Fetal growth restriction

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Chapter 4

General movements after fetal growth restriction in relation to prenatal Doppler flow patterns

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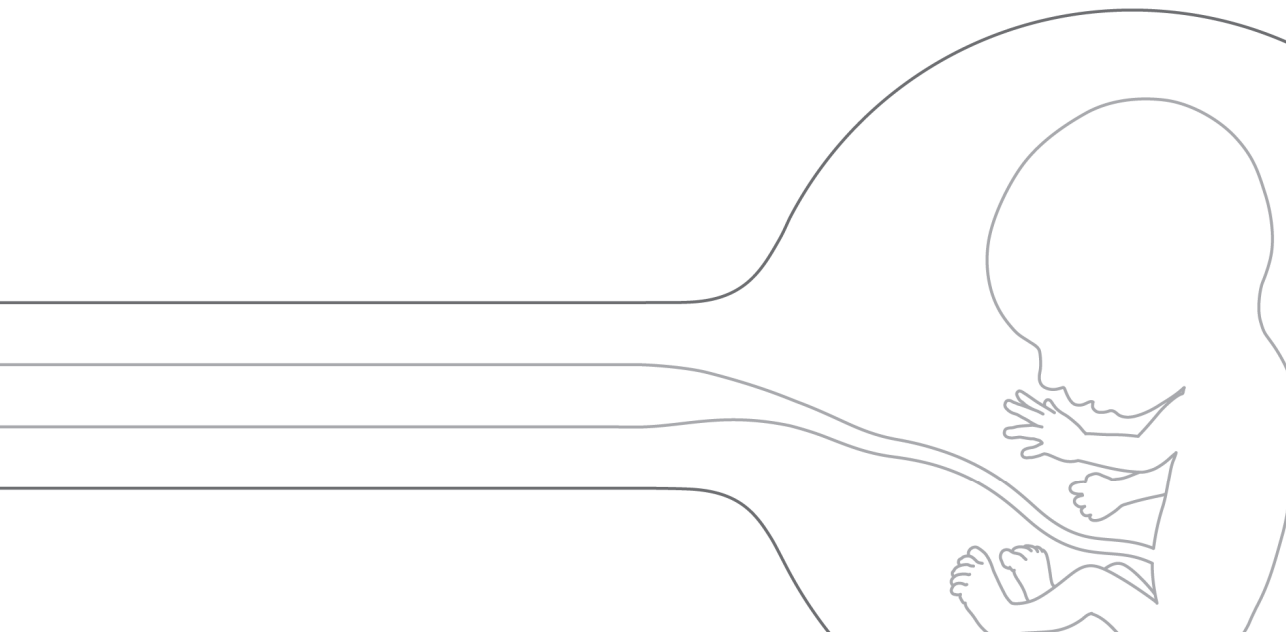

Abstract

Aim

To investigate whether in fetal growth restriction (FGR) Doppler PI measurements of the fetal circulation are associated with neonatal general movements (GMs).

Method

FGR diagnosis was based on abdominal circumference or estimated fetal weight <P10 or deflecting fetal growth. Fetal Doppler parameters of the umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV) were measured maximally 1 week prior to delivery. Cerebroplacental ratio (CPR) was calculated as MCA divided by UA PI. We assessed the quality of GMs on day 7 after birth, around the due date if cases were born preterm, and at three months post term. Additionally, we performed a detailed analysis of the motor repertoire by calculating a motor optimality score (MOS).

Results

Forty-eight FGR cases were included with a median GA of 35 (range 26-40) weeks. UA PI, MCA PI, and CPR correlated strongly (rho .374-.472, p<.01) with MOS on day 7 after birth, DV did not. Doppler PI measurements did not correlate with MOS at three months post term.

Conclusion

Fetal arterial Doppler measurements are associated with the quality of neonatal GMs one week after birth, but this association is no longer evident at three months post term age. Brain sparing in particular associated strongly with abnormal quality of GMs.

Introductory section

Fetal growth restriction (FGR) is one of the leading causes of perinatal and long-term adverse outcomes.(1) FGR occurs in both early and late stages of pregnancy, each with its own pathofysiological mechanism. During fetal life, Doppler pulsatility index (PI) measurements of arterial and venous vessels are used for fetal monitoring. Previous studies suggest that abnormal PI values of the umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV) are predictive of perinatal outcome including long-term neurodevelopment.(2-4) Specifically, absent or reversed end-diastolic flow (AREDF) of the UA is associated with long-term neurodevelopmental delay.(3) It is unknown, however, whether the entire range of Doppler measurements are associated with neurodevelopmental delay, and how abnormal PI of the UA, MCA, and DV affect neurologic development shortly after birth. Previous studies report a higher incidence of abnormal general movements (representative of neurological functioning) in growth restricted infants when compared to controls.(5,6) However, they did not compare these results with fetal Doppler measurements. Therefore, it remains unknown whether fetal Doppler measurements are associated with short-term neurological functioning of the newborn in FGR, and if so, which Doppler measurements.

A reliable method to determine neurological functioning, is Prechtl's method of assessing quality of general movements (GMs).(7,8) Chronologically, two types of GMs can be distinguished. Up to term age, GMs are normally characterized by variability, complexity, and fluency. At three months post term, fidgety GMs (FMs) emerge, defined as continuous small, circular movements of moderate speed in all directions. The quality of GMs and FMs are predictive of abnormal neurological development.(8) Therefore, abnormal GMs in FGR infants may be a reflection of possible brain damage.

To gain insight into the relationship between prenatal Doppler PI measurements and short term postnatal neurology in FGR, we aimed to determine associations between Doppler PI of the UA, MCA, and DV and the qualitative and quantitative assessment of GMs and FMs. Since preterm and term-born FGR infants might have different underlying pathofysiological mechanisms, we also aimed to study associations for both groups separately.

Methods

Participants

A prospective observational cohort study was performed from June 2012 to September 2014 at the Departments of Obstetrics and Fetal Medicine of University Medical Center Groningen (UMCG) in The Netherlands. Exclusion criteria were multiple pregnancy, structural and/or chromosomal abnormalities or evidence of fetal infection. All pregnancies were delivered at UMCG and, if indicated, neonates were admitted to the Neonatology ward of the same hospital. Data on obstetric, birth, and neonatal characteristics were collected from the two departments. Written informed parental consent was obtained in all cases. The study was approved by the hospital Medical Board and Medical Research Ethics Committee.

We defined FGR as a fetal abdominal circumference or estimated fetal weight (9) below the 10th centile, or deflecting fetal growth of at least 30 centiles with respect to previous measurements (reduced growth according to the fetus' expected growth potential). On average, prior to maternal admission, fetal Doppler parameters were measured serially once a week, and twice a week for the duration of admission. Care was taken to perform the last measurement as close to the day of delivery as possible and never at an interval of more than one week to delivery. Only the last measurement was used for analysis. Measurements included PI of UA, MCA, and DV. Left and right maternal uterine artery Dopplers were measured during the first visit, then mean uterine artery (UtA) PI was calculated. Two experienced operators performed all measurements. All the measurements were transformed to *z* scores (standard deviation from the gestational age mean) for further analysis.(10,11) In case of absent end diastolic flow in the UA, the PI was calculated by manually tracing the end diastolic velocity along the time axis. The cerebroplacental ratio (CPR) was calculated as MCA PI divided by UA PI.(12)

Recording of general movements

We video recorded each infant's general movements for 30 to 60 minutes on day 7 after birth. Preterm-born infants were again recorded around due date (40 weeks GA) with the same recording time. At three months post term, all infants were recorded for 10 minutes. Timing and duration of recording were as advised by Einspieler et al.(8) The infants were filmed naked or wearing only a diaper, lying in supine position, and being able to move their limbs and trunk freely. We placed the video camera high above the infant at the foot of the changing mat or playpen, or in case of preterm born or ill infants, the incubator. GMs during crying, hiccupping, or sucking on a dummy were excluded from analysis.

Analysis of general movements

Two of the authors (JCT and AFB) assessed the quality of GMs according to Prechtl's method, on the basis of visual Gestalt perception.(7) They did so blinded for the prenatal data. Both are certified by the GM Trust. Interobserver reliability was not determined in this study, but has previously been studied extensively and reported as good to excellent.(8) Normal GMs involve the infant's entire body, can last a few seconds to several minutes, and are characterized by a complex and variable sequence of arms, legs, neck, and trunk. GMs are scored as abnormal if they lack complexity, variability, and fluency. There are three types of abnormal GMs that apply to the preterm and term period: poor repertoire, chaotic, and cramped-synchronized GMs.(5,13) If GMs are absent or very short (<3 s), the infant was assessed as being hypokinetic.(14) Next we performed a detailed analysis by calculating a motor optimality score (MOS) using the GM Optimality List.(14) Eight different aspects, including GM quality, are distinguished. MOS ranges from 8 to 18 (low to high optimality).

At approximately the end of the second month post term, during the so-called major neural transformation, GMs acquire a fidgety character.(15) Normal fidgety movements (FMs) are circular movements of small amplitude, moderate speed, and variable acceleration of neck, trunk, and limbs in all directions.(16) FMs are scored as being abnormal when circular movements resembling FMs are present, but with exaggerated speed, amplitude or jerkiness. They are scored as absent (severely abnormal) if they are never observed during video recordings between 9 and 16 weeks post term. Next, we used the Motor Optimality List for Fidgety Movements to assess a MOS.(17) Five aspects, including FM quality, are distinguished. During this period, MOS ranges from 5 to 28 (low to high optimality).

Statistical analysis

We performed a sample size calculation. We expected Doppler PI of the UA to be abnormal in two third of the cases (ratio 2:1). Our main endpoint was MOS at 3 months post term age, range 8-18, standard deviation 3.1. We considered a difference of 4 MOS points relevant. Therefore, at a power of 0.8 and *P* value 0.05, 38 infants should be included in this study. However, due to a not normal distribution of the MOS, we add 10% to this number, and the minimum number of inclusion should be 42. Due to practicalities we followed 43 infants up until 3 months post term.

We used the Spearman rank order correlation test to determine correlations between Doppler parameters and MOS, and BW centiles and MOS. The analyses were repeated in the preterm FGR group (below 37 weeks GA) and in the term FGR group (≥37 weeks GA), and in a mild FGR group (BW >P5) and severe FGR group (BW ≤P5). Chi square test was used to evaluate categorised Doppler and GM variables, and when significant univariate and multiple logistic regression analyses were performed. A *P* value of <.05 was considered statistically significant.

Table 1. Patient characteristics of preterm and term groups

	Preterm	Term
Maternal demographics		
Patients	24	24
Antenatal steroids	21 (88%)	2 (8%)
Cesarean section	22 (92%)	8 (33%)
Preeclampsia	8 (33%)	0
HELLP syndrome	3 (13%)	0
(Stopped) smoking*	8 (33%)	13 (54%)
Maternal BMI	26 (23-30)	20 (19-24)
Caucasian mother	20 (83%)	20 (83%)
Caucasian father	20 (83%)	20 (83%)
Perinatal variables		
Gender (male)	13 (54%)	10 (42%)
GA at birth (weeks)	31 (28-32)	38 (37-39)
BW (grams)	1105 (843-1448)	2490 (2016-2647)
BW z score	-1.38 (-1.87 to -.99)	-1.51 (-1.80 to -1.13)
BW <10th centile	14 (60%)	18 (75%)
Head circumference (cm)	27.0 (24.0-28.5)	31.5 (31.0-32.5)
Apgar 1'	6 (3-8)	8 (7-9)
Apgar 5'	8 (6-9)	9 (8-10)
pH venous (n=17/19)	7.28 (7.23-7.33)	7.26 (7.23-7.31)
pH arterial (n=18/19)	7.24 (7.18-7.29)	7.21 (7.15-7.25)
Base excess (n=/20)	-4 (-6 to -2)	-6 (-7 to -4)
NICU admission	24 (100%)	3 (13%)
Days of admission	16 (6-27)	4 (3-6)
Mechanical ventilation	13 (54%)	2 (8%)
RDS	13 (54%)	0
BPD	4 (17%)	0
Sepsis	4 (17%)	0
NEC	2 (8%)	0
IVH	3 (13%)	0
Doppler assessment		
Abnormal Doppler		
UA (>95th centile or AREDF)	19 (79%)	10 (42%)
MCA (<5th centile)	11 (46%)	3 (13%)
CPR (<1)	14 (58%)	4 (17%)
DV (>95th centile)	12 (50%)	13 (54%)
UtA (>95th centile)	11 (46%)	2 (8%)

Median (IQR) or number (percentage). BMI body mass index, GA gestational age, BW birth weight, NICU neonatal intensive care unit, RDS respiratory distress syndrome, BPD bronchopulmonary dysplasia, NEC necrotizing enterocolitis, IVH intraventricular haemorrhage, UA umbilical artery, AREDF absent or reversed end diastolic flow, MCA middle cerebral artery, CPR cerebroplacental ratio, DV ductus venosus, UtA uterine artery.
* Percentage of patients that smoked during pregnancy or stopped smoking after the first trimester of pregnancy.

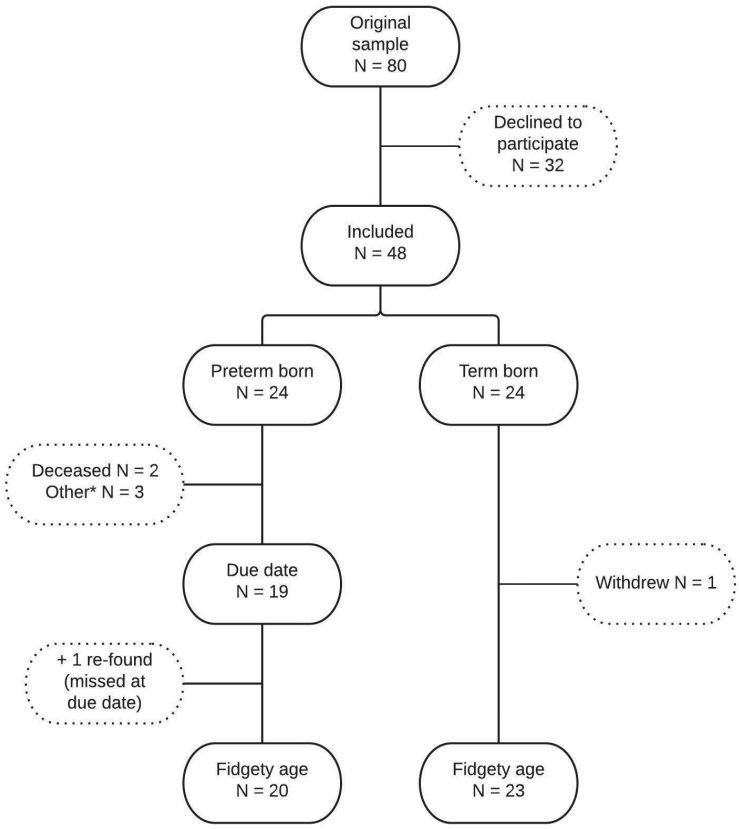

Figure 1. Study flow diagram
*Other: 1 withdrew, 1 bad quality of video, 1 video not carried out

Results

Patient characteristics

We included 48 FGR cases, of which 43 cases were followed-up until 3 months post term (Figure 1). Two cases died before they reached the age of 3 months post term, in two cases the parents withdrew from the study before reaching 3 months post term, and one case was excluded from analysis due to bad quality of the video recording. In the preterm group, the video recording of one case was not carried out at term age, due to logistic reasons. Background characteristics of the initial group (N=48) are presented in Table 1.

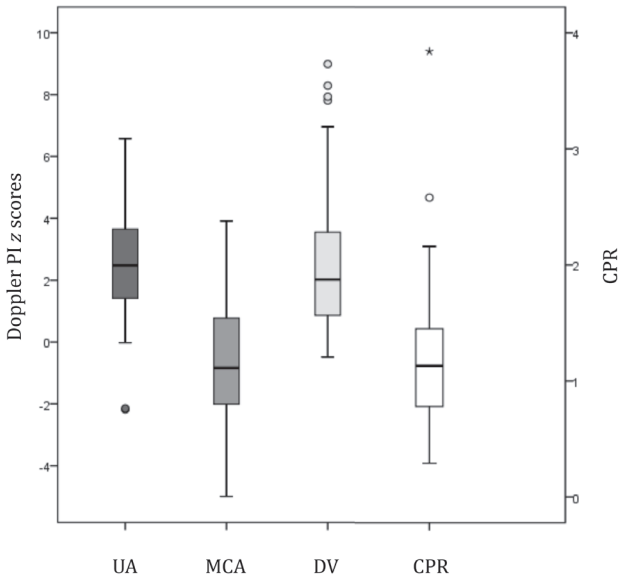

Figure 2. Doppler PI *z* scores of the UA, MCA, and DV and CPR

Doppler measurements

In Figure 2 we show the distribution of *z* scores of mean UtA, UA, MCA, and CPR. Abnormal Doppler PI values were found in 60% of cases for the UA (>95th centile), 30% abnormal for the MCA (<5th centile), 39% abnormal for the CPR (<1), 58% abnormal for the DV (>95th centile), and 28% abnormal for the mean maternal uterine artery (>95th centile). In nine out of 48 cases diastolic flow in the UA was absent and reversed in one case.

General movements

Quality of GMs on day 7 was normal in 22 cases (45%), poor repertoire in 24 cases (50%), cramped synchronized movement in one case (2%), and dyskinetic in one case (2%). At the assessment at term of the preterm group, 4 cases were normal (21%), 14 showed poor repertoire (74%), and one cramped synchronized movement (5%). Median (interquartile range, IQR) MOS on day 7 (N=48) was 13 (11-17), median MOS at the assessment of the preterm group at approximately term age (N=19) was 11 (10-13).

The quality of FMs was scored as absent FMs in one case (2%) and normal in all others. At three months post-term age, median fidgety MOS (N=43) was 25 (IQR 23-26).

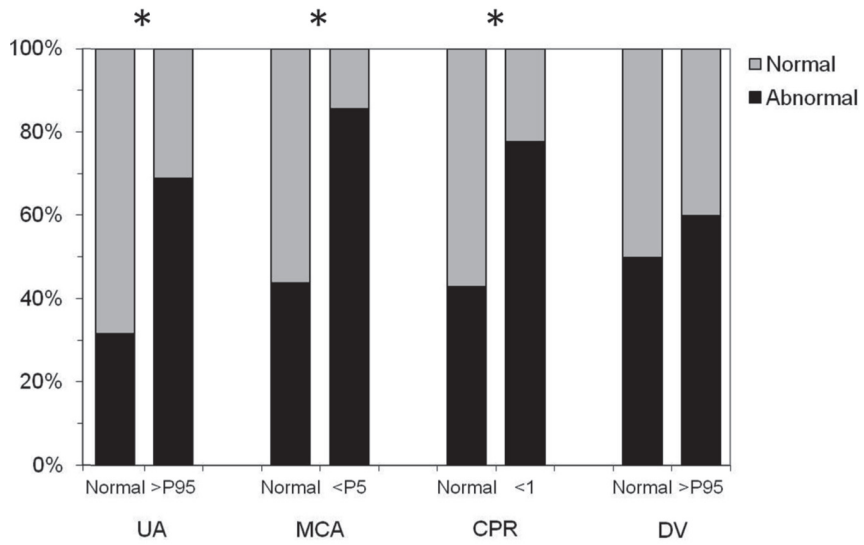

Figure 3. Categorised Doppler PI with categorised GMs day 7
*P<.05, black = abnormal GMs (poor repertoire, cramped synchronised, dyskinetic), grey = normal GMs

Categorization and correlation coefficients of Doppler PI measurements and GMs

In Figure 3 we present the distribution of normal and abnormal (i.e. poor repertoire, cramped-synchronized, hypokinetic) GMs per normal and abnormal Doppler measurements of each vessel. Groups of abnormal UA PI, MCA PI, and CPR had significantly more cases with abnormal GMs on day 7 (poor repertoire, cramped synchronized, or dyskinetic), with odds ratios of 4.82 (95% confidence interval [CI] 1.38 - 16.8, explained variance 17.1%) for UA PI; 7.71 (95% CI 1.48 - 40.2, explained variance 20.5%) for MCA PI; and 4.67 (95% CI 1.22 - 17.8, explained variance 15.6%) for CPR. Multiple logistic regression analysis, entering UA PI, MCA PI, and CPR in the model, revealed that MCA PI remained solely in the model, indicating that abnormal UA PI and CPR did not contribute to the prediction of abnormal GMs above MCA PI.

High correlation coefficients were found between Doppler PI of UA and MCA, and CPR and MOS of writhing GMs (Table 2). No significant correlation coefficients were found between DV PI and GMs. Furthermore, none of the Doppler measurements were correlated to FMs. Of note, we additionally calculated correlation coefficients on day 7 for preterm and term groups separately, which yielded high correlation coefficients in the term group between UA PI, MCA PI, and CPR and GMs but not in the preterm group.

When separated into mild (BW >P5) and severe FGR (BW ≤P5), we found high correlation coefficients between Doppler PI of UA and MCA, and CPR and MOS of writhing GMs in both groups (data not shown). BW centiles tended to correlate with MOS of writhing GMs, but not with fidgety movements 3 months post term (Table 2).

Table 2. Correlation coefficients (rho values) between Doppler PI and MOS of writhing and fidgety movements

	Day 7	Day 7	Day 7	40 weeks GA	3 months post term
Group	Preterm + Term	Preterm	Term	Preterm only	Preterm + Term
N	48	24	24	19	43
UA PI	-.374 *P*=.009	-.258 *P*=.223	-.348 *P*=.096	-.058 *P*=.815	-.134 *P*=.390
MCA PI	.472 *P*=.001	.140 *P*=.523	.509 *P*=.013	-.147 *P*=.561	.082 *P*=.611
CPR	.431 *P*=.003	.218 *P*=.318	.485 *P*=.019	.161 *P*=.525	.158 *P*=.325
DV PI	-.137 *P*=.380	-.067 *P*=.769	-.299 *P*=.188	-.234 *P*=.366	-.176 *P*=.289
BW centile	.279 *P*=.055	.396 *P*=.056	.196 *P*=.358	.287 *P*=.233	.056 *P*=.721

Discussion

In this study we demonstrate that fetal Doppler measurements in FGR are associated with the quality of GMs on day 7 after birth. This pertains to the UA, MCA, and CPR. In addition, when categorized into normal versus abnormal Doppler groups, infants with abnormal UA, MCA, and CPR more often have an abnormal quality of GMs. These associations, however, have disappeared by 3 months post term. DV Doppler measurements were not associated with the quality of GMs, and thus with short-term neurological outcome.

Previous studies report UA PI to be predictive of neurodevelopmental outcome at the age of 2 to 12 years.(3,18) However, this only applies to AREDF in the UA. We here demonstrate that considerably more infants with increased resistance to flow in the UA (PI >95th centile) have abnormal GMs on day 7 after birth, i.e. even before AREDF. Our findings suggest that abnormal UA PI is also associated with neurological outcome, even though AREDF might reflect a more seriously compromised placental function, which is a better predictor for long-term neurodevelopmental outcome. In the present study, particularly low MCA PI is strongly associated with abnormal GMs on day 7, although not with FMs at 3 months. This is in agreement with the literature. Figueras et al. found lower scores on behavior at term in a group with abnormal MCA, and Baschat et al. found no association between brain sparing and neurodevelopment at 2 years.(3,4) A recent systematic review reinforces the association between abnormal cerebral perfusion and altered neurological and cognitive functions.(19)

None of the fetal Doppler measurements were associated with GMs at 3 months post term. Since we found abnormal GMs at term in half of our study group, GMs seem to normalize between term and 3 months post term. Similarly, Zuk et al. found

that out of 32 growth restricted infants, 16 had abnormal GMs at term and 7 of them normalized at 9-11 weeks post term (one infant dropped out).(6) Bos et al. also found that the majority of growth restricted infants with abnormal GMs at preterm and term period had normalized at approximately 3 months post term.(5) In Zuk's study, all of the 7 infants with normalized GMs had a normal neurodevelopmental outcome at 2 years. However, abnormal GMs in preterm infants recorded prior to 8 weeks post term, despite normalization later on, are associated with a lower IQ at school age.(20) Apparently, in spite of normalization, abnormal GMs at term in FGR infants may be a reflection of possible brain damage. More specifically, abnormal GMs around term are associated with cerebral white matter pathology.(21) We speculate that FGR infants with normalization of GMs from term to 3 months post term are still at risk of later cognitive delay and subtle brain dysfunction.

Associations between UA, MCA, and CPR and GMs at day 7 seem to be mainly due to the term FGR group. We performed extra analyses for preterm and term FGR groups separately, and found that in the term group, associations were even stronger than in the entire group, whereas in the preterm group associations were weaker and lost significance. One possible explanation is a higher incidence of comorbidity in the preterm group.(22) Serious complications in the first days after birth may induce abnormal GMs, and obscure the original association between Doppler measurements and GMs. Conversely, infants born at term after FGR are less likely to have comorbidity, since their FGR was mild enough to allow a full-term pregnancy. In these cases, GMs purely reflect the neonatal neurological status.

In previous studies DV was predictive of poor neonatal outcome,(2,23) postnatal brain function seems to be positively influenced by a clinical management of FGR based on DV changes.(24) GMs on day 7 to 3 months post term were not associated with DV in our study. Therefore, we believe that abnormality in DV flow, a late event only present in early and severe FGR, may have a more complex relationship with neurological outcome, than, for instance, a long lasting abnormal cerebral perfusion.(19) An unexpected and inexplicable finding was that the proportion of cases with abnormal DV PI in the term group was higher than the proportion of abnormal UA PI.

We recognize several strengths and limitations in this study. A strength is that we performed an extensive postnatal neurological follow-up, until 3 months post term age. A limitation may be the heterogeneity of the group (early and late FGR, variable severity of the condition), preventing statistically significant associations. Because of the inclusion criteria (abdominal circumference below the 10th centile, or deflecting growth pattern), the study group consists mainly of mild FGR, as suggested by the fact that only one case had absent FMs at 3 months post term age.

Our findings might have clinical implications. Despite the loss of association with Doppler measurements in the fidgety period, normalization of GMs from term to

3 months post term might still be a risk factor for subtle brain dysfunction. Medical caregivers, such as neonatologists, general paediatricians, and nurses should be aware of the consequences of fetal brain sparing in infants born after FGR.

Conclusion

This is the first report on the association between fetal Doppler parameters and GMs in FGR. UA, MCA, and CPR are strongly associated with GMs on day 7, but the association is no longer evident at 3 months post term age. Brain sparing in particular associated strongly with abnormal quality of GMs.

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Part III

Follow-up at school age after FGR