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Fetal brain development in fetal growth restriction using MRI: a systematic review

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Abstract

Background This systematic review investigates potential differences in brain development between growth restricted (FGR)-fetuses compared to appropriate for gestational age (AGA) fetuses using MRI.

Methods PubMed, Embase, Cochrane Library and Web of Science databases were searched from 1985 to 2023. FGR was defined as an estimated fetal weight (EFW) < p10 and/or an abdominal circumference (AC) < p10, or 20% reduction in EFW or AC using a minimum interval of two weeks. Outcomes included volumetrics, biometrics, apparent diffusion coefficients (ADC), ^{1}H-MRS-metabolites, and oxygenation of the fetal brain. Risk of bias was assessed using Newcastle-Ottawa Scale (NOS). A meta-analysis was conducted on variables when reported in at least three studies, calculating the mean difference (MD) with a 95% confidence interval (CI).

Results Twenty-nine studies were included after three-phase screening, 13 used the FGR consensus definition according to the Delphi procedure. Total brain volume and cerebellar volume were significantly reduced in FGR fetuses ($n = 183$; 74) when compared to AGA fetuses ($n = 283$; 166) with a MD of -30.84 cm^3 ($p < 0.01$) and -2.24 cm^3 ($p < 0.01$). ADC values in the frontal white matter (FWM), occipital white matter (OWM), temporal white matter (TWM), thalami, centrum semiovale (CSO), basal ganglia, pons and cerebellum, significantly lower in growth restricted fetuses (-0.07×10^{-3} mm^2/s ($p < 0.01$); -0.06×10^{-3} mm^2/s ($p < 0.01$); -0.07×10^{-3} mm^2/s ($p < 0.01$); -0.10×10^{-3} mm^2/s ($p < 0.01$); -0.06×10^{-3} mm^2/s ($p < 0.01$); -0.07×10^{-3} mm^2/s ($p < 0.01$); -0.07×10^{-3} mm^2/s ($p < 0.01$); -0.02×10^{-3} mm^2/s ($p < 0.01$); respectively). ^{1}H-MRS showed reduced levels of N-acetyl aspartate (NAA): Choline (Cho) and NAA: Creatine(CR) levels in the frontal lobe and central brain tissue, whilst contradictive findings concerning Cho: Cr and Inositol(Ino): Cho ratios were found. Two studies investigated the cerebral hemodynamic changes in FGR fetuses showing no difference in fractional moving blood volume, similar venous blood oxygenation in the superior sagittal sinus and no difference in T2* in the fetal brain.

Discussion MRI provides additional information on fetal brain development in a growth restricted population. Smaller total brain and cerebellar volumes and lower ADC values in the FWM, OWM, TWM, thalami, CSO, basal ganglia, pons and cerebellum have been observed in FGR. These conclusions are drawn on relatively small sample sizes with high heterogeneity resulting from diverse study populations and MRI techniques. Furthermore, how these findings correlate to long-term neurocognitive abnormalities associated with FGR remains to be elucidated. A large cohort study comparing brain maturation, myelination, metabolic and hemodynamic status between brain-sparing FGR fetuses to healthy age-matched controls is needed.

Keywords Fetal growth restriction, Fetal MRI, Brain development, Systematic review

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Background

Fetal growth restriction (FGR) complicates 5–10% of pregnancies and affects approximately 30 million pregnancies per year worldwide [1, 2]. It is most often caused by placental insufficiency and leads to significant perinatal morbidity and mortality [3]. Placental insufficiency reduces both the supply of oxygen and nutrients to the fetus [2]. The fetal circulation changes by shifting cardiac output towards the brain to 'spare' it from possible hypoxia and undernutrition; this phenomenon is commonly known as brain-sparing [4].

Even though brain-sparing serves as a fetal survival mechanism, the term is misleading since it does not automatically spare the brain from altered development [5]. FGR is associated with the development of brain injury, structural deficits in brain development, and long-term neurodevelopmental abnormalities [2, 6, 7]. Such abnormalities include impaired motor and cognitive functions (e.g. cerebral palsy, lower intelligence quotient (IQ) and attention deficit hyperactivity disorder) [8].

The timing of altered brain development and the identification of FGR infants at risk for adverse neurodevelopmental outcomes remains challenging. Early identification of the FGR fetuses at risk offers an opportunity to prevent or reduce adverse neurodevelopmental outcome secondary to altered brain development. This could be done by optimizing timing of delivery before irreversible brain damage occurs and by identifying a potential therapeutic window for new medications [9, 10].

The current clinical standard to evaluate fetal brain development is ultrasound (US). However, magnetic resonance imaging (MRI) can complement US by assessing brain development and maturation based on gyrification, myelination, metabolic status, ischemia, and hemodynamics using various modalities [7, 11–36] Conventional T2-weighted sequences provide a detailed depiction of the fetal brain. This allows for qualitative assessment of brain injury or structural deficits and segmentation, suitable for volume calculations and quantification of gyrification. Additional sequences used in the FGR population are diffusion-weighted imaging (DWI), proton magnetic resonance spectroscopy (^{1}H-MRS), susceptibility-weighted (SWI) MRI and transverse relaxation time (T2*) [7, 11–33, 37] (Fig. 1 and Appendix 3). All these sequences might contribute to a better understanding of brain development and altered cerebral hemodynamics in FGR fetuses.

This systematic review aims to outline the differences in fetal brain development between FGR-fetuses and appropriate for gestational age (AGA) fetuses using various MRI-techniques.

Methods

Protocol and registration

This systematic review was written according to the PRISMA 2020 guidelines and preregistered on PROSPERO on the 7th of January 2022 (CRD42022302227).

Eligibility criteria, information sources, search strategy

PubMed and Embase databases were first searched on the 14th of July 2022 by two independent researchers (IvO and LM). The search was repeated and expanded including Cochrane Library and Web of Science databases on the 1st of November 2023. Our search contained terms for "Magnetic Resonance Imaging", "Fetus", "Fetal Growth Retardation", and "Brain" (search string in Appendix 1). All gestational ages, all publication years and all languages

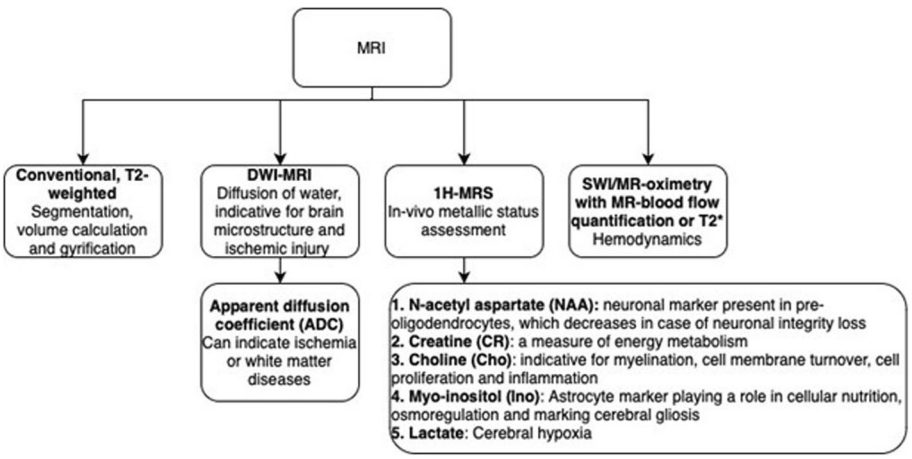

Fig. 1 Different MRI techniques available to provide insight in fetal brain development. DWI: Diffusion-weighted, ^{1}H-MRS: proton magnetic resonance spectroscopy, MRI: magnetic resonance imaging, SWI: susceptibility-weighted

were included. Post-mortem studies or animal studies were excluded. Appendix 2 depicts a flowchart on the screening and exclusion process performed by the same two researchers (IvO and LM). References lists were screened for additional inclusions. Inclusion criteria were human observational case-control and cohort studies investigating the brain development using fetal MRI in growth restricted fetuses compared to a control group. Since the definition of FGR was reached by Delphi consensus in 2016, we extended our study population to SGA as well to comply with no publication year restrictions and to include retrospective observational studies.

FGR was defined as an estimated fetal weight (EFW) < p10 and/or an abdominal circumference (AC) < p10 or 20% reduction in EFW or AC using a minimum interval of two weeks [38]. An inclusion requirement was availability of a control group. Studies were excluded in case of multifetal pregnancies, chromosomal anomalies, congenital anomalies or infections.

Data extraction

Data was extracted by two independent researchers (IvO and LM) and discrepancies were resolved by consensus decision. Data was extracted on type of MRI, definition of FGR, Doppler measurement, sex of the included fetuses and gestational age (GA) at time of MRI. Our primary outcomes included brain volumetrics, brain biometrics (e.g. corpus callosum length and sulcus depth), apparent diffusion coefficients, ^{1}H-MRS-metabolites, and blood oxygenation. If research groups continued to recruit patients after the first publication, we used the latest publication for the meta-analysis. When data was presented in graphs the authors were contacted via email. If no response was received after two emails, data from the graphs was extracted using apps.automeris.io. software (Pacifica, California, USA).

Assessment of risk of bias

The quality of the studies was assessed using the Newcastle-Ottawa Quality Assessment scale by two independent researchers (IvO and LM) [39].

Statistical analysis

If more than three studies reported on the same variable a meta-analysis was conducted to provide insight in the pooled effect. Meta-analysis was performed using R (version 4.0.3). The mean difference (MD) with a 95% confidence interval was calculated to compare the outcomes for FGR and AGA fetuses. If outcomes were reported as median with interquartile rage, the mean and standard deviation (SD) was calculated [40]. When studies lacked to report a SD, the highest SD included in the meta-analysis was imputed for the missing value [41]. Heterogeneity was evaluated using I^2 where less than 25% was considered low, 25–50% moderate and over 50% high heterogeneity [42].

Results

Inclusion/selection of studies

The literature search yielded 1166 studies, the removal of duplicates resulted in a total of 626 studies (Appendix 2). Our three-phase screening resulted in 29 included studies [7, 11–33, 37, 43–46].

Twelve studies reported on brain volumetrics and nine studies reported on other brain biometric parameters. Seven studies implemented DWI-MRI measuring ADC-values and five studies used ^{1}H-MRS to investigate fetal brain metabolism. Two studies looked at cerebral hemodynamics (Tables 1 and Appendix 3). A meta-analysis was performed on the following outcomes: total brain volume, ADC-values in the frontal white matter (FWM), occipital white matter (OWM), temporal white matter (TWM), thalami, centrum semiovale (CSO), basal ganglia, pons and the cerebellum.

Risk of Bias of included studies

Five studies scored seven out of nine points in the risk of bias analysis [13, 15, 16, 22, 27]. Overall, risk of bias was high, with 13 studies receiving four or less points. Most frequently studies scored low on comparability and appropriate follow up (Appendix 4).

Study characteristics

Thirteen studies implemented the FGR definition according to the Delphi procedure, nine of them included a definition of brain-sparing as part of the inclusion criteria for FGR [11, 13, 20, 23–25, 28, 30, 31]. Five studies investigated a more severe FGR population with EFW below 5th percentile where all other studies used an EFW under the 10th percentile [13, 20, 23, 28, 33]. 19 studies reported the sex of the included fetuses, in four of those studies the percentage of included males varied > 20% between FGR and controls [25, 27, 30, 44]. The GA at the MRI varies from 20 to 40 weeks and in six studies the GA at time of scanning differed more than a week between FGR and controls [13, 17, 30–32, 37].

Synthesis of results

For brain volumetrics raw data was received from Duncan et al. and Zhu et al. [14, 20]. The data was extracted from graphs for Baker et al. [12]. The highest SD included in the meta-analysis was imputed for Andescavage et al. since no standard deviation was reported [11, 41]. The units for the ADC meta-analyses were recalculated to x 10^{-3} mm^2/s for Kutuk et al. and Sanz-Cortes et al. For

Table 1 Overview of studies with baseline characteristics and reported outcomes

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Volumetrics											
Baker [12] 1995 UK Retrospective study	T2-weighted (Modulus-blipped EPI), 0.5T, slice thickness 1 cm, manual segmentation, no motion correction	BW < p10	Not defined as inclusion criteria	Suspected problems with placental site, uterine anomalies, unexplained antepartum hemorrhage, nonproteinuric hypertension	11	34.5 ± 1.8*	21	35.0 ± 1.8*	Graphic	=	TBV was not different in FGR compared to controls when plotted against gestational age.
Duncan [14] 2005 UK Prospective, observational study	T2-weighted (Multi-slice EPI), 0.5T, slice thickness 7 mm, manual segmentation, no motion correction, repeated scan in case of motion	AC < p10 and confirmed BW < p10	Not defined as inclusion criteria	No abnormalities at 6 weeks postnatal life	37	34.4 ± 3.3*	33	34.4 ± 3.3*	TBV: 278.81 ± 75.24 cm^3 vs. 332.16 ± 81.85 cm^3	↓	TBV was significantly reduced in FGR compared to controls when plotted against gestational age.
Damodaram° [13] 2012 UK Prospective, observational study	T2-weighted (SSFSE), 1.5T, slice thickness 4 mm, manual segmentation, no motion correction, repeated scan in case of motion	EFW < p5	5 groups: (1) UA PI > p95, (2) + MCA PI < p5, (3) Absent flow, (4) Reversed, (5) Absent or reversed a wave in DV	Structurally normal fetuses	20	26.6 ± 3.4	19	29.3 ± 2.7	Graphic	=	TBV was not different in FGR compared to controls when plotted against gestational age.
Egana-Ugrinovic [15] 2013 Spain Prospective, observational study	T2-weighted (HASTE), 3.0T, slice thickness 3.5 mm, semiautomatic segmentation, no motion correction, repeated scan in case of motion	EFW and confirmed BW < p10	Normal UA PI	Normal term fetuses with EFW > p10 and confirmed BW > p10	52 (62%)	37.5 ± 0.8	50 (52%)	37.7 ± 0.8	ICV: 441.25 ± 56.01 cm^3 vs. 515.82 ± 36.63 cm^3 ($p < 0.01$) TBV: 276.47 ± 52.61 cm^3 vs. 312.07 ± 40.85 cm^3 ($p < 0.01$) LOV: 2.52 ± 0.69 cm^3 vs. 3.02 ± 0.71 cm^3 ($p < 0.01$)	↓	Lower ICV, TBV and LOV in FGR compared to controls. No differences in ROV.
Egana-Ugrinovic [22] 2014b Spain Prospective, observational study	T2-weighted (HASTE), 3.0T, slice thickness 3.5 mm, manual delineation, no motion correction, repeated scan in case of motion	EFW and confirmed BW < p10	Normal UA PI	Normal term fetuses with EFW > p10 and confirmed BW > p10	65 (59%)	37.5 ± 0.8	59 (56%)	37.6 ± 0.9	LIV: 0.904 ± 0.274 cm^3 vs. 1.099 ± 0.283 cm^3 ($p < 0.01$) RIV: 0.860 ± 0.258 cm^3 vs. 1.059 ± 0.287 cm^3 ($p < 0.01$)	↓	Smaller left and right insular volumes in FGR when compared to controls.
Sanz-Cortes [19] 2014 Spain Prospective, observational study	T2-weighted (SSFSE), 3.0T, slice thickness 3.5 mm, semiautomatic segmentation, no motion correction, repeated scan in case of motion	EFW and confirmed BW < p10	Normal UA PI	EFW and confirmed BW > p10	51 (53%)	37.3 ± 0.9	47 (53%)	37.5 ± 0.8	0.042 ± 0.01 mm vs. 0.038 ± 0.00 mm ($p = 0.04$)	↑	Larger cerebellar volume/total intracranial volume in FGR when corrected for sex, maternal smoking and gestational age

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Zhu [20] 2016 Canada Prospective, observational study	T2-weighted (3D-SSFP), 1.5T, slice thickness 1 mm, automatic mapping, no motion correction	Scoring system. FGR≥2: - BW < p3 or 20% drop. - Ponderal index < 2.2 (grams per cm3) - Lowest CPR after 30 weeks < p5 - placenta histology meets underperfusion criteria	Some cases CPR < p5	FGR scores < 2	14	35.4 ± 2.4	26	35.9 ± 0.9	249 ± 55 g vs. 300 ± 29 g ($p = 0.005$)	↓	Smaller brain weights in FGR compared to controls
Andescavage° [11] 2017 USA Prospective, observational study	T2-weighted (SSFSE), 1.5T, slice thickness 2 mm, automatic atlas-based segmentation with motion correction and manual correction (3D reconstruction)	EFW < p10	either UA PI > p95 or CPR < 1 or evidence of AC lagging HC > 1 week	Normal prenatal history, including screening laboratory and ultrasound studies	35 (40%)	30.2 ± 4.3*	79 (41%)	29.6 ± 6.3*	TBV: 147.4 cm^3 vs. 169.9 cm^3 ($p < 0.01$) Cerebrum: 138.32 cm^3 vs. 157.9 cm^3 ($p < 0.01$) Cerebellum: 6.17 cm^3 vs. 7.8 cm^3 ($p < 0.01$) Brainstem: 2.50 cm^3 vs. 2.53 cm^3 ($p = 0.88$)	↓	TBV, cerebrum and cerebellar volumes were significantly smaller, brainstem volumes were not different for FGR and controls.
Polat° [7] 2017 Israel Retrospective study	T2-weighted (SSFSE), 1.5T, slice thickness 3–4 mm, manual segmentation, no motion correction	EFW < p10	UA PI > 3 or absent/reversed flow or abnormal UtA and/or thickened placenta, or low amniotic fluid	Suspicious non-cerebral ultrasound findings, a family history of developmental delay, inborn malformations or genetic background, extracranial malformation, and insignificant genetic finding. No overt pathologic MRI findings were found	13 (46%)	31.6 ± 1.1	21 (52%)	32.3 ± 0.6	STB: 162.0 ± 30.4 mL vs. 197.0 ± 21.8 mL ($p = 0.002$) STC: 215.8 ± 42.7 mL vs. 271.6 ± 32.7 mL ($p = 0.001$) LH: 80.6 ± 14.9 mL vs. 98.6 ± 10.9 mL ($p = 0.001$) RH: 81.4 ± 15.6 mL vs. 98.4 ± 10.9 mL ($p = 0.003$) LT: 8.9 ± 2.0 mL vs. 11.3 ± 1.3 mL ($p = 0.001$) RT: 9.2 ± 2.0 mL vs. 11.4 ± 1.5 mL ($p = 0.004$) TT: 18.0 ± 4.0 mL vs. 22.8 ± 2.7 mL ($p = 0.001$) Cerebellum: 6.3 ± 1.6 mL vs. 9.1 ± 1.6 mL ($p = 0.001$)	↓	Smaller STB, STC, LH, RH, LT, RT, TT and cerebellum in FGR when compared to controls.

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Javor [17] 2018 Austria Prospective, observational study	T2-weighted, DWI (b = 0 and b = 700s/mm2) 1.5T, manual segmentation, no motion correction	EFW < 10	If available, UA PI > p95	Mild ventricular asymmetry, diaphragmatic hernia, bone malformation, heart malformation and renal cysts (known genetic abnormalities and congenital heart disease were excluded)	34	29.1 ± 5.2	72	30.8 ± 5.9	TBV: 127.0 ± 69.5 cm^3 vs. 124.6 ± 66.9 cm^3 ($p = 0.22$)	=	TBV was not different in FGR compared to controls when plotted against gestational age.
Li [18] 2021 China Retrospective study	3D- FIESTA with breath hold 12–18 s, 1.5T, slice thickness 2 mm, semi-automatic segmentation, no motion correction	BW < p10	Not defined as inclusion criteria	Infant with BW p10-p90	42	32.1 ± 3.1	105	31.2 ± 3.8	N/A	N/A	Higher fetal brain: liver volume has a high sensitivity to identify FGR
Peretz [43] 2022 Israel Historical cohort study	T2-weighted, 1.5T, semiautomatic segmentation with manual corrections in case of motion	BW or EFW < p10	Notch in UA, high resistance in UA, abnormal systolic-diastolic flow ratio in UA, increased diastolic flow in UA, abnormal MCA PI, pathologic or thickened placenta, low amniontic fluid	No abnormal findings and BW > p10	26 (57%)	33.3 ± 2.8	66 (48%)	34.1 ± 2.6	ST: 179.9 ± 45.7 mL vs. 210.7 ± 49.0 mL ($p < 0.01$) RH: 88.4 ± 22.0 mL vs. 105.3 ± 24.6 mL ($p < 0.01$) LH: 88.8 ± 22.7 mL vs. 105.2 ± 24.8 mL ($p < 0.01$) Cerebellum: 10.3 ± 3.5 mL vs. 12.2 ± 3.3 mL ($p = 0.02$)	↓	Significantly smaller volumes for ST, RH, LH and cerebellum in FGR. However, the effect of FGR on brain volumes is smaller than on BW.
Biometrics											
Abe [21] 2004 Japan Retrospective study	T2-weighted (HASTE), 1.5T, slice thickness 6–8 mm, manual scoring, no motion correction	BW < p10 (MRI indications: Uterine fibroma, ovarian cysts, cervical cancer, placental anomalies, abnormal amniotic fluid volume and suspected fetal abnormalities on US)	Not defined as inclusion criteria	BW > p10 (MRI indications: Uterine fibroma, ovarian cysts, cervical cancer, placental anomalies, abnormal amniotic fluid volume and suspected fetal abnormalities on US)	37	28–39	123	18–39	N/A	=	Gyrus and sulcus formation did not differ between FGR and controls between 28–39 weeks

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Egana-Ugrinovic [15] 2013 Spain Prospective, observational study	T2-weighted (HASTE), 3.0T, slice thickness 3.5 mm, semiautomatic delineation, no motion correction, repeated scan in case of motion	EFW and confirmed BW < p10	Normal UA PI	Normal term fetuses with EFW > p10 and confirmed BW > p10	52 (62%)	37.5 ± 0.8	50 (52%)	37.7 ± 0.8	LID: 0.293 ± 0.052 vs. 0.267 ± 0.029 ($p = 0.02$) RID: 0.379 ± 0.066 vs. 0.318 ± 0.075 ($p < 0.01$) Left cingulate fissure: 0.096 ± 0.016 vs. 0.087 ± 0.019 ($p = 0.03$)	↑	Deeper LID, RID and left cingulate fissure when divided by BPD in FGR compared to controls. No differences in right cingulate fissure, left and right lateral fissures, parietooccipital fissures and calcarine fissures.
Egana-Ugrinovic [16] 2014a Spain Prospective, observational study	T2-weighted (HASTE), 3.0T, slice thickness 3.5 mm, semiautomatic delineation, no motion correction, repeated scan in case of motion.	EFW and confirmed BW < p10	Normal UA PI	Normal term fetuses with EFW > p10 and confirmed BW > p10	117 (58%)	37	73 (55%)	37	Total area: 1.40 ± 0.26 vs. 1.66 ± 0.31 ($p < 0.01$) Genu area: 0.160 ± 0.067 vs. 0.21 ± 0.084 ($p < 0.01$) Rostral body area: 0.315 ± 0.06 vs. 0.382 ± 0.076 ($p < 0.01$) Anterior midbody area: 0.172 ± 0.038 vs. 0.201 ± 0.042 ($p = 0.02$) Posterior midbody area: 0.164 ± 0.036 vs. 0.189 ± 0.044 ($p = 0.04$) Isthmus area: 0.14 ± 0.031 vs. 0.169 ± 0.04 ($p < 0.01$) Splenium area: 0.358 ± 0.09 vs. 0.396 ± 0.109 ($p = 0.03$)	↓	Smaller total area, genu area, rostral body area, anterior midbody area, posterior midbody area, isthmus area, splenium area of the CC when divided by cephalic index in FGR compared to controls. No difference in length, anterior-, middle- and posterior thickness, and rostrum area.

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Egana-Ugrinovic [22] 2014b Spain Prospective, observational study	T2-weighted (HASTE), 3.0T, slice thickness 3.5 mm, semiautomatic delineation, no motion correction, repeated scan in case of motion	EFW and confirmed BW < p10	Normal UA PI	Normal term fetuses with EFW > p10 and confirmed BW > p10	65 (59%)	37.5 ± 0.8	59 (56%)	37.6 ± 0.9	Left anterior ICT: 0.044 ± 0.011 vs. 0.051 ± 0.014 ($p < 0.01$) Left middle ICT: 0.047 ± 0.011 vs. 0.054 ± 0.013 ($p < 0.01$) Left posterior ICT: 0.048 ± 0.011 vs. 0.053 ± 0.014 ($p = 0.02$) Right anterior ICT: 0.038 ± 0.011 vs. 0.046 ± 0.013 ($p < 0.01$) Right middle ICT: 0.040 ± 0.011 vs. 0.048 ± 0.014 ($p < 0.01$) Right posterior ICT: 0.038 ± 0.012 vs. 0.046 ± 0.013 ($p < 0.01$)	↓	Thinner insular cortical thickness when divided by insular lobe depth in FGR when compared to controls.
Sanz-Cortes [19] 2014 Spain Prospective, observational study	T2-weighted (SSFSE), 3.0T, slice thickness 3.5 mm, manual delineation, no motion correction	EFW and confirmed BW < p10	Normal UA PI	EFW and confirmed BW > p10	51 (53%)	37.3 ± 0.9	47 (53%)	37.5 ± 0.8	Pontine width: 0.143 ± 0.01 mm vs. 0.135 ± 0.01 mm ($p < 0.01$) Medullar width: 0.088 ± 0.01 mm vs. 0.083 ± 0.01 mm ($p = 0.01$) Vermian width: 0.181 ± 0.03 mm vs. 0.162 ± 0.02 mm ($p < 0.01$) Vermian height: 0.235 ± 0.03 mm vs. 0.222 ± 0.01 mm ($p < 0.01$) Primary fissure depth: 0.041 ± 0.01 mm vs. 0.035 ± 0.03 mm ($p = 0.01$)	↑	Higher brainstem and cerebellar ratios in FGR, increased pontine width, medullar width, vermian width and height and deeper cerebellar primary fissures when divided by BPD and corrected for sex, maternal smoking and gestational age.

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Sanz-Cortes [29] 2015 Spain Prospective, observational study	T2-weighted (HASTE), H-MRS, 3.0T, slice thickness 3.5 mm, semiautomatic delineation, no motion correction	EFW and confirmed BW < p10	Normal UA PI	EFW and confirmed BW > p10	64 (55%)	37.7 ± 3.3	55 (49%)	38.4 ± 6.4	BPD: 89.28 ± 3.30 mm vs. 94.61 ± 3.5 mm (< p0.01) FOD: 109.22 ± 4.99 mm vs. 115.49 ± 4.28 mm ($p < 0.01$) CC total area: 1.05 ± 0.17 vs. 1.165 ± 0.23 ($p = 0.03$) CC genu area: 0.121 ± 0.04 vs. 0.145 ± 0.06 CC rostral body area: 0.235 ± 0.04 vs. 0.266 ± 0.05 ($p < 0.01$) CC isthmus area: 0.105 ± 0.02 vs. 0.118 ± 0.03 ($p = 0.01$) LID: 0.299 ± 0.05 vs. 0.267 ± 0.03 ($p < 0.01$) RID: 0.38 ± 0.06 vs. 0.326 ± 0.07 ($p < 0.01$) LCD: 0.099 ± 0.01 vs. 0.088 ± 0.01 ($p = 0.01$) RCD: 0.098 ± 0.01 vs. 0.088 ± 0.01 ($p = 0.02$)	↓ / ↑	Decreased biparietal diameters, smaller FODs, smaller CCs. Greater insular and cingular sulci depths when divided by BPD for FGR compared to controls when corrected for smoking, gestational age and maternal BMI. No differences in sylvian, parietooccipital and calcarine fissure depths.
Junior° [23] 2021 Brazil Prospective, observational study	T2-weighted (SSFSE), 3.0T, manual delineation, no motion correction.	EFW < p3 or p3-p10	UA RI > p95 with/without CPR < 1	Gestational age matched healthy fetuses with BW p10-p90 referred for MRI due to maternal diseases, suspected fetal congenital anomalies, obesity and suspected placental disease.	13 (39%)	32.0 ± 3.9*	13 (54%)	32.0 ± 3.9*	Brain BPD: 67.8 mm (53.5–82.5) vs. 71.6 mm (56.4–86.7) ($p < 0.01$) eCSF: 5.3 mm (3.7–9.2) vs. 8.2 mm (6.2–12.1) ($p < 0.01$) Left axial IOD: 11.8 mm (2.6–14.3) vs. 16.3 mm (5.9–20.2) ($p = 0.02$) Right axial IOD: 9.8 mm (2.6–14.6) vs. 13.9 (4.3–18.3) ($p < 0.01$)	↓	Smaller brain BPD, lower eCSF and reduced axial left and right IODs in FGR when compared to controls. No difference in brain OFD, CC parameters, brainstem parameters, cerebellar parameters, left and right atrial diameter and left and right coronal IODs.

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Moradi [44] 2021 Iran Prospective, observational study	T2-weighted (SSFSE), 3.0T, slice thickness 4 mm, manual delineation, no motion correction	EFW < p10	Not defined as inclusion criteria	BW and EFW > p10 extra-central nervous system pathologies	42 (47.6%)	34.1*	28 (78.6%)	34*	Insular cortex: 0.034 ± 0.007 mm vs. 0.043 ± 0.012 mm ($p < 0.01$) Temporal lobe: 0.036 ± 0.007 mm vs. 0.047 ± 0.027 mm ($p = 0.01$) Hippocampus: 0.017 ± 0.008 cm^2 vs. 0.0125 ± 0.003 cm^2 ($p < 0.01$) Cerebellum: 0.147 ± 0.021 cm^2 vs. 0.130 ± 0.019 cm^2 (< 0.01) Whole brain area: 0.806 ± 0.170 cm^2 vs. 0.812 ± 0.027 cm^2 ($p = 0.03$)	↓	FGR fetuses had significantly thinner insular and temporal lobe cortex and smaller hippocampal, cerebellar and whole brain surface area compared to controls. No difference in cortical thickness was found for the frontal and occipital lobe. Surface area for the frontal, temporal, occipital lobe, midbrain and pons was also not significantly different between FGR and AGA.
Zheng° [46] 2022 China Retrospective study	T2-weighted (SSFSE), DWI (b = 0 and 600s/mm^2) 1.5T, slice thickness 4 mm, manual delineation and region of interest plotting, no motion correction	PE or GH according to ACOG criteria with AC < p10	UA or uterine PI > p95	PE or GH with AC > p10	56 (42.9%)	33.6 ± 2.5	56 (42.9%)	33.6 ± 2.5	CC length: 0.4284 [0.4079–0.4470] mm vs. 0.4614 [0.4461–0.4944]mm ($p < 0.01$) CC area: 1.0779 ± 0.1931 mm^2 vs. 1.1896 ± 0.1803 mm^2 ($p < 0.01$)	↓	Decreased CC length and area adjusted for cephalic index were found in the FGR group. Furthermore, the splenium showed altered macro- and microstructural development in FGR. The abnormal structure of the splenium correlated significantly to adverse perinatal outcomes in the PE/GH with FGR group.
				Normotensive pregnancy with isolated polyydramnios with normal karyotypes and morphological features, maternal placental disorders and benign gynaecologic tumors			56 (35%)	33.6 ± 2.6	CC length: 0.4284 [0.4079–0.4470]mm vs. 0.4591[0.4310–0.4927]]mm ($p < 0.01$) CC area: 1.0779 ± 0.1931 mm^2 vs. 1.1438 ± 0.1935 mm^2 ($p = 0.02$)		

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
ADC											
Sanz-Cortes [27] 2010 Spain Prospective observational study	DWI (b = 0 and 1000s/mm^2), 1.5T, slice thickness 4 mm, manual region of interest plotting, no motion correction.	EFW and confirmed BW < p10	Normal UA PI	EFW and confirmed BW > p10	8 (75%)	37.2 ± 0.8	5 (100%)	37.0 ± 0.8	Pyramidal tract: $119.87 \pm 12.03 \times 10^{-5}$ mm^2/s vs. $105.11 \pm 11.07 \times 10^{-5}$ mm^2/s ($p = 0.04$)	↑ / =	Higher ADC values in pyramidal tract in FGR compared to controls. No differences for FWM, OWM, basal ganglia and CC.
Arthurs° [33] 2017 France Retrospective study	DWI (b = 0 and 700 s/mm^2), 1.5T, slice thickness 4 mm, manual segmentation, manual regions of interest plotted on ADC map, no motion correction	EFW < p3	UA absent or reversed flow	Family history for cerebral malformation, suspicion of cerebral abnormality or low cerebral biometry on US not confirmed on MRI, mild uni- or bilateral ventriculomegaly < 12 mm, isolated extracranial malformations and isolated polyhydramnions all with normal karyotype or maternal disease with possible consequences on fetal cerebral development without abnormalities on MRI.	30 (52%)	30.2 ± 1.6	24 (50%)	30.7 ± 1.4	FWM: $1.97 \pm 0.23 \times 10^{-3}$ mm^2/s vs. $2.17 \pm 0.22 \times 10^{-3}$ mm^2/s ($p < 0.01$) Thalami: $1.04 \pm 0.15 \times 10^{-3}$ mm^2/s vs. $1.13 \pm 0.10 \times 10^{-3}$ mm^2/s ($p < 0.01$) CSO: $1.86 \pm 0.22 \times 10^{-3}$ mm^2/s vs. $1.97 \pm 0.23 \times 10^{-3}$ mm^2/s ($p = 0.01$) Pons: $0.85 \pm 0.19 \times 10^{-3}$ mm^2/s vs. $0.94 \pm 0.12 \times 10^{-3}$ mm^2/s ($P = 0.04$)	↓	Lower ADC values in FWM, thalami, CSO and pons for FGR compared to controls. No significant difference in OWM and cerebellar hemispheres.
Kutuk° [24] 2018 Turkey Prospective observational study	DWI (b = 0–1000 s/mm^2), 1.5T, slice thickness 4 mm, manual ADC mapping, no motion correction, repeated scan in case of motion	EFW < p10	4 groups: UA PI > p95, +MCA PI < p5, absent flow, reversed flow	Suspected ventriculomegaly, intra-abdominal cyst, adnexal mass, verbtral anomalies and placental invasion anomalies whose fetal MRI, ante- and postnatal follow-up revealed normal outcome	54	30.4 ± 2.3	15	29.6 ± 1.8	PWM: $1687 \pm 17.9 \times 10^{-6}$ mm^2/s vs. $1789.8 \pm 34.3 \times 10^{-6}$ mm^2/s ($p = 0.01$) FWM: $1735.5 \pm 16.1 \times 10^{-6}$ mm^2/s vs. $1808.96 \pm 30.7 \times 10^{-6}$ mm^2/s ($p = 0.038$) Thalamus: $1190.2 \pm 15.5 \times 10^{-6}$ mm^2/s vs. $1291.9 \pm 29.7 \times 10^{-6}$ mm^2/s ($p < 0.01$) Basal ganglia: $1320.9 \pm 14.6 \times 10^{-6}$ mm^2/s vs. $1401.7 \pm 27.9 \times 10^{-6}$ mm^2/s ($p = 0.013$)	↓	Lower ADC values in PWM, FWM, thalami and basal ganglia for FGR compared to controls. No significant difference for the cerebellum and pons.

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Razek ° [26] 2019 Egypt Prospective observational study	DWI (b = 0, 500, 1000 s/mm^2), 1.5T, slice thickness 5 mm, manual placement of regions of interest, no motion correction.	EFW or AC < p10	UA PI > p95	Normal EFW and Dopplers and non-FGR-related fetal pathologies with normal MR imaging of the placenta, brain, liver and kidney of the fetus.	32	35.0 ± 2.3*	15	35.0 ± 2.3*	0.97 ± 0.2 × 10^{-3} mm^2/s vs. 1.23 ± 0.1 × 10^{-3} mm^2/s ($p < 0.01$)	↓	Lower ADC values in the fetal brain in FGR compared to controls.
Moradi° [25] 2020 Iran Prospective observational study	DWI (b = 0–700 s/mm^2), 3.0T, slice thickness 4–5 mm, manual placement of regions of interest, no motion correction, repeated scan in case of motion	EFW < p10	Severe: EFW < p3 and/or abnormal UA/UtA PI and/or CPR < p5	Suspected ventriculomegaly, duodenal atresia, oesophageal atresia, mega cisterna magna, posterior urethral vale, macrosomia, syndactyly, hemivertebra, cleft lip and palate, pulmonary cysts and those with normal fetal MRI	38 (23 severe, 15 non severe) (53%)	34.3	18 (78%)	34	Thalami: 1.205 ± 0.170 × 10^{-3} mm^2/s vs. 1.275 ± 0.158 × 10^{-3} mm^2/s ($p = 0.03$) Cerebral hemispheres: 1.239 ± 0.164 × 10^{-3} mm^2/s vs. 1.280 ± 0.188 × 10^{-3} mm^2/s ($p = 0.05$) Caudate nucleus: 1.319 ± 0.173 × 10^{-3} mm^2/s vs. 1.394 ± 0.166 × 10^{-3} mm^2/s ($p = 0.04$)	↓	Lower ADC values in thalami, cerebellar hemispheres and caudate nucleus in FGR compared to controls. No difference for FWM, OWM, TWM, pons, hippocampal cortex, rolandic cortex and CSO.
Zheng° [46] 2022 China Retrospective study	T2-weighted (SSFSE), DWI (b = 0 and 600s/mm^2) 1.5T, slice thickness 4 mm, manual delineation and region of interest plotting, no motion correction	PE or GH according to ACOG criteria with AC < p10	UA or uterine PI > p95	PE or GH with AC > p10	56 (42.9%)	33.6 ± 2.5	56 (42.9%)	33.6 ± 2.5	Anterior third of CC: 1.49 (1.35–1.59) x 10^{-3} mm^2/s vs. 1.59 (1.49–1.68) x 10^{-3} mm^2/s ($p < 0.05$) Splenium CC: 1.47 (1.38–1.57) x 10^{-3} mm^2/s vs. 1.57 (1.53–1.63) x 10^{-3} mm^2/s ($p < 0.05$)	↓	Significantly lower ADC values in the anterior third and splenium of the CC in PE/GH + FGR when compared to PE/GH with FGR and normotensive pregancies.
				Normotensive pregnancy with isolated polyydramnios with normal karyotypes and morphological features, maternal placental disorders and benign gynaecologic tumors			56 (35%)	33.6 ± 2.6	Anterior third of CC: 1.49 (1.35–1.59) x 10^{-3} mm^2/s vs. 1.58 (1.48–1.69) x 10^{-3} mm^2/s ($p < 0.05$) Splenium CC: 1.47 (1.38–1.57) x 10^{-3} mm^2/s vs. 1.63 (1.50–1.70) x 10^{-3} mm^2/s ($p < 0.05$)	↓	

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Zheng [45] 2023 China Retrospective study	DWI (b = 0 and 600 s/ mm^2 1.5T, slice thickness 4 mm, manual placement of regions of interest, no motion correction	PE or GH according to ACOG criteria with AC < p10 and BW < p10	Not defined as inclusion criteria	PE or GH according to ACOG criteria with BW > p10	40 (45%)	33.8 ± 2.5	40 (45%)	33.5 ± 2.7	CSO: $1.81 \pm 0.13 \times 10^{-3}$ mm^2/s vs. $1.90 \pm 0.14 \times 10^{-3}$ mm^2/s ($p < 0.05$) PWM: 1.86 (1.77, 1.95) x 10^{-3} mm^2/s vs. 1.94 (1.86, 2.05) x 10^{-3} mm^2/s ($p < 0.05$)	↓	Significantly lower ADC-values in the CSO and PWM for PE/GH + FGR compared to PE/GH without FGR
		Normotensive, AC and BW < p10	Not defined as inclusion criteria	Normotensive, BW > p10 with Isolated polyhydramnios with normal karyotypes and morphology, maternal placental disorder, gynaecological benign tumors	40 (27.5%)	33.8 ± 2.6	40 (35%)	33.9 ± 2.5	PWM: 1.91 (1.82, 1.95) x 10^{-3} mm^2/s vs. 1.99 (1.91, 2.05) x 10^{-3} mm^2/s ($p < 0.05$) OWM: $1.73 \pm 0.14 \times 10^{-3}$ mm^2/s vs. $1.83 \pm 0.20 \times 10^{-3}$ mm^2/s ($p < 0.05$) TWM: $1.72 \pm 0.12 \times 10^{-3}$ mm^2/s vs. $1.80 \pm 0.15 \times 10^{-3}$ mm^2/s ($p < 0.05$)	↓	Significantly lower ADC-values in the PWM, OWM and TWM in normotensive FGR compared to healthy controls.
Metabolism											
Sanz-Cortes [27] 2010 Spain Prospective observational study	^{1}H-MRS, 1.5T, slice thickness 4 mm, manual region of interest plotting,. Examinations with significant motion were discarded.	EFW and confirmed BW < p10	Normal UA PI	EFW and confirmed BW > p10	8 (75%)	37.2 ± 0.8	5 (100%)	37.0 ± 0.8	Ino/Cho: 0.57 (0.28) vs. 0.25 (0.10) ($p = 0.04$)	↑ / =	Increased levels of Ino/Cho in FGR compared to controls in the left frontal lobe. No differences for NAA/Cho, Cho/Cr and Cr/Cho.
Story° [30] 2011 UK Prospective observational study	^{1}H-MRS, 1.5T, slice thickness 4 mm, jMRUI software, imaging was repeated after spectral acquisition to ensure no significant fetal movement had occurred	EFW < p10	Abnormal (UA PI > 95, or absent/reversed and MCA < p5)	Appropriately grown fetuses with normal anatomy ultrasound scan	28. 19 interpretable for ^{1}H-MRS data analysis (21%)	27.9 ± 4.2*	41. 28 interpretable for ^{1}H-MRS data analysis (50%)	29.8 ± 4.5*	Graphic	↓ / =	Lower NAA/Cr and NAA/Cho over central brain tissue encompassing both central grey and white matter in FGR compared to controls when corrected for gestation, no difference in Cho/Cr. Lactate was present in 5 FGR fetuses compared to 3 AGA.

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Story° [31] 2013 UK Prospective observational study	^{1}H-MRS, 1.5T, slice thickness 4 mm, jMRUI software, imaging was repeated after spectral acquisition to ensure no significant fetal movement had occurred	EFW < p10	UA PI > p95 (= 5, 16 had absent, 1 reversed) and MCA PI < p5 (all)	Appropriately grown fetuses with normal Dopplers and normal anatomy ultrasound scan	28. 24 interpretable for ^{1}H-MRS data analysis (54%)	27.9 ± 4.2*	47. 26 interpretable for ^{1}H-MRS data analysis (50%)	30.5 ± 3.8*	Graphic	=	No difference in Cho/Cr, Ino/Cr or Ino/Cho levels over central brain tissue encompassing both central grey and white matter in FGR when compared to controls when corrected for gestation.
Sanz-Cortes [28] 2014 Spain Prospective observational study	^{1}H-MRS, 3.0T, slice thickness 3.5 mm, LCModel, repeated scan in case of motion	BW < p3 or EFW < p10	If EFW p3-p10 then MCA PI < p5 and/or uterine > p95	EFW and confirmed BW > p10	31 (65%)	37.5 ± 0.9	30 (50%)	38.4 ± 6.4	NAA/Cho: 1.189 ± 0.22 vs. 1.372 ± 0.21 ($p < 0.01$)	↓ / =	Lower NAA/Cho ratios in the frontal lobe in FGR compared to controls. No difference in NAA/Cr and Cho/Cr. After correction for maternal smoking and gestational age at MRI NAA/Cho levels remained significantly lower.
Sanz-Cortes [29] 2015 Spain Prospective observational study	^{1}H-MRS, 3.0T, slice thickness 3.5 mm, LCModel, repeated scan in case of motion	EFW and confirmed BW < p10	Normal UA PI	EFW and confirmed BW > p10	64 (55%) 43 interpretable for ^{1}H-MRS data analysis	37.7 ± 3.3	55 (49%) 34 interpretable for ^{1}H-MRS data analysis	38.4 ± 6.4	NAA/Cho: 1.203 ± 0.241 vs. 1.371 ± 0.278 ($p = 0.02$)	↓ / ↑ / =	Lower NAA/Cho ratios in FGR compared to controls in the frontal lobe when corrected for smoking, gestational age and maternal BMI. Cho/Cr was significantly elevated without correction for confounders but lost significance when corrected. No difference in Ino/Cho levels.

Table 1 (continued)

Author Year Country Study design °= FGR Delphi consensus	MRI technique	FGR definition	Doppler abnormalities	Inclusion criteria control group	Number of FGR (% male if reported)	GA of FGR during MRI (in wks)	Number of controls (% male if reported)	GA of control during MRI (in wks)	Results FGR vs. Control	Effect for FGR	Summary of reported outcomes
Hemodynamics											
Yadav° [32] 2020 USA Prospective, observational study	SWI, 3.0T, slice thickness 3.0–3.5 mm, manual plotting of region of interest, no motion correction	EFW < p10	UA PI > p95	EFW p10-p90 with normal fetal anatomy and normal Dopplers	10	35.5 ± 2.9*	33	30.0 ± 5.8*		=	No difference in fractional moving blood volume and venous blood oxygenation in the superior sagittal sinus between FGR and AGA
Baadsgaard [37] 2022 Denmark Prospective observational study	T2*-weighted, 1.5T, slice thickness 5 mm, manual plotting of region of interest, no motion correction	BW < p2.3	Not defined as inclusion criteria	BW p10-p90	31	33.2 ± 1.6*	57	35.3 ± 2.8*		=	There was no significant difference of T2* in the brain in FGR compared to controls and no significant correlation was found between BW and fetal brain T2*

° = Delphi consensus definition FGR; *= based on raw data received from author or recalculation from median and range to mean and standard deviation according to "S.P. Hozo, B. Djulbegovic, and I. Hozo, "Estimating the Mean and Variance from the Median, Range, and the Size of a Sample," *BMC Medical Research Methodology* 2005, **5**:13"; ↓ = decreased for FGR; ↑ = increased for FGR; '=' no difference for FGR; *AC* abdominal circumference, *ADC* apparent diffusion coefficient, *BPD* biparietal diameter, *BW* birthweight, *CC* corpus callosum, *CPR* cerebroplacental ratio, *CSO* centrum semiovale, *DWI* diffusion-weighted imaging, *eCSF* extracerebral cerebrospinal fluid (skull BPD – brain BDP), *EFW* estimated fetal weight, *FGR* fetal growth restriction, *FOD* frontoccipital diameter, *EPI* echo planar imaging, *FWM* frontal white matter, *HASTE* Half-Fourier-Acquired Single-shot Turbo spin Echo, *GH* gestational hypertension, *ICT* insular cortical thickness, *ICV* intracranial volume, *IOD* interopercular distances, *LCD* left cingular depth, *LH* left cerebral hemisphere, *LID* left insular depth, *LIV* left insular volume, *LOV* left opercular volume, *LT* left temporal lobe, *MCA* middle cerebral artery, *OFD* occipitofrontal diameter, *OWM* occipital white matter, *PE* preeclampsia, *PWM* parietal white matter, *RCD* right cingular depth, *RH* right cerebral hemisphere, *RID* right insular depth, *RIV* right insular volume, *RT* right temporal lobe, *ST* supratentorial brain volume, *SSTSE* single shot turbo spin echo sequence, *STB* Supratentorial brain, *STC* supratentorial cavity, *TBV* total brain volume, *TT* total temporal lobes, *TWM* temporal white matter, *ROV* right opercular volume, *UA* umbilical artery

Zheng et al. some ADC-values were recalculated to mean and standard deviation. [24, 27, 40, 41, 45].

Meta-analyses of primary outcomes

Total brain volume was lower for FGR fetuses when compared to AGA fetuses with an MD of −30.84 cm^3 [−42.90; −18.78] ($p<0.01$) at a mean gestational age of 33.5 ± 3.12 weeks for FGR and 33.8 ± 3.03 weeks for AGA. (Fig. 2). $I^2=42\%$ ($p=0.13$) meaning moderate, yet insignificant, heterogeneity. Cerebellar volume was also significantly lower for FGR fetuses with an MD of −2.24 cm^3 [−2.99; −1.48] ($p<0.01$) at a mean gestational age of 31.9 ± 1.28 for FGR and 33.2 ± 1.27 for AGA with a heterogeneity of $I^2=0\%$ ($p=0.38$) (Fig. 3).

ADC values in the FWM, OWM, TWM, thalami, CSO, basal ganglia, pons and cerebellum, were significantly lower in growth restricted fetuses when compared to AGA fetuses. (-0.07×10^{-3} mm^2/s ($p<0.01$); -0.06×10^{-3} mm^2/s ($p<0.01$); -0.07×10^{-3} mm^2/s ($p<0.01$); -0.10×10^{-3} mm^2/s ($p<0.01$); -0.06×10^{-3} mm^2/s ($p<0.01$); -0.07×10^{-3} mm^2/s ($p<0.01$); -0.07×10^{-3} mm^2/s ($p<0.01$); -0.02×10^{-3} mm^2/s ($p<0.01$); respectively) (Appendix 5). The mean gestational ages reached from 32.5 to 34.0 weeks for FGR and 32.3–33.8 weeks for AGA. The associated heterogeneity was 65% ($p=0.01$), 12% ($p=0.34$), 0% ($p=0.80$), 0% ($p=0.44$), 9% ($p=0.35$), 76% ($p<0.01$), 51% ($p=0.09$), 0% ($p=0.95$). When I^2 was 0%, significance was not reached, but either all included studies found the same direction of MD with small confidence intervals or in case of FWM, basal ganglia and pons some studies found the opposite direction of effect contributing to higher heterogeneity.

Brain volumetrics

Andescavage et al. found significantly reduced volumes of the total brain, cerebrum, and cerebellum in 35 FGR fetuses compared to 79 controls around 30 weeks of gestation. Brain stem volume was not significantly different [11]. Duncan et al. support these findings by showing reduced total brain volumes across GAs when comparing FGR to AGA [14]. Between 30 and 34 weeks of gestation, Polat et al. also illustrated significantly lower volumes in the supratentorial brain with and without cerebrospinal fluid (CSF), cerebral hemispheres, temporal lobes, and cerebellum in FGR fetuses [7]. Peretz et al. found significantly smaller volumes of the supratentorial brain, left and right hemisphere and cerebellum at 33–34 weeks of gestation [43]. Zhu et al. recalculated brain volumes to fetal brain weights which were significantly lower as well for in FGR fetuses at 35 weeks of gestation when compared to AGA fetuses [20]. At 37 weeks, Egana-Ugrinovic et al. found smaller intracranial, brain and left opercular volumes in FGR fetuses. Right opercular volumes were similar to AGA fetuses [15]. In a different study by the same research group the left and right insular volumes were smaller in FGR when compared to controls [22].

Controversially, across 20.5–36.6 weeks GA Damodaran et al. found no difference in brain volume when comparing 20 FGR fetuses to 19 AGA fetuses [13]. Baker et al. found similar brain volumes when comparing FGR to AGA at GAs ranging from 30.8–37.1 [12]. At 29.1 weeks GA Javor et al. also did not find any differences in brain volumes when comparing FGR to AGA fetuses [17]. Sanz-Cortes et al. even found larger cerebellar volumes in FGR fetuses at 37 weeks of gestation [19].

Other brain biometrics

Abe et al. found no difference in cortical gyrus and sulcus formation for FGR fetuses from gestational week 28–39 [21]. Between 26 and 38 weeks GA Junior et al. illustrated that FGR fetuses have smaller skull biparietal and occipitofrontal diameters (BPD and OFD), with lower extracerebral spinal fluid (skull BPD – brain BPD), reduced vermis area percentiles and smaller left and right interopercular distances. However, corpus callosum lengths and areas, the widths and heights of the pons and vermis and the cerebellar diameter were not significantly different in FGR fetuses [23]. Zheng et al. did find smaller corpus callosum lengths and areas corrected for cephalic index for FGR fetuses in hypertensive pregnancy compared to hypertensive pregnancies without FGR or normotensive pregnancies at 33.6 weeks of gestation [46]. Around 34 weeks of gestation Moradi et al. described thinner insular and temporal lobe cortex and smaller hippocampal, cerebellar, and whole brain surface areas in FGR compared to AGA [44]. At 37 weeks Sanz-Cortes et al. found significantly larger brainstem and cerebellar ratios in FGR fetuses [19]. Additionally, at this term FGR fetuses showed significantly thinner insular cortical thickness in combination with smaller corpus callosi, which is in line with the findings mentioned previously. [16, 22, 29, 44, 46]. Moreover, the left and right insula and cingulate depths were significantly deeper and the left cingulate fissure significantly lower in FGR fetuses [15, 29]. Yet no differences in lateral-, parietooccipital-, right cingulate- and calcarine fissures were observed [15].

ADC-values

Around 30 weeks GA, FGR fetuses showed significantly lower ADC values in the FWM, thalami, centrum semiovale and pons, but no differences were found for OWM and cerebellar hemispheres by Arthurs et al. [33]. At 30 weeks Kutuk et al. also demonstrated reduced ADC-values in the periatrial white matter, FWM, thalami and

basal ganglia. However, ADC-values were not reduced in the pons and cerebellum [24]. Around 34 weeks ADC values in the thalami, cerebellar hemispheres and caudate nucleus are also significantly lower [25]. Zheng et al. found significantly lower ADC-values in the CSO and parietal white matter in hypertensive FGR pregnancies compared to hypertensive pregnancies without FGR. This study group also compared normotensive FGR with normotensive AGA and found reduced ADC-values in the parietal white matter, OWM and TWM [45]. Furthermore, they describe lower ADC-values in the corpus callosum anterior third and splenium [46]. When measuring the ADC-value of the brain at 35 weeks GA it remains significantly lower for FGR fetuses compared to AGA [26]. At 37 weeks GA Sanz-Cortes et al. found higher ADC-values in the pyramidal tract, but no differences in the frontal lobe, occipital lobe, basal ganglia and corpus callosum [27].

Brain metabolism

Story, et al. conducted two studies using ^{1}H-MRS placing a $20\times20\times20$ mm^3 voxel over central brain tissue including both grey as well as white matter. Brain-sparing FGR fetuses showed reduced levels of NAA: Cho and NAA: Cr ratios across various GAs [30]. No differences in Cho: Cr and Ino: Cho were detected in brain-sparing FGR compared to healthy controls [31].

Sanz-Cortes et al. investigated the metabolic status in fetal brains using ^{1}H-MRS in non-brain-sparing late onset FGR at GA 37 weeks. The FGR fetuses showed a significant increase in Ino: Cho ratio in the left frontal lobe, suggesting high levels of inositol [27]. Furthermore, NAA: Cho levels were reduced for both small for gestational age (SGA) and late-onset FGR fetuses [28, 29]. Cho: Cr was only significantly elevated before correction for confounders. No differences in Ino: Cho ratios were found [29].

Hemodynamics

Yadav et al. quantified venous blood oxygenation using SWI MRI and found that FGR fetuses have slightly higher, yet insignificant, fractional moving blood volume (FMBV) and similar venous blood oxygenation (SvO_2) in the superior sagittal sinus compared to normal growth fetuses across gestation (FMBV: $26.9\pm3.9\%$ vs. $21.9\pm1.1\%$ $p=0.09$ and SvO_2: $60.6\pm5.3\%$ vs. $63.9\pm3.2\%$, $p=0.44$) [32]. T2* is an alternative method to provide an estimation of oxygenation, however Baadsgaard

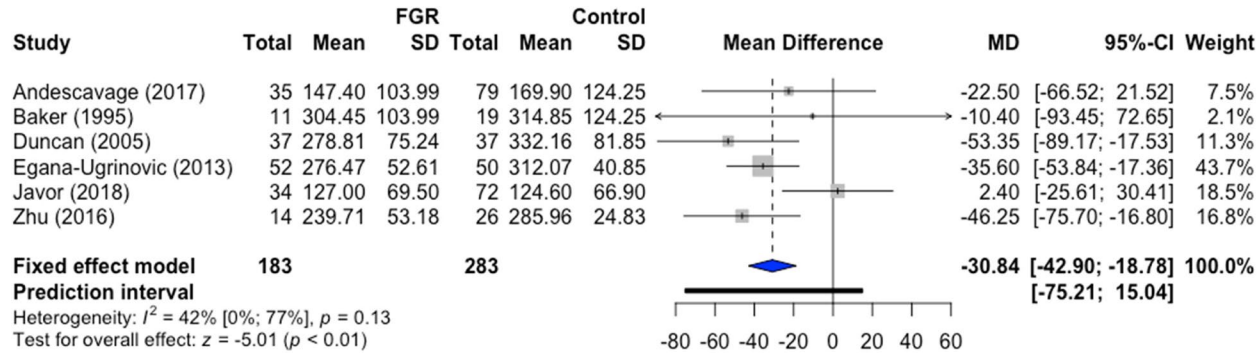

Fig. 2 Total brain volume in cm^3. CI: Confidence interval, FGR: Fetal growth restriction, MD: Mean difference, SD: Standard deviation

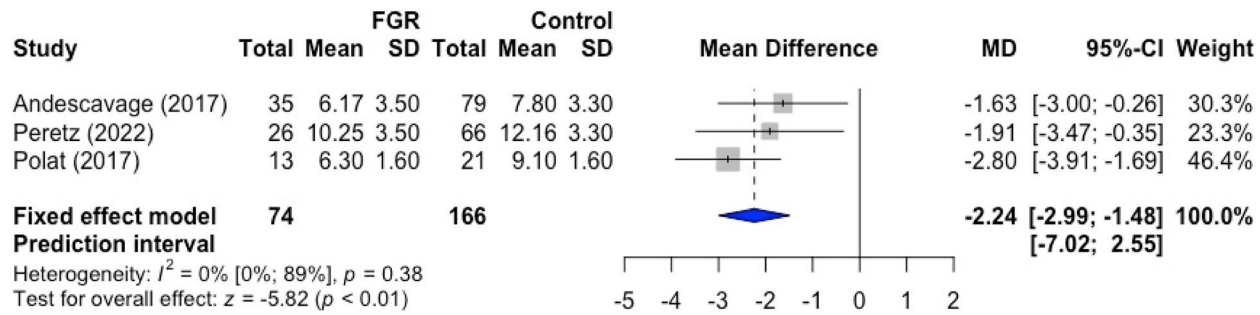

Fig. 3 Cerebellar volume in cm^3. CI: Confidence interval, FGR: Fetal growth restriction, MD: Mean difference, SD: Standard deviation

et al. found no difference in T2* in the fetal brain when comparing FGR to AGA fetuses. Brain T2* was significantly correlated the MCA Doppler and to placenta T2* ($R=0.23$ ($p=0.032$) and $R=0.41$ ($p<0.01$)) [37].

Discussion

Our systematic review showed significantly reduced total brain and cerebellar volumes and lower ADC values in the FWM, OWM, TWM, thalami, CSO, basal ganglia, pons and cerebellum in growth restricted fetuses when compared to AGA fetuses. ^{1}H-MRS measurements found reduced levels of NAA: Cho and NAA: CR, while contradictive findings concerning Cho: Cr and Ino: Cho ratios were described (Fig. 4).

Smaller brain volumes in FGR: macroscopic in line with microscopic results

Chronic hypoxia causes total brain volume reductions due to neuronal degeneration and hypomyelination in FGR [1, 47–54]. Preoligodendrocytes, the precursors of myelin producing oligodendrocytes, are sensitive to hypoxia, accounting for the hypomyelination in FGR [2, 55]. Postmortem studies of the FGR brain confirm a reduced number of neuronal cells and hypomyelination [49, 56]. How these reduced volumes correlate to neurodevelopmental outcomes remains to be elucidated, however total brain volume is significantly correlated with IQ scores later in life [57, 58]. Additionally, one study described a correlation between the cerebellar: supratentorial volume ratio and the Vineland-II Adaptive Behavior Scales (VABS-II), yet no difference in score was found between FGR and AGA children at the age of 4 years [59].

Some of the included studies describe no differences in brain volumes or even larger brainstem and cerebellar ratios in FGR fetuses [12, 13, 17, 19]. Damodaram et al. included FGR fetuses with a mean gestational age of 26.6 weeks describing no differences in total brain volume whereas the meta-analysis included gestational ages 29–38 weeks [11–15, 17, 20]. Potentially neuronal degeneration has not occurred yet, prolonged exposure to chronic hypoxia might contribute to lower total brain volume [1, 47–54]. Another reason could be the occurrence of asymmetric FGR, where preserved head circumference presumably accounts for brain volumes [60]. Furthermore, brain-sparing is suggested to occur hierarchically, as chronic hypoxia continues vasodilation shifts to the more posterior regions of the brain, sparing those structures the longest [61–63]. Additionally, a single voxel represents a relatively large proportion of small structures like the brainstem and cerebellum, causing a larger variation by motion and partial volume effects [64]. Other reasons why three studies did not find reduced brain volumes could be the use of lower Tesla MRI, manual segmentation, and most importantly the lack of motion correction [12, 13, 17].

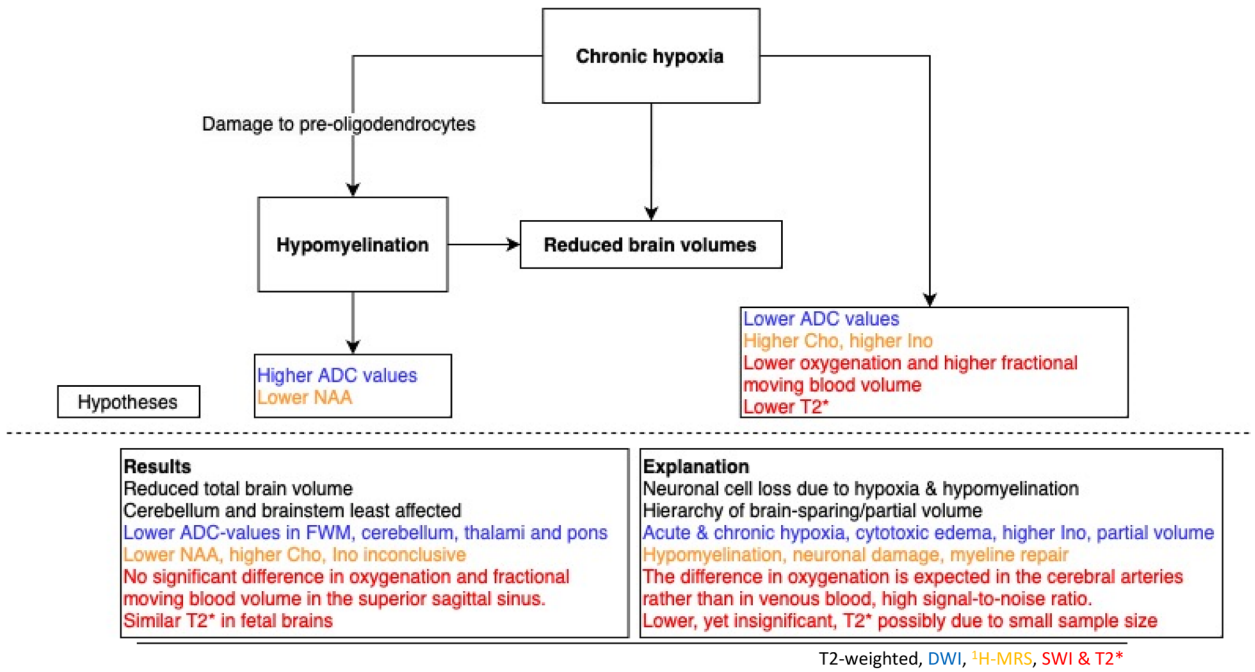

Fig. 4 Graphic overview of results. ADC: Apparent diffusion coefficient, Cho: Choline, FWM: frontal white matter, Ino: Myoinositol, NAA: N-Acetyl Aspartate

The impact of FGR on maturation

Gyral formation has been used as an indicator of brain maturation, other methods to analyze in vivo fetal brain maturation include cortical surface area, sulcal organization, cortical curvature, and shape indexes [65]. But there is no standardized fetal brain maturation method yet, considering the many structural variations between individuals [66]. This might explain the absence of differences in gyral formation reported by Abe et al. [21]. Potentially, there is no difference in brain maturation as gyrification in preterm babies was similar for FGR and AGA neonates [53].

Apparent diffusion coefficients: a measure of chronic hypoxia?

Our meta-analyses show significantly lower ADC values in FWM, OWM, TWM, thalami, CSO, basal ganglia, pons and cerebellum. ADC-values are a measure of water diffusion, which is reduced by myelination or after acute hypoxia-ischemia [25, 33, 67, 68]. Hypomyelination in FGR should translate to higher ADC-values, yet the process of myelination starts around 30 weeks of gestation which is the mean GA at time of MRI for two of the included studies [24, 33, 69]. The ADC-value meta-analyses included gestational ages reaching from 30 to 38 weeks. The observed lower ADC-values occurred across gestational ages for all studies implementing the FGR consensus definition, Sanz-Cortes et al. included late SGA [24, 25, 27, 33].

The decreased values could be due to cerebral redistribution affecting maturation, myelination, and diffusion or ongoing ischemic lesions [24, 25, 33, 67].

Two pregnancies were terminated in Arthurs et al. and autopsies of the fetal FGR brains revealed acute and chronic hypoxic injuries, potentially accounting for the lower ADC-values [33]. Altered cellular metabolism in FGR might lead to swelling, resulting in reduced diffusion and lower ADC-values, but brain-sparing might stabilize ADC values [24]. Additionally, a partial volume effect including both gray and white matter in the region of interest might have led to lower ADC-values since ADC is lowest in white matter [70]. At last, increased levels of myo-inositol (Ino) that have been described in FGR brains are also associated with lower ADC-values [27, 71].

In vivo metabolic status in FGR

Ino is an osmoregulator and a marker of astrocyte activation which is characteristic for perinatal hypoxia and of reactive gliosis [27]. Sanz-Cortes et al. found higher levels of Ino in the left frontal lobe where Story et al. found no differences between FGR and AGA [27, 31]. FGR fetuses show reduced levels of NAA across various GAs, marking impaired myelination and neuronal integrity loss due to injury [2, 28, 30, 36, 49]. NAA: Cho, is strongly associated with corpus callosum development possibly accounting for smaller corpus callosi with worse neurocognitive outcomes in FGR [16, 29]. Two studies describe higher Cho: Cr ratios and lower NAA: Cho ratios meaning Cho levels are elevated in FGR, fitting a status of injury and myelin repair [29, 28].

The clinical feasibility of altered brain hemodynamics on MRI

Hemodynamic MRI evaluation would be interesting in FGR fetuses due to their hemodynamic adaptations in the brain, but Yadav et al. did not show altered oxygenation and fractional moving blood volume in the superior sagittal sinus in FGR fetuses [32]. T2* is an alternative method to provide an in vivo estimation of oxygenation, but Baadsgaard et al. found no difference in T2* in the fetal brain when comparing FGR to AGA fetuses. Improved MRI methods, such as T2-mapping and 2D flow MRI, can evaluate oxygenation and quantify blood velocity [72]. Additional sequences like blood oxygen level-dependent (BOLD)-MRI and T2* show promising results when assessing oxygenation in fetal organs, the placenta and animal models for FGR [73–79]. BOLD-MRI with hypercapnic challenge can distinguish normoxia from early- and late-onset hypoxia in mice, where neuroapoptosis only occurred in early-onset hypoxia. This means that BOLD-MRI can potentially identify chronic fetal hypoxia before it leads to irreversible brain damage [73]. The high spatial resolution needed to visualize small structures like blood vessels, in combination with fetal movement, increase the signal to noise ratio making hemodynamic MRI challenging [20, 72].

Strengths and limitations

Our systematic review including meta-analyses provides an overview of all fetal MRI data investigating cerebral differences between FGR and AGA fetuses at all gestational ages.

However, there are a few limitations, mostly due to the quality of the included literature. Only one study included a sample size > 100, therefore some studies might have based their results on a type I error [16, 80]. Furthermore, not all data in our outcomes was available for data extraction [12, 13, 18, 19]. Heterogeneity, resulting from diverse study populations and MRI techniques limits interpretation. By implementing motion correction in fetal MRI, the interpretation and reproducibility could have reduced heterogeneity in the results. Only 1 included study implemented 3-dimensional reconstruction and automatic segmentation with manual correction [11]. An example of an accurate, open source analysis method with appropriate motion correction could be the use of the slice to volume correction reconstruction

(SVR) toolkit [81]. None of the included studies have implemented this method. Furthermore, differentiation on GA is lacking, 7 out of 13 studies implementing the consensus definition of FGR would classify as early-onset FGR. Our meta-analyses cannot provide absolute reference values for either volumes or ADC-values.

Lastly, our inclusion criteria for FGR entail both FGR and SGA, early and late-onset FGR and brain-sparing and non-brain-sparing whereas multiple control groups might have included large for gestational age (LGA) as well. If either study characteristics or primary outcome and MRI technique were more comparable, subgroup analyses (e.g. onset, severity of FGR and gender) could have aided in identifying the FGR fetuses at risk for altered brain development. If we had included only FGR according to the consensus definition, we expect to find a more severe phenotype. Our baseline table shows conflicting results on volumetric and biometric parameters. ADC values tend to be lower in FGR across seven studies, one study group found reduced NAA/Cr and NAA/Cho ratios and no differences in fractional moving blood volume, venous oxygenation in the superior sagittal sinus and T2* in the fetal brain were described.

Future perspectives

Future studies should implement a standardized approach to assess fetal brain maturation and include cerebral hemodynamic MRI in FGR. These factors are likely to differ from healthy controls due to hypoxia-mediated injury.

A large cohort study comparing brain maturation based on a standardized method, myelination, metabolic and hemodynamic status between brain-sparing FGR fetuses to healthy age-matched controls is needed. Such a study should use fetal brain 3-dimensional reconstruction and automatic segmentation including manual correction if needed to correct for fetal motion (e.g. SVR toolkit). By performing subgroup analyses the fetuses most at risk for and the timing of altered brain development can be identified. Ultimately, the altered brain development should be linked to neurodevelopmental outcomes by performing long-term follow-up.

Conclusion

MRI provides additional information on fetal brain development in a growth restricted population at risk for altered brain development. Smaller total brain and cerebellar volumes and lower ADC values in the FWM, OWM, TWM, thalami, CSO, basal ganglia, pons and cerebellum have been observed in FGR. How these findings correlate to long-term neurocognitive abnormalities associated with FGR remains to be elucidated.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Declarations

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