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Increased Fetal Brain Perfusion and Neonatal Neurobehavioral Performance in Normally Grown Fetuses

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Key Words
Brain perfusion · Neurobehavioral outcome · Doppler

Abstract
Objective: To explore the association between fetal cerebroplacental ratio (CPR) and frontal brain perfusion at third trimester with neonatal neurobehavioral performance in normally grown fetuses. ***Methods:*** CPR and frontal brain perfusion measured by fractional moving blood volume (FMBV) were assessed in 258 consecutive healthy fetuses at routine third trimester scan (32–35.6 weeks). Neonates were evaluated with the Neonatal Behavioral Assessment Scale. The association between Doppler parameters and neurobehavior was analyzed by MANCOVA (multiple analysis of covariance) and logistic regression, with adjustment for smoking, socioeconomic class, mode of delivery, gestational age at birth, postnatal days at examination and gender. ***Results:*** Fetuses with increased FMBV (in the upper quartile) had lower neurobehavioral scores in all areas, reaching significance in motor (5.6 vs. 5.8; $p = 0.049$), social (6 vs. 6.4; $p = 0.006$) and attention (5.3 vs. 5.9; $p = 0.032$). Fetuses with increased FMBV had higher risk of abnormal (<10th centile) motor (OR 3.3; 95% CI 1.36–8.1), social (OR 2.9; 95 CI% 1.33–6.5) and attention (OR 2.5; 95% CI 1.1–5.8) scores. Fetuses with lower CPR (in the lower quartile) did not differ in their neurobehavioral scores from those with normal values. ***Conclusions:*** Normally grown fetuses with increased frontal brain perfusion have poorer neurobehavioral competences, suggesting a disrupted neurological maturation. The results support the existence of forms of placental insufficiency not detected by current definitions of growth restriction.

Introduction

As hypoxia secondary to placental insufficiency progresses, hemodynamic adaptation occurs with blood flow redistribution preferentially to the brain, i.e. the brain-sparing effect. This sign was first described in early-onset intrauterine growth restriction (IUGR) [1], being considered a protective mechanism by preserving brain oxygenation [2]. Later, several studies in the same population

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suggested that brain-sparing was not an entirely protective response, being associated with neurodevelopmental disruptions [3, 4]. More recently, this notion has been extended to late-onset small-for-gestational age (SGA) cases, where brain-sparing has been associated with adverse perinatal [5–7] and neurodevelopmental [4, 8, 9] outcomes.

Clinically, the standard parameter to assess fetal brain circulation and to define brain-sparing has been the evaluation of the middle cerebral artery by pulsed Doppler that combined in a ratio with the umbilical artery Doppler constitutes the cerebroplacental ratio (CPR). This parameter has been demonstrated in animal [10] and clinical [11] models to be more sensitive to hypoxia than its individual components, and correlates better with adverse outcome [12]. More recently, fractional moving blood volume (FMBV), a quantitative methodology that has been validated against gold standards for fetal evaluation [13], has been used to demonstrate that cerebral blood perfusion increases earlier and in a higher proportion of cases than other spectral Doppler indices [14, 15] and is associated with the risk of abnormal neonatal neurobehavioral performance in full-term SGA fetuses [16].

The terms SGA and IUGR have often been used interchangeably, but not all small babies are growth-restricted, and not all growth-restricted babies are small. Therefore, the identification of at-risk babies only by weight may be missing a significant proportion of cases with latent placental insufficiency that may have already been exposed to hypoxia. This latent and mild hypoxia could be only detected by sensitive methods, with FMBV being suitable for a such purpose. No previous studies have evaluated the consequences of brain-sparing as assessed by increased FMBV in normally grown fetuses.

In this study we aimed to explore in the general population of fetuses whether changes in fetal brain Doppler are associated with neonatal neurobehavior.

Patient and Methods

Subjects

A cohort was created of consecutive singleton pregnancies that attended our institution between March 2011 and August 2011 for a routine third-trimester scan. Inclusion criteria were: (i) an estimated fetal weight >10 centile according to local standards and (ii) an umbilical artery Doppler pulsatility index (PI) below the 95th centile [17]. Exclusion criteria were: (i) congenital malformations (including chromosomopathies and infections), (ii) a birth weight below the 10th centile, or (iii) maternal diseases, including diabetes, chronic hypertension, autoimmune and other systemic diseases. Pregnancies were dated by the first-trimester crown-rump length measurement [18]. Deliveries were attended by a staff obstetrician blinded to the Doppler results. The study protocol was approved by the ethics committee and parents provided written informed consent.

Brain Doppler Assessment

Prenatal Doppler ultrasound examinations were performed in all cases at the time of routine ultrasound (32.0–35.6 weeks) by one of two experienced observers (R.M. and S.S.), using an Acuson Antares Premium Edition (Siemens, Mountain View, Calif., USA) ultrasound machine equipped with a 2.3–4 MHz transabdominal transducer. With color directional Doppler scans, the study included umbilical artery PI, obtained from a free-floating portion of the umbilical cord, and middle cerebral artery PI, obtained in a transversal view of the fetal head at the level of its origin from the circle of Willis. The CPR was calculated as the ratio between middle cerebral artery PI and umbilical artery PI. Doppler recordings were performed in the absence of fetal movements and voluntary maternal suspended breathing. Pulsed Doppler parameters were performed automatically from ≥3 consecutive waveforms, with the angle of insonation as close to 0 as possible. A high-pass wall filter of 70 Hz was used to record low flow velocities and to avoid artifacts.

With power Doppler ultrasound, frontal brain perfusion was evaluated in a sagittal view of the fetal head. The power Doppler color box was placed to include all the frontal part of the brain. Five consecutive high-quality images with no artifacts were recorded with the use of the following fixed ultrasound setting: gray-scale image for obstetrics, medium persistence, wall filter of 1, gain level of 1, and pulsed repetition frequency of 610 Hz. All images were examined offline, and FMBV was estimated with the statistical software (MATLAB version 7.5; The MathWorks, Natick, Mass., USA), as previously described [19]. The mean FMBV from all 5 images was considered to be representative for that specific case and was expressed as percentage. The region of interest was delineated as described elsewhere; anteriorly by the internal wall of the skull, inferiorly by the base of the skull, and posteriorly by an imaginary line drawn at 90° at the level of the origin of the anterior cerebral artery and parallel to an imaginary line in the front of the face (fig. 1).

Frontal FMBV and CPR were converted into centiles according to normal reference ranges [12, 20], and dichotomized using the 75th and 25th centile for FMBV and CPR, respectively, as cut-offs.

Neurobehavioral Outcome

Neurobehavioral performance was evaluated at 40-week (+1) corrected age with the Neonatal Behavioral Assessment Scale (NBAS) [21] that assesses both cortical and subcortical functions by evaluating 35 items rated on a 1–9 scale (9 being the best performance) except for 8 curvilinear scale items which, according to the manual, are re-scored as linear on a 5-, 6-, or 8-point scale. Items are grouped into clusters, including motor (general tone, elicited activity, spontaneous activity and motor maturity), social-interactive (responses to visual, animate and inanimate auditory stimuli and alertness), organization of state (irritability, state lability, maximum excitation and reaction time), regulation of state (self-quieting and hand-to-mouth responses) and attention (alertness, quality of the alert responsiveness and cost of attention). The social-interactive cluster was subscored for visual and auditory stimuli. All 5 clusters were averaged to construct a mean NBAS score.

All evaluations were performed by one of three trained examiners, accredited by The Brazelton Institute (Harvard Medical School, Boston, Mass., USA), that had been previously tested for

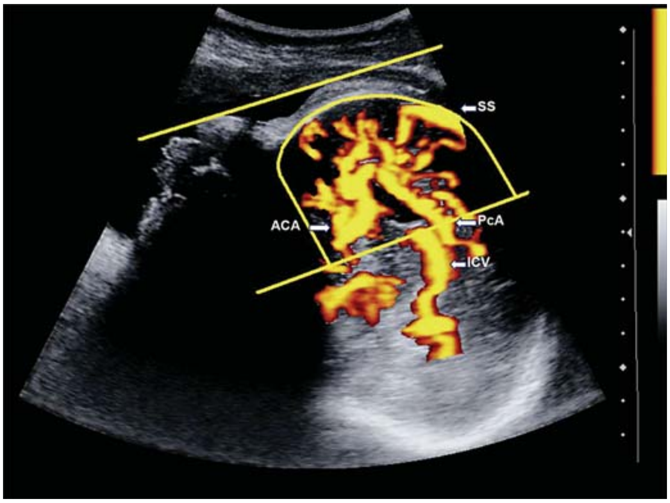

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Fig. 1. Power Doppler image from the region of interest, where frontal lobe perfusion was estimated. ACA = Anterior cerebral artery; SS = sagittal sinus; PcA = pericallosal artery; ICV = internal cerebral vein.

Table 1. Clinical characteristics of the population (n = 258)

Primiparity	162 (62.8)
Non-Caucasian ethnicity	85 (32.9)
Maternal age, years	31.8±4.9
Maternal age <21 years	14 (5.4)
Body mass index at booking	23.4±4.3
Low socioeconomic level*	22 (8.5)
Smoking	
Non-smoking	222 (86)
1–9 cigarettes/day	18 (7)
10–19 cigarettes/day	14 (5.4)
20+ cigarettes/day	4 (1.6)
Alcohol consumption >170 g/week	4 (1.6)
Gestational age at scan, weeks	34.5±0.88
Estimated fetal weight, g	2,445±415
Estimated fetal weight centile	48±27

Values are mean ± SD or n (%). * Routine occupations, long-term unemployment or never worked (UK National Statistics Socio-Economic Classification).

reliability achieving an inter-rater reliability level above 90%. The examiners were blinded to the prenatal variables. Neonates were assessed in the afternoon, between two feedings, in a small, semi-dark, quiet room with a temperature between 22 and 27°C and in the presence of at least one parent.

Statistical Analysis

The Student's t test for independent samples and Pearson-χ^2 test were used to compare quantitative and qualitative data, respectively. Multivariate analysis was conducted by multiple analysis of covariance (MANCOVA) and logistic regression, whereby a model was run for each different set of skills (motor, social-interactive, state organization, state regulation and attention) including the study group as a factor and as covariates the following variables: (i) smoking during pregnancy: no smoking, 1–9 cigarettes/day, 10+ cigarettes/day; (ii) low socioeconomic level, defined as routine occupations, long-term unemployment or never worked (UK National Statistics Socio-Economic Classification); (iii) mode of delivery (vaginal delivery vs. cesarean section); (iv) gestational age at delivery; (v) postnatal days at evaluation (log-transformed), and (vi) gender. For each MANCOVA and logistic model, assumptions were checked and multivariate significance was obtained from F's and Wald's values. The software package SPSS 19.0 was used for the statistical analysis.

Results

A total of 265 women fulfilled the inclusion and exclusion criteria. In all included infants, a neurobehavioral assessment visit was scheduled at 40 weeks (+1) of corrected age. Parents of 7 infants later declined to participate, leaving a final population of 258 infants. Tables 1 and 2 depict the clinical characteristics at inclusion and the perinatal outcome of the population.

Table 2. Perinatal outcome of the population (n = 258)

Gestational age at delivery, weeks	40.1±1.2
Epidural anesthesia	220 (85.3)
Birth weight, g	3,359±425
Birth weight centile	46.7±29
Male gender	120 (46.5)
Cesarean section	61 (23.6)
Labor induction	58 (22.5)
Operative delivery for fetal distress	39 (15.1)
5-min Apgar score <7	0
Umbilical artery pH <7.15 at delivery	19 (7.4)
Neonatal unit admission	0

Values are mean ± SD or n (%).

Neonatal neurobehavior was assessed at 4.8 (SD 3.2) days of life. A total of 62 (24%) fetuses had an increased FMBV whereas 60 (23.3%) had a decreased CPR. Interestingly, fetuses with increased FMBV had lower neurobehavioral scores in all areas, reaching significance in motor (5.6 vs. 5.8; adjusted p 0.049), social (6 vs. 6.4; adjusted p 0.006) and attention (5.3 vs. 5.9; adjusted p 0.032). The averaged score was also significantly lower for fetuses with increased FMBV (4.9 vs. 5.2; adjusted

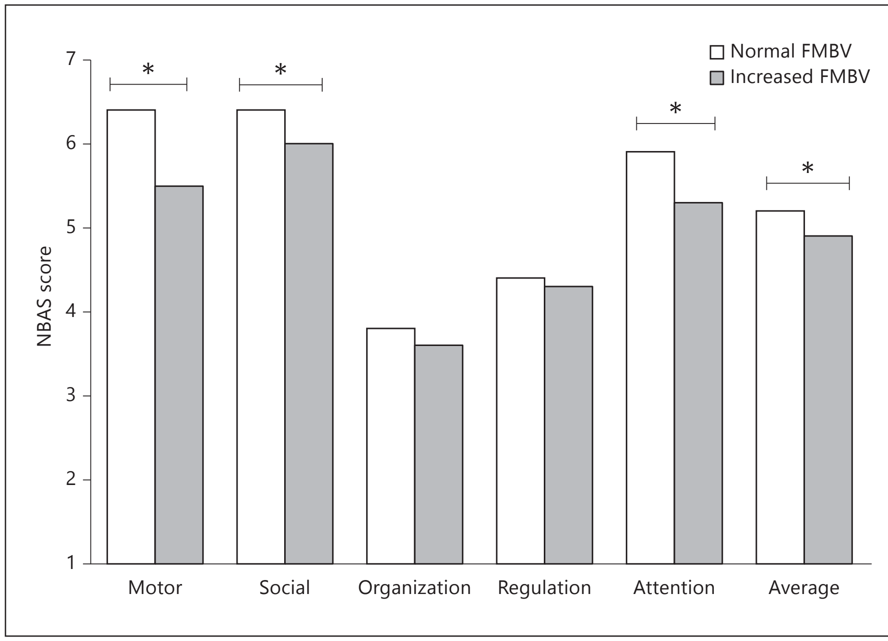

Fig. 2. Neurobehavioral score by NBAS area. * p = 0.049, 0.006, 0.032, 0.015 (motor, social, attention and averaged scores, respectively).

Table 3. Clusters of NBAS scores by study group (mean ± SD)

	Normal FMBV (n = 196)	Increased FMBV (n = 62)	p^+	p*	Normal CPR (n = 198)	Decreased CPR (n = 60)	p^+	p*
Motor	5.8±0.64	5.6±0.7	0.029	0.049	5.72±0.65	5.72±0.7	0.94	0.87
Social-interactive	6.4±1.24	6±1.44	0.031	0.006	6.34±1.28	6.28±1.39	0.78	0.46
Visual	6.1±1.4	5.35±1.6	0.009		5.97±1.46	5.99±1.44	0.89	
Auditory	7.03±1.17	6.15±1.42	0.078		6.69±1.23	6.62±1.28	0.7	
Organization of state	5.91±1.56	5.23±1.81	0.58	0.98	3.5±0.98	3.7±0.98	0.15	0.18
Regulation of state	4.09±1	4.02±0.92	0.99	0.44	4.42±1.6	4.27±1.54	0.54	0.73
Attention	5.94±1.7	5.3±1.7	0.012	0.032	5.82±1.7	5.6±1.84	0.49	0.87
Averaged score	5.2±0.79	4.9±0.94	0.03	0.015	5.11±0.88	5.15±0.82	0.78	0.89

$^+$ Student's t test. * Adjusted for smoking, maternal socioeconomic level, mode of delivery, gestational age at delivery, postnatal days at evaluation and gender by multivariate analysis (MANCOVA).

p 0.015). Regarding CPR, fetuses with decreased and normal values did not significantly differ in their neurobehavioral scores. Table 3 and figure 2 detail the neurobehavioral outcome by NBAS area.

Fetuses with increased FMBV had higher risk of abnormal (<10th centile) motor (OR 3.3; 95% CI 1.36–8.1), social (OR 2.9; 95 CI% 1.33–6.5) and attention (OR 2.5; 95% CI 1.1–5.8) scores. Figure 3 shows the adjusted OR of increased FMBV for abnormal neurobehavioral scores. Fetuses with lower CPR did not differ in their neurobehavioral scores from those with normal values.

Discussion

It is well known that IUGR secondary to placental insufficiency is associated with behavioral, sensitive and cognitive dysfunctions in premature babies [4, 22, 23]. More recently this association has also been found in term SGA infants: a recent systematic review [24] including 7,861 term SGA showed that standardized neurodevelopmental scores in SGA babies was 0.32 SD below those for normally grown controls. This finding suggests that even mild and latent degrees of placental insufficien-

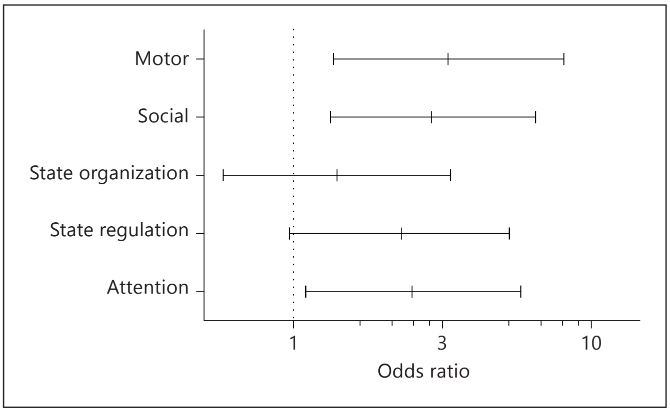

Fig. 3. Adjusted odds ratios of increased frontal perfusion for abnormal neurobehavioral scores.

cy, not yet reflected in the umbilical artery Doppler, also pose the fetus at risk for the consequences of chronic hypoxia. Our study extends the consequences of chronic hypoxia on neurobehavior to normally grown newborns and it adds to previous evidence suggesting that fetal weight alone is a perfectible marker of placental function [25].

Few studies have showed that signs of fetal brain-sparing were associated with infant problem neurobehavior in normally grown babies. A small series [4] including 73 preterm infants revealed that those with brain-sparing had poorer cognitive function at 5 years of age. The same cohort was evaluated at 11 years [26], when neurological outcome did not differ between those with and without brain-sparing. Roza et al. [27] followed up a cohort of 935 fetuses (mixing together small and normally grown fetuses) with Doppler evaluation at 28–32 weeks and found that whereas anterior CPR was associated (OR 1.22 per SD) with behavioral problems at 18 months, middle cerebral artery showed a weaker and non-significant association. This finding is consistent with the results of the current study, where anterior perfusion rather than middle CPR was associated with neurobehavioral problems. Our study adds to the current knowledge that this association is already present at birth, a time when the confounding effect of environmental factors, such as socioeconomic level or nutrition, are not major determinants of the child behavior [28]. Instead of applying only conventional spectral Doppler, in the present study we used frontal brain perfusion measured by FMBV to demonstrate fetal circulatory redistribution. Previous studies on term SGA have demonstrated that FMBV is more sensitive to hypoxia than conventional Doppler [29] and, accordingly, is more predictive of abnormal neurobehavior [8]. Our results suggest that this contention is also true in normally grown fetuses.

The data that have been provided by this study add to the body of evidence suggesting that increased brain perfusion is a deleterious mechanism. During the second half of gestation, profound changes in brain organization take place that involve critical neural connections and myelination of important neural tracts [30]. It is not known how the susceptibility of the brain changes as such maturation progresses, but it is plausible that even mild degrees of hypoxia can induce permanent epigenetic changes that are the result of the adaptation of the developing brain to a hypoxic and undernourished environment. There is structural [31, 32] and functional [23] evidence suggesting that the frontal brain is particularly susceptible to the hypoxic insult. One potential explanation is that the frontal areas are phylogenetically recently acquired, therefore maturation and myelinization processes of these areas occur late in fetal development, making these structures vulnerable during a long period [33].

From a clinical perspective, our results strengthen the idea that fetal weight alone is a reliable parameter to assess fetal growth. In obstetrical practice, SGA is normally defined as an estimated fetal weight below the 10th centile [34]. This definition is known to be inaccurate and to miss many instances of true restriction [35]. Since we do not know the 'ideal weight' of each fetus, there is no standard way of identifying when restriction is occurring. Customized birth weight standards represent an attempt to overcome this limitation, whereby growth is assessed against an individual growth potential according to gender and maternal characteristics [35]. However, despite using such a definition, our results suggest that a proportion of babies with normal growth still have placental insufficiency, underlining the importance not merely of conditions that severely constraint fetal growth but, rather, the entire range of factors that influence growth. In a large cohort [36] of healthy children it has consistently been shown that even within normal birth size range, there is a correlation between birth weight and intelligence at 7–9 years of age. Thus, in the search of a better predictive and personalized fetal medicine, a refined definition of growth restriction and placental insufficiency is required, which uses the weight but combines it with other markers. Further studies are needed to ascertain whether FMBV could improve the way IUGR is defined.

This study has several limitations. First, as any imaging method, FMBV is an indirect estimate of blood perfusion. However, the technique has shown an excellent correlation with gold standards in the estimation of true tissue perfusion in animal experiments [13]. The method has also shown good reproducibility in the assessment of fetal brain perfusion in different regions [37]. Second, it was beyond the objective of this study to describe the pathophysiological pathways leading to increase blood perfusion. Several mechanisms, including increased blood pressure and vascular resistance, may be involved. Third, the clinical application is also limited because current ultrasound equipment does not yet incorporate FMBV algorithms for the automatic calculation of tissue perfusion. We recognize that the time consumed in the offline image process in estimating FMBV is also a limitation (approx. 5 min). Finally, although NBAS is a gold standard to evaluate the neonate's capacity to respond to the environment and reflects brain maturation, it only assesses neurobehavior and not cognitive function [38]. It could be argued that neonatal assessment may not correlate with later cognitive and intellectual performance. However, several studies have demonstrated the correlation between neonatal neurobehavior and later intelligence and cognitive development in preterm and term infants. Remarkably, Feldman and Eidelman [22] studied the correlation of neurobehavioral and later cognitive function with the Bayley Scale of Infant Development in SGA premature neonates. They found that neonatal motor maturity correlated with the psychomotor development outcome at 2 years of age. Another study [39] in full-term healthy babies reported that levels of self-regulation were also correlated with the infants' levels of cognitive development and with sleeping disorders at 2 years of age. Finally, Canals et al. [40] found neonatal self-regulation behavior to be a good predictor of infant development and intelligence at 6 years.

In conclusion, this study demonstrates that 'normally grown babies' may experience increased frontal brain perfusion which is related with poorer neurobehavioral competences, suggesting the existence of placental insufficiency. Thus, FMBV as an indicator for brain-sparing can help identify a subgroup fetuses with chronic hypoxia, unable to be detected using EFW alone.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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