/MCA-PI ratio, as well as increases in both the DAo-PI and in the DAo-PI/MCA-PI ratio, were associated with adverse cognitive performance in univariate analysis (Table 3). Although the associations were generally similar when the effect of confounding factors was controlled for, only the DAo-PI and UA-PI/MCA-PI ratio remained statistically significant. When brain pathology was added to the model, the estimated regression coefficient decreased only slightly, which suggests that brain pathology was not the mediating factor. Once cerebral volume was added to the regression model, the association between Doppler findings and cognitive outcome was no longer statistically significant.

DISCUSSION

Pathological antenatal Doppler flow was associated with adverse cognitive outcome but not with motor development at 2 years of corrected age. This study supports the hypothesis that inadequate circulation impairs the growth potential of the developing brain, which leads to reduced cerebral volume. This reduced cerebral volume is associated with poorer neurodevelopment in VLBW infants at 2 years of age. Our findings suggest that cerebral volume could be a mediating factor between abnormal fetoplacental flow and cognition. In contrast, brain macropathology was not found to be a mediating factor.

Table 1 Maternal and infant characteristics and surveillance parameters of the study group

Parameter	*Study infants with antenatal Doppler and outcome variables* (n = *83*)	*Infants with abnormal UA-PI/MCA-PI ratio* (n = *16*)*	*Infants with normal UA-PI/MCA-PI ratio* (n = *54*)*
Maternal characteristics			
Age of mother (years)	31 ± 5.2 (16–40)	31 ± 5.4 (20–39)	31 ± 5.5 (16–40)
Mother's educational level			
< 9 years' education	11/81 (14)	3/15 (20)	6/53 (11)
9–12 years' education	21/81 (26)	3/15 (20)	15/53 (28)
> 12 years' education	49/81 (60)	9/15 (60)	32/53 (60)
Nulliparous	44/72 (61)	8 (50)	31/46 (67)
Pre-eclampsia			
None	59/80 (74)	7/15 (47)	39/52 (75)
Mild	6/80 (8)	5/15 (33)	1/52 (2)
Severe	15/80 (19)	3/15 (20)	12/52 (23)
Premature rupture of membranes	29 (35)	0	20 (37)
Antenatal steroids	79 (95)	12 (75)	54 (100)
Multiple birth	25 (30)	1 (6)	15 (28)
Mode of delivery			
Vaginal	29/82 (35)	1/15 (7)	21 (39)
Cesarean			
Elective	18/82 (22)	6/15 (38)	10 (19)
Non-elective	32/82 (39)	9/15 (56)	20 (37)
Emergency	3/82 (4)	0	3 (6)
Infant characteristics			
Gestational age at delivery (weeks)	28 + 4 (23 + 6 to 34 + 6)	29 + 4 (25 + 6 to 34 + 6)	28 + 3 (23 + 6 to 33 + 4)
Male	44 (53)	7 (44)	30 (56)
Birth weight (g)	1043 ± 299 (400–1500)	968 ± 284 (580–1420)	1071 ± 292 (565–1500)
Median birth weight (g)	1080	847	1090
Birth weight *Z*-score	−1.67 ± 1.3 (−5 to 0.9)	−2.69 ± 1.2 (−4.4 to −0.1)	−1.36 ± 1.2 (−4.1 to 0.9)
Small-for-gestational age	32 (39)	13 (81)	16 (30)
Weight at term (g)	2675 ± 487 (1588–3735)	2153 ± 333 (1588–2825)	2765 ± 462 (1750–3735)
Infant surveillance parameters			
Umbilical artery pH (after birth)	7.32 (7.06–7.50)	7.27 (7.06–7.35)	7.33 (7.19–7.45)
5-min Apgar score	6.8 ± 2.2 (2–10)	7.4 ± 2.3 (3–10)	6.8 ± 2.1 (2–10)
Sepsis/meningitis/NEC	16 (19)	5 (31)	10 (19)
Patent ductus arteriosus	10 (12)	2 (13)	6 (11)
Total stay on ventilator (days)	9 ± 13.3 (0–60)	10 ± 13.1 (0–49)	8 ± 13.2 (0–60)
Chronic lung disease	14 (17)	3 (19)	10 (19)
Postnatal steroids	12 (15)	1 (6)	6 (11)
Brain volume (mL)	359.4 ± 50.2 (233–465.7)	330.3 ± 40.4 (233–391)	370.9 ± 50.2 (261–465.7)
Brain pathology			
Normal	19/81 (23)	2 (13)	14/52 (26)
Intermediate	29/81 (36)	5 (31)	18/52 (33)
Major	33/81 (41)	9 (56)	20/52 (38)
MDI	102.5 ± 14.1 (68–128)	94.1 ± 16.8 (68–122)	106.2 ± 12.7 (74–128)
HINE	73.6 ± 3.9 (52–78)	73.4 ± 2.9 (67.5–78)	74 ± 3.7 (52–78)

Data are expressed as median, mean (range), mean ± SD (range) or *n* (%). Denominators in rows are provided for data with missing values. HINE, Hammersmith Infant Neurological Examination; MDI, Mental Developmental Index of the Bayley Scales of Infant Development (2nd edition); NEC, necrotizing enterocolitis; UA-PI/MCA-PI, umbilical artery/middle cerebral artery pulsatility index ratio. *UA-PI/MCA-PI was measured in 70 cases.

It is difficult to make comparisons with earlier studies because the study population differs in terms of birth weight[40,41], degree of fetoplacental flow abnormalities[11,40], gestational age[42], morbidity[11] and mortality[11,40]. Several factors have been associated with the neurodevelopment of preterm infants in earlier studies, including maternal education[43,44], gestational age[2,11,45], administration of prenatal corticosteroids[46], gender[2] and neonatal condition[47]. Significant pathology in fetoplacental circulation, such as AREDF in the UA[17] or abnormal UA-PI/MCA-PI ratio[19], or negative net blood flow in the aortic isthmus[48], has been associated with impaired cognitive outcome. AREDF in the UA has been related both to cerebral palsy[11] and to normal motor outcome[49]. In a previous study of IUGR children an association was found between abnormal blood flow in the DAo and adverse cognitive capacity[50]. There are incongruent results concerning the effect that decreased MCA-PI has on neurodevelopment[11,43]. Similarly to earlier studies, our study representing a cohort of non-selected VLBW infants with antenatal Doppler characteristics found that abnormal UA-PI/MCA-PI ratio and increased impedance to blood flow in the descending aorta were associated

Table 2 Comparison of antenatal Doppler blood flow velocities between appropriate-for-gestational age (AGA) and small-for-gestational age (SGA) fetuses among the 99 pregnancies that underwent prenatal Doppler ultrasound examination

Parameter	*AGA fetuses (n = 60)*	*SGA fetuses (n = 39)*
AREDF in UA	2/55 (3.6)	8/39 (20.5)
AREDF in DV	2/55 (3.6)	1/37 (2.7)
Retrograde net flow in the aortic isthmus	1/43 (2.3)	1/27 (3.7)
Abnormal UA-PI	4/59 (6.8)	17/38 (44.7)
Abnormal UA-PI/MCA-PI ratio	3/48 (6.2)	18/36 (50)
UA-PI mean	1.10 ± 0.35	1.64 ± 0.82
UA-PI/MCA-PI ratio	0.64 ± 0.40	1.19 ± 0.70
DAo-PI/MCA-PI ratio	0.95 ± 0.30	1.43 ± 0.77

Data are expressed as *n* (%) or mean ± SD. AREDF, absent or reversed flow; DAo, descending aorta; DV, ductus venosus; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

with adverse cognitive outcomes. The low impedance in the MCA itself was not associated with adverse neurodevelopment at 2 years of age. Most of the fetuses in this study were delivered if gross abnormality in the fetoplacental blood flow was anticipated, which may be one reason why the motor outcome of these children was good and why most infants had normal cognitive outcome at the 2-year examination. Most of the measured blood flow velocity waveforms indicate early placental insufficiency[40,51]. Earlier studies on the association of abnormal fetal Doppler characteristics with cognitive outcome have focused on growth restricted infants[5,8,11,14–16,40] or have compared growth restricted infants with infants of normal weight[19,42]. While SGA infants were included in our study, most of the infants were appropriate for gestational age. Although the present study found an association between pathological fetoplacental blood flow and SGA status, SGA status was not found to be associated with adverse neurodevelopment.

As we have reported earlier, the UA-PI/MCA-PI ratio, which is known to reflect placental insufficiency, seems to be the best Doppler parameter predicting decreased brain volume[20]. Similarly, Tolsa *et al.*[52] found that placental insufficiency, as defined by abnormal antenatal Doppler measurements and IUGR, is associated with reduced cerebral cortical gray matter at term. This suggests that placental dysfunction is predominantly reflected as diminished cerebral volume. The vulnerability of the developing and growing brain to under-nutrition was shown in animal models nearly 30 years ago[53]. It has been speculated that decreased regional brain volumes at term indicate later adverse cognitive outcome in preterm infants[21,54], which is supported by our findings because the role of the brain volume meets the criteria for a mediating factor[55].

This study represents antenatal Doppler studies in a non-selected group of VLBW infants. However, it was not possible to include all VLBW infants owing to the fact that preterm delivery may be an acute emergency situation. The effect of the confounding factors was controlled for in the statistical analysis of the current data. The infants were carefully evaluated using both ultrasonography and conventional MRI in order to study their brain volumetry, morphology and pathology. This is the first prospective study to use the established and widely used BSID-II method to systematically assess cognitive outcome at 2 years of age for all study infants in relation to antenatal Doppler findings. In earlier studies assessing the effects of antenatal fetoplacental blood flow velocity waveforms on cognitive outcome, either a local intelligence test was applied[19] or the study population was not systematically tested[11].

As a limitation, it can be seen that conventional MRI or ultrasound may not reveal all pathology that could negatively influence cognitive development[56]. In statistical analyses, no correction was made for multiple testing, which means that some of the reported significant findings could reflect false-positive results.

In conclusion, the study shows that placental dysfunction, that is associated with Doppler abnormalities such as elevated UA-PI/MCA-PI, has an adverse effect on cognitive development at 2 years of age and this seems to be mediated through cerebral growth delay.

Table 3 Association of antenatal Doppler flow with Mental Developmental Index (MDI) at 2 years of corrected age

		Multivariate analysis		
Parameter	*Univariate analysis*	*With confounding factors*	*With confounding factors and brain pathology*	*With confounding factors and brain volume*
Abnormal UA-PI	−7.85 (3.77), $P = 0.04$	−6.55 (4.15), $P = 0.12$	−6.10 (4.44), $P = 0.17$	−5.60 (4.16), $P = 0.18$
Abnormal UA-PI/MCA-PI ratio	−12.06 (3.89), $P = 0.003$	−11.35 (4.44), $P = 0.01$	−10.59 (4.72), $P = 0.03$	−8.24 (4.55), $P = 0.08$
DAo-PI/MCA-PI ratio	−7.63 (3.05), $P = 0.02$	−5.55 (4.05), $P = 0.18$	−4.79 (4.40), $P = 0.28$	−3.92 (5.55), $P = 0.48$
DAo-PI	−6.51 (2.93), $P = 0.03$	−7.46 (3.28), $P = 0.03$	−6.79 (3.48), $P = 0.06$	−6.14 (3.44), $P = 0.08$
MCA-PI	3.86 (3.51), $P = 0.28$	2.60 (3.76), $P = 0.43$	2.99 (3.99), $P = 0.46$	2.83 (3.72), $P = 0.45$

Results are given for univariate analyses, for multivariate analyses including confounding factors and for multivariate analyses including confounding factors and brain pathology or brain volume and are expressed as estimated regression coefficient (standard error). Estimated regression coefficient describes change in MDI when UA-PI and UA-PI/MCA-PI ratio are abnormal and when DAo-PI/MCA-PI, DAo-PI and MCA-PI are elevated by one unit; minus symbol indicates decrease in MDI. DAo, descending aorta; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

APPENDIX

The PIPARI Study Group

The PIPARI Study Group includes: Satu Ekblad, RN, Eeva Ekholm, MD, PhD, Leena Haataja, MD, PhD, Mira Huhtala, MD, Pentti Kero, MD, PhD, Riikka Korja, PhD, Harry Kujari, MD, Helena Lapinleimu MD, PhD, Liisa Lehtonen, MD, PhD, Hanna Manninen, MD, Jaakko Matomäki, MSc, Jonna Maunu, MD, Petriina Munck, MA, Pekka Niemi, PhD, Pertti Palo, MD, PhD, Riitta Parkkola, MD, PhD, Jorma Piha, MD, PhD, Marika Leppänen, MD, Annika Lind, MA, Liisi Rautava, MD, Päivi Rautava, MD, PhD, Milla Reiman, MD, PhD, Hellevi Rikalainen, MD, Katriina Saarinen, Physiotherapist, Elina Savonlahti, MD, Matti Sillanpää, MD, PhD, Suvi Stolt, PhD, Päivi Tuomikoski-Koiranen, RN, Anniina Väliaho, MA, Tuula Äärimaa, MD, PhD.

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