Ultrasound Obstet Gynecol 2011; **37**: 501–514
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.9008

Neurodevelopment following fetal growth restriction and its relationship with antepartum parameters of placental dysfunction

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KEYWORDS: biophysical profile; Doppler ultrasound; fetal growth restriction; neurodevelopment

ABSTRACT

Placental dysfunction leading to fetal growth restriction (FGR) is an important risk factor for neurodevelopmental delay. Recent observations clarify that FGR evolves prenatally from a preclinical phase of abnormal nutrient and endocrine milieu to a clinical phase that differs in characteristics in preterm and term pregnancies. Relating childhood neurodevelopment to these prenatal characteristics offers potential advantages in identifying mechanisms and timing of critical insults. Based on available studies, lagging head circumference, overall degree of FGR, gestational age, and umbilical artery (UA), aortic and cerebral Doppler parameters are the independent prenatal determinants of infant and childhood neurodevelopment. While head circumference is important independent of gestational age, overall growth delay has the greatest impact in early onset FGR. Gestational age has an overriding negative effect on neurodevelopment until 32–34 weeks' gestation. Accordingly, the importance of Doppler status is demonstrated from 27 weeks onward and is greatest when there is reversed end-diastolic velocity in the UA or aorta. While these findings predominate in early-onset FGR, cerebral vascular impedance changes become important in late onset FGR. Abnormal motor and neurological delay occur in preterm FGR, while cognitive effects and abnormalities that can be related to specific brain areas increase in frequency as gestation advances, suggesting different pathophysiology and evolving vulnerability of the fetal brain. Observational and management studies do not suggest that fetal deterioration has an independent impact on neurodevelopment in early-onset FGR. In late-onset FGR further research needs to establish benefits of perinatal intervention, as the pattern of vulnerability and effects of fetal deterioration appear to differ in the third trimester. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

The management of pregnancies complicated by fetal growth restriction (FGR) continues to challenge obstetricians because our understanding about many aspects of this disease is still evolving[1]. Two different patterns of clinical deterioration, determined primarily by the gestational age of disease onset and the placental blood flow resistance, have recently been characterized more clearly[2–5]. The importance of gestational age at delivery as a determinant of many critical postpartum outcomes is becoming more apparent[6–8]. Accordingly, the balance of fetal versus post-delivery risks and the optimal timing of delivery has been a key issue in FGR management for years[9,10]. A central hypothesis driving this management focus is based on the observation that fetal acidemia rather than hypoxemia carries the greater risk for irreversible developmental delay[11,12]. Because the likelihood of acidemia increases with clinical signs of fetal deterioration, two randomized management trials have been designed around the hypothesis that timing of delivery and degree of compromise at birth can modify infant neurodevelopment. The Growth Restriction Intervention Trial (GRIT) randomized to immediate versus delayed delivery when obstetricians were unsure about management. The Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) randomized delivery timing based on specific test thresholds (computerized cardiotocography (CTG) versus ductus venosus (DV) Doppler abnormalities)[13]. While randomization has only just been completed for TRUFFLE, short- and long-term outcomes have been reported for GRIT. Two-year outcomes showed increased prematurity-related developmental morbidity with immediate delivery before 32 weeks' gestation[14]. However, at 6–13 years, childhood neurodevelopment was identical in both management arms of the trial[15]. While this may suggest that timing of delivery is less relevant than was

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Accepted: 21 March 2011

thought, it also raises the question as to whether neurodevelopment is determined mainly before delivery decisions become relevant[16]. Systematic examination of this question based on available studies is difficult because of heterogeneity of endpoints and study designs. The aim of this review is to provide a detailed summary of studies that evaluate this relationship, with emphasis on the potential timing and mechanisms of the neurodevelopmental impact of placental dysfunction.

CLINICAL EVOLUTION OF PLACENTAL DYSFUNCTION AND POTENTIAL DEVELOPMENTAL CONSEQUENCES

The proportion of essential substrates that are metabolized aerobically in the liver and their ability to drive the endocrine growth axis of the fetus is influenced by the degree of DV shunting[17–20]. In the preclinical phase of FGR, decreased umbilical venous volume flow can result in venous redistribution of blood flow towards the fetal heart, potentially affecting substrate availability in the liver and the endocrine and nutritional milieu of all downstream organs[21–23]. With decreased glycogen storage in the liver, the growth rate of the abdominal circumference begins to slow down, resulting in fetal asymmetry[24]. With more advanced placental dysfunction, increased villous vascular resistance produces proportional elevation in the umbilical artery (UA) Doppler indices, while falling oxygen levels may result in decreasing middle cerebral artery (MCA) Doppler indices[25–27]. Before Doppler indices in these vessels exceed their individual abnormal thresholds, the cerebroplacental Doppler ratio (CPR = MCA/UA Doppler index) decreases[28,29]. A rise in placental blood flow resistance increases the right ventricular afterload, while a fall in cerebral blood flow resistance decreases the left ventricular afterload. At the level of the ventricles, this results in a relative increase of left ventricular output. The amount of this central 'redistribution' is greater when UA end-diastolic velocity is absent (UA-AEDV), producing a measurable relative increase in left ventricular output[30]. In addition, the net direction of aortic isthmus blood flow is determined passively by this relationship of right- and left-sided afterload and the output of each ventricle. With increasing central redistribution, partly depleted blood from the descending aorta reverses back towards the cerebral circulation through the aortic isthmus[31]. When nutritional deficiency is sufficiently severe, or has persisted for a sufficiently long period, the growth rate of all fetal measurements slows down and the sonographically estimated fetal weight eventually drops below the 10th percentile[1,24,29] (Figure 1).

Once the clinical diagnosis of FGR has been made, the progression differs in preterm and term pregnancies. In early-onset FGR before 34 weeks, late cardiovascular

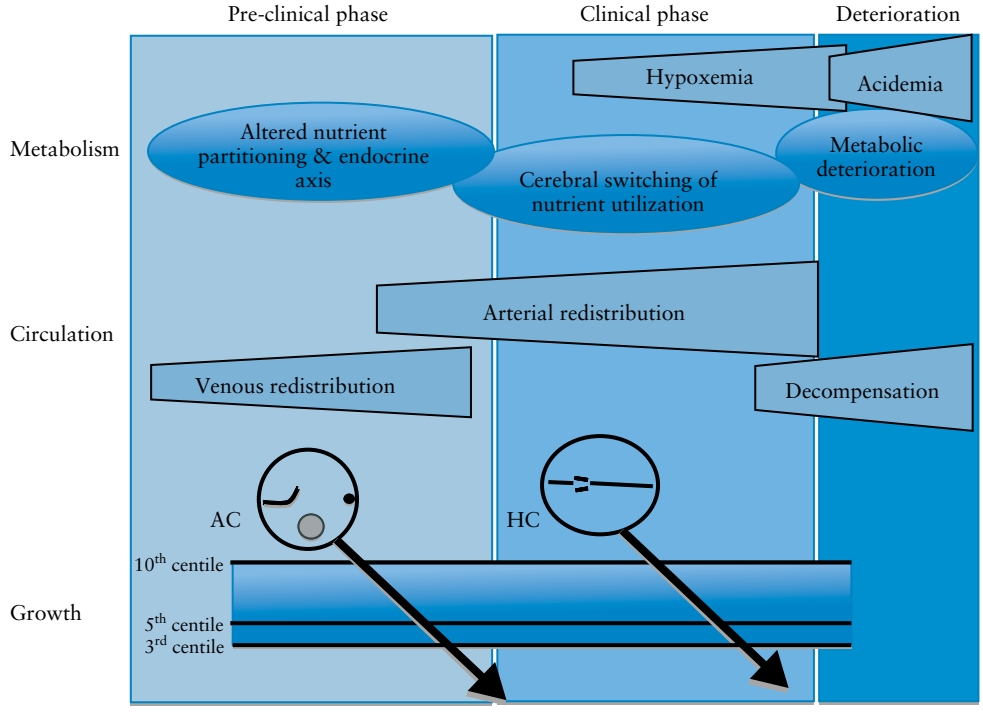

Figure 1 The phases of placental dysfunction can be subdivided broadly into preclinical phase, clinical phase and deterioration. During the preclinical phase, reduction of blood flow volume and blood nutritional content in the umbilical venous blood triggers venous redistribution. The diversion of blood away from the fetal liver and decreased glycogen deposition are responsible for slowing of abdominal circumference (AC) growth. At the same time, many downstream organs are exposed to an altered nutritional and endocrine milieu. Detection of growth delay, often associated with arterial Doppler findings, defines the clinical phase of growth delay. With progressive nutrient deficiency, the brain switches its major fuel sources to ketone bodies and lactate and head circumference (HC) growth may slow as well. When placental insufficiency limits the beneficial effects that can be achieved through arterial redistribution, chronic hypoxemia can progress to acidemia. This is associated with circulatory, behavioral and metabolic signs of deterioration, which vary between early- and late-onset fetal growth restriction.

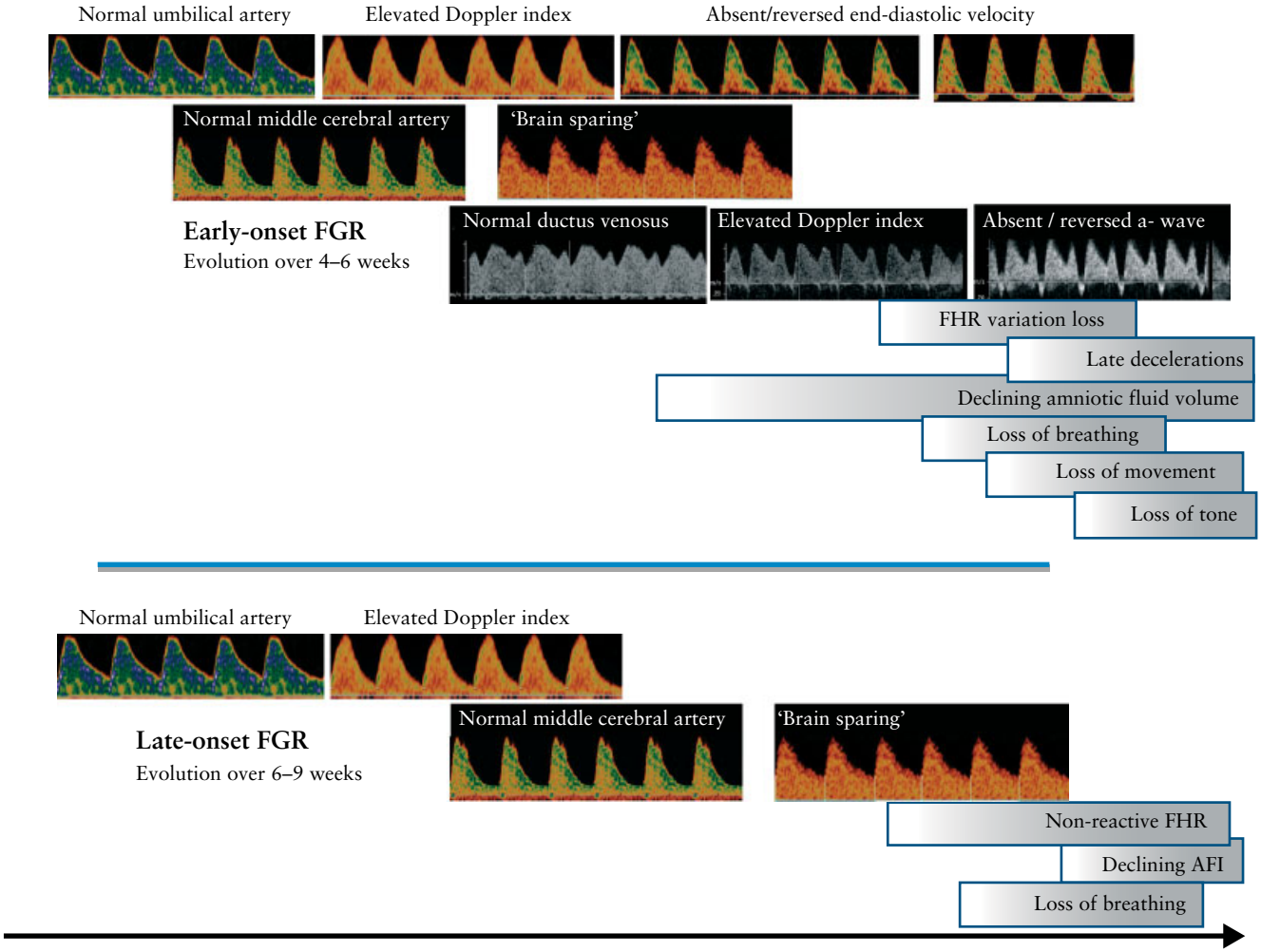

Figure 2 The pattern of clinical progression in fetal growth restriction (FGR) is determined by the gestational age at onset and the blood flow resistance in the umbilical circulation. Early-onset FGR presenting prior to 34 weeks' gestation is associated with escalating blood flow resistance in the umbilical artery, accompanied by brain sparing, and followed by deterioration of venous Doppler parameters and the biophysical profile score. Progression occurs over 4 to 6 weeks and is determined by how quickly umbilical artery end-diastolic velocity becomes absent or reversed. In contrast, late-onset FGR is associated with mildly elevated, or even normal, umbilical artery Doppler parameters and isolated brain sparing. The deterioration of biophysical parameters is equally subtle and therefore often hard to detect. AFI, amniotic fluid index; FHR, fetal heart rate.

manifestations of placental dysfunction become more likely when the UA end-diastolic velocity is reversed (UA-REDV)[32]. The typical pattern of deterioration progresses from escalating abnormalities in UA and venous Doppler parameters to abnormal biophysical parameters[2,4,7,32–35]. In this setting, the metabolic status and the diminishing supply of glucose forces the brain and heart to metabolize lactate and ketones as their primary energy sources[36,37]. With increasing severity of placental dysfunction, transfer of these important nutrients also becomes impaired and their deficiency has been linked independently to a range of neurodevelopmental disorders[38,39]. The rate of deterioration of UA Doppler parameters determines the overall speed of deterioration in early-onset FGR, often necessitating preterm delivery[4,7]. Accordingly, fetuses are forced to make critical adjustments in the cerebral metabolism of essential nutrients prior to delivery.

In contrast, in late-onset FGR presenting after 34 weeks, cardiovascular abnormalities do not extend beyond the cerebral circulation. As placental vascular dysfunction is less severe, a decreased CPR, with either normal or only minimally elevated UA Doppler indices, may be observed[2,4,5,40–42]. This is followed by intracerebral redistribution of blood flow towards the basal ganglia, at the expense of the frontal lobe[43,44], and a decreased MCA Doppler index that may occur as an isolated finding without a preceding increase in the UA Doppler index. Although term FGR does not present with the same degree of clinical deterioration as does early-onset disease, abnormal brain microstructure and metabolism have been documented independent of the degree of Doppler abnormalities[45] (Figure 2).

Thus, the preclinical phase of FGR is characterized by alterations in nutrient partitioning. This is followed by a clinical phase that potentially leads to deprivation of specific nutrients and modification of nutrient utilization. Clinical deterioration is associated with acid–base abnormalities and significant changes of vascular dynamics that

are determined by the relationship between gestational age at disease onset and the degree of abnormality in the umbilical circulation.

EVIDENCE OF FETAL NEURODEVELOPMENTAL DELAY IN PLACENTAL DYSFUNCTION

Examination of fetal behavior is potentially the most direct method with which to study the effects of placental dysfunction on neurodevelopment prior to delivery. The recognized sequence of fetal developmental milestones coincides with accelerating synapse formation and reflects the increasing sophistication of central regulation of physiological and behavioral variables[46–48]. Diurnal variation of fetal movement and heart-rate patterns, with increased activity in the second half of the day, appears from 20–22 weeks onwards[49]. Coupling of physiological inputs (e.g. linking of fetal breathing frequency to maternal glucose levels) and periodic rest–activity cycles become evident from 26–28 weeks[50,51]. Fetal heart-rate reactivity in response to movement, fully established by 32 weeks' gestation, allows correlation of heart-rate patterns to behavioral states. Fetal behavioral states 1F–4F, which correspond to their neonatal counterparts, are established between 32 and 36 weeks' gestation[52,53]. Integration of behavioral and cardiovascular control enables the fetus to modulate vascular impedance between behavioral states. For example, during state 2F, changes in cerebral and thoracic aortic blood flow impedance and central cardiac output distribution are consistent with preferential redistribution of blood flow to the brain[54–58].

The effect of placental dysfunction on fetal behavior has been studied by assessing behavioral maturation in the clinical phase and by relating fetal deterioration to the biophysical profile score (BPS). Prior to the establishment of behavioral states, the percentage of coincidence of fetal heart rate and movement variables can be used as an index of development[50]. In FGR, the percentage of coincidence is lower and state transitions take longer compared to appropriate-for-gestational-age (AGA) controls[59–61]. Delayed central integration of activity and heart-rate control is responsible for elevated baseline heart rate, lower short- and long-term variation and delayed development of heart-rate reactivity in FGR[62–65]. Even after behavioral states are established, movement quality, coincidence, coupling and state transitions may remain abnormal[66–69]. Moreover, disorganization of state transitions increases with fetal deterioration, suggesting that progressive nutritional deprivation may potentiate cortical dysfunction[70]. The developmental delays are more marked in fetuses with increased placental blood flow resistance and their association with abnormal biochemical markers of brain development points towards decreased myelination and neurotransmitter depletion as potential causes[71–74]. Yet, despite these developmental delays, intrafetal consistency in behavior and overall responsiveness to hypoxemia is maintained[75,76]: in FGR the fetus responds to worsening hypoxemia with declining global fetal activity and to acidemia with an abnormal BPS[77,78]. However, the parameters and thresholds that define an abnormal BPS are designed to detect fetal deterioration and are therefore too crude to study neurodevelopment. Accordingly, the BPS becomes abnormal late in the cascade of fetal deterioration and therefore serves more as a surveillance and management tool rather than a neurodevelopmental test[1].

Although a relationship between placental dysfunction and delayed achievement of fetal developmental milestones is recognized, there is limited information regarding how such delay affects long-term neurodevelopment. Among the individual components of fetal behavior, abnormal movement quality has a stronger relationship with neurodevelopment than does the quantity of gross fetal movement[79]. Abnormal quality of general movement, classified as poor repertoire, cramped-synchronized and chaotic, is more readily recognized postnatally than it is in the fetus[80]. Poor-quality movements are observed in FGR and their persistence after birth correlates with abnormal motor outcome at 2 years of age[81–83].

In summary, there is evidence that placental dysfunction is associated with delayed achievement of behavioral state organization prior to deterioration of fetal status. A recent study documented suboptimal scores for social-interactive, attention capacity, state organization and motor skills among growth-restricted neonates that had abnormal prenatal MCA Doppler studies[84]. This finding suggests that the prenatal delay in neurodevelopment can have measurable neonatal behavioral impact. However, because the fetal behavioral states are established late in pregnancy and their investigation is labor-intensive, there is limited information on the relationship between delayed fetal neurodevelopment and long-term outcome. The fetal BPS can be performed from viability onwards and, while there are no studies specific to FGR, application of the BPS management algorithm is associated with a significant decrease in the cerebral palsy rate in tested pregnancies[85,86].

FETAL GROWTH CHARACTERISTICS

With the recognition that birth weight needs to be expressed by percentiles rather than absolute values it became possible to diagnose growth deficiency independent of gestational age. Accordingly, it was recognized as early as the 1970s that placental dysfunction and subsequent growth delay had neurodevelopmental impact apparently independent of gestational age[87]. Applying the concept of percentiles to sonographically estimated fetal weight allowed a more refined examination of the relationship between prenatal growth dynamics and neurodevelopment.

Harvey *et al.*[88] were among the first to recognize that slowing of fetal head growth with early-onset growth delay before 26 weeks' gestation had a stronger impact on cognitive and motor development than did the decrease in overall growth percentile. The impact

of delayed abdominal circumference growth, especially if this occurs in the third trimester, is more difficult to demonstrate. In a study by Roth *et al.*[89], slower abdominal circumference growth was used to distinguish FGR from small-for-gestational age (SGA), and neonates that were defined prenatally by this criterion had higher rates of obstetric complications and limb hypotonia at birth. At age 1 year, significant motor disability (hemiplegia or spastic diplegia) was present in 6% of small infants, and mild motor disability in approximately 30%, irrespective of growth pattern or perinatal factors. Despite similar cognitive scores at age 1, over 50% of these infants subsequently required additional educational support when re-evaluated at age 8 years[90]. Evaluation of body symmetry either by head circumference/abdominal circumference ratio or by cephalization index (head circumference/body weight) provides another estimate of growth deficiency, with an added emphasis on head growth. An abnormal cephalization index, especially in later gestation, is associated with a greater likelihood of cerebral palsy and severe psychomotor retardation[91]. Studies with larger sample sizes allow detection of the impact of subtle growth abnormality, and have demonstrated that a 1 SD deviation in weight or symmetry parameters increases the risk of suboptimal development by 11–13%[92].

In addition to the degree and pattern of fetal growth delay, gestational age at delivery is an important determinant of the type and frequency of adverse neurodevelopmental outcome. Sung *et al.*[93] matched SGA infants with two AGA control groups; while significant developmental impact could be demonstrated for SGA infants compared with gestational age-matched controls, those AGA infants delivered at earlier gestational ages had comparable developmental outcomes secondary to a higher neonatal complication rate. In case–control studies of near-term pregnancies, the impact of growth delay becomes less apparent. A study by Gortner *et al.*[94] compared SGA and AGA infants that were delivered at a median gestational age of 34 weeks. The SGA group was associated with a higher prevalence of maternal hypertensive disorders and oligohydramnios, potentially leading to delivery prior to fetal deterioration. At 2 years of age, the growth-restricted children continued to have smaller head circumference and body weight, but the Griffiths developmental quotient (DQ) was comparable with the AGA controls (82.2 vs. 81.9). While a trend towards lower cognitive scores in SGA infants did not reach statistical significance, motor, social and cognitive subscales correlated highly with birth weight and gestational age at delivery.

In summary, these observations suggest that early-onset growth delay, severity of FGR and prematurity significantly increase the risk for neurological sequelae and motor and cognitive delay. Slowing of head growth in particular is associated with decrease in perceptional performance, motor ability, cognition, concentration ability and defects in short-term memory, with subsequently poorer school achievement[95]. Studies with a higher proportion of patients delivered for maternal deterioration fail to demonstrate consistent differences compared with AGA controls (Table S1). One significant confounder of studies that consider growth parameters in isolation is that the degree of fetal compromise is not accounted for.

UMBILICAL ARTERY DOPPLER STUDIES

The UA waveform defines key aspects of placental dysfunction in FGR: the dimensions of the villous vascular tree, the blood flow resistance in the fetal compartment of the placenta and the relative risk for nutritional and metabolic deficiency[1,4]. The developmental impact of UA end-diastolic velocities has been investigated in case–control studies and by stratification of FGR cohorts according to the degree of UA Doppler abnormality (Table S2).

Early-onset fetal growth restriction

Three studies evaluated growth-restricted infants delivered prior to 29 weeks' gestation. Vossbek *et al.*[96], who studied FGR cases with absent/reversed end-diastolic velocity (AREDV) and AGA controls delivered at 27 weeks, found significantly lower Bayley motor development index (MDI) scores at 2 years of age (77 vs. 98) and lower Kaufman mental processing composite scores after 2.5 years (75 vs. 87). Similarly, the rate of mental retardation was significantly higher following FGR (44% vs. 25%). A recent study confirmed lower verbal and full-scale intelligence quotients (IQs) in FGR survivors with UA-AREDV delivered before 29 weeks' gestation[97]. This study also suggested that boys may be at greater risk than girls for abnormal development. In contrast, Brodszki *et al.*[98] found similar rates of cerebral palsy in FGR pregnancies with UA-AREDV that were delivered prior to fetal deterioration compared with AGA controls (14% and 17%, respectively). Padilla *et al.*[99] compared 1-year Bayley scores and neurological findings between growth-restricted and gestational age-matched AGA infants that were delivered at a median of 30 weeks' gestation. Although cases and controls had no statistical differences in testing, growth-restricted infants had smaller head circumferences and trends for lower psychomotor development (PDI) scores. In FGR children, gestational age and birth weight correlated with the MDI, while head circumference and cephalization index correlated with the PDI.

Shand *et al.*[100] found that 28% of growth-restricted infants with AEDV or REDV that were delivered before 32 weeks' gestation died or had moderate to severe disability at age 2 years. However, after correcting for gestational age at birth, there was no relationship with UA Doppler abnormality and neurodevelopment, suggesting that the increased need for preterm delivery in the setting of UA-AREDV was the determining factor. At 6 years of age, UA-AREDV survivors delivered by 32 weeks had an increased incidence of major and

minor neurological sequelae compared with controls with positive end-diastolic velocity (major 21% vs. 9%, minor 35% vs. 27%), while IQs were similar[101]. In children delivered later (median, 34 weeks' gestation) findings were different. At 6 years of age, ARED flow survivors scored lower in 20–22% of fine motor and neuropediatric tests and had significantly lower scores in all domains of the Kaufman assessment battery for children[102]. Kaufman scores correlated with birth weight, and REDV survivors tended to have lower scores than did those with AEDV. Schreuder *et al.*[103] examined a larger cohort of adolescents and found the most significant differences for children that had UA-REDV prenatally. Cognitive delay was observed in 14% of the study group and REDV survivors had lower neurological test scores, had 56% risk for visual impairment and scored higher in tests indicating hyperactivity problems. Even after correction for gestational age, poorer cognitive and motor performance remained related to REDV.

Late-onset fetal growth restriction

In 282 SGA infants delivered at a median gestational age of 36 weeks, McCowan *et al.*[104] related the 2-year cognitive development to several important perinatal factors, including the UA Doppler status. Delivery for maternal hypertensive disorders was associated with a lower rate of abnormal mental development index scores. A low behavior rating index was associated with smaller head size, lower ponderal index and higher base deficit at birth, while abnormalities in the PDI were related to the length of stay in a neonatal intensive care unit and lack of breast feeding at 3 months. In this study, a subgroup of 15% of SGA infants with normal UA Doppler, that would nowadays be defined as late-onset FGR infants, had suboptimal neurodevelopment. More recently, Figueras *et al.*[105] confirmed that infants with third-trimester growth delay with normal UA Doppler score significantly lower in the attention, habituation, motor, social-interactive and state-regulation domains of the neonatal behavioral assessment score. Cesarean section, gestational age at delivery and low socioeconomic level were identified as independent cofactors affecting habituation and social-interactive scores. Longer-term follow-up of a similar group of patients at 2 years using the ages and stages questionnaire (ASQ) demonstrated significantly lower scores in the problem solving and social domains compared to AGA controls[106]. These domains are related to frontal lobe function and several observations support the concept that this area of the brain is especially vulnerable to fetal nutrient deficiency in the third trimester[45,107–109]. However, it needs to be noted that, in one of these studies[106], maternal smoking, which has the potential to affect similar areas of the maturing brain, was an important confounder[110,111].

In summary, it appears that the associations between UA Doppler and neurodevelopment manifest differently across gestational ages and patterns of fetal growth delay. In early-onset FGR, the risk of abnormal neurodevelopment increases as end-diastolic velocity decreases. Due to the high rate of prematurity-related morbidity, independent impacts on motor development are more difficult to demonstrate at very early gestational ages. Between 28 and 34 weeks' gestation, the neurological and cognitive impact of increased UA blood flow resistance emerges more clearly as a factor independent of lagging head growth, severity of growth delay or condition at birth. In FGR presenting near term, abnormal UA Doppler is a less prominent feature and developmental abnormalities emerge in other domains that appear to be related to specific brain areas and higher brain functions.

CEREBRAL ARTERY DOPPLER STUDIES

Cerebral artery Doppler in FGR is important because it corroborates significant placental dysfunction. Reduction of the Doppler index can be observed by itself (brain sparing), in association with an elevated UA Doppler index, by a reduction of the CPR or by an increase of its inverse, the umbilical–cerebral Doppler ratio (UCR). When any of these changes is observed in the context of established FGR, a degree of clinical progression is implied.

Early-onset fetal growth restriction

Scherjon *et al.*[112] followed a group of children delivered between 25 and 33 weeks' gestation over an 11-year period and recorded their outcomes in a series of studies[113–115]. Patients were recruited if they had prenatal ultrasound biometry as well as UA and cerebral artery Doppler that allowed calculation of the UCR. Because FGR was not a prenatal inclusion criterion, approximately 30% of infants were classified as SGA based on their birth weight. At 6 months, SGA infants had shorter visual evoked potential (VEP) latencies, which were related to an increased UCR but not to head circumference. At 3 years of age, detailed assessment of neurological function coupled with a cognitive questionnaire showed that 9/96 (9.4%) survivors had abnormal neurological testing; three had mild and six had major motor deficits[113]. Interestingly, these occurred predominantly in patients with normal UCR. Neonatal intracranial hemorrhage, as well as a small head circumference at age 3 years, were the major determinants of motor dysfunction. At 5 years of age, children with brain sparing had a 9-point lower IQ and 54% had a score below 85 compared with 20% in children who had a normal UCR[114]. Factors that were predictive of abnormal cognitive function were UCR, VEP latencies at 6 months, abnormal neurological testing at age 3 years and maternal education level. The findings led the authors to reconsider shortening of VEPs at 6 months as a negative prognostic sign. At age 11 years, behavioral testing scores were similar between both groups and the major determinants of abnormal behavior were the degree of FGR, low 5-min Apgar score, oxygen dependence at age 28 days,

neonatal intracerebral hemorrhage and an IQ < 85 at age 5 years[115]. One important confounder in this cohort was that antenatal steroids were administered almost exclusively to patients with FGR with abnormal UCR. Prolonged neonatal oxygen dependence and intracranial hemorrhage are known consequences in infants who did not receive antenatal steroids[116]. It is therefore possible that a proportion of abnormal neurodevelopment in appropriately grown children with normal UCR was attributable to the lack of antenatal steroids, thereby minimizing differences between normal and FGR cases.

Kutschera *et al.*[117] examined three groups of children with Kaufman ABC, Snijders Omen Intelligence testing and neurological examination at 3–6 years of age. Children with UA-ARED, increased UA pulsatility index (PI) or abnormal MCA Doppler index were matched with AGA controls. Growth-restricted children had smaller head circumferences at the time of developmental assessment and significantly lower scores for all domains of the Kaufman and Snijders Omen tests. There were no differences in the scores among SGA children. However, in the matched pair analysis in the SGA group, only one child with UA-ARED had a higher Kaufman score compared with his control with positive UA end-diastolic velocity.

Late-onset fetal growth restriction

Eixarch *et al.*[118] examined infants with late-onset FGR and AGA controls using the ASQ. Test results were stratified according to growth characteristics and the presence of a decreased MCA-PI. Brain sparing was associated with a higher rate of acidosis at birth. While there were no differences in ASQ scores between SGA infants with normal MCA Doppler and AGA controls, brain sparing was associated with significantly lower scores in communication, problem solving and personal-social areas. Roza *et al.*[119] carried out behavioral testing in over 900 children and related these results to fetal growth as well as the UCR Doppler ratios of the anterior cerebral artery and MCA. In this study, maternal smoking lowered the MCA-PI. Each SD increase in the anterior cerebral artery UCR increased emotional-reactive, attention and somatic complaint scores by 23–26%. In contrast, MCA Doppler parameters were related only to somatic complaint scores. This large study demonstrates differential impact of regional alterations in cerebral blood flow impedance on development, consistent with recent findings in the neonatal period[120].

In summary, cerebral artery Doppler studies in early-onset FGR provide little additional information over those utilizing UA Doppler alone. Since UA-AREDV is frequent and associated with central blood flow redistribution, the incremental effect of an additional decrease in MCA Doppler index is difficult to demonstrate. Nevertheless, observations in early-onset FGR further support the concept that the severity of placental dysfunction, as reflected in the UA waveform, affects child neurodevelopment independently. In late FGR, cerebral artery Doppler studies provide important new findings because regional alterations in blood flow resistance and the pattern of observed developmental abnormalities suggest an increased vulnerability of frontal lobe areas. In the neonate, this manifests as social-interactive and attention deficits, while in infancy and early childhood, performance attention, communication, problem solving, emotion and social function may be affected. In contrast, blood flow impedance that is more likely to affect the motor cortex is also reflected in decreased motor performance in the neonate[120] (Table S3).

DOPPLER OF THE AORTA AND AORTIC ISTHMUS

Blood-flow resistance in the descending aorta is determined by the sum of the vascular impedance in downstream vascular beds, including the placenta. An increase in blood flow resistance in this vessel is associated with a relative increase in right ventricular afterload and redistribution of cardiac output towards the left ventricle and therefore the upper part of the body[30]. Direction of forward flow in the aortic isthmus depends on input pressure and downstream vascular impedance and may reverse as blood flow resistance in the placenta rises or cerebral artery blood flow impedance falls[31]. Accordingly, examination of these vessels allows us to relate developmental outcome to left ventricular redistribution of well-oxygenated blood towards the brain and retrograde delivery of descending aortic blood with a lower nutritional content through the aortic isthmus.

A series of studies evaluated various aspects of neurodevelopment in near-term FGR cases and AGA controls in relationship to blood flow classes (BFC) in the fetal descending aorta. At 7 years of age, children with BFC II and III (AREDV) had lower verbal and global IQs compared with controls. Information, comprehension and arithmetic domains of the verbal IQ showed the greatest deviation. The strongest single antenatal predictor of low verbal IQ < 85 was aortic BFC; performance IQ < 85 was related to head size, gestational age at delivery and socioeconomic status; global IQ < 85 was determined by aortic BFC, gestational age at delivery and socioeconomic status[121]. Mild forms of minor neurological dysfunction were more frequent in cases with BFC II compared with BFC 0 (8/11 vs. 35/91) and severe forms of minor neurological dysfunction were observed most frequently (8/21, 38%) in children who had had REDV in the aorta[122]. Neurological dysfunction was determined by the degree of FGR, head circumference at birth and aortic BFC. In adolescence, FGR cases with decreased or absent end-diastolic velocities in the aorta performed worse in school and had significantly lower scores for executive cognitive functions compared with controls[123]. Although psychological testing was comparable to that of normal controls, attention deficit was observed only in the FGR group.

Blood flow in the aortic isthmus reverses early in cases with elevated placental blood flow resistance. Fouron *et al.*[124] evaluated the relationship between

neurodevelopment at 2–4 years of age and prenatal net retrograde flow in the aortic isthmus in 44 infants delivered at 33 weeks' gestation. The flow pattern was determined retrospectively from recordings. Of the 19 (49%) infants with composite suboptimal development, nine had a Griffiths DQ < 85 and five had abnormal motor findings on the neurological examination. Non-optimal outcome was more frequent after net reversal of isthmus blood flow independent of the UA Doppler flow pattern. A follow-up study described the calculation of the isthmus flow index, which provides a numerical quantification of flow direction and accordingly allows calculation of a predictive cut-off[125]. In this study, an isthmic flow index < 0.7 increased the likelihood ratio for non-optimal development five-fold and provided 58% sensitivity and 89% specificity. However, this finding could not be confirmed in two studies that also evaluated concurrently the MCA Doppler index as a marker of left ventricular afterload[126,127]. The study by Kaukola *et al.*[126] demonstrated a significant decline in left and right cardiac outputs and therefore loss of redistribution as a more important factor than is isthmic blood flow reversal for adverse neurodevelopment before 30 weeks' gestation.

These studies suggest that marked increase in aortic blood flow resistance is associated with abnormal neurodevelopment in preterm and early term pregnancies. Net reversal of aortic isthmus blood flow is a plausible mechanism by which retrograde circulation of depleted blood may affect brain development[125]. However, since blood flow directionality in the isthmus is regulated passively, it is difficult to establish if developmental effects are independent of the changes in cardiac output or peripheral vascular impedance. In addition, gestational age may affect brain vulnerability to changes in isthmus blood flow direction[126] (Table S4).

VENOUS DOPPLER, CENTRAL HEMODYNAMIC AND BIOPHYSICAL PARAMETERS

Abnormal venous blood flow, declining forward cardiac function, abnormal heart-rate variation and an abnormal BPS indicates late responses to placental insufficiency that are typically associated with an increased risk for metabolic derangement or stillbirth[1,2,4,7,32]. Evaluating these parameters can potentially answer the important question as to whether fetal deterioration beyond the early responses to placental insufficiency increases the rate of abnormal neurodevelopment.

There have been relatively few studies in early-onset FGR that analyzed venous Doppler findings as prognostic factors for neurodevelopment (Table S5). Kaukola *et al.*[126] performed Doppler measurements of the UA, MCA, precordial veins, cardiac output and aortic isthmus as well as computerized analysis of fetal heart-rate short-term variation in early-onset FGR before 32 weeks' gestation. In addition to these cardiovascular parameters, placental histology and multiple inflammatory markers were related to the Griffiths DQ at age 1 year. Seven cases (one with severe and four with moderate neuromotor dysfunction and two with DQ < 97) were compared with 10 controls. Abnormal neurodevelopment was seen with higher UA and venous Doppler indices and lower weight-indexed fetal cardiac outputs. Leppänen *et al.*[127] reported a large cohort of very preterm FGR cases delivered before 30 weeks' gestation that were evaluated with UA, MCA, descending aorta, aortic isthmus and DV Doppler and had 2-year assessment of cognitive and motor performance. Interestingly, while UA, aortic and MCA Doppler parameters predicted cognitive performance, motor development was unrelated to Doppler. However, when the measurement of brain volume was considered, the association with Doppler parameters was no longer significant. Accordingly, the authors conclude that the reduction of brain volume associated with severe placental dysfunction is the primary mediator of cognitive dysfunction.

Our group performed arterial and venous Doppler as well as BPS in early-onset FGR and related the findings to 2-year developmental outcome[128]. In this analysis, gestational age at delivery, birth weight and UA-REDV were the primary determinants of cerebral palsy, neurodevelopmental delay and global delay, respectively. Neither venous Doppler parameters nor deterioration of the BPS impacted on neurodevelopment. This finding is consistent with 5–10-year follow-up findings in children with UA-ARED stratified by their antenatal management strategy and BPS deterioration prior to delivery[129]. Torrance *et al.*[130] also studied 180 FGR pregnancies delivered before 34 weeks' gestation with UA and MCA Doppler in addition to computerized CTG. The frequency of a normal Bayley or Griffiths DQ > 85 increased from 0% at 26 weeks to 80% at 32 weeks' gestation. A low test score was predicted by birth weight $< 2.3^{rd}$ percentile, UA cord pH < 7.00 and placental villitis; these three factors accounted for 24% of this outcome. Interestingly, gestational age was not a cofactor.

In summary, studies that incorporate venous Doppler and biophysical information are heterogeneous and focus on early-onset FGR. However, none of these studies demonstrates an independent contributory role of venous Doppler parameters or biophysical deterioration to adverse neurodevelopment. Furthermore, they do not suggest a contributory effect of abnormal aortic isthmus blood flow. Indeed, the majority of factors identified by these studies predate the clinical deterioration leading to delivery, suggesting a small contributory role of fetal deterioration to neurodevelopment.

IMPACT OF DELIVERY TIMING

While we await the results of the TRUFFLE study, the GRIT is the only study that allows us to estimate the potential role of delivery timing. A critical difference between the two studies is that the TRUFFLE evaluates a specific management strategy, while the GRIT randomized the delivery timing without a specific delivery trigger and

utilized a Bayesian analytical approach[16]. In the GRIT, 98% of patients were followed up at 2 years and while both arms had comparable rates of death or disability, cerebral palsy was more frequent with immediate delivery prior to 31 weeks' gestation[14]. A smaller proportion of patients completed standardized assessment of cognition, language, behavior and motor ability at 6–13 years. There were no differences in the rates of severe disability and individual domain scores between the two delivery arms. Moreover, results were comparable to other preterm cohorts without FGR[15]. Conclusions that can be drawn from the GRIT include that judgments made around the time of delivery have little impact on longer-term neurodevelopment.

SUMMARY OF RISK FACTORS FOR ABNORMAL NEURODEVELOPMENT

Despite the heterogeneity of study designs presented in this review, there are several consistent observations in these investigations. Motor, neurological, behavioral and cognitive deficiencies of children with growth delay appear to result from different pathophysiology, which probably explains why their clinical emergence is variable. Motor dysfunction is evident as early as birth and certainly by 2 years of age. At this time, neurological abnormalities are also typically well documented. The significance of behavioral abnormalities in the neonatal period is difficult to gauge as they may simply be the postnatal correlate of delayed evolution of fetal behavioral states. The behavioral and cognitive liabilities of placental dysfunction become more apparent with longer-term follow-up studies into early childhood and adolescence. There is little evidence that the preclinical phase of FGR has measurable long-term impact. However, when growth delay is clinically established, there are several prenatal variables that predominate as consistent risk factors for adverse neurodevelopment. These include lagging head growth and overall severity of growth delay, gestational age at delivery and UA, aortic and cerebral Doppler parameters.

As a risk factor for suboptimal neurodevelopment, decrease of head growth overrides the overall degree of FGR in importance[88,91]. Smaller head and brain dimensions are associated with psychomotor retardation, cognitive delay and abnormal behavior rating index in infancy, followed by persistent cognitive delay, speech delay, motor dysfunction and lower scholastic performance from childhood all the way to adolescence[88,95,99,104,117,121,122]. These associations have been documented for early- and late-onset FGR independent of Doppler parameters[127]. The overall severity of growth delay, expressed in absolute birth weight or as a low birth-weight percentile, correlates predominantly with parameters of motor development in infancy and early childhood[99,102,127,128,130] and to a lesser degree with social and cognitive scales[94]. These associations are reported for early-onset FGR independent of Doppler parameters and BPS.

Preterm delivery predisposes to neonatal complications such as intracerebral hemorrhage which is associated with long-term risks for suboptimal neurodevelopment[93,115,125,131]. Because of this specific risk factor, prematurity is associated predominantly with motor dysfunction and cerebral palsy in infancy[13,98,128,132] and to a lesser degree with a decreased global IQ in childhood[121]. It is important to recognize that gestational age overrides the effects of the fetal cardiovascular condition until 32–34 weeks' gestation[94,100]. Therefore, independent associations between Doppler status and neurodevelopment can be demonstrated only for children with the most severe forms of placental dysfunction[103,126]. This explains why studies of cohorts defined postnatally only demonstrate an independent contribution of FGR to cerebral palsy for children delivered between 34 and 37 weeks' gestation[133]; it is likely that this threshold is actually closer to 32 weeks' gestation.

Neurodevelopment is affected by umbilical artery and aortic blood flow impedance in early-onset FGR and by cerebral artery blood flow dynamics in late-onset disease. For the UA and aorta, the developmental impact is proportional to the degree of decrease in end-diastolic velocity, with the worst outcomes if REDV develops by 27 weeks' gestation[96]. AREDV is associated with suboptimal motor development in infancy and childhood cognitive and neurological dysfunction that may persist all the way into adolescence[96,97,101,103,121–123,128]. In the setting of early-onset FGR, there is little evidence to suggest that cerebral artery Doppler impedance affects long-term development independently[117]. Similarly, isthmic flow reversal, which is probably important pathophysiologically, is determined passively by changes in peripheral impedance and cardiac performance and does not appear to have an impact that is independent of these underlying parameters. In late-onset FGR, when the UA waveform is frequently normal, the changes in cerebral artery impedance are associated with behavioral, psychological and cognitive testing abnormalities[104,118,119]. These observations are consistent with an increased overall and regional vulnerability of the brain at a gestational epoch during which up to 40 000 new synapses may be formed per second[48].

Fetal deterioration appears to play an insignificant role in early-onset FGR. Abnormal venous Doppler parameters or an abnormal BPS does not increase measurably the rate of abnormal infant neurodevelopment if the fetus is delivered[127,128]. It is only when significant cardiovascular decompensation or metabolic deterioration to a level of potential hypoxic ischemic encephalopathy occurs that an independent contribution to development is observed[126,130]. The GRIT study confirms that deterioration to a level that is tolerated by most obstetricians does not affect infant or childhood development in early-onset FGR[14,15]. The TRUFFLE study[13] will clarify if additional parameters of deterioration require consideration. In late-onset FGR, fetal deterioration may have an independent impact, as babies delivered in poorer condition tend to perform worse in infancy while those

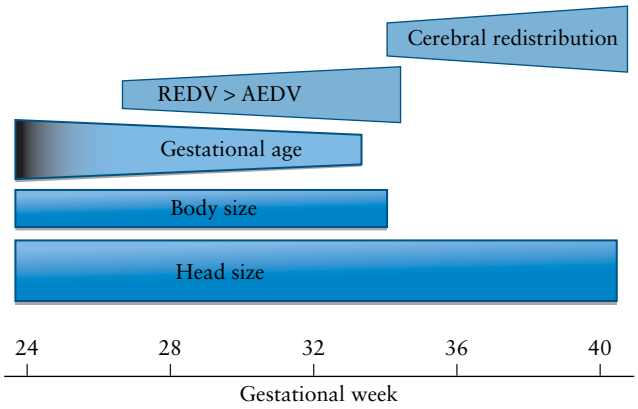

Figure 3 The four primary determinants of neurodevelopment are fetal head size, overall body size, gestational age at delivery and the Doppler parameters in the umbilical artery, descending aorta and cerebral vessels. The negative impact of small head size is independent of gestational age and associated Doppler parameters. Body size is an independent contributor for early-onset fetal growth restriction (FGR), losing its importance near term. Equally, gestational age is important for preterm deliveries up to 34 weeks' gestation. Umbilical or aortic parameters are important for early-onset FGR and cerebral parameters are important for late onset disease. Because of the importance of gestational age, reversed end-diastolic velocity (REDV) has a stronger negative impact than does absent end-diastolic velocity (AEDV), which is evident from approximately 27 weeks onwards.

delivered prior to deterioration have similar testing to AGA controls[89,94,104]. However, the overall contribution of this effect is difficult to quantify (Figure 3).

CONCLUSIONS

With the improved delineation of the clinical progression of early and late placental dysfunction and the appreciation of the perinatal and long-term risks, neurodevelopmental endpoints have moved increasingly into our management focus. The traditional concept has been that progressive fetal deterioration predisposes to abnormal neurodevelopment and that perinatal management that is based on accurate fetal monitoring can minimize long-term risks. However, on critical review it becomes evident that the pattern of growth abnormality, the gestational age at its onset and fetal vascular responses to placental dysfunction lead to long-term consequences prior to the onset of fetal deterioration. Accordingly, it is unlikely that perinatal management strategies in early-onset FGR will affect neurodevelopment. In late-onset FGR, additional studies are required to establish the potential benefit of perinatal interventions as the pattern of vulnerability of the brain appears to differ in the third trimester.

REFERENCES

1. Baschat AA. Fetal growth restriction – From observation to intervention. *J Perinat Med* 2010; **38**: 239–246.
2. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackelöer BJ, Kok HJ, Senat MV, Visser GH. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. *Ultrasound Obstet Gynecol* 2001; **18**: 564–570.
3. Baschat AA, Turan O, Berg C, Turan S, Moyano D, Bhide A, Galan H, Thilaganathan B, Bower S, Gembruch U, Nicolaides KH, Harman CR. Integration of venous Doppler and biophysical profile provides optimal delivery timing in fetal growth restriction (FGR). *Am J Obstet Gynecol* 2007; **198**: S29.
4. Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, Nicolaides KH, Harman CR, Baschat AA. Progression of Doppler abnormalities in intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2008; **32**: 160–167.
5. Oros D, Figueras F, Cruz-Martinez R, Meler E, Munmany M, Gratacos E. Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses. *Ultrasound Obstet Gynecol* 2011; **37**: 191–195.
6. GRIT study group. A randomized trial of timed delivery for the compromised preterm fetus: Short term outcomes and Bayesian interpretation. *BJOG* 2003; **110**: 27–32.
7. Bilardo CM, Wolf H, Stigter RH, Ville Y, Baez E, Visser GH, Hecher K. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2004; **23**: 119–125.
8. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, Germer U, Moyano D, Turan S, Hartung J, Bhide A, Müller T, Bower S, Nicolaides KH, Thilaganathan B, Gembruch U, Ferrazzi E, Hecher K, Galan HL, Harman CR. Predictors of neonatal outcome in early-onset placental dysfunction. *Obstet Gynecol* 2007; **109**: 253–261.
9. Romero R, Kalache KD, Kadar N. Timing the delivery of the preterm severely growth-restricted fetus: venous Doppler, cardiotocography or the biophysical profile? *Ultrasound Obstet Gynecol* 2002; **19**: 118–121.
10. GRIT study group. When do obstetricians recommend delivery for a high-risk preterm growth-retarded fetus? The GRIT Study Group. Growth Restriction Intervention Trial. *Eur J Obstet Gynecol Reprod Biol* 1996; **67**: 121–126.
11. Soothill PW, Ajayi RA, Campbell S, Ross EM, Candy DC, Snijders RM, Nicolaides KH. Relationship between fetal acidemia at cordocentesis and subsequent neurodevelopment. *Ultrasound Obstet Gynecol* 1992; **2**: 80–83.
12. Soothill PW, Ajayi RA, Campbell S, Ross EM, Nicolaides KH. Fetal oxygenation at cordocentesis, maternal smoking and childhood neuro-development. *Eur J Obstet Gynecol Reprod Biol* 1995; **59**: 21–24.
13. Lees C, Baumgartner H. The TRUFFLE study–a collaborative publicly funded project from concept to reality: how to negotiate an ethical, administrative and funding obstacle course in the European Union. *Ultrasound Obstet Gynecol* 2005; **25**: 105–107.
14. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M; GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. *Lancet* 2004; **364**: 513–520.
15. Walker DM, Marlow N, Upstone L, Gross H, Hornbuckle J, Vail A, Wolke D, Thornton JG. The Growth Restriction Intervention Trial: long-term outcomes in a randomized trial of timing of delivery in fetal growth restriction. *Am J Obstet Gynecol* 2010; **204**: 34.e1–9.
16. Baschat AA, Odibo AO. Timing of delivery in fetal growth restriction and childhood development: Some uncertainties remain. *Am J Obstet Gynecol* 2011; **204**: 2–3.
17. Nicolini U, Hubinont C, Santolaya J, Fisk NM, Coe AM, Rodeck CH. Maternal-fetal glucose gradient in normal pregnancies and in pregnancies complicated by alloimmunization and fetal growth retardation. *Am J Obstet Gynecol* 1989; **161**: 924–927.
18. Battaglia FC, Regnault TR. Placental transport and metabolism of amino acids. *Placenta* 2001; **22**: 145–161.

19. Fant ME, Weisoly D. Insulin and insulin-like growth factors in human development: implications for the perinatal period. *Semin Perinatol* 2001; **25**: 426–435.
20. Kiserud T. The ductus venosus. *Semin Perinatol* 2001; **25**: 11–20.
21. Haugen G, Hanson M, Kiserud T, Crozier S, Inskip H, Godfrey KM. Fetal liver-sparing cardiovascular adaptations linked to mother's slimness and diet. *Circ Res* 2005; **96**: 12–14.
22. Kiserud T, Kessler J, Ebbing C, Rasmussen S. Ductus venosus shunting in growth-restricted fetuses and the effect of umbilical circulatory compromise. *Ultrasound Obstet Gynecol* 2006; **28**: 143–149.
23. Rigano S, Bozzo M, Ferrazzi E, Bellotti M, Battaglia FC, Galan HL. Early and persistent reduction in umbilical vein blood flow in the growth-restricted fetus: a longitudinal study. *Am J Obstet Gynecol* 2001; **185**: 834–838.
24. Divon MY, Chamberlain PF, Sipos L, Manning FA, Platt LD. Identification of the small for gestational age fetus with the use of gestational age-independent indices of fetal growth. *Am J Obstet Gynecol* 1986; **155**: 1197–1201.
25. Morrow RJ, Adamson SL, Bull SB, Ritchie JW. Effect of placental embolization on the umbilical artery velocity waveform in fetal sheep. *Am J Obstet Gynecol* 1989; **161**: 1055–1060.
26. Thompson RS, Stevens RJ. Mathematical model for interpretation of Doppler velocity waveform indices. *Med Biol Eng Comput* 1989; **27**: 269–276.
27. Arbeille P, Maulik D, Fignon A, Stale H, Berson M, Bodard S, Locatelli A. Assessment of the fetal PO2 changes by cerebral and umbilical Doppler on lamb fetuses during acute hypoxia. *Ultrasound Med Biol* 1995; **21**: 861–870.
28. Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A. Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. *Obstet Gynecol* 1992; **79**: 416–420.
29. Harrington K, Thompson MO, Carpenter RG, Nguyen M, Campbell S. Doppler fetal circulation in pregnancies complicated by pre-eclampsia or delivery of a small for gestational age baby: 2. Longitudinal analysis. *Br J Obstet Gynaecol* 1999; **106**: 453–466.
30. Al Ghazali W, Chita SK, Chapman MG, Allan LD. Evidence of redistribution of cardiac output in asymmetrical growth retardation. *Br J Obstet Gynaecol* 1987; **96**: 697–704.
31. Bonnin P, Fouron JC, Teyssier G, Sonesson SE, Skoll A. Quantitative assessment of circulatory changes in the fetal aortic isthmus during progressive increase of resistance to umbilical blood flow. *Circulation* 1993; **88**: 216–222.
32. Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, Battaglia FC, Galan HL. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. *Ultrasound Obstet Gynecol* 2002; **19**: 140–146.
33. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. *Ultrasound Obstet Gynecol* 2001; **18**: 571–577.
34. Cosmi E, Ambrosini G, D'Antona D, Saccardi C, Mari G. Doppler, cardiotocography, and biophysical profile changes in growth-restricted fetuses. *Obstet Gynecol* 2005; **106**: 1240–1245.
35. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, Rodis JF. Relationship between fetal biophysical activities and umbilical cord blood gas values. *Am J Obstet Gynecol* 1991; **165**: 707–713.
36. Vannucci RC, Vannucci SJ. Glucose metabolism in the developing brain. *Semin Perinatol* 2000; **24**: 107–115.
37. Fisher DJ, Heymann MA, Rudolph AM. Fetal myocardial oxygen and carbohydrate consumption during acutely induced hypoxemia. *Am J Physiol* 1982; **242**: H657–H661.
38. Baschat AA. Fetal responses to placental insufficiency – an update. *BJOG* 2004; **111**: 1031–1041.
39. Ward PE. Potential diagnostic aids for abnormal fatty acid metabolism in a range of neurodevelopmental disorders. *Prostaglandins Leukot Essent Fatty Acids* 2000; **63**: 65–68.
40. Hecher K, Spernol R, Stettner H, Szalay S. Potential for diagnosing imminent risk to appropriate- and small-for-gestational-age fetuses by Doppler sonographic examination of umbilical and cerebral arterial blood flow. *Ultrasound Obstet Gynecol* 1992; **2**: 266–271.
41. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, Mari G. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. *Am J Obstet Gynecol* 1999; **180**: 750–756.
42. Baschat AA, Berg C, Turan O, Turan S, Galan H, Thilaganathan B, Nicolaides K, Gembruch U, Harman CR. Natural history of stillbirth in placenta based fetal growth restriction – implications for surveillance. Annual Meeting of the Society for Maternal-Fetal Medicine. *Am J Obstet Gynecol* 2008; **199**: S198.
43. Hernandez-Andrade E, Figueroa-Diesel H, Jansson T, Rangel-Nava H, Gratacos E. Changes in regional fetal cerebral blood flow perfusion in relation to hemodynamic deterioration in severely growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2008; **32**: 71–76.
44. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Puerto B, Gratacós E. Longitudinal brain perfusion changes in near-term small-for-gestational-age fetuses as measured by spectral Doppler indices or by fractional moving blood volume. *Am J Obstet Gynecol* 2010; **203**: 42.e1–6.
45. Sanz-Cortés M, Figueras F, Bargalló N, Padilla N, Amat-Roldan I, Gratacós E. Abnormal brain microstructure and metabolism in small-for-gestational-age term fetuses with normal umbilical artery Doppler. *Ultrasound Obstet Gynecol* 2010; **36**: 159–165.
46. Nijhuis JG. Behavioural states: concomitants, clinical implications and the assessment of the condition of the nervous system. *Eur J Obstet Gynecol Reprod Biol* 1986; **21**: 301–308.
47. Pillai M, James D. Development of human fetal behavior: a review. *Fetal Diagn Ther* 1990; **5**: 15–32.
48. Bourgeois JP. Synaptogenesis, heterochrony and epigenesis in the mammalian neocortex. *Acta Paediatr Suppl* 1997; **422**: 27–33.
49. de Vries JI, Visser GH, Mulder EJ, Prechtl HF. Diurnal and other variations in fetal movement and heart rate patterns at 20–22 weeks. *Early Hum Dev* 1987; **15**: 333–348.
50. Arduini D, Rizzo G, Giorlandino C, Valensise H, Dell'Acqua S, Romanini C. The development of fetal behavioural states: a longitudinal study. *Prenat Diagn* 1986; **6**: 117–124.
51. Manning FA. Fetal biophysical profile. *Obstet Gynecol Clin North Am* 1999; **26**: 557–577.
52. Nijhuis JG, Prechtl HF, Martin CB Jr, Bots RS. Are there behavioural states in the human fetus? *Early Hum Dev* 1982; **6**: 177–195.
53. Arduini D, Rizzo G, Giorlandino C, Vizzone A, Nava S, Dell'Acqua S, Valensise H, Romanini C. The fetal behavioural states: an ultrasonic study. *Prenat Diagn* 1985; **5**: 269–276.
54. van Eyck J, Wladimiroff JW, Noordam MJ, Tonge HM, Prechtl HF. The blood flow velocity waveform in the fetal descending aorta: its relationship to fetal behavioural states in normal pregnancy at 37–38 weeks. *Early Hum Dev* 1985; **12**: 137–143.
55. van Eyck J, Wladimiroff JW, van den Wijngaard JA, Noordam MJ, Prechtl HF. The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relation to fetal behavioural states in normal pregnancy at 37–38 weeks. *Br J Obstet Gynaecol* 1987; **94**: 736–741.
56. van Eyck J, Stewart PA, Wladimiroff JW. Human fetal foramen ovale flow velocity waveforms relative to behavioral states in normal term pregnancy. *Am J Obstet Gynecol* 1990; **163**: 1239–1242.
57. van der Mooren K, van Eyck J, Wladimiroff JW. Human fetal ductal flow velocity waveforms relative to behavioral states

in normal term pregnancy. *Am J Obstet Gynecol* 1989; **160**: 371–374.
58. Rizzo G, Arduini D, Valensise H, Romanini C. Effects of behavioural states on cardiac output in the healthy human fetus at 36–38 weeks of gestation. *Early Hum Dev* 1990; **23**: 109–115.
59. Arduini D, Rizzo G, Caforio L, Boccolini MR, Romanini C, Mancuso S. Behavioural state transitions in healthy and growth retarded fetuses. *Early Hum Dev* 1989; **19**: 155–165.
60. Arduini D, Rizzo G, Romanini C, Mancuso S. Computerized analysis of behavioural states in asymmetrical growth retarded fetuses. *J Perinat Med* 1988; **16**: 357–363.
61. Nijhuis IJ, ten Hof J, Nijhuis JG, Mulder EJ, Narayan H, Taylor DJ, Visser GH. Temporal organisation of fetal behaviour from 24-weeks gestation onwards in normal and complicated pregnancies. *Dev Psychobiol* 1999; **34**: 257–268.
62. Nijhuis IJ, ten Hof J, Mulder EJ, Nijhuis JG, Narayan H, Taylor DJ, Visser GH. Fetal heart rate in relation to its variation in normal and growth retarded fetuses. *Eur J Obstet Gynecol Reprod Biol* 2000; **89**: 27–33.
63. Henson G, Dawes GS, Redman CW. Characterization of the reduced heart rate variation in growth-retarded fetuses. *Br J Obstet Gynaecol* 1984; **91**: 751–755.
64. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses. *Br J Obstet Gynaecol* 1991; **98**: 820–823.
65. Smith JH, Anand KJ, Cotes PM, Dawes GS, Harkness RA, Howlett TA, Rees LH, Redman CW. Antenatal fetal heart rate variation in relation to the respiratory and metabolic status of the compromised human fetus. *Br J Obstet Gynaecol* 1988; **95**: 980–989.
66. van Vliet MA, Martin CB Jr, Nijhuis JG, Prechtl HF. The relationship between fetal activity and behavioral states and fetal breathing movements in normal and growth-retarded fetuses. *Am J Obstet Gynecol* 1985; **153**: 582–588.
67. Dornan JC, Ritchie JW, Ruff S. The rate and regularity of breathing movements in the normal and growth-retarded fetus. *Br J Obstet Gynaecol* 1984; **91**: 31–36.
68. van Vliet MA, Martin CB Jr, Nijhuis JG, Prechtl HF. Behavioural states in growth retarded human fetuses. *Early Hum Dev* 1985; **12**: 183–197.
69. Vindla S, James D, Sahota D. Computerised analysis of unstimulated and stimulated behaviour in fetuses with intrauterine growth restriction. *Eur J Obstet Gynecol Reprod Biol* 1999; **83**: 37–45.
70. Visser GH, Bekedam DJ, Ribbert LS. Changes in antepartum heart rate patterns with progressive deterioration of the fetal condition. *Int J Biomed Comput* 1990; **25**: 239–246.
71. Rizzo G, Arduini D, Pennestri F, Romanini C, Mancuso S. Fetal behaviour in growth retardation: its relationship to fetal blood flow. *Prenat Diagn* 1987; **7**: 229–238.
72. Longo LD, Packianathan S. Hypoxia-ischemia and the developing brain: hypotheses regarding the pathophysiology of fetal neonatal brain damage. *Br J Obstet Gynaecol* 1997; **104**: 652–662.
73. Romanini C, Valensise H, Ciotti G, Arduini D, Giorgi P. Tryptophan availability and fetal behavioral states. *Fetal Ther* 1989; **4** (Suppl. 1): 68–72.
74. Gazzolo D, Visser GH, Lituania M, Sarli R, Bruschettini M, Michetti F, Bruschettini PL. S100B protein cord blood levels and development of fetal behavioral states: a study in normal and small-for-dates fetuses. *J Matern Fetal Neonatal Med* 2002; **11**: 378–384.
75. Pillai M, James D. Continuation of normal neurobehavioural development in fetuses with absent umbilical arterial end-diastolic velocities. *Br J Obstet Gynaecol* 1991; **98**: 277–281.
76. Groome LJ, Singh KP, Bentz LS, Holland SB, Atterbury JL, Swiber MJ, Trimm RF 3rd. Temporal stability in the distribution of behavioral states for individual human fetuses. *Early Hum Dev* 1997; **48**: 187–197.
77. Ribbert LS, Nicolaides KH, Visser GH. Prediction of fetal acidaemia in intrauterine growth retardation: comparison of quantified fetal activity with biophysical profile score. *Br J Obstet Gynaecol* 1993; **100**: 653–656.
78. Ribbert LS, Visser GH, Mulder EJ, Zonneveld MF, Morssink LP. Changes with time in fetal heart rate variation, movement incidences and haemodynamics in intrauterine growth retarded fetuses: a longitudinal approach to the assessment of fetal well being. *Early Hum Dev* 1993; **31**: 195–208.
79. Bos AF, van Loon AJ, Martijn A, van Asperen RM, Okken A, Prechtl HF. Spontaneous motility in preterm, small-for-gestational age infants. I. Quantitative aspects. *Early Hum Dev* 1997; **50**: 115–129.
80. Einspieler C, Prechtl HF, Ferrari F, Cioni G, Bos AF. The qualitative assessment of general movements in preterm, term and young infants–review of the methodology. *Early Hum Dev* 1997; **50**: 47–60.
81. Bekedam DJ, Visser GH, de Vries JJ, Prechtl HF. Motor behaviour in the growth retarded fetus. *Early Hum Dev* 1985; **12**: 155–165.
82. Prechtl HF, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. An early marker for neurological deficits after perinatal brain lesions. *Lancet* 1997; **349**: 1361–1363.
83. Bos AF, van Loon AJ, Hadders-Algra M, Martijn A, Okken A, Prechtl HF. Spontaneous motility in preterm, small-for-gestational age infants. II. Qualitative aspects. *Early Hum Dev* 1997; **50**: 131–147.
84. Cruz-Martinez R, Figueras F, Oros D, Padilla N, Meler E, Hernandez-Andrade E, Gratacos E. Cerebral blood perfusion and neurobehavioral performance in full-term small-for-gestational-age fetuses. *Am J Obstet Gynecol* 2009; **201**: 474.e1–7.
85. Manning FA, Bondagji N, Harman CR, Casiro O, Menticoglou S, Morrison I. Fetal assessment based on the fetal biophysical profile score: relationship of last BPS result to subsequent cerebral palsy. *J Gynecol Obstet Biol Reprod* 1997; **26**: 720–729.
86. Manning FA, Bondaji N, Harman CR, Casiro O, Menticoglou S, Morrison I, Berck DJ. Fetal assessment based on fetal biophysical profile scoring. VIII. The incidence of cerebral palsy in tested and untested perinates. *Am J Obstet Gynecol* 1998; **178**: 696–706.
87. Lagercrantz H. Better born too soon than too small. *Lancet* 1997; **350**: 1044–1045.
88. Harvey D, Prince J, Bunton J, Parkinson C, Campbell S. Abilities of children who were small-for-gestational-age babies. *Pediatrics* 1982; **69**: 296–300.
89. Roth S, Chang TC, Robson S, Spencer JA, Wyatt JS, Stewart AL. The neurodevelopmental outcome of term infants with different intrauterine growth characteristics. *Early Hum Dev* 1999; **55**: 39–50.
90. Roth SC, Baudin J, Pezzani-Goldsmith M, Townsend J, Reynolds EO, Stewart AL. Relation between neurodevelopmental status of very preterm infants at one and eight years. *Dev Med Child Neurol* 1994; **36**: 1049–1062.
91. Harel S, Tomer A, Barak Y, Binderman I, Yavin E. The cephalization index: a screening device for brain maturity and vulnerability in normal and intrauterine growth retarded newborns. *Brain Dev* 1985; **7**: 580–584.
92. van Batenburg-Eddes T, de Groot L, Steegers EA, Hofman A, Jaddoe VW, Verhulst FC, Tiemeier H. Fetal programming of infant neuromotor development: the generation R study. *Pediatr Res* 2010; **67**: 128–129.
93. Sung IK, Vohr B, Oh W. Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. *J Pediatr* 1993; **123**: 618–624.
94. Gortner L, van Husen M, Thyen U, Gembruch U, Friedrich HJ, Landmann E. Outcome in preterm small for gestational age infants compared to appropriate for gestational age preterms

at the age of 2 years: a prospective study. *Eur J Obstet Gynecol Reprod Biol* 2003; **110** (Suppl 1): S93–S97.
95. Parkinson CE, Scrivener R, Graves L, Bunton J, Harvey D. Behavioural differences of school-age children who were small-for-dates babies. *Dev Med Child Neurol* 1986; **28**: 498–505.
96. Vossbeck S, de Camargo OK, Grab D, Bode H, Pohlandt F. Neonatal and neurodevelopmental outcome in infants born before 30 weeks of gestation with absent or reversed end-diastolic flow velocities in the umbilical artery. *Eur J Pediatr* 2001; **160**: 128–134.
97. Morsing E, Asard M, Ley D, Stjernqvist K, Marsál K. Cognitive function after intrauterine growth restriction and very preterm birth. *Pediatrics* 2011; **127**: e874–882.
98. Brodszki J, Morsing E, Malcus P, Thuring A, Ley D, Marsál K. Early intervention in management of very preterm growth-restricted fetuses: 2-year outcome of infants delivered on fetal indication before 30 gestational weeks. *Ultrasound Obstet Gynecol* 2009; **34**: 288–296.
99. Padilla N, Perapoch J, Carrascosa A, Acosta-Rojas R, Botet F, Gratacós E. Twelve-month neurodevelopmental outcome in preterm infants with and without intrauterine growth restriction. *Acta Paediatr* 2010; **99**: 1498–1503.
100. Shand AW, Hornbuckle J, Nathan E, Dickinson JE, French NP. Small for gestational age preterm infants and relationship of abnormal umbilical artery Doppler blood flow to perinatal mortality and neurodevelopmental outcomes. *Aust N Z J Obstet Gynaecol* 2009; **49**: 52–58.
101. Valcamonico A, Accorsi P, Battaglia S, Soregaroli M, Beretta D, Frusca T. Absent or reverse end-diastolic flow in the umbilical artery: intellectual development at school age. *Eur J Obstet Gynecol Reprod Biol* 2004; **114**: 23–28.
102. Wienerroither H, Steiner H, Tomaselli J, Lobendanz M, Thun-Hohenstein L. Intrauterine blood flow and long-term intellectual, neurologic, and social development. *Obstet Gynecol* 2001; **97**: 449–453.
103. Schreuder AM, McDonnell M, Gaffney G, Johnson A, Hope PL. Outcome at school age following antenatal detection of absent or reversed end diastolic flow velocity in the umbilical artery. *Arch Dis Child Fetal Neonatal Ed* 2002; **86**: F108–F114.
104. McCowan LM, Pryor J, Harding JE. Perinatal predictors of neurodevelopmental outcome in small-for-gestational-age children at 18 months of age. *Am J Obstet Gynecol* 2002; **186**: 1069–1075.
105. Figueras F, Oros D, Cruz-Martinez R, Padilla N, Hernandez-Andrade E, Botet F, Costas-Moragas C, Gratacos E. Neurobehavior in term, small-for-gestational age infants with normal placental function. *Pediatrics* 2009; **124**: e934–941.
106. Figueras F, Eixarch E, Meler E, Iraola A, Figueras J, Puerto B, Gratacos E. Small-for-gestational-age fetuses with normal umbilical artery Doppler have suboptimal perinatal and neurodevelopmental outcome. *Eur J Obstet Gynecol Reprod Biol* 2008; **136**: 34–38.
107. Capilla-González A, Fernández-González S, Campo P, Maestú F, Fernández-Lucas A, Mulas F, Ortiz T. Magnetoencephalography in cognitive disorders involving frontal lobes. *Rev Neurol* 2004; **39**: 183–188.
108. Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R. White-matter abnormalities in attention deficit hyperactivity disorder: a diffusion tensor imaging study. *Hum Brain Mapp* 2009; **30**: 2757–2765.
109. Makhoul IR, Soudack M, Goldstein I, Smolkin T, Tamir A, Sujov P. Sonographic biometry of the frontal lobe in normal and growth-restricted neonates. *Pediatr Res* 2004; **55**: 877–883.
110. Jacobsen LK, Picciotto MR, Heath CJ, Frost SJ, Tsou KA, Dwan RA, Jackowski MP, Constable RT, Mencl WE. Prenatal and adolescent exposure to tobacco smoke modulates the development of white matter microstructure. *J Neurosci* 2007; **27**: 13491–13498.
111. Gallinat J, Meisenzahl E, Jacobsen LK, Kalus P, Bierbrauer J, Kienast T, Witthaus H, Leopold K, Seifert F, Schubert F, Staedtgen M. Smoking and structural brain deficits: a volumetric MR investigation. *Eur J Neurosci* 2006; **24**: 1744–1750.
112. Scherjon S, Oosting H, Ongerboer de Visser B, de Wilde T, Zondervan HA, Kok JA. Fetal brain sparing is associated with shortening of visual evoked potential latencies. *Am J Obstet Gynecol* 1996; **175**: 1569–1575.
113. Scherjon SA, Oosting H, Smolders-DeHaas H, Zondervan HA, Kok JH. Neurodevelopmental outcome at three years of age after fetal 'brain-sparing'. *Early Hum Dev* 1998; **52**: 67–79.
114. Scherjon S, Briet J, Oosting H, Kok J. The discrepancy between maturation of visual-evoked potentials and cognitive outcome at five years in very preterm infants with and without hemodynamic signs of fetal brain-sparing. *Pediatrics* 2000; **105**: 385–391.
115. van den Broek AJ, Kok JH, Houtzager BA, Scherjon SA. Behavioural problems at the age of eleven years in preterm-born children with or without fetal brain sparing: a prospective cohort study. *Early Hum Dev* 2010; **86**: 379–384.
116. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Duncan CC, Makuch RW. Antenatal steroids, delivery mode, and intraventricular hemorrhage in preterm infants. *Am J Obstet Gynecol* 1995; **172**: 795–800.
117. Kutschera J, Tomaselli J, Urlesberger B, Maurer U, Häusler M, Gradnitzer E, Burmucic K, Müller W. Absent or reversed end-diastolic blood flow in the umbilical artery and abnormal Doppler cerebroplacental ratio–cognitive, neurological and somatic development at 3 to 6 years. *Early Hum Dev* 2002; **69**: 47–56.
118. Eixarch E, Meler E, Iraola A, Illa M, Crispi F, Hernandez-Andrade E, Gratacos E, Figueras F. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. *Ultrasound Obstet Gynecol* 2008; **32**: 894–899.
119. Roza SJ, Steegers EA, Verburg BO, Jaddoe VW, Moll HA, Hofman A, Verhulst FC, Tiemeier H. What is spared by fetal brain-sparing? Fetal circulatory redistribution and behavioral problems in the general population. *Am J Epidemiol* 2008; **168**: 1145–1152.
120. Oros D, Figueras F, Cruz-Martinez R, Padilla N, Meler E, Hernandez-Andrade E, Gratacos E. Middle versus anterior cerebral artery Doppler for the prediction of perinatal outcome and neonatal neurobehavior in term small-for-gestational-age fetuses with normal umbilical artery Doppler. *Ultrasound Obstet Gynecol* 2010; **35**: 456–461.
121. Ley D, Tideman E, Laurin J, Bjerre I, Marsal K. Abnormal fetal aortic velocity waveform and intellectual function at 7 years of age. *Ultrasound Obstet Gynecol* 1996; **8**: 160–165.
122. Ley D, Laurin J, Bjerre I, Marsal K. Abnormal fetal aortic velocity waveform and minor neurological dysfunction at 7 years of age. *Ultrasound Obstet Gynecol* 1996; **8**: 152–159.
123. Tideman E, Marsál K, Ley D. Cognitive function in young adults following intrauterine growth restriction with abnormal fetal aortic blood flow. *Ultrasound Obstet Gynecol* 2007; **29**: 614–618.
124. Fouron JC, Gosselin J, Amiel-Tison C, Infante-Rivard C, Fouron C, Skoll A, Veilleux A. Correlation between prenatal velocity waveforms in the aortic isthmus and neurodevelopmental outcome between the ages of 2 and 4 years. *Am J Obstet Gynecol* 2001; **184**: 630–636.
125. Fouron JC, Gosselin J, Raboisson MJ, Lamoureux J, Tison CA, Fouron C, Hudon L. The relationship between an aortic isthmus blood flow velocity index and the postnatal neurodevelopmental status of fetuses with placental circulatory insufficiency. *Am J Obstet Gynecol* 2005; **192**: 497–503.
126. Kaukola T, Rasanen J, Herva R, Patel DD, Hallman M. Suboptimal neurodevelopment in very preterm infants is related to fetal cardiovascular compromise in placental insufficiency. *Am J Obstet Gynecol* 2005; **193**: 414–420.

127. Leppänen M, Ekholm E, Palo P, Maunu J, Munck P, Parkkola R, Matomäki, Lapinleimu H, Haataja L, Lehtonen L, Rautava P, and the PIPARI Study group. Abnormal antenatal Doppler velocimetry and cognitive outcome in very-low birth weight infants at 2 years of age. *Ultrasound Obstet Gynecol* 2010; **36**: 178–185.
128. Baschat AA, Viscardi RM, Hussey-Gardner B, Hashmi N, Harman C. Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters. *Ultrasound Obstet Gynecol* 2009; **33**: 44–50.
129. Gerber S, Hohlfeld P, Viquerat F, Tolsa JF, Vial Y. Intrauterine growth restriction and absent or reverse end-diastolic blood flow in umbilical artery (Doppler class II or III): A retrospective study of short- and long-term fetal morbidity and mortality. *Eur J Obstet Gynecol Reprod Biol* 2006; **126**: 20–26.
130. Torrance HL, Bloemen MC, Mulder EJ, Nikkels PG, Derks JB, de Vries LS, Visser GH. Predictors of outcome at 2 years of age after early intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2010; **36**: 171–177.
131. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. *Am J Obstet Gynecol* 2000; **182**: 198–206.
132. Hutton JL, Pharoah PO, Cooke RW, Stevenson RC. Differential effects of preterm birth and small gestational age on cognitive and motor development. *Arch Dis Child Fetal Neonatal Ed* 1997; **76**: F75–F81.
133. Walker DM, Marlow N. Neurocognitive outcome following fetal growth restriction. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**: F322–F325.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Studies on fetal growth characteristics and neurodevelopment

Table S2 Umbilical artery Doppler and neurodevelopment

Table S3 Cerebral arterial Doppler and neurodevelopment

Table S4 Doppler of the descending aorta or aortic isthmus and neurodevelopment

Table S5 Doppler of venous and central hemodynamics and biophysical parameters