Antenatal Doppler Measurements and Early Brain Injury in Very Low Birth Weight Infants

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Objective To determine the correlation between fetoplacental blood flow and brain injury and volumes in very low birth weight (VLBW) infants.

Study design Antenatal blood flow from the umbilical artery (UA), middle cerebral artery (MCA), and descending aorta was determined in 70 VLBW infants. The directions of the total diastolic flow of the aortic isthmus and the end-diastolic flow of ductus venosus also were measured. Serial brain ultrasound examinations and MRI at term were performed to assess brain abnormalities. On the basis of brain imaging findings, the newborn infants were classified as normal (n = 14), intermediate brain pathology (n = 31), and major pathology (n = 25) groups.

Results Abnormalities in fetoplacental blood flow were not related to anatomic brain lesions. However, an abnormal UA/MCA pulsatility index ratio was associated with reduced total brain volume (mean, 360 mL; SD, 32.5 mL) and reduced cerebral volume (344 mL; SD, 28.4 mL) compared with infants with normal UA/MCA pulsatility index ratio (mean, 405 mL; SD, 51.3 mL, $P = .01$, and mean, 368 mL; SD, 52.3 mL, $P = .012$), respectively.

Conclusions Redistribution of fetal blood flow in VLBW infants is associated with reduced brain volume at term age. Neurodevelopmental follow-up of this cohort will clarify the significance of these blood flow changes on development. *(J Pediatr 2007;150:51-6)*

The optimal timing of delivery of a preterm infant with abnormal fetal blood flow has remained controversial. Impairment of fetoplacental circulation must be balanced against the risks of prematurity. Placental insufficiency with an absent or reversed end-diastolic flow (EDF) of umbilical artery (UA) has been shown to be associated with increased perinatal mortality and neonatal morbidity[1-7] and with poor developmental outcome[2-4] in preterm infants. Interestingly, a large, randomized, multicenter study including 588 infants (GRIT, 2004)[8] showed that delaying the delivery for 4 days for cases with absent or reversed EDF of the UA increased intrauterine mortality but did not impair cognitive development at 2 years of age in the surviving preterm infants. The ratio of pulsatility indexes (PIs) between UA and middle cerebral artery (MCA) elevates with prolonged hypoxia when the fetus redistributes blood perfusion to the brain and myocardium at the cost of peripheral blood flow. An elevated UA/MCA PI ratio has been associated with fetal death and growth restriction,[9,10] with poor neonatal outcome in small for gestational age (SGA) infants[10-14] and with poor cognitive outcome in very low birth weight (VLBW) infants.[15] In addition, venous blood flow abnormalities were strongly associated with adverse neonatal outcomes in preterm SGA fetuses.[16-19]

The aim of this study was to assess how fetoplacental blood flow relates to brain injuries from birth to term and regional brain volumes at term in VLBW infants. We hypothesized that abnormal fetoplacental flow patterns result in brain pathology and decreased regional brain volumes in VLBW infants.

METHODS

This prospective study is a part of a multidisciplinary project (the PIPARI Study) for VLBW infants born at Turku University Hospital in 2001 to 2006. The PIPARI

CLD	Chronic lung disease	NEC	Necrotizing enterocolitis
DAo	Descending aorta	PI	Pulsatility index
EDF	End-diastolic flow	SGA	Small for gestational age
FSE	Fast spin echo	UA	Umbilical artery
MCA	Middle cerebral artery	VLBW	Very low birth weight

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project is a follow-up study of development and functional outcome of VLBW infants from infancy to school age.

The PIPARI study population consists of VLBW infants (birth weight ≤1500 grams) who were preterm (<37 gestational weeks), of Finnish- or Swedish-speaking families living in the hospital catchment area; 123 eligible VLBW infants were born at Turku University Hospital between July 2001 and July 2004. All of their families chose to participate in the follow-up study. The additional inclusion criteria for participation were (1) antenatal Doppler ultrasound examinations within 1 week before delivery and (2) serial cranial ultrasound examinations of survivors during neonatal intensive care and at term and (3) brain magnetic resonance imaging (MRI) of survivors at term.

Antenatal Doppler examinations were successfully performed within 1 week before delivery for 70 of 123 (57 %) infants. These 70 infants met the other inclusion criteria. SGA was determined as birth weight below −2.0 SD from the mean in Finnish growth charts. Accordingly, there were 26 SGA and 44 non-SGA infants. Seven infants (10 %) died before 40 weeks of gestational age. Brain ultrasound and MRI at term were successfully done for all of the remaining 63 infants.

Classification of the Study Groups

To evaluate the relation between fetoplacental blood flow and brain pathology, the infants were categorized into three groups, based on the most pathological brain image detected either with ultrasound or MRI: (1) normal group, (2) intermediate group with a finding of unclear clinical significance, and (3) major pathology group with definite brain pathology or neonatal death. The normal group consisted of VLBW infants with normal brain anatomy and the width of extracerebral space ≤4 mm. The intermediate brain pathology group consisted of VLBW infants with intraventricular hemorrhages grades 1 to 2, dilation of one horn of the lateral ventricles, caudothalamic cysts, or width of the extracerebral space of 5 mm. The infants with intraventricular hemorrhages grades 3 to 4; white matter cysts or ventriculomegaly with 2 to 4 horns dilated; abnormal T1 or T2 signals in cortex, basal ganglia, thalamus, cerebellum, or internal capsule; hypoplasia of corpus callosum; increased width of extracerebral space (≥6 mm); or ventriculitis or other major brain anomaly were included in the major pathology group.

Antenatal Doppler Recordings

Doppler examinations were performed with a 3.5- to 5-MHz convex transducer (Acuson Sequoia, Mountain View, Calif). Blood flow velocity waveforms from the UA, MCA, and descending aorta (DAo) were assessed. The PI was calculated as described by Gosling and King[20] [PI= (systolic velocity − diastolic velocity)/mean velocity] from a mean of three consecutive waveforms of UA, MCA, and DAo. The ratios of PIs between fetal peripheral vessels (ie, UA, DAo) and MCA were calculated. The direction of net blood flow of the aortic isthmus and end-diastolic flow of ductus venosus were determined as antegrade, retrograde, or absent.

The interval between Doppler measurements and delivery was a maximum of 7 days. All the Doppler measurements were performed by one of the two perinatologists.

Serial Cranial Ultrasound Examinations

Cranial ultrasound examinations were performed for all study infants once at 3 to 5 days, once at 7 to10 days, at 1 month of age and, thereafter, monthly until discharge from the hospital. The ultrasound examinations in the intensive care unit were performed by using a 7-MHz vector transducer (Sonos 5500 Hewlett-Packard, Andover, Mass). These examinations were done as a part of clinical routine by the attending neonatologist.

A pediatric radiologist who was blinded to the clinical data of the study infants performed the cranial ultrasound at term. These ultrasound examinations were performed with a 7.5-MHz sector transducer (Aloka SSD 2000, Aloca Co, Ltd, Tokyo, Japan) during January 2001 to August 2002 and an 8-MHz vector transducer (General Electric Logic 9) during September 2002 to July 2004. All the ultrasound examinations were tape-recorded for later reading and measurements.

The classification of intraventricular hemorrhage (grades I to IV) was done according to Papile et al.[21] Only multiple cysts with typical location were classified as cystic periventricular leukomalacia.

The reference values for VLBW infants at term introduced by Virkola[22] were used to define ventriculomegaly. The oblique widths of the frontal horns of the lateral ventricles were measured from the coronal plane at the level of the foramen of Monro. The cutoff value for a dilated frontal horn was 0.3 cm (1 SD above the mean according to VLBW population). On parasagittal views, the sagittal diameters of the trigone of the posterior horns were measured. The cutoff value for a dilated posterior horn was 1.15 cm (1 SD above the mean according to VLBW population). Ventriculomegaly was defined as mild if one horn only was dilated and as severe if at least two of the four horns of the lateral ventricles were dilated.

Magnetic Resonance Imaging of the Brain

An MRI of the brain was performed at term on the same day as the ultrasound examination on all the infants. The imaging took place during postprandial sleep without sedation. The infants were swaddled to calm them and to reduce movement artifacts in the imaging. The MRI equipment was an open 0.23-Tesla Outlook GP (Philips Medical Inc, Vantaa, Finland), equipped with a multipurpose flexible coil fitting the head of the infant. The open MR equipment permitted good visual control and easy access to the baby. Axial T2-weighted fast spin echo (FSE) images with a repetition time (TR) of 9999 ms and echo time (TE) of 200 ms were obtained. In this sequence, the flip angle was 90 degrees, the slice thickness was 6 mm, the field of view was