Detection and assessment of brain injury in the growth-restricted fetus and neonate

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Fetal growth restriction (FGR) is a common complication of pregnancy and, in severe cases, is associated with elevated rates of perinatal mortality, neonatal morbidity, and poor neurodevelopmental outcomes. The leading cause of FGR is placental insufficiency, with the placenta failing to adequately meet the increasing oxygen and nutritional needs of the growing fetus with advancing gestation. The resultant chronic fetal hypoxia induces a decrease in fetal growth, and a redistribution of blood flow preferentially to the brain. However, this adaptation does not ensure normal brain development. Early detection of brain injury in FGR, allowing for the prediction of short- and long-term neurodevelopmental consequences, remains a significant challenge. Furthermore, in FGR infants the detection and diagnosis of neuropathology is complicated by preterm birth, the etiological heterogeneity of FGR, timing of onset of growth restriction, its severity, and coexisting complications. In this review, we examine existing and emerging diagnostic tools from human and preclinical studies for the detection and assessment of brain injury in FGR fetuses and neonates. Increased detection rates, and early detection of brain injury associated with FGR, will offer opportunities for developing and assessing interventions to improve long-term outcomes.

Fetal growth restriction (FGR) or intrauterine growth restriction (IUGR) affects more than 10% of pregnancies worldwide, with substantial implications for short-term and long-term well-being of the infant. FGR is strongly associated with stillbirth, preterm birth, and, in newborn survivors, increased risk of developing neonatal complications (1). FGR is also a causal factor in the development of adverse neurodevelopmental sequelae in childhood (2,3).

FGR defines a fetus that has failed to reach its genetically determined birth weight. Unfortunately, there is a lack of a consensus definition for fetal growth restriction. Pragmatically, FGR is defined by the criteria of estimated fetal weight, or birth weight, being less than the 10th centile for age and sex. However, many studies do not discriminate between

infants whose birth weight is less than the 10th centile for age but who are small and otherwise healthy, termed small for gestational age (SGA), compared with the pathologically small babies who did not grow fully (true FGR). Further, some fetuses will be growth-restricted, but have a birth weight >10th centile. Such fetuses remain at an increased risk of stillbirth or perinatal morbidity.

The causes of FGR are diverse, including fetal, maternal, or placental factors (4). Poor placental function is the most important contributor clinically (5–7), resulting in chronic fetal hypoxia and hypoglycemia in an otherwise normal fetus (8–10). In turn, chronic fetal hypoxemia and nutrient insufficiency directly decrease fetal growth rate, and hypoxia induces a redistribution of cardiac output (11–14). This redistribution of fetal cardiac output tends to protect brain and heart growth relative to other organs, termed brain-sparing or central redistribution, but this does not ensure normal brain growth (4,9,15).

The specific neuropathology of FGR is complex and distinct from that in both infants born preterm without FGR and in term infants exposed to a severe acute hypoxic event (2,16). Human FGR imaging studies and postmortem examination, together with animal experimental studies of placental insufficiency and FGR, describe reduced total brain volume, with loss of both gray and white matter substructure. At the cellular level, gray matter areas are shown to have reduced cell number (17) with sparse and disorganized cortical structure (18). The white matter of the FGR brain is described as immature, with delayed oligodendrocyte maturation (19), more unmyelinated axons, and thinner myelin coverage (20), with evidence of astrogliosis and inflammation (21). More recently, it has also been shown that the structural connectivity of the FGR brain is significantly altered, particularly along motor and cortico-striatal-thalamic tracts. Importantly, these measures of reduced tractography correlate with poor neurodevelopmental outcomes in young children who were born FGR (22,23).

FGR is associated with an increased risk for neurodevelopmental impairment, with the degree of impairment

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Received 12 September 2016; accepted 14 January 2017; advance online publication 17 May 2017. doi:10.1038/pr.2017.37

Figure 1. Timeline for the detection and assessment tools available for FGR-related brain injury.

Figure 2. Current status of fetal and neonatal imaging for FGR-related brain injury.

related to (i) the severity of growth restriction, (ii) the onset of FGR (early or late), and (iii) gestation at birth (preterm or term) (2). FGR children born preterm or with evidence of brain-sparing are considered to be at greatest risk for deficits in brain development (24). The neurodevelopmental outcomes of children born after early-onset FGR are worse than outcomes for late-onset FGR. This likely reflects both a greater degree of placental dysfunction and hypoxia adversely affecting brain development, and the impact of preterm birth (25). In addition, preterm FGR infants demonstrate an elevated risk for neonatal complications such as pulmonary hypertension, metabolic disturbances, and necrotizing enterocolitis, which in turn may induce acute

hypoxia/ischemia leading to increased brain injury (26). Late-onset FGR infants are also at risk for altered outcomes, particularly infants with brain-sparing, who show abnormal neurobehavior in the neonatal period and at 2 years of age (27–29). Impairments in school-age children who have FGR encompass gross and fine motor deficits, cognition and learning problems, and behavioral dysfunctions (30,31), and neurological dysfunctions continue into older childhood and adolescence (32). Furthermore, FGR is associated with high risk for diagnosis of cerebral palsy. The rate of cerebral palsy for early-onset FGR is up to 12% for infants delivered at <32 weeks of gestation (25,33,34).

The complex and heterogeneous adverse outcomes observed in FGR children demonstrate the need for accurate neurological assessments that can be applied either antenatally or postnatally, and for the provision of a diagnostic link between the injury observed and long-term consequences. The objective of this review is to bring together the available evidence for the detection and assessment of brain injury linked to FGR, in both the fetus and neonate. We acknowledge that, with no strict definition for FGR, this is imperfect; however, here we have only included published work in which the population was described as “FGR” or “IUGR”.

ASSESSMENT OF FGR-RELATED BRAIN INJURY IN THE FETUS

Fetal Ultrasound

Ultrasound-based fetal surveillance is an established component of modern perinatal care of high-risk pregnancy, including the monitoring of FGR (Figures 1 and 2) (35–37). A major aspect of assessment of fetal well-being and, indirectly, neuropathology in FGR relies on Doppler assessment of fetal and uteroplacental circulations. As placental pathology is considered the principal cause of true FGR (7,10), recent definitions of FGR include fetal umbilical artery Doppler flow velocimetry assessment (36,38). However, it is suggested that a definition of true FGR should not rely on parameters of fetal umbilical artery Doppler alone, as this parameter identifies only severe, early-onset placental insufficiency (39). Instead, FGR should be diagnosed by the presence of poor fetal growth combined with any Doppler observation associated with suboptimal perinatal outcome in umbilical or uterine artery (UA), or cerebral arteries. A recent study in a cohort of FGR fetuses confirmed that evaluation of Doppler parameters, rather than gestational age at birth, allowed better risk stratification of FGR preterm fetuses for neonatal neuropathologies (40).

Fetal ultrasound—umbilical artery Doppler. Growth-restricted fetuses with absent or reversed end-diastolic flow in the UA have increased rates of fetal and neonatal mortality, and a higher incidence of long-term permanent neurologic damage (41). The importance of following UA Doppler status is demonstrated particularly in early-onset FGR, where end-diastolic velocity is reversed in the UA or aorta, whereas cerebral vascular impedance changes are apparent in both early- and late-onset FGR (38). Absent diastolic flow in the UA is a sign of placental resistance and vascular stress, with increasing placental resistance leading to reversal of flow in an already compromised fetal placental unit. Fetal Doppler indices, such as absent or reversed end-diastolic flow in the UA and absent or reversed “a” wave in the ductus venosus (DV), are considered good predictors of neonatal intraventricular hemorrhage (IVH) and death in growth-restricted infants (42,43). Infants who demonstrate an altered UA have poorer motor outcomes at 2 years and at school age when compared with their appropriately grown preterm or term counterparts (44,45). It is pertinent to note that the detection of placental and fetal circulatory abnormalities via ultrasound

does not provide a direct assessment of brain injury but, along with fetal head circumference, severity of growth restriction, and gestational age at delivery, they are very useful determinants of the degree of placental dysfunction, which is, in turn, associated with neurodevelopmental outcomes (46). The overall sensitivity and specificity of reverse end-diastolic flow in UA or DV and adverse perinatal outcomes is 60–80%, with a positive predictive value (PPV) of ~50% and negative predictive value (NPV) of 80% (47,48).

Fetal ultrasound—cerebral doppler. Assessment of the fetal cerebral circulation is particularly useful to observe hemodynamic changes associated with chronic hypoxia and the severity of FGR. The gold standard for fetal brain hemodynamic evaluation is middle cerebral artery (MCA) flow (3) and pulsatility index (49). Reduced pulsatility index in the MCA demonstrates cerebral vasodilatation (and brain-sparing), and a number of studies show that MCA vasodilatation predicts neurodevelopmental deficits after birth (28,50–52). All available data to date indicate that vasodilation of the MCA reflects an advanced and severe stage of growth restriction and brain injury, with high risk for abnormal neurodevelopment (53,54). The anterior and posterior cerebral arteries might also provide cerebral hemodynamic insight, characteristic of the onset and the degree of brain-sparing (50). Scherjon and colleagues showed that fetal brain-sparing with elevated umbilical/cerebral ratio was associated with normal neurodevelopmental outcome at 3 years of age but, at 5 years, infants with brain-sparing had an IQ score 9 points lower than expected (30,55). Fetal blood flow redistribution in favor of the fetal brain can also be detected and quantified by the Doppler cerebral/umbilical ratio (C/U ratio = cerebral resistance index (CRI)/umbilical resistance index) (56) and the fractional moving blood volume estimation (57). Fetal deterioration in chronic and severe hypoxia is characterized by the disappearance of physiological cerebral vascular variability, followed by an increase in cerebral vascular resistance (56). However, studies on growth-restricted and hypoxic human fetuses have shown that perinatal brain lesions can develop even before the loss of cerebrovascular variability (27). The cerebroplacental ratio (ratio of Doppler indices of MCA and UA) is an important predictor of adverse perinatal and later outcomes. The sensitivity and specificity of an abnormal cerebroplacental ratio for an adverse perinatal outcome lies between 60% and 80% (58).

Fetal ultrasound—others doppler studies. Aortic isthmus Doppler has been proposed as a novel method to interrogate oxygenation of the cerebral circulation in the presence of brain-sparing. When downstream placental vascular resistance is high and cerebral vascular resistance is low, blood leaving the right ventricle may take the path of least resistance and flow retrograde through the aortic isthmus. This results in poorly oxygenated blood from the right ventricle, destined for the placenta, instead being shunted through the aortic isthmus to the cerebral circulation (59). In the setting of early-onset severe FGR, retrograde flow increases the likelihood of IVH and periventricular leukomalacia (60). Not surprisingly, such

retrograde flow has been linked with adverse neurodevelopmental outcomes at the age of 2–5 years (61).

UA Dopplers have also been studied, but their role in the assessment of brain injury or outcomes in FGR is not clear (62). Overall, fetal Dopplers greatly assist in the assessment and prediction of FGR, particularly the more severe cases, and, although these Doppler indices do not detect brain injury *per se*, they provide an essential first screening to identify fetuses at greatest risk of brain injury. Less severe FGR fetuses are more difficult to detect via Doppler assessments and, therefore, FGR and associated neuropathology may be missed.

Fetal ultrasound—direct assessment of brain structure. In addition to assessment of the fetoplacental circulation, ultrasound also offers opportunities to assess fetal brain structure. Prenatal 3D ultrasound can detect smaller brain volume in FGR fetuses (63), and can detect coexistent neuropathologies including intracranial hemorrhage and hydrocephalus, which may not be due to FGR but contribute to adverse outcomes (64). FGR fetuses show differences in the volume of many intracranial structures compared with appropriate for gestational age fetuses, with the largest difference observed in the frontal region. Nomograms exist for the ultrasonographic dimensions of the fetal corpus callosum, allowing for prenatal diagnosis of abnormal callosal development (65,66). Cerebellar size, measured by ultrasound, is correlated with the severity of FGR, and therefore the trans-cerebellar diameter may also have prognostic significance (67). Although there are some studies that have correlated fetal corpus callosum and trans-cerebellar diameter changes with neurobehavior and neurodevelopment (68–70), these remain relatively rudimentary detecting only the most overt structural changes.

Fetal ultrasound—assessment of fetal behavior. Fetal biophysical profile, which assesses fetal tone, breathing, and body movements, has been traditionally used in the surveillance of high-risk pregnancies, and its accuracy in prediction of perinatal and neonatal outcomes continues to be debated (7). Kurjak *et al.* (71) proposed a scoring system for the assessment of fetal neurological status by 4D sonography named “Kurjak Antenatal Neurodevelopmental Test (KANET)”. This test assesses fetal behavior in a qualitative and quantitative manner (72); however, it remains unvalidated in large studies by independent operators and requires skill development and expertise that currently limits its widespread use.

In summary, a number of fetal ultrasound tools are available to directly and indirectly detect, assess, and prognosticate on neurological outcomes of FGR fetuses. Comprehensive evaluation of heterogeneous FGR fetuses in large studies will aid elucidation of the most reliable and feasible neuroimaging assessments capable of predicting neurodevelopmental outcomes.

Fetal MRI

Fetal brain MRI has revolutionized early detection of intrauterine CNS injury in high-risk fetal and pregnancy

conditions. Fetal MRI can be technically challenging, with acquisition of diagnostic quality fetal brain MRI affected by the trans-abdominal intrauterine environment and fetal movement. Fetal MRI brain is ideally done in a center with good radiological expertise, in late gestation when the fetal head is fixed in the maternal pelvis. In FGR, fetal brain MRI is currently used predominantly as a clinical tool to exclude gross brain malformations, and as a research tool for the evaluation of FGR-related brain injury; hence, predictive values for adverse outcomes are not yet available.

Fetal MRI—brain structure. Fetal MRI provides a sensitive and detailed assessment of the developing brain in high-risk conditions, including for growth-restricted fetuses, with the capacity to correlate fetal brain structural anomalies with neurodevelopmental outcomes (73). MRI of the fetus and the fetal brain has been used to confirm circulatory redistribution—brain-sparing—in FGR fetuses via assessment of fetal organ volumetry (13) or superior vena caval and umbilical vein perfusion (74). Fetal brain MRI has also been used in late-onset FGR fetuses to demonstrate an abnormal pattern of cortical development (75). Brain function, especially childhood development, is tightly linked to the development of the cortex in late gestation, and MRI with post-processing image analyses can provide insight into cortical development (76). This is reflected in the use of conventional MRI and diffusion tensor imaging (DTI) of appropriately grown and FGR fetuses, which has elucidated the relationship between changes in intracortical layering and cortical folding, where FGR is associated with altered cortical development (76). Fetal MRI of the corpus callosum has also confirmed that this structure is significantly smaller in FGR fetuses, and this is correlated with adverse neonatal neurobehavioral outcomes (68).

Fetal MRI—brain metabolism. Magnetic resonance spectroscopy (MRS) is a standard tool used in the early neonatal period to examine brain biochemistry wherein changes in MRS can predict neurological outcomes in perinatal brain injury, especially birth asphyxia (77). More recently, MRS has been successfully undertaken on the fetal brain, and to date demonstrates similar findings to those observed in neonatal populations with respect to altered brain metabolite concentrations within the compromised brain. MRS is particularly useful when subtle changes are present on conventional fetal MRI sequences (78). Brain-sparing in FGR fetuses is associated with altered brain metabolism evidenced by a reduction in the peak ratios of the metabolites N-acetylaspartate: Choline (NAA:Cho) and N-acetylaspartate: Creatine (NAA:Cr) (79). NAA is a very useful marker of neuronal cell integrity, and therefore reduction in these ratios principally reflects a loss of neurons within the FGR brain. Furthermore, frontal lobe NAA:Cho ratio in FGR and appropriately grown fetuses shows a strong association with corpus callosum development (80). The brain metabolite myo-inositol, considered a good marker of glial astrocyte cells, has also been examined in FGR and appropriately grown fetuses via

MRS, but levels in key brain regions are not shown to be significantly different between cohorts (81).

In summary, a number of promising MRI and MRS tools for use in the fetus are currently being investigated. It is apparent that they can provide excellent direct assessments of structure and biochemistry of the developing brain, and to date results suggest that fetal MRI and MRS outcomes show strong predictive value for long-term neurodevelopmental outcomes. Fetal MRI is, however, not readily available across obstetric and birth centers, and requires specialist expertise, adequate training of radiology personnel involved, and resources to obtain reliable, clinically useful, and relevant information. Moving forward, it will be critical for individual centers to evaluate the pros and cons of obtaining fetal brain MRI assessments, with consideration for the expertise and resources available.

DETECTION OF BRAIN INJURY IN THE FGR NEONATE

In high-resource clinical settings, approximately half of the FGR fetuses are detected antenatally (82) (Figures 1 and 2). The findings presented above demonstrate that fetal assessment of the FGR brain could effectively be incorporated into routine clinical care to detect neuropathology associated with FGR, particularly in the most severe cases. However, in the remaining (antenatally undiagnosed) FGR neonates, it is critical that effective screening and detection strategies are in place for the assessment of neuropathology after birth. In the first instance, an important consideration is therefore the neonatal identification of the growth-restricted infant who would be appropriate for a newborn imaging examination. This allows for the possibility of neuroprotective strategies to treat FGR-related brain injury to commence shortly after birth, and certainly provides clinicians and parents with knowledge regarding diagnosis and follow-up requirements across the spectrum of potential outcomes.

Neonatal Ultrasound

Cranial ultrasound enables bedside, easily available serial cerebral assessment, and is commonly used as the primary brain-imaging modality in high-risk neonates, especially those born preterm. It is well described that significant brain abnormalities evident on neonatal cranial ultrasound are associated with adverse neurodevelopment (83). Neonatal cranial ultrasound is considered the gold-standard screening method for neonatal brain injury, for the detection of major or significant abnormalities of the brain, most notably severe IVH or cystic periventricular leukomalacia in the preterm infant. It is, however, not generally considered sensitive enough to detect and assess subtle or diffuse brain pathologies in the neonatal period (84), and most term-born growth-restricted infants are unlikely to have a brain lesion easily identifiable by neonatal cranial ultrasound. Overall, the sensitivity of neonatal ultrasound to detect any brain injury predictive of adverse motor outcomes at 2–3 years ranges between 20% and 60%, with specificity of 80–95% especially

with severe injury, PPV of 20–60%, and NPV of 85–100% (85).

The interaction of prematurity and FGR on neonatal hemorrhagic and ischemic brain damage, as detected by cranial ultrasound, has been described and debated for over 20 years (86,87). There is inconsistent evidence on whether placental insufficiency and FGR is directly linked to IVH and other neonatal cranial ultrasound abnormalities (88–91). Some studies have shown FGR to be associated with an increased prevalence of IVH and white matter damage detectable on ultrasound brain scans in preterm neonates (92–94). In contrast, other studies have reported a reduced rate of IVH in FGR infants (95,96) or have shown no change in the incidence of neonatal cranial ultrasound abnormalities in FGR infants compared with appropriately grown preterm infants (91,97,98). More recently, two studies have found an increase in cranial ultrasound abnormalities in preterm FGR infants compared with matched controls (40,99). This spectrum of outcomes may exist because of different definitions of FGR, inclusion criteria, and quality of ultrasound technology used.

Neonatal MRI

MRI of the brain in the neonatal period is a gold standard for non-invasive structural assessment of the brain with excellent sensitivity and prognostic utility. Neonatal brain MRI is considered supplementary to routine and sequential cranial ultrasound, and is most commonly used in term and preterm infants with suspected brain injury or in infants considered high risk (for example, infants born extremely preterm). Advances in MRI technology and post-processing have greatly progressed our understanding of, and ability to detect, neonatal neuropathology, resulting in a broad shift from simply using neonatal MRI for the detection of severe cystic brain lesions toward the assessment of subtle and/or diffuse injury, or injury that is region-specific (84). MRI provides for a range of assessments of the neonatal brain that can be correlated with outcome measures of childhood motor and cognitive function, behavior, and learning (100). Specifically for motor outcomes, neonatal MRI demonstrates 80–100% sensitivity and specificity, PPV between 30 and 90%, and NPV of 90–100% (85).

Neonatal MRI—brain structure. More than a decade ago, Tolsa and colleagues used echo-planar MRI to demonstrate that FGR neonates imaged within 2 weeks after preterm birth demonstrate region-specific alterations in brain development, with decreased total brain volume and cortical (gray matter) volume compared with appropriately grown infants. A second MRI at term-equivalent age confirmed that the reduction in total intracranial and gray matter volume in FGR infants, with reduced cortical volume at term, correlated with worse behavioral outcomes (27). MRI examination of preterm-born FGR and appropriately grown infants at term-equivalent age found no differences in the incidence of gross brain lesions, or in the degree of morphological brain maturation between the

two groups; however, there was a delay in myelination within the FGR cohort (101). Preterm FGR neonates have also been shown to have discordant gyrification and cortical folding observed on MRI soon after birth, which can predict term-equivalent-age cerebral volumes and neurobehavioral development (18). There are a number of studies that have shown structural differences (including in the gray matter) in the brain of FGR infant as compared with the appropriately grown infant at a later age (70,102).

The hippocampus is a highly vulnerable brain structure that is altered in response to chronic fetal hypoxia and therefore frequently reported as abnormally developed in human and animal experimental FGR (2). The hippocampal structure of preterm-born FGR infants has been examined using 3D MRI at term-equivalent age, demonstrating reduced hippocampal gray matter volume. Hippocampal volume reduction was associated with functional behavioral differences at term-equivalent age, but not at 24 months of corrected age (103).

Neonatal MRI—brain metabolism. Although MRS is regularly used in the early assessment and diagnosis for acute neonatal encephalopathy associated with birth asphyxia (hypoxic ischemic encephalopathy), MRS has not been routinely used for assessment of the neonatal FGR brain. This is likely contributed by the difficulty in imaging FGR neonates very soon after birth, at a time when brain biochemical metabolites may be still be influenced by the chronic disturbances resultant from placental insufficiency. A recent study in neonatal FGR rabbits showed reduced NAA in the cerebral cortex and hippocampus, likely because of a loss of neuronal cells, and higher levels of glycine in the striatum. These metabolic changes were correlated with decreased brain volume (104). Similarly, regional differences in brain neurochemical profiles have been observed in FGR rats (105).

Neonatal MRI—brain organization and networks. A relatively new imaging tool allows the examination of brain organization using diffusion MRI, which we now appreciate, has the potential to describe complex brain connection networks, and to correlate these with neurodevelopmental outcomes. Specifically, MRI-based connectomics is an emerging approach to extract information from MRI data that exhaustively maps inter-regional connectivity within the brain to build a graph model of the neural circuitry forming the brain network (106,107).

DTI assessment of fractional anisotropy (FA), which provides microstructural information on the density and organization of white matter tracts, provides an excellent assessment modality for white matter development within the brain. FGR is associated with a complex pattern of brain reorganization (as demonstrated by FA) in specific regions of the brain, as determined from voxel-based analysis in the neonatal period (107,108). A recent study in FGR neonates showed hyper-connected but poorly organized brain networks that were most notable within the frontal, cingulate, and lingual cortices (109). A number of further brain connectivity

studies have been performed at a later age (typically around 1 year of age or beyond) showing altered brain network organizations in infants born growth-restricted (22,23,102,110–112). Importantly, two recent studies demonstrate that brain connectivity is predictive of subsequent functional delays in preterm and/or FGR infants (23,113). The future study of neuropathology in FGR infants should incorporate examination of brain connectivity, which is emerging as a predictive assessment of complex brain reorganization that occurs in FGR infants in response to placental insufficiency.

In summary, advanced neonatal MRI of brain structure and microstructure, incorporating the use of DTI, is increasingly being used for the detection and assessment of FGR-related brain injury in infants after birth. MRI provides high resolution and therefore the capability for detecting subtle, but clinically important, brain-imaging information. It is becoming apparent that neonatal brain examination of FGR infants must incorporate detection of white matter injury and altered brain connectivity, and link with robust follow-up data. Altogether, these will provide evaluation on how brain microstructural changes correlate with long-term neurodevelopmental outcomes in FGR infants.

OTHER TOOLS AND TECHNIQUES TO DETECT FGR-RELATED BRAIN INJURY

A range of indirect assessment tools that have been used to identify the presence or severity of brain injury have been the subject of trials in growth-restricted fetuses and newborns. Visual evoked responses using magnetoencephalography provide a simple and non-invasive assessment of brain function, and are delayed in FGR fetuses (114). A number of other tools available in the neonatal period may predict long-term neurodevelopmental outcomes in FGR infants. In the first instance, this may be as simple as the measure of smaller head circumference in FGR infants, which is a good predictor for poor neurodevelopmental outcome (115). Although head circumference is an important predictor of neurodevelopmental outcome independent of gestational age, overall growth delay in the fetal period as impacted by the severity of FGR probably has the greatest impact in early-onset FGR (46). Overall, postnatal growth restriction, especially poor head growth, can have an additive impact on adverse neurodevelopment (116). Higher postnatal venous hematocrit and lower cerebral blood flow velocity have also been suggested as prognostic markers for adverse neurodevelopment in FGR neonates (117). Nuclear magnetic resonance spectroscopy-based analysis of umbilical vein blood in FGR infants has shown interesting patterns of metabolite change. Increased lipid levels were present in umbilical vein samples from both early and late FGR infants, whereas glucose was decreased and acetone increased in early FGR infants. FGR cases also showed increased glutamine and creatine levels, whereas the amounts of choline, valine, leucine, phenylalanine, and tyrosine were decreased in cord blood samples (118). S100B is a glial astrocyte protein that is

released from brain astrocytes in response to injury, and elevated cord blood levels of S100B are associated with subsequent diagnosis of cerebral palsy (119).

Last, qualitative assessment of general movements (GMs) (120) is a powerful diagnostic method to evaluate brain dysfunction in “at-risk” preterm and term infants (121). Many infants with growth restriction have transient abnormal GMs in the early newborn period, indicating the importance of obtaining serial observations. As is the case with preterm infants, the quality of fidgety movements (when examined at 12 weeks post term age) is predictive for neuromotor outcome in term and preterm FGR infants (122,123). Irrespective of imaging and other diagnostic modalities used, FGR infants should be closely followed up after birth to ascertain the impact of FGR on long-term neurodevelopmental outcomes, incorporating motor, cognition, and behavioral assessments, in this vulnerable population.

CONCLUSIONS

Detection and assessment of neuropathology in the fetus or neonate is a major challenge for modern perinatal medicine, allowing for timely delivery of the fetus, prediction of long-term consequences, and neuroprotective interventions. FGR is a common complication of pregnancy, and FGR infants have a greatly elevated risk for fetal and neonatal brain injury, such that strategies for the detection and treatment of FGR neuropathology are of great interest. We suggest that optimizing outcomes for FGR infants requires a collaborative approach, incorporating improved detection of true FGR infants during pregnancy via Doppler assessment of the degree of growth restriction. These infants in whom FGR is confirmed antenatally should provide a reference group for further validation studies incorporating biomarkers of brain injury, general movement assessment after birth, and direct assessment of the brain via cranial ultrasound and MRI in the neonatal period. For all FGR newborns, it is clear that early assessment of brain abnormalities should be a principal aim and, where possible, advanced MRI should be incorporated to provide clinicians and parents with accurate diagnostic information. There are currently no interventions or treatments that are available to improve brain development in FGR infants, and this should be a research focus to reduce the burden of neurodevelopmental impairments associated with FGR.

ACKNOWLEDGMENTS

AM is supported by a Royal Australasian College of Physicians Foundation Research Scholarship; GRP is supported by a National Health and Medical Research Council Fellowship; and SM is supported by an Australian Research Council Future Fellowship. We would also wish to acknowledge the Victorian Government's Operational Infrastructure Support program.

Disclosure: The authors declare no conflict of interest.

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