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

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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. 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. The importance of gestational age at delivery as a determinant of many critical postpartum outcomes is becoming more apparent. 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. 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. 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). 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. However, at 6–13 years, childhood neurodevelopment was identical in both management arms of the trial. While this may suggest that timing of delivery is less relevant than was...
thought, it also raises the question as to whether neurodevelopment is determined mainly before delivery decisions become relevant\textsuperscript{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\textsuperscript{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\textsuperscript{21–23}. With decreased glycogen storage in the liver, the growth rate of the abdominal circumference begins to slow down, resulting in fetal asymmetry\textsuperscript{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\textsuperscript{25–27}. Before Doppler indices in these vessels exceed their individual abnormal thresholds, the cerebroplacental Doppler ratio (CPR = MCA/UA Doppler index) decreases\textsuperscript{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\textsuperscript{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\textsuperscript{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 10\textsuperscript{th} percentile\textsuperscript{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

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manifestations of placental dysfunction become more likely when the UA end-diastolic velocity is reversed (UA-REDV)\textsuperscript{32}. The typical pattern of deterioration progresses from escalating abnormalities in UA and venous Doppler parameters to abnormal biophysical parameters\textsuperscript{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\textsuperscript{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\textsuperscript{38,39}. The rate of deterioration of UA Doppler parameters determines the overall speed of deterioration in early-onset FGR, often necessitating preterm delivery\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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. 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. 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. 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 by 32 weeks’ gestation, allows correlation of heart-rate patterns to behavioral states. Fetal behavioral states 1F–4F, which correspond to their neonatal counterparts, patterns to 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.

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. In FGR, the percentage of coincidence is lower and state transitions take longer compared to appropriate-for-gestational-age (AGA) controls. 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. Even after behavioral states are established, movement quality, coincidence, coupling and state transitions may remain abnormal. Moreover, disorganization of state transitions increases with fetal deterioration, suggesting that progressive nutritional deprivation may potentiate cortical dysfunction. 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. Yet, despite these developmental delays, intrafetal consistency in behavior and overall responsiveness to hypoxemia is maintained; in FGR the fetus responds to worsening hypoxemia with declining global fetal activity and to acidemia with an abnormal BPS. 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.

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. Abnormal quality of general movement, classified as poor repertoire, cramped-synchronized and chaotic, is more readily recognized postnatally than it is in the fetus. Poor-quality movements are observed in FGR and their persistence after birth correlates with abnormal motor outcome at 2 years of age.

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-interaction, attention capacity, state organization and motor skills among growth-restricted neonates that had abnormal prenatal MCA Doppler studies. 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.

**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. 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. 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., 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. 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. 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%. 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. 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. 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 perceptual performance, motor ability, cognition, concentration ability and defects in short-term memory, with subsequently poorer school achievement. 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. 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., 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. This study also suggested that boys may be at greater risk than girls for abnormal development. In contrast, Brodzski et al. 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. 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. 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 similar101. 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 neuropsychiatric tests and had significantly lower scores in all domains of the Kaufman assessment battery for children102. 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, would be considered to have normal UCR (brain sparing), in association with an elevated UA Doppler index. More recently, Figueiras 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 controls106. 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 trimester45,107–109. However, it needs to be noted that, in one of these studies106, maternal smoking, which has the potential to affect similar areas of the maturing brain, was an important confounder110,111.

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 studies113–115. 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 deficits113. 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 UCR114. 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. 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. 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. 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. 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. 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.

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 (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. 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. 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. 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. 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. 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. Furon et al. 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 < 8.5 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. 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. The study by Kaukola et al. 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. 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 directionality in the aortic isthmus (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. 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. 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. 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. 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-AREDV stratified by their antenatal management strategy and BPS deterioration prior to delivery. Torrance et al. 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 < 2.3rd 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\textsuperscript{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\textsuperscript{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\textsuperscript{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, neurobehavioral 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\textsuperscript{48,91}. 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\textsuperscript{48,95,99,104,117,121,122}. These associations have been documented for early- and late-onset FGR independent of Doppler parameters\textsuperscript{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\textsuperscript{99,102,127,128,130} and to a lesser degree with social and cognitive scales\textsuperscript{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\textsuperscript{93,115,125,131}. Because of this specific risk factor, prematurity is associated predominantly with motor dysfunction and cerebral palsy in infancy\textsuperscript{13,98,128,132} and to a lesser degree with a decreased global IQ in childhood\textsuperscript{121}. It is important to recognize that gestational age overrides the effects of the fetal cardiovascular condition until 32–34 weeks’ gestation\textsuperscript{98,100}. Therefore, independent associations between Doppler status and neurodevelopment can be demonstrated only for children with the most severe forms of placental dysfunction\textsuperscript{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\textsuperscript{131}; 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\textsuperscript{96}. AREDV is associated with suboptimal motor development in infancy and childhood cognitive and neurological dysfunction that may persist all the way into adolescence\textsuperscript{96,97,101,103,121,123,129}. In the setting of early-onset FGR, there is little evidence to suggest that cerebral artery Doppler impedance affects long-term development independently\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{14,15}. The TRUFFLE study\textsuperscript{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
delivered prior to deterioration have similar testing to AGA controls. 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.

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**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