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Additional value of advanced neurosonography and magnetic resonance imaging in fetuses at risk for brain damage

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KEYWORDS: acquired brain damage; fetus; MRI; neonate; neurodevelopment; ultrasound

CONTRIBUTION

What are the novel findings of this work?
Multiplanar neurosonography should be performed in fetuses at risk for acquired brain anomalies. Fetal magnetic resonance imaging showed no additional value to that of the standard axial ultrasound planes or multiplanar neurosonography in a diverse population at high risk of acquired fetal brain anomalies.

What are the clinical implications of this work?
Prenatal specialists should become familiar with the execution and interpretation of the fetal neurosonographic examination.

ABSTRACT

Objective *To assess the additional value of fetal multiplanar (axial, coronal and sagittal) neurosonography and magnetic resonance imaging (MRI) to that of the standard axial ultrasound planes in diagnosing brain damage in fetuses at high risk.*

Methods *This was a prospective, multicenter, observational study. Women were eligible for participation if their fetus was at risk for acquired brain anomalies. Risk factors were congenital infection, alloimmune thrombocytopenia, fetal growth restriction, trauma during pregnancy, fetal hydrops, monochorionic twins and prior ultrasound finding suggestive of an acquired brain anomaly. Examinations of the fetal brain before birth comprised axial ultrasound and advanced neurosonography biweekly and MRI once. After birth, neonatal cranial ultrasound was performed at < 24 h and at term-equivalent age. Neonatal brain MRI was performed once at term-equivalent age. An expert panel blinded to medical information, including imaging findings by the other methods, evaluated the presence of periventricular echogenicity (PVE) changes, peri- and intraventricular hemorrhage (IVH) and changes in basal ganglia and/or thalami echogenicity (BGTE) on ultrasound, and the equivalent signal intensity (SI) changes on MRI. Conclusions on imaging findings were generated by consensus. The children were followed up with examinations for psychomotor development at 1 year of age, using the Touwen examination and Alberta Infant Motor Scale, and at 2 years of age using Bayley Scale of Infant Development-III (BSID-III) and behavioral, sensory profile and linguistic questionnaires; scores > 1 SD below the mean were considered suspicious for neurodevelopmental sequelae.*

Results *Fifty-six fetuses were examined, and in 39/56 fetuses, all fetal-imaging modalities were available. PVE/SI changes were observed in 6/39, 21/39 and 2/39 fetuses on axial ultrasound planes, multiplanar neurosonography and MRI, respectively. IVH was found in 3/39, 11/39 and 1/39 fetuses, and BGTE/SI changes*

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in 0/39, 12/39 and 0/39 fetuses, respectively. Outcome was suspicious for neurodevelopmental sequelae in 13/46 infants at 1 year, and at 2 years, 41/41 children had scores within 1 SD of the mean on BSID-III and 20 had scores > 1 SD below the mean on the behavioral (5/38), sensory profile (17/37) and/or linguistic (6/39) questionnaires.

Conclusions *In this cohort of fetuses at risk for brain damage, the severity of acquired brain anomalies was limited. Nevertheless, multiplanar neurosonography detected more fetal PVE changes, IVH and/or BGTE changes compared to the standard axial ultrasound planes and MRI. Fetal MRI did not demonstrate any anomalies that were not seen on neurosonography. Neurodevelopmental outcome at 2 years of age showed no or mild impairment in most cases.* © *2019 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The increasing quality of ultrasound and magnetic resonance imaging (MRI) of the fetal brain has enabled the assessment of subtle changes, for example, in the white matter and peri- and intraventricular areas, which are prone to hypoxia/ischemia or infection[1–6].

In addition to the regular axial planes, multiplanar neurosonography (referred to herein as the neurosonogram/neurosonography) allows for evaluation of coronal and sagittal planes, through the fetal fontanels and sagittal suture, using transvaginal ultrasound in cases of cephalic presentation and transabdominal ultrasound in cases of breech presentation[7,8]. Neurosonography provides assessment of the fetal brain in the same systematic way as in the neonate and can be performed serially[9]. The value of MRI lies in its ability to visualize all brain areas, as well as those in proximity to the fetal skull, regardless of fetal position, and depict small differences in tissue composition[10,11]. Performing brain ultrasound and MRI in the same manner, before and after birth in fetuses at risk for brain damage, facilitates the evaluation of which technique is most predictive for neurological sequelae in infancy. Acknowledged risk factors for fetal brain injury are, amongst others, placental insufficiency, congenital infection, physical maternal trauma, fetal hydrops and fetal thrombocytopenia.

Despite an abundance of literature on neurosonography and brain MRI, there is no consensus on which is the preferred neuroimaging technique in detecting and monitoring acquired brain anomalies[1,12–14]. Until now, various disciplines, obstetricians, pediatricians and radiologists have used their own disciplinary or local guidelines. The aim of this prospective, multidisciplinary study was to examine the additional value of fetal neurosonography and MRI compared to the standard axial ultrasound planes in fetuses at risk for acquired brain anomalies, applying the same brain-imaging protocol after birth. We hypothesized that neurosonography and MRI are of additional value to the standard axial ultrasound planes in the detection of brain damage. The specific items that were examined were: the prevalence of echogenicity changes visible on axial ultrasound planes and neurosonography; and the corresponding signal intensity (SI) changes on MRI, according to imaging modality and indication. The evolution of these changes, from before to after birth, and the neurodevelopmental outcome of these infants at 2 years of age were assessed.

METHODS

This was a prospective multicenter, multidisciplinary cohort study (fetal brain-imaging (FBI) study) conducted in two tertiary medical centers in The Netherlands (Amsterdam UMC, location VUmc, and University Medical Centre, Utrecht) between October 2011 and July 2014. All consecutive pregnant women beyond 20 weeks of gestation with a high risk of fetal brain damage were eligible to participate. Inclusion criteria were maternal cytomegalovirus (CMV) or toxoplasmosis infection, maternal trauma, alloimmune thrombocytopenia, early-onset fetal growth restriction (FGR; defined as abdominal circumference or estimated fetal weight $< 10^{th}$ centile, with Doppler evidence of placental insufficiency before 30 weeks), fetal hydrops, monochorionic twin pregnancy or prior ultrasound findings suggestive of acquired brain anomalies. Exclusion criteria were maternal age below 18 years, a serious language or communication barrier, presence of a pacemaker (with respect to the MRI examination), a familial metabolic disorder and/or a confirmed fetal chromosomal or a suspected syndromic or metabolic disorder.

Fetal and neonatal brain ultrasound

The first fetal examination took place as soon as informed consent was given and biweekly thereafter. The regular fetal brain ultrasound examination consisted of three axial planes[8] and the neurosonogram comprised an additional six coronal and five sagittal planes, as described by van Gelder-Hasker *et al.*[4]. The axial planes consisted of the transventricular plane, the transcerebellar plane and a third plane parallel to the transventricular plane, through the frontoparietal subcortical white matter. The coronal planes comprised the transfrontal plane, the transcaudate plane, the transthalamic plane, a plane containing the bodies of the lateral ventricles and the posterior portions of the temporal lobes, the transcerebellar plane and a sixth coronal plane through the occipital subcortical white matter. The sagittal planes comprised the midsagittal plane, the parasagittal plane (both sides) and a plane through the temporal subcortical white matter with the Sylvian fissure (both sides). Images were obtained using a Voluson E8 or Voluson Expert 730 machine (GE Healthcare, Zipf, Austria) by B.J.v.d.K., J.I.P.d.V. and/or L.R.P. Still images as well as coronal (frontal to occipital) and sagittal (from left-to-right lateral) videoclips were stored digitally.

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Neonatal cranial ultrasound (cUS) was performed within 24 h after birth (and weekly thereafter until discharge, in cases of hospital admission) and at term-equivalent age (TEA). The same coronal and sagittal planes (still images and videoclips) were obtained, as well as an additional plane through the mastoid fontanel to visualize the cerebellum, as axial ultrasound planes cannot be obtained in the same manner in the neonate as in the fetus. The cUS examinations were performed by B.J.v.d.K., J.I.M.L.V., I.Z. and/or L.S.d.V. using a ProSound Alpha 7 (Hitachi Aloka Medical Ltd., Tokyo, Japan) or Toshiba Aplio (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) machine. All images and sweeps were stored for offline analysis.

Assessment of the fetal neurosonogram and cUS consisted primarily of evaluation for periventricular echogenicity (PVE) changes, peri- and intraventricular hemorrhage (IVH), including germinal matrix hemorrhage, and changes in basal ganglia and/or thalami echogenicity (BGTE)[4,15]. These and all other items that were assessed on ultrasound are presented in Table S1[2,4,16–19]. On multiplanar ultrasound, the presence of echogenicity changes was confirmed in two directions (coronal, sagittal and/or axial planes). In cases in which an echogenicity change was seen in one plane only, the item was considered inconclusive. For analysis of the prevalence of echogenicity changes according to indication, the ultrasound examination with the highest grade of echogenicity changes per case was used.

Fetal and neonatal brain MRI

A fetal MRI examination was scheduled for approximately 2–3 weeks after the first ultrasound examination. A sedative (flunitrazepam, 1 mg) to minimize movement artifacts was advised, but not obligatory. Fetal MRI was performed using a 1.5-Tesla scanner (Sonata or Avanto; Siemens Medical Solutions, Erlangen, Germany or Ingenia; Philips Healthcare, Best, The Netherlands) and the research protocol, containing T2 and T1 (inversion–recovery) sequences in three directions, a T1 sequence in the axial direction and a diffusion-weighted imaging sequence in the axial direction, was applied. Detailed information about the sequences and settings is provided in Appendix S1.

A neonatal MRI examination was performed at TEA. The neonates were not sedated, but comfortably swaddled after feeding. Hearing protection was applied, and heart rate and saturation were monitored during the MRI. The neonatal MRI examinations were performed using a 1.5-Tesla scanner (Sonata or Avanto; Siemens Medical Solutions or Ingenia; Philips Healthcare) with a pediatric head coil. The neonatal sequences are provided in detail in Appendix S1[20–21].

The focus of the assessment of fetal and neonatal MRI was on the grading of SI changes of the white matter (corresponding to PVE changes on ultrasound), signs of IVH and SI changes in the basal ganglia and thalami (corresponding to BGTE changes on ultrasound). These and all other items that were assessed on MRI are presented in Table S2.

Image assessment

The assessments of all images were performed by a panel of experts, comprising the primary investigator (B.J.v.d.K.) with 4 years' experience as a physician/sonographer, J.I.P.d.V. with 20 years' experience as a gynecologist/perinatologist, I.A.Z. with 12 years' experience as a neonatologist, R.J.V. with 18 years' experience as a pediatric neurologist and L.S.d.V. with 30 years' experience as a neonatologist/neonatal neurologist. Fetal neurosonograms and standard axial ultrasound examinations were assessed by B.J.v.d.K. and J.I.P.d.V., neonatal cUS examinations by I.A.Z., R.J.V., L.S.d.V. and J.I.P.d.V. and fetal and neonatal MRI examinations by R.J.V. and L.S.d.V.. For the purpose of this study, all conclusions on imaging findings were based on consensus agreement between the observers, due to previously reported poor interobserver agreement for assessment of mild echogenicity changes[22–24]. The panelists were blinded to all medical information, including imaging findings by the other methods; only gestational age (GA) in weeks at each examination was provided.

Neurodevelopmental outcome

At TEA, the neurological examination was performed according to Prechtl[25]. At the age of 12 months, the neurological investigations were performed according to Touwen[26] and the Alberta Infant Motor Scale (AIMS; in a subgroup, the Griffiths Mental Development Scale (GMDS) was used instead).

The Prechtl and Touwen neuromotor examinations were considered normal when there were no tone and posture abnormalities; suspicious for neurodevelopmental sequelae in cases of mildly abnormal tone and posture, with no or moderate delay in motor development; and poor in cases of definite abnormalities in tone and posture, resulting in delayed motor development. For the AIMS, *Z*-scores below −1 were considered suspicious for neurodevelopmental sequelae[27]. For the GMDS, the mean ± SD developmental quotient score for the general population is 100 ± 12, and scores > 1 SD below the mean were considered suspicious; correction for prematurity was applied[28].

At 2 years of age, neurodevelopmental outcome was examined using the Bayley Scale of Infant Development-III (BSID-III). The composite motor and cognitive scales were used for analyses, and correction for prematurity applied. For both scales, the mean ± SD score for the general population is 100 ± 15, and scores > 1 SD below the mean were considered suspicious for neurodevelopmental sequelae. Furthermore, a lexi quotient, reflecting linguistic comprehension and with an average score of 100 ± 15 in the general population, was calculated; scores > 1 SD below the average were considered suspicious. The parents

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filled out a Child Behavior Checklist (CBCL) and an Infant and Toddler Sensory Profile (ITSP) questionnaire during the visit at 2 years of age; the latter is used to assess sensory processing problems, which are associated with white matter damage[29]. Clinical interpretation of CBCL T-scores for narrow-band scales was as follows: < 65, normal behavior; 65–69 (93rd–97th centile), borderline behavior, indicating problems rated high enough to be of concern, but not clearly deviant; and > 69 ($> 97^{th}$ centile), clinical range, indicating problems of clinically relevant deviance. CBCL T-scores for broad-band scales were interpreted as: ≤ 60, normal behavior; 60–63 (84^{th}–90^{th} centile), borderline behavior; and ≥ 63 ($> 90^{th}$ centile), clinical range[30]. For the ITSP, scores > 1 SD below the mean were considered suspicious for neurodevelopmental sequelae[29].

Statistical analysis

The estimated percentage of ultrasound anomalies[31–36] for the various indications was 45% and the estimated percentage of neurologically affected[32,34,37–42] neonates was 15%. Power and size analysis with bioequivalence of proportions statistics, or the paired Student's *t*-test, showed that a study size of 400 fetuses would detect an absolute difference of 5% in the incidence of abnormal findings on axial ultrasound *vs* neurosonography, as well as axial ultrasound *vs* MRI, with alpha 0.05 and power 80%. The same number of fetuses would have a power of $> 90\%$ to demonstrate a correlation of > 0.1 between imaging findings and neurological abnormalities. The eligible population in the three initially involved centers was calculated to be a total of 324 pregnant women annually.

The prevalence of different grades of echogenicity or SI changes visible on axial ultrasound, the neurosonogram and MRI was analyzed in each fetus for which all imaging modalities were available, using the Friedman two-way analysis of variance by ranks, with a McNemar test for *post-hoc* analyses.

For all axial ultrasound and neurosonography examinations (irrespective of whether fetal MRI examinations were available), presence of echogenicity changes (yes/no) in the three regions of interest was analyzed using the McNemar test in cases with sufficient imaging. Indication for participation, position (breech or cephalic) and GA were compared between those with sufficient and those with insufficient imaging using the Fisher's exact test or Pearson chi-square for categorical variables and the Mann–Whitney *U*-test for continuous variables. For all tests, $P < 0.05$ was considered significant and the Bonferroni correction for multiple testing was applied as appropriate. All analyses were performed using IBM SPSS Statistics version 22.0 for Windows (IBM Corp., Armonk, NY, USA.).

Approval from the local medical ethical committees was obtained; all participating women, and their partners if present, gave written informed consent.

RESULTS

Participation in the FBI study is summarized in Figure 1. Fifty-six fetuses with at least one available fetal-imaging modality were included. The calculated sample size of 400 participants was not met in the three study years, due to an unexpected low rate of study participation in eligible women[43] and financial issues, which meant that one initially involved center could not participate.

The earliest neurosonogram was performed at 20 weeks of gestation and the latest at 36 weeks, with a median (IQR) of 27 (25–30) weeks. The fetal MRI examinations were performed at a median (range) GA of 30 (24–38) weeks, 2.5 (−2 to 9) weeks after the first ultrasound examination and 3 (−1 to 9) weeks after study inclusion. The median (range) time between the fetal MRI and a follow-up neurosonogram was 0 (−2 to 6) weeks; 53% of the fetal MRI examinations were performed either on the same day as, the day prior to or the day after a follow-up neurosonogram. All but three fetuses had a neurosonogram and a MRI examination within 2 weeks.

Prevalence of echogenicity and signal-intensity changes

In 39 of 56 fetuses, all three fetal-imaging techniques were available (Figure 1). The prevalence of echogenicity changes visible on axial ultrasound and the neurosonogram and SI changes on MRI are depicted in Table 1. The prevalence of PVE/SI changes ($P < 0.001$), IVH ($P = 0.001$) and BGTE/SI changes ($P = 0.008$) was significantly different between the three imaging modalities. *Post-hoc* analysis showed that the neurosonograms revealed more PVE changes, IVH and BGTE changes compared to axial ultrasound ($P = 0.001$, $P = 0.039$ and $P = 0.031$, respectively) and the corresponding SI changes on MRI ($P < 0.001$, $P = 0.004$ and $P = 0.031$, respectively). The five fetuses with an anomaly on MRI (two with SI changes of the white matter, one with IVH and ventriculomegaly (VM) and two with isolated VM) were all identified as having an anomaly on a neurosonogram, and four of five had an anomaly on axial ultrasound. The findings in the 17/56 fetuses, with one or more fetal-imaging modality missing, are presented in Table 2.

In 52/56 fetuses (Figure 1), axial ultrasound and neurosonographic examinations were available. The prevalence of echogenicity changes visible on axial ultrasound and neurosonography for all ultrasound examinations ($n = 143$) is shown in Table 3.

Whether the neurosonography and axial ultrasound examinations were sufficient for assessment was not influenced by the indication for study participation ($P = 0.063$ and $P = 0.885$, respectively) or fetal position ($P = 0.121$ and $P = 0.770$, respectively). For neurosonography, GA did not influence whether the examination was sufficient for assessment ($P = 0.110$), whereas axial ultrasound examinations considered as insufficient for assessment were performed at a higher GA (median, 32 weeks) compared with those that were sufficient for assessment (median, 29 weeks) ($P = 0.049$).

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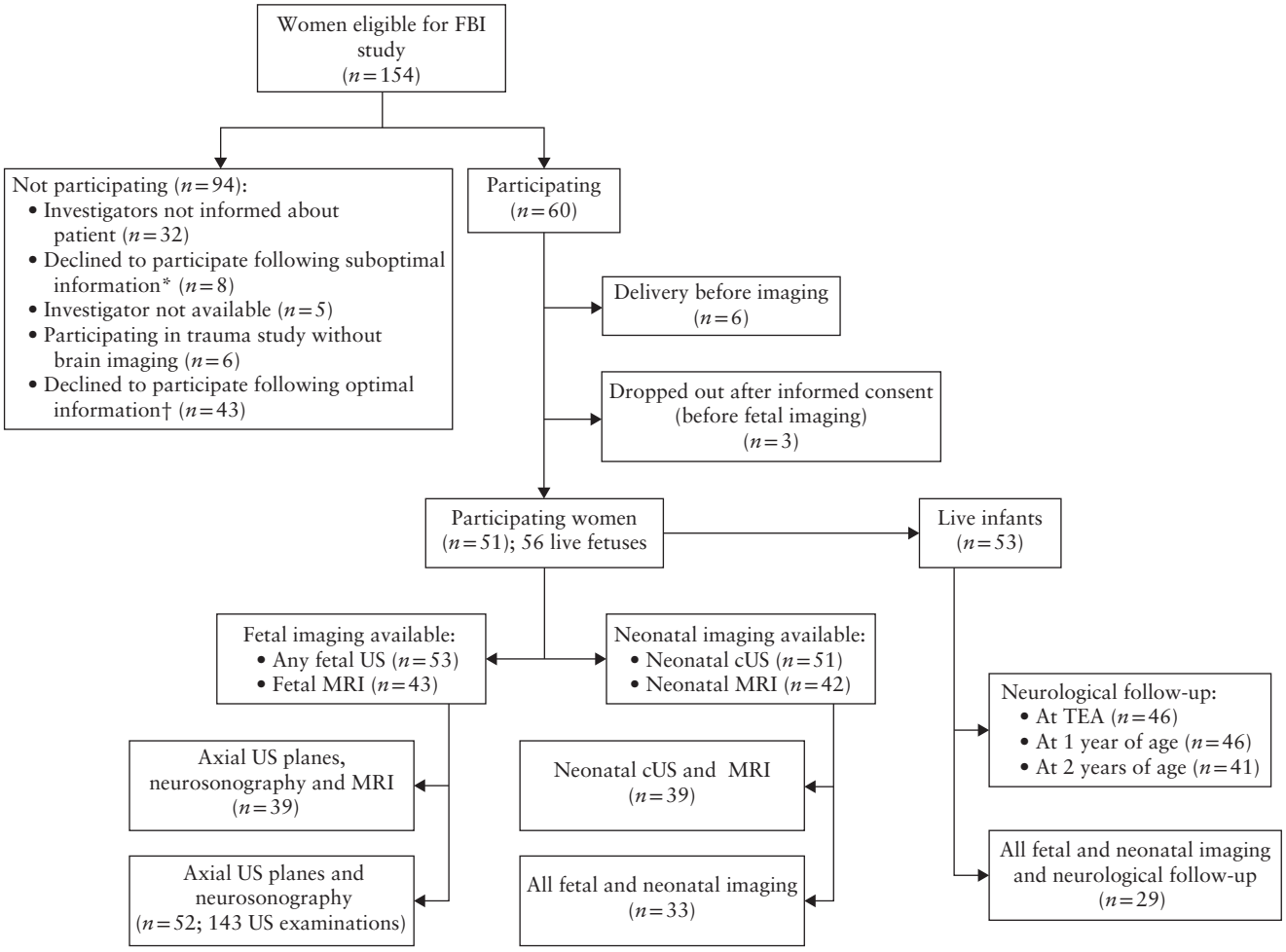

Figure 1 Flowchart summarizing study inclusion. *Study information given by physician on duty. †Study information given by investigator. cUS, cranial ultrasound; FBI, fetal brain imaging; MRI, magnetic resonance imaging; TEA, term-equivalent age; US, ultrasound.

Table 4 depicts information on echogenicity changes and other findings on axial ultrasound or neurosonography, according to indication for study participation.

Evolution of echogenicity and/or signal-intensity changes from before to after birth

Data regarding evolution of echogenicity or SI changes in each fetus are shown in Table S3. One case (indication, maternal trauma) withdrew from further study participation after two fetal neurosonograms.

Table 5 shows the evolution of echogenicity changes in fetuses with an anomaly on neurosonography. There were six fetuses with an anomaly on fetal MRI and three with fetal MRI examinations only. In the six fetuses with SI changes ($n=4$) or ventriculomegaly ($n=2$) on fetal MRI, the findings were persistent after birth. Five of these fetuses also had an anomaly on fetal neurosonography and are presented accordingly in Table 5. The sixth fetus had a fetal MRI examination, but no fetal axial ultrasound or neurosonography; this fetus is presented below (fetuses with severe anomalies). Two other fetuses had fetal MRI without fetal ultrasound examinations. One of these had a suspected anomaly (VM) on routine fetal ultrasound, but showed no anomalies on fetal MRI; after birth, neonatal MRI showed moderate VM, irregular ventricular wall and a germinolytic cyst. The other fetus (inclusion criterion, FGR) had no fetal MRI anomalies but showed mild VM and enlarged cerebrospinal fluid (CSF) spaces on both neonatal cUS and MRI.

Neurodevelopmental outcome at term-equivalent age and 1 and 2 years of age

One infant (indication, FGR) with postnatally diagnosed trisomy 21 was excluded from neurodevelopmental outcome analysis. Another neonate (indication, monochorionic twin) died shortly after birth.

Neurological outcome at TEA, 1 year and 2 years is shown in Table 6. The indications for study participation in those with scores suspicious for neurodevelopmental sequelae are provided in Table 7. Five of 13 children with suspicious AIMS/GMDS scores at 1 year did not attend the 2-year follow-up examination. Indication for participation was monochorionic twins in three of these cases. The other two were examined at 5 years of age, showing neurodevelopmental delay in one (indication, suspected anomaly on ultrasound) and normal development in the other (indication, FGR).

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Table 1 Prevalence of echogenicity changes on standard axial ultrasound (US) planes and multiplanar neurosonography, and corresponding signal intensity (SI) changes on magnetic resonance imaging (MRI), of brain in 39 fetuses at high risk for acquired brain anomalies

Finding	*Axial US planes*	*Neurosonography*	*MRI*
PVE/SI changes			
Absent	19	13*	36
Grade IA/IB	5	20	1
Grade II	0	0	0
Grade III	1	1	1
Insufficient imaging	14	5	1
IVH			
Absent	27	24*	37
Grade I/II	3	9	1‡
Grade III/IV	0	2	0
Insufficient imaging	9	4	1
BGTE/SI changes			
Absent	35	24†	38
Inhomogeneous	0	11	0
Central echogenicities	0	1	0
Insufficient imaging	4	3	1

Data are given as *n*. Details of grading of echogenicity and SI changes are explained in Tables S1 and S2, respectively. In *two cases and in †one case, finding was absent on one side, while imaging on other side was insufficient. ‡Case of Grade-II peri- and intraventricular hemorrhage (IVH) on MRI was classified on neurosonography as Grade-IV IVH. BGTE, basal ganglia and/or thalami echogenicity; PVE, periventricular echogenicity; SI, signal intensity.

Table 2 Prevalence of brain-imaging findings in 17 fetuses at high risk for acquired brain anomalies, which had one or more missing fetal-imaging modalities

Finding	*Missing axial US (n = 1)**	*Missing axial US and NS (n = 3)†*	*Missing MRI (n = 13)‡*
Axial US and/or NS			
No anomaly	0	—	5
PVE changes only	1	—	1
IVH only	0	—	1
BGTE changes only	0	—	1
Multiple echogenicity changes	0	—	2
Other findings	0	—	2§
Insufficient imaging	0	—	1
MRI			
No anomaly	1	2	—
IVH	0	1	—

Data are given as *n*. *Axial ultrasound (US) images not stored properly; fetal neurosonography (NS) showed Grade-IA periventricular echogenicity (PVE) changes. †Three fetuses had only fetal magnetic resonance imaging (MRI) examination due to image storage problem; one fetus (inclusion criterion, anomalies (peri- and intraventricular hemorrhage (IVH) Grade IV and severe ventriculomegaly (VM) of lateral 3rd and 4th ventricles) on routine US) showed IVH Grade IV with VM of lateral 3rd and 4th ventricles on fetal MRI and other two (inclusion criteria, fetal growth restriction and suspicion of acquired anomalies (VM) on routine US) showed no anomalies on fetal MRI. ‡MRI not performed because MRI was declined ($n = 6$), delivery occurred before MRI ($n = 5$), MRI was not arranged ($n = 1$) or participant withdrew from study ($n = 1$). §Lenticulostriate vasculopathy ($n = 1$) and enlarged cerebrospinal fluid spaces ($n = 1$). BGTE, basal ganglia and/or thalami echogenicity.

Cases with severe anomalies on fetal brain imaging

The focus of this study was on recognition of early signs of mild acquired brain anomalies. Fetal and neonatal ultrasound and MRI images in a fetus with mild echogenicity changes are depicted in Figure 2. Below, we present the trajectory of imaging findings in four fetuses with higher grading of echogenicity/SI changes on FBI.

The first fetus had routine fetal ultrasound suspicious for PVE changes as the indication for study participation. The neurosonogram showed, amongst other findings, Grade-III PVE changes, IVH Grade III and BGTE changes. Fetal MRI demonstrated similar findings, except that IVH was not seen. Most anomalies were persistent on neonatal cUS and MRI, including Grade-IV PVE changes, severe VM, enlarged CSF spaces, cortical delay and calcifications in the parenchyma. A selection of MRI and ultrasound images from this case is presented in Figure 3. Multifactorial etiology was suspected. The infant was lost to neurodevelopmental follow-up.

The second fetus had routine fetal ultrasound suspicious for IVH as the indication. An ultrasound data storage problem meant that fetal axial ultrasound and neurosonography examinations were not available. Fetal MRI showed large IVH and severe posthemorrhagic VM. Neonatal MRI showed extensive SI changes, Grade-III IVH and severe VM; findings were similar on neonatal

Table 3 Prevalence of echogenicity changes on 143 axial ultrasound (US) and neurosonography examinations obtained in 52 fetuses at high risk for acquired brain anomalies

Finding	*Axial US planes*	*Neurosonography*	P *(McNemar)*
PVE changes			
Absent	49	63*	0.496
Grade IA/B	6	29	< 0.001
Grade III	2	1†	1.00
Insufficient imaging	86	50	< 0.001
IVH			
Absent	90	86‡	0.243
Grade I/II	9	21	0.023
Grade III/IV	0	4	0.125
Insufficient imaging	44	32	0.067
BGTE changes			
Absent	101	92§	0.100
Inhomogeneous	11	24	0.003
Central echogenicities	0	1	—
Insufficient imaging	31	26	0.345

Data are given as *n*. Details of grading of echogenicity changes are explained in Table S1. In *20, ‡four and §two cases, finding absent on one side, while imaging insufficient on other. †Grade-III periventricular echogenicity (PVE) changes suspected on axial US planes during two separate examinations and findings confirmed on neurosonography once; other neurosonographic examination in this case considered insufficient for assessment. Any observed *P*-value less than Bonferroni-corrected *P*-value (0.0045) considered significant. BGTE, basal ganglia and/or thalami echogenicity; IVH, peri- and intraventricular hemorrhage.

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Table 4 Prevalence of echogenicity changes on standard axial ultrasound (US) planes or neurosonography in 53 fetuses at high risk for acquired brain anomalies, according to indication for participation

	Indication					
Variable	*Congenital infection (n = 13)*	*Maternal trauma (n = 15)**	*FGR (n = 9)*	*Suspected brain anomaly on US (n = 2)*	*Mono-chorionic twin (n = 14)*	*Total (n = 53)*
GA at first neurosonography (weeks)	26.5 (20–36)	28.5 (20–36)	28 (26–32)	27 (25–29)	26 (23–30)	27 (20–36)
Any echogenicity changes†	10/12 (83)	8/12 (67)	2/7 (29)	1/1 (100)	7/13 (54)	28/45 (62)
PVE changes						
Absent	3	6	6	0	7	22
Grade IA/IB	9	6	1	0	6	22
Grade II/III	0	0	0	1	0	1
Insufficient imaging	1	3	2	1	1	8
IVH						
Absent	9	13	7	0	9	38
Grade I/II	4	1	1	0	4	10
Grade III/IV	0	0	0	2	0	2
Insufficient imaging	0	1	1	0	1	3
BGTE changes						
Absent	7	9	9	0	12	37
Inhomogeneous	5	4	0	2	1	12
Central	1	0	0	0	0	1
Insufficient imaging	0	2	0	0	1	3
Other findings on US‡	11	7	1	2	8	29
VM/slit-like/asymmetrical ventricles	5	1	0	2	4	12
Thick/irregular ventricular wall	4	1	0	2	3	10
Choroid plexus cyst(s)	6	4	0	2	2	14
Echogenicities in caudothalamic groove	5	3	0	1	4	13
Enlarged cerebrospinal fluid spaces	1	1	1	1	4	8
Germinolytic cyst(s)	0	2	0	0	0	2
Occipital bleeding	1	0	0	0	0	1
Lenticulostriate vasculopathy	1	0	0	0	0	1

Data are given as median (range), *n*/*N* (%) or *n*. Details of grading of echogenicity changes are explained in Table S1. *One woman in maternal trauma group withdrew from further study participation after two fetal neurosonograms performed. †In fetuses with sufficient imaging to assess periventricular echogenicity (PVE) changes, US examination demonstrating highest grade of echogenicity changes included for each case. ‡Other findings without echogenicity changes observed in 3/11 cases in congenital infection group, 1/1 case in fetal growth restriction (FGR) group, 3/8 cases in monochorionic twin group and no cases in groups with maternal trauma or brain anomaly on US. BGTE, basal ganglia and/or thalami echogenicity; GA, gestational age; IVH, peri- and intraventricular hemorrhage; VM, ventriculomegaly.

Table 5 Persistence after birth of echogenicity changes observed on fetal neurosonography in fetuses at high risk for acquired brain anomalies

	Echogenicity/SI change on neonatal imaging	
Finding	*Yes*	*No*
PVE changes	21/23	2/23
IVH	12/12	0/12
BGTE changes	12/13	1/13
No	6/11	5/11

Data are given as *n*/*N*. BGTE, basal ganglia and/or thalami echogenicity; IVH, peri- and intraventricular hemorrhage; PVE, periventricular echogenicity; SI, signal intensity.

cUS. As mentioned above, the fetus had a poor outcome at TEA and a GMDS *Z*-score < -1 at 1 year of age. Movement ABC score at 5 years of age was $< 2.3^{rd}$ centile.

The third fetus had routine fetal ultrasound suspicious for IVH as the indication for study participation. On fetal neurosonography, there were findings of IVH Grade IV, BGTE changes and moderate VM. After birth, there were punctate white matter lesions, IVH Grade II and mild VM on neonatal MRI. Follow-up was normal at 1 and 2 years of age. At 5 years of age, the total movement-ABC score was on the 5^{th} centile, which reflects suspicious development.

The fourth fetus had congenital CMV infection as the indication. The fetal neurosonogram showed severe lenticulostriate vasculopathy (LSV). Neonatal cUS showed Grade-IA PVE changes, LSV and calcifications in the parenchyma. On neonatal MRI, there were irregular SI changes in the frontal and occipital lobes and temporal cysts. Neurological outcome was poor on the Touwen examination and AIMS *Z*-score was < -1 at 1 year. Outcome was normal on BSID-III, CBCL, lexi and ITSP at 2 years of age.

Except for the first abovementioned case with severe anomalies, the children who were lost to follow-up were, with respect to findings on fetal imaging, comparable to those who attended the neurodevelopmental examinations.

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Table 6 Neurodevelopmental outcome at term-equivalent age (TEA), 1 year and 2 years in fetuses at high risk for brain damage

	Anomaly on fetal brain imaging		
Neurodevelopmental outcome	*Yes*	*No*	*Total*
TEA ($n=46$)			
Prechtl assessment			
Suspicious or poor	3	1	4
Normal	31	11*	42
1 year ($n=46$)			
Touwen examination ($n=43$)			
Suspicious or poor	2	0	2
Normal	30	11*	41
AIMS/GMDS ($n=46$)			
Suspicious	8	5	13
Normal	25	8*	33
2 years ($n=41$)			
BSID-III ($n=41$)			
Suspicious	0	0	0
Normal	20	21	41
CBCL ($n=38$)			
Suspicious	4	1	5
Normal	26	7*	33
ITSP ($n=37$)			
Suspicious	13	4	17
Normal	16	4	20
Lexi quotient ($n=39$)			
Suspicious	4	2*	6
Normal	27	6	33

Data are given as *n*. *Including two cases with insufficient neurosonography that had no anomalies on fetal axial ultrasound and/or fetal magnetic resonance imaging. AIMS, Alberta Infant Motor Scale; BSID-III, Bayley Scale of Infant Development-III; CBCL, Child Behavior Checklist; GMDS, Griffiths Mental Development Scale; ITSP, Infant and Toddler Sensory Profile.

Table 7 Indication for study participation in fetuses at high risk for brain damage, with follow-up assessments suspicious for neurodevelopmental sequelae

Indication	*Suspicious/ poor score on Prechtl assessment* (n = *4*)	*Suspicious score on AIMS* (n = *13*)	*Suspicious score on ITSP/CBCL/lexi* (n = *20*)
Congenital infection	1	5*	5†
Maternal trauma	1	—	7*
Fetal growth restriction	1	4	3†
Suspected brain anomaly on US	1	1*	—
Monochorionic twin	—	3	5

Data are given as *n*. *Including fetus with suspicious score on Prechtl assessment. †Including two fetuses with suspicious Alberta Infant Motor Scale (AIMS) score. CBCL, Child Behavior Checklist; ITSP, Infant and Toddler Sensory Profile; US, ultrasound.

DISCUSSION

The findings of this study confirmed our hypothesis that multiplanar neurosonography has value additional to that of the standard axial ultrasound planes in the detection of acquired brain anomalies, in a population of fetuses at risk for brain damage. However, no additional value was found for fetal MRI compared to axial ultrasound or neurosonography. To our knowledge, this is the first prospective study comparing the value of neurosonography, fetal MRI and the standard axial ultrasound planes in a diverse population at risk for acquired brain anomalies. Low-grade echogenicity changes (PVE, IVH, BGTE) were found more often using neurosonography compared to axial ultrasound planes and the corresponding SI changes on fetal MRI. Evolution of echogenicity changes studied by serial multiplanar ultrasound examinations demonstrated persistence of IVH before birth and in a large proportion after birth. PVE and BGTE changes appeared to be transient in the majority of cases; however, > 90% of those with PVE or BGTE changes showed changes in other areas of the brain. All children attending the follow-up examinations at 2 years of age had normal neurodevelopmental outcome on BSID-III, but 51% (20/39) had score(s) suspicious for neurodevelopmental sequelae on ITSP, CBCL and/or lexi quotient. Of the four children with high-grade anomalies on fetal imaging, two had normal outcome at 2 years of age, one had scores suspicious for neurodevelopmental sequelae at 5 years and one was lost to follow-up. A small number of fetuses with echogenicity changes on neurosonography showed no anomalies on neonatal imaging (Table 5) and had normal neurodevelopmental outcome. In these children, echogenicity changes may have reflected physiological changes, or the echogenicities did not result in neurodevelopmental sequelae at an early age.

In order to examine the brain at the correct time, one has to be aware of the interval between risk-factor exposure and onset of brain damage. Risk factors such as maternal trauma and the death of a monochorionic twin may induce intracranial hemorrhage, which can be visualized directly. Other risk factors, such as chronic hypoxia/ischemia in growth-restricted fetuses and congenital infection, cause damage gradually over time, if any damage does occur. The earliest signs may appear after about 1 week, including increased echogenicity/SI in the injured area, followed by cysts, replacement of damaged areas by fibrillary processes, thinning of brain areas and deposition of minerals[1].

Implementation of multiplanar neurosonography for fetal central nervous system assessment has been advocated by experts in the field of ultrasound[7] since as early as 1996. The findings of this study support this. Accuracy of the neurosonogram was not influenced by fetal cephalic or breech position, indication or GA. This underlines the usefulness of transvaginal ultrasound in cases of cephalic position.

This study, assessing the value of axial ultrasound, neurosonography and MRI, paves the way to prevent unnecessary MRI in cases with sufficient fetal neurosonography, as we did not find an additional value of MRI in this limited population of fetuses at risk of acquired brain anomalies. The usefulness of MRI has been shown in cases with established acquired fetal-brain anomalies[6]; however, the value of MRI in a population at

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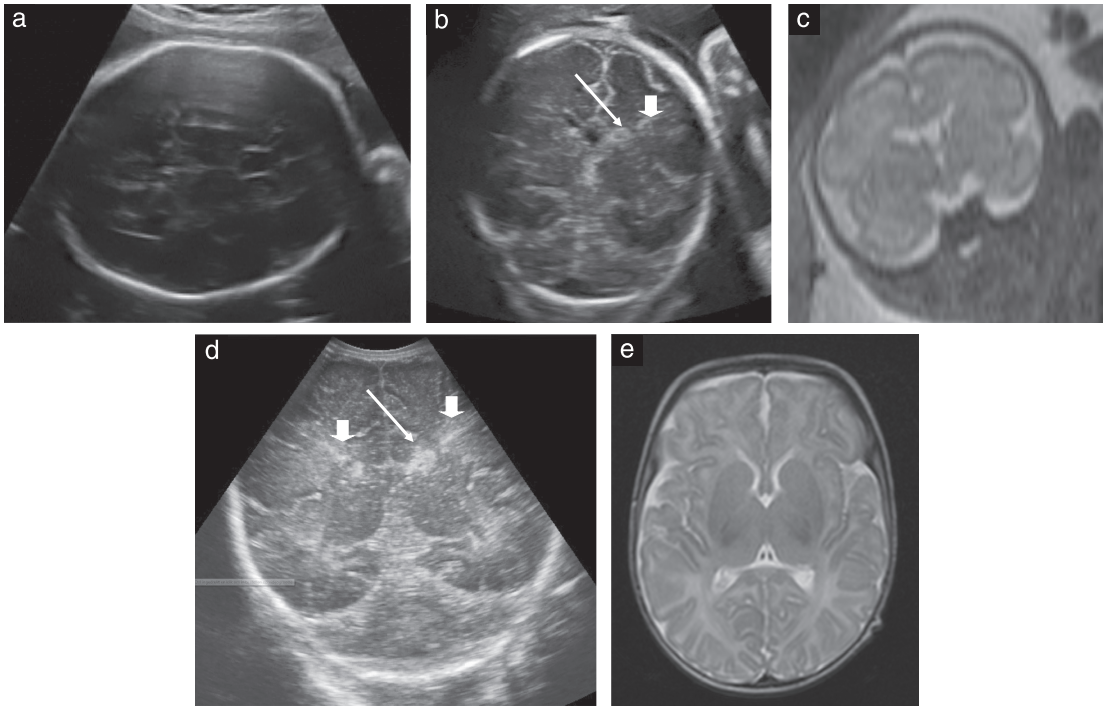

Figure 2 Fetal and neonatal brain imaging in pregnancy at high risk for acquired fetal brain anomalies that had low-grade echogenicity changes. (a–c) Fetal axial (a) and coronal (b) ultrasound (US) images and fetal coronal T2-weighted magnetic resonance imaging (MRI) (c) at 30 + 4 weeks of gestation. (d) Neonatal coronal cranial US image < 24 h after birth at 37 + 5 weeks. (e) Neonatal axial T1-weighted MRI at term-equivalent age. (b,d) Intraventricular hemorrhage Grade I–II (thin arrows) and Grade-IA periventricular echogenicity changes (thick arrows) were seen; echogenicity changes were confirmed in sagittal plane. (c) Fetal MRI showed no anomalies. (e) Neonatal MRI showed Grade-IA periventricular signal intensity changes; no coronal images were available.

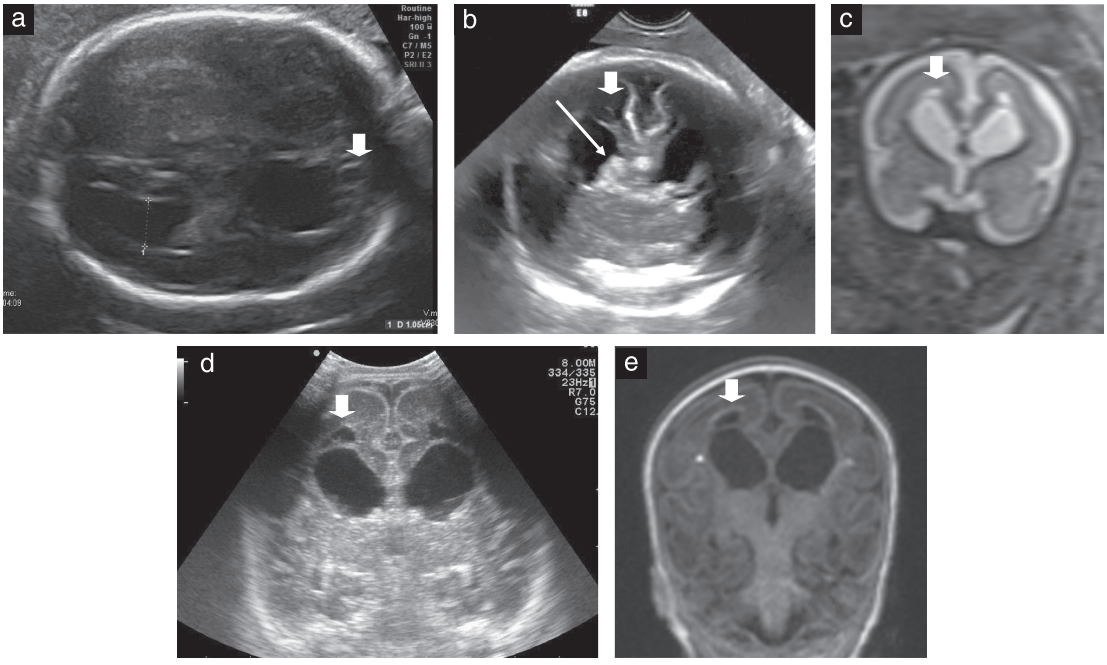

Figure 3 Fetal and neonatal brain imaging in pregnancy at high risk for acquired fetal brain anomalies that had high-grade echogenicity changes. (a,b) Fetal axial (a) and coronal (b) ultrasound (US) images at 29 + 3 weeks of gestation. (c) Fetal coronal T2-weighted magnetic resonance imaging (MRI) at 30 + 3 weeks. (d) Neonatal coronal cranial US image on day 5 after birth at 32 + 1 weeks. (e) Neonatal coronal T1-weighted MRI on day 15. (a–e) Grade-III periventricular echogenicity changes (cystic periventricular leukomalacia) were seen (thick arrows), as well as intraventricular hemorrhage Grade II–III (long arrow) (b). Furthermore, there was severe ventriculomegaly and delayed cortical development. Neonatal studies were performed at these ages for clinical reasons. Case was lost to follow-up at term-equivalent age.

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risk for acquired anomalies, and in comparison with neurosonography, has not. This is attributed to the fact that fetal MRI is generally complementary after an inconclusive ultrasound examination or a suspected anomaly on ultrasound[14,44], and no large multicenter study comparing neurosonography and fetal MRI has been performed. The FBI study was conducted to fill this gap in the literature.

The results of this study seem to contradict those of other studies. Two recent publications have emphasized the value of fetal MRI. First, the MERIDIAN group reported, in a large cohort study, improved diagnostic accuracy (23–29%) when fetal MRI is used in addition to ultrasound[45]; they examined prospectively 823 fetuses that underwent MRI after a suspected brain anomaly was found on ultrasound. Patients were eligible for recruitment if a detailed ultrasound scan suggested a brain anomaly; however, there were no specific requirements for the ultrasound technique. The most common anomalies on ultrasound were VM, posterior fossa anomalies and failed commissuration of the corpus callosum. Similar indications were included in a systematic review by van Doorn and colleagues[46]. They analyzed a large population of 1184 cases from 27 studies and reached the conclusion that addition of fetal MRI improved the diagnostic accuracy of neurosonography, even though it was not mentioned in the included studies whether a dedicated neurosonogram or axial ultrasound planes only was performed[46].

Strengths and limitations

A strength of our study is the systematic and multidisciplinary set up, in which all three imaging modalities were applied in a population of fetuses at risk for, but not yet diagnosed with, acquired anomalies. Second, image assessment by expert panelists generating consensus scores enhances the reliability of our findings. A third strength is the follow-up of children after birth by means of imaging as well as extensive neurodevelopmental examinations.

The main limitation of this study is the large number of women who declined study participation, resulting in a relatively small study population, and this prohibited subgroup analyses of several inclusion criteria. We have reported previously that, in this study population, an important reason for declining participation was the MRI examination[43]. Another limitation is the relatively low frequency of higher-grade echogenicity and/or SI changes. Furthermore, it is important to bear in mind that the quality of sequences and settings used in fetal MRI may have progressed over the years since the initiation of the study. It is possible that a stronger relationship between neurosonography and fetal MRI would be present using new magnetic resonance techniques.

While we did not find a relationship between low-grade echogenicity or SI changes and early neurodevelopmental outcome at 2 years, they may still have an effect on outcome at school age.

Conclusions

We recommend transvaginal multiplanar neurosonography for evaluating the brain in fetuses at risk for brain damage, as it is the most accurate imaging technique for depicting early signs of damage in predilection areas. It can be used easily to assess the evolution of echogenicity changes serially over time. In cases with absent or mild echogenicity changes on neurosonography, fetal MRI has no additional value in this population. A multidisciplinary approach, in which obstetricians, neonatologists, child neurologists and radiologists work together, increases reliability in recognition of early signs of brain damage.

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SUPPORTING INFORMATION ON THE INTERNET

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

Appendix S1 Fetal and neonatal magnetic resonance imaging (MRI) procedures and sequences

Table S1 Items assessed on ultrasound examination of fetal brain, in accordance with Rosier-van Dunné *et al.*[15]

Table S2 Items assessed on magnetic resonance imaging (MRI) examination of fetal brain

Table S3 Evolution of echogenicity or signal intensity (SI) changes on brain imaging and neurodevelopmental outcome in fetuses at high risk for acquired brain anomalies, per fetus

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