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# Brain Development in Fetuses of Mothers with Diabetes: A Case-Control MR Imaging Study

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Offspring exposed to maternal diabetes are at increased risk of neurocognitive impairment, but its origins are unknown. With MR imaging, we investigated the feasibility of comprehensive assessment of brain metabolism ( $^1\text{H}$ -MRS), microstructure (DWI), and macrostructure (structural MRI) in third-trimester fetuses in women with diabetes and determined normal ranges for the MR imaging parameters measured.

**MATERIALS AND METHODS:** Women with singleton pregnancies with diabetes ( $n = 26$ ) and healthy controls ( $n = 26$ ) were recruited prospectively for MR imaging studies between 34 and 38 weeks' gestation.

**RESULTS:** Data suitable for postprocessing were obtained from 79%, 71%, and 46% of women for  $^1\text{H}$ -MRS, DWI, and structural MRI, respectively. There was no difference in the NAA/Cho and NAA/Cr ratios (mean [SD]) in the fetal brain in women with diabetes compared with controls (1.74 [0.79] versus 1.79 [0.64],  $P = .81$ ; and 0.78 [0.28] versus 0.94 [0.36],  $P = .12$ , respectively), but the Cho/Cr ratio was marginally lower (0.46 [0.11] versus 0.53 [0.10],  $P = .04$ ). There was no difference in mean [SD] anterior white, posterior white, and deep gray matter ADC between patients and controls (1.16 [0.12] versus 1.16 [0.08],  $P = .96$ ; 1.54 [0.16] versus 1.59 [0.20],  $P = .56$ ; and 1.49 [0.23] versus 1.52 [0.23],  $P = .89$ , respectively) or volume of the cerebrum (243.0 mL [22.7 mL] versus 253.8 mL [31.6 mL],  $P = .38$ ).

**CONCLUSIONS:** Acquiring multimodal MR imaging of the fetal brain at 3T from pregnant women with diabetes is feasible. Further study of fetal brain metabolism in maternal diabetes is warranted.

**ABBREVIATIONS:** T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; GDM = gestational diabetes; sMRI = structural MRI

Diabetes is the most common medical disorder of pregnancy with the prevalence of type 1 (T1DM), type 2 (T2DM), and gestational diabetes (GDM) all increasing among women of child-bearing age in resource-rich settings. The perinatal complications of maternal diabetes, which reflect altered metabolic function in utero, include major congenital malformations, macrosomia, and stillbirth.<sup>1</sup> Long-term, children born to mothers with diabetes are

at increased risk for cognitive impairment,<sup>2,3</sup> inattentiveness,<sup>4</sup> impaired working memory,<sup>5</sup> and altered language development.<sup>6</sup> These adverse outcomes are not fully explained by postnatal events; this question focuses research attention on the vulnerability of the developing brain during fetal life. Identification of the nature and timing of alterations to brain structure and function that underlie neurocognitive impairment could help the development of strategies designed to improve the long-term outcome of children of diabetic mothers.

During fetal life, the predominant source of brain energy is glucose, which crosses the placenta by facilitated diffusion.<sup>7</sup> While severe perturbations in glucose homeostasis after birth are associated with neonatal brain injury, the effect of chronic fluctuant glucose concentration experienced by fetuses of women with diabetes on in utero brain development has not been investigated, to our knowledge. Maternal diabetes is also associated with disturbances in fatty acid metabolism: Umbilical venous blood docosahexaenoic acid concentration is reduced; this reduction reflects lower docosahexaenoic acid transfer to the fetus.<sup>8</sup> Docosahexaenoic acid accumulates in the brain in abundance from the

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third trimester and is essential for neurogenesis, neurotransmission, and protection from oxidative stress. Reduced bioavailability of this key metabolite has been suggested as a putative mechanism for programming altered neurodevelopment.<sup>8,9</sup>

Advances in proton MR spectroscopy (<sup>1</sup>H-MRS) and diffusion-weighted and structural MR imaging (sMRI) have led to the development of objective and sensitive measures of fetal brain structure and metabolism. Use of these technologies has revealed alterations in the cerebral NAA:choline ratio and gyrification in fetuses with congenital heart disease,<sup>10</sup> temporal lobe volumes in fetuses with congenital cytomegalovirus infection,<sup>11</sup> and ADC values and parenchymal volume in antenatal ventriculomegaly.<sup>12,13</sup> Historically, most fetal imaging studies have been undertaken at 1.5T. However, although an increasing number of studies have been performed at 3T field strength,<sup>14–20</sup> which has benefits over 1.5T due to improved signal-to-noise and is likely to be advantageous for depicting fetal anatomy,<sup>21</sup> to date, there have been no studies assessing the feasibility of recruiting women with diabetes for fetal neuroimaging.

Early-life metrics derived from <sup>1</sup>H-MRS, DWI, and sMRI are associated with function in childhood. After preterm birth, NAA/Cho and Cho/Cr ratios are associated with neurodevelopmental outcome at 2 years of age,<sup>22</sup> lactate/NAA predicts outcome following hypoxic-ischemic encephalopathy,<sup>23</sup> and abnormalities in the NAA/Cr and Cho/Cr ratios in neonates<sup>24</sup> and older children<sup>25</sup> predict developmental delay. Increased ADC values in white matter are associated with diffuse white matter injury following preterm birth<sup>26</sup> and with poor outcome after hypoxic-ischemic encephalopathy in term infants.<sup>27,28</sup> Finally, reduced regional and whole-brain volumes are associated with specific preterm comorbidities,<sup>29,30</sup> and structural alteration predicts long-term impairment after preterm birth.<sup>31,32</sup>

On the basis of disturbances to fetal glucose and fatty acid metabolism associated with maternal diabetes and the neurocognitive profile of offspring, we aimed to investigate the feasibility of comprehensive fetal brain assessment by acquiring measurements of NAA/Cho, NAA/Cr, and Cho/Cr ratios; regional apparent diffusion coefficient measurements; and volume of the cerebrum during the third trimester of pregnancy from women with diabetes and from healthy controls by using 3T MR imaging. The secondary aim was to determine normal values for these measures for future studies designed to investigate the effect of maternal disease on fetal brain development and in utero origins of neurodevelopmental impairment.

## MATERIALS AND METHODS

### Study Population

Ethics approval was obtained from the National Research Ethics Committee (South East Scotland Research Ethics Committee), and written informed consent was obtained. Women with a pregnancy complicated by diabetes ( $n = 26$ ) and healthy controls ( $n = 26$ ) were recruited prospectively from antenatal diabetes clinics at the Simpson Centre for Reproductive Health at the Royal Infirmary, Edinburgh, UK. The inclusion criteria were a singleton pregnancy and a fetal anomaly scan with normal findings at 20 weeks' gestation. Women with diabetes were eligible to participate if they had gestational diabetes, diagnosed by using the Scottish Intercollegiate Guideline Network diagnostic criteria<sup>33</sup> as a

fasting venous plasma glucose of  $\geq 5.1$  mmol/l or 2-hour glucose of  $\geq 8.5$  mmol/l after a 75-g oral glucose tolerance test or pregestational type 1 or type 2 diabetes. Exclusion criteria were serious coexisting maternal systemic disease other than maternal diabetes and women with any contraindications to MR imaging, including metal implants and pacemakers.

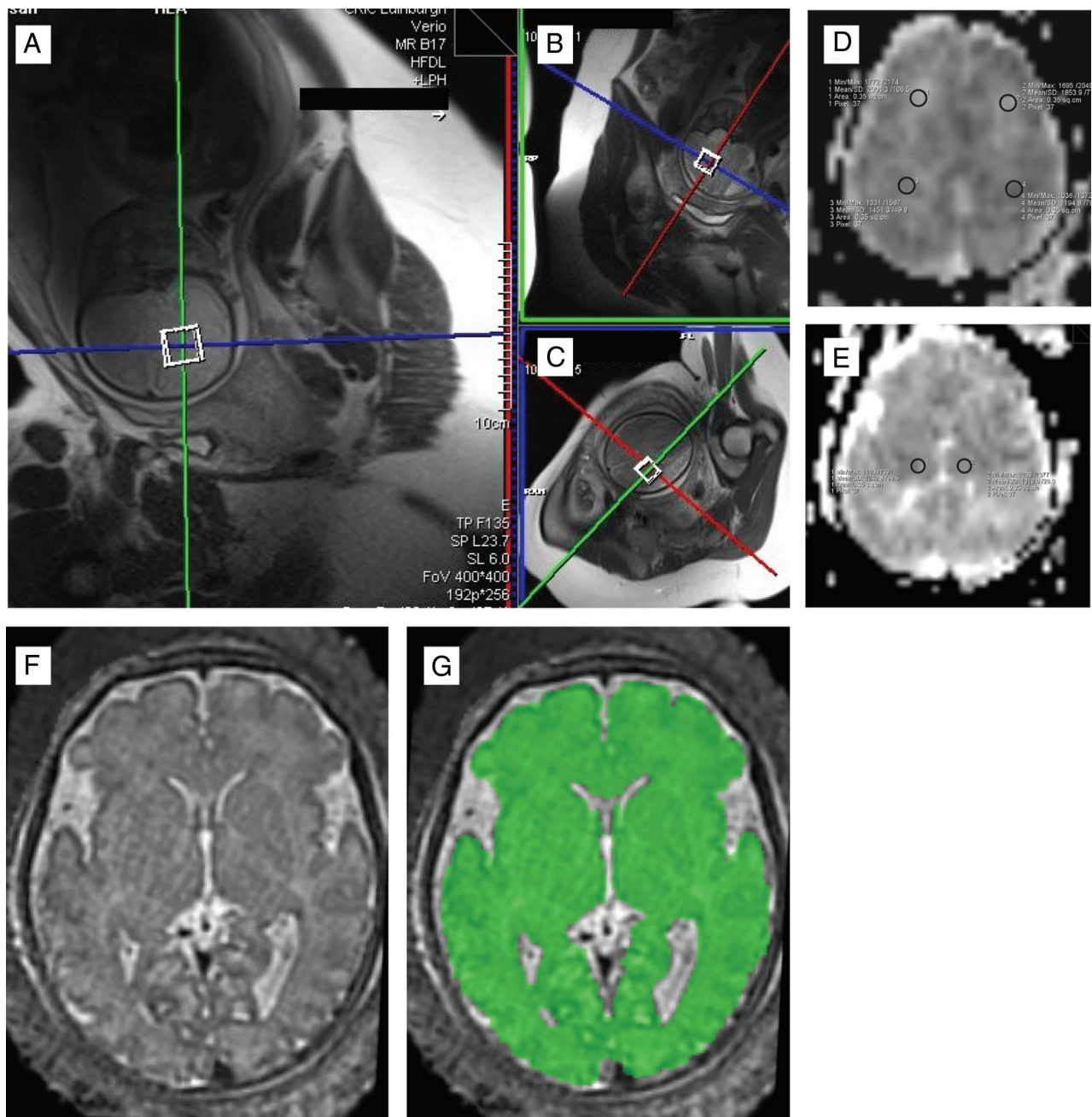
### MR Image Acquisition

MR imaging studies were performed at the Clinical Research Imaging Centre in the Queen's Medical Research Institute, University of Edinburgh, UK, by using a Magnetom Verio 3T MR imaging clinical scanner (Siemens, Erlangen, Germany). To avoid vena-cava compression, we placed women in a left-lateral tilt, with blood pressure being constantly monitored by using a Veris MR imaging vital signs monitor (Medrad, Indianola, Pennsylvania). No fetal sedation was used, women were limited to spending 45 minutes in the scanner, and data were acquired with women free-breathing throughout. MR images were obtained between 34 and 38 weeks' gestation. A radiologist with experience in MR imaging reported all images.

T2-weighted half-Fourier-acquisition single-shot turbo spin-echo images were acquired of the fetal brain in sagittal, coronal, and transverse orientations (HASTE: TR/TE = 1800/86 ms, FOV = 400 × 400 mm, matrix = 192 [phase] × 256 [frequency], section thickness = 8 mm, acquisition time = 18 seconds). These images were used to plan the position of the single 20-mm<sup>3</sup> spectroscopy voxel within the fetal brain. The scanner bed was moved to ensure that the fetal brain was positioned at the isocenter, and the voxel was positioned within 1 hemisphere of the fetal brain, avoiding ventricles and contaminant signal from surrounding tissue. An optimized semiautomated shimming protocol was systematically applied until the full width at half maximum of the water peak was <20 Hz. A single-voxel point-resolved spectroscopy technique was applied with TR/TE = 1500/30 ms, 96 signal averages, bandwidth = 2000 Hz, and a water suppression bandwidth = 50 Hz. The spectral acquisition took 2 minutes 30 seconds. Signal was received from selected elements of the spine matrix coil and body matrix surface coils positioned to allow adequate coverage of the fetal brain. A postspectroscopy 3-plane HASTE acquisition was then compared with the prespectroscopy HASTE images to allow visual assessment of fetal movement during the spectral acquisition. If the expert operator observed evidence of movement between HASTE acquisitions, then the spectroscopy voxel was repositioned and the spectral acquisition was repeated. No additional filtering or quality-control limiting of data was applied during the processing stage. We therefore processed all the MR spectroscopy data that were acquired. An example of voxel positioning for the MR spectroscopy acquisition is shown in Fig 1A.

Transverse DWIs of the whole fetal brain (TR/TE = 7300/106 ms, FOV = 400 × 400 mm, matrix = 128 × 128, section thickness = 3 mm, b-values = 0, 500, and 1000 s/mm<sup>2</sup>) were acquired. DWI was checked at the point of acquisition for obvious signs of fetal motion and was repeated if required. ADC maps were generated automatically from the diffusion-weighted images.

Finally, additional transverse HASTE images were acquired with identical coverage to the DWIs to aid subsequent ROI anal-



**FIG 1.** Examples of MR spectroscopy voxel placement in the fetal brain (A–C). ROIs for DWI in anterior white matter and posterior white matter (right and left) (D) and deep gray matter (right and left) (E), and tissue segmentation in the brain, highlighted in green (F–G).

ysis and to enable construction of the 3D motion-corrected brain volumes.

#### **Data Analysis: <sup>1</sup>H-MRS**

Spectral analysis was performed by using the QUEST algorithm available in jMRUI ([www.mrui.uab.es/mrui/mrui\\_download/](http://www.mrui.uab.es/mrui/mrui_download/)).<sup>34</sup> This technique estimates metabolite amplitudes by using a non-linear least-squares fit of simulated metabolite signals to the acquired spectrum. A metabolite basis set was generated by using the NMR-Scope function available in jMRUI<sup>35</sup> and included contributions from NAA (2.01, 2.49, and 2.70 ppm), Cho (3.20, 3.53, and 4.08 ppm), and Cr (3.04 and 3.93 ppm). We then calculated the following ratios: NAA/Cho, NAA/Cr, and Cho/Cr.<sup>36,37</sup> The

QUEST algorithm calculates errors associated with the estimated metabolite amplitudes by using an extended version of the Cramer–Rao lower bounds calculation.<sup>35</sup> The errors for each of the calculated metabolite ratios were derived through error propagation of the jMRUI output.

#### **Data Analysis: Diffusion and sMRI**

**Apparent Diffusion Coefficients.** ROI analysis was performed on ADC maps by using standard software on the 3T Magnetom Verio MR imaging system (Siemens). First, ROIs within white matter and gray matter were identified from the HASTE images acquired in the same plane and with the same coverage as the diffusion-

**Table 1: Demographics, MRI details, and delivery outcomes**

|                                                | Control (n = 26) | Diabetes     |              |               |              |
|------------------------------------------------|------------------|--------------|--------------|---------------|--------------|
|                                                |                  | All (n = 26) | GDM (n = 13) | T1DM (n = 12) | T2DM (n = 1) |
| Maternal demographics                          |                  |              |              |               |              |
| Maternal age (mean) (SD) (yr)                  | 31 (5)           | 31 (5)       | 32 (5)       | 30 (6)        | 34           |
| Parity (median) (range)                        | 0 (0–3)          | 0 (0–3)      | 1 (0–2)      | 0 (0–3)       | 0            |
| Current smoker (No.) (%)                       | 1 (4)            | 3 (12)       | 1 (8)        | 2 (17)        |              |
| Deprivation (No.) (%)                          |                  |              |              |               |              |
| SIMD 1–3                                       | 13 (50)          | 13 (50)      | 6 (46)       | 6 (50)        | 1            |
| SIMD 4–5                                       | 13 (50)          | 13 (50)      | 7 (54)       | 6 (50)        |              |
| MRI details                                    |                  |              |              |               |              |
| Gestation at MRI (mean) (SD) (wk)              | 36.1 (0.9)       | 36.0 (0.8)   | 36.0 (0.8)   | 36.0 (0.9)    | 36.7         |
| MRI-to-delivery interval (mean) (SD) (wk)      | 3.6 (1.6)        | 2.1 (1.2)    | 2.6 (1.2)    | 1.6 (1.1)     | 15           |
| Neonatal outcome                               |                  |              |              |               |              |
| Gestation delivery (mean) (SD) (wk)            | 39.7 (1.5)       | 38.1 (1.4)   | 38.6 (1.1)   | 37.6 (1.5)    | 38.9         |
| Birthweight (mean) (SD) (g)                    | 3372 (467)       | 3551 (627)   | 3629 (483)   | 3508 (780)    | 3040         |
| Sex (male/female)                              | 13:13            | 9:17         | 6:7          | 2:10          | Male         |
| Occipitofrontal circumference (mean) (SD) (cm) | 34.4 (1.4)       | 34.8 (1.8)   | 35 (1.6)     | 35 (2.2)      | 36           |

**Note:**—SIMD indicates Scottish Index of Multiple Deprivation; SIMD 1, most deprived; SIMD 5, most affluent.

weighted images. A section above the ventricles was identified as white matter, and a section at the level of the thalami was identified as deep gray matter by using landmarks described in Boardman et al.<sup>38</sup> The identical sections were then identified on the corresponding ADC map; 4 ROIs were positioned in the white matter (2 posterior and 2 anterior) and 2 were positioned in the gray matter. Due to differences in fetal brain volume, we used an anatomically appropriate ROI size for each individual brain, taking care to avoid partial volume effects from adjacent structures and artifacts. The mean (SD) ADC value for each ROI was recorded. The mean white matter ROI size was  $0.30 \pm 0.12$ , and the mean gray matter ROI size was  $0.32 \pm 0.13$ . Sample ROI placements for white and gray matter are shown in Fig 1B. Interrater agreement was checked by 2 independent investigators (D.A., G.M.).

**sMRI.** For each participant, a single 3D motion-corrected brain volume was reconstructed by using a section-to-volume registration method (Fig 1C).<sup>39</sup> The fetal brain was extracted from surrounding fetal and maternal tissue by using an atlas-based approach.<sup>40</sup> All reconstructed images were nonlinearly aligned to the closest age-matched template from a publicly available 4D fetal brain atlas.<sup>41</sup> Then, an automatic method based on an expectation-maximization framework for brain tissue segmentation was used, in which the priors of brain tissues were propagated by using prior probabilities provided by the 4D atlas. Finally, binary masks of the cerebrum (intracranial contents excluding intraventricular CSF, extra-axial CSF, and the choroid plexus, brain stem, cerebellum, and pons structures) and the intracranial volume (GM, WM, and CSF) were deformed to the subject's native space, and volumes were calculated.

### Statistical Analysis

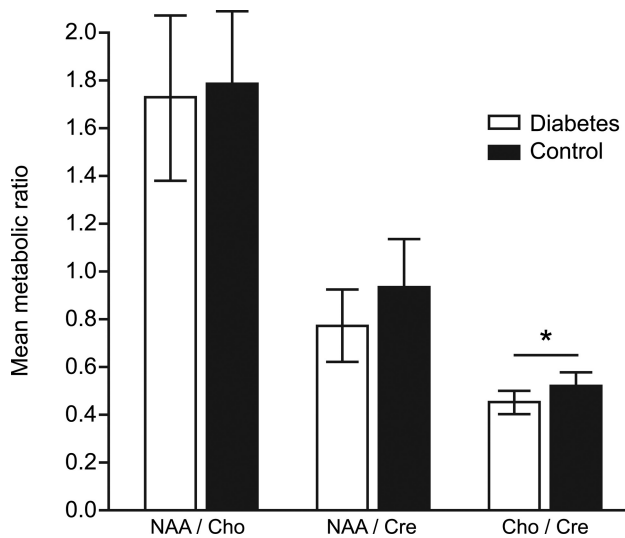
This was a feasibility study, so a formal power calculation for sample size was not required.<sup>42,43</sup> For normally distributed data, the mean and SD are reported, and for non-normally distributed data, the median and interquartile range are reported. For group-wise comparisons of normally distributed variables, an independent-sample *t* test was used, and for skewed data, the Mann-Whitney *U* test was used. To analyze regional ADC values, we first

tested for evidence of laterality in the anterior and posterior white matter and deep gray matter values with a paired-samples *t* test, and if there were no significant differences between left and right, the values were averaged to compute mean anterior white matter ADC, mean posterior white matter ADC, and mean deep gray matter ADC per individual. The distributions were assessed for normality, and an independent-samples *t* test was used for group-wise comparisons of regional ADC. Interobserver agreement in ADC measurements was assessed for each region in a randomly selected subset of 20 participants by using Bland-Altman statistics. For group-wise analysis of NAA/Cho, NAA/Cr, and Cho/Cr ratios and cerebral and intracranial volumes, an independent-samples *t* test was used after assessing the equality of variance between groups. Statistical analyses were performed by using SPSS 21 (IBM, Armonk, New York) with statistical significance defined as  $P < .05$ .

## RESULTS

### Participants

The maternal demographics and delivery outcomes of the study population are shown in Table 1. All women tolerated the MR imaging well, and no scan had to be abandoned due to maternal discomfort or claustrophobia. Of the women with diabetes, 13 were diagnosed with GDM during pregnancy, 12 had T1DM, and 1 had T2DM. In women with GDM, the median gestation at diagnosis and diagnosis-to-scan interval were 27.1 weeks (interquartile range, 12.0–31.0 weeks) and 8.9 weeks (interquartile range, 4.4–23.6 weeks), respectively. Only 1 woman with GDM was treated with diet alone. The other 12 were treated with metformin ( $n = 9$ ) or metformin and insulin ( $n = 3$ ) to achieve glycemic control. All women with T1DM were insulin-treated, and the 1 woman with T2DM was treated with insulin and metformin. The hemoglobin A1c (glycolated hemoglobin) at booking (11–13 weeks' gestation) for women with T1DM and T2DM was 51.9 mmol/mol (16.6 mmol/mol). Two women with GDM, 4 women with T1DM, and 1 control had antenatal steroids for fetal lung maturation before MR imaging. Three neonates of women with T1DM were admitted to the neonatal unit for <72 hours. The reasons for admission were suspected sepsis (culture negative



**FIG 2.** Metabolite ratios for NAA/Cho, NAA/Cr, and Cho/Cr in the fetal brain in women with diabetes and healthy controls. Data are presented as mean  $\pm$  SD.

for bacteria) and transient low blood glucose ( $n = 1$ ), a fractured clavicle sustained during a forceps delivery with shoulder dystocia, and a duplication cyst that was not diagnosed antenatally. No neonates born to healthy controls required admission. All neonates were discharged home alive and well.

There was no difference in the gestation in weeks at MR imaging between women with diabetes and healthy controls (mean [SD]) (36.0 weeks [0.8 weeks] versus 36.1 weeks [0.9 weeks],  $P = .69$ ). No adjustment was therefore made for gestational age in the statistical analysis. No congenital anomalies, acquired brain injuries, or incidental findings were detected by MR imaging.

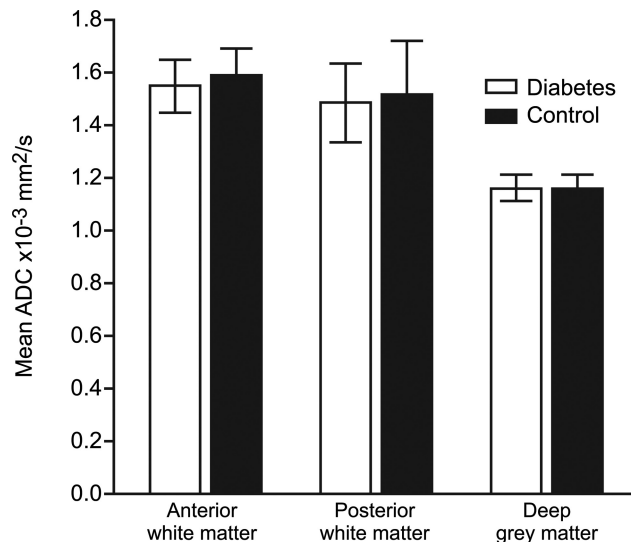
### MR Spectroscopy

In utero  $^1\text{H}$ -MRS of the fetal brain of suitable quality for analysis was obtained in 41/52 (79%) women in the study population, 22/26 (85%) with diabetes and 19/26 (73%) healthy controls. There was no difference in the clinical characteristics of women in whom interpretable data were acquired compared with those in whom they were not (data not shown). There was no difference in the NAA/Cho and NAA/Cr ratios in the fetal brain in women with diabetes compared with controls (1.74 [0.70] versus 1.79 [0.64],  $P = .81$ ; and 0.78 [0.28] versus 0.94 [0.36],  $P = .12$ , respectively). The Cho/Cr ratio was marginally lower in the fetal brain in women with diabetes compared with controls (0.46 [0.11] versus 0.53 [0.10],  $P = .04$ ) (Fig 2).

### Diffusion-Weighted Imaging: ADC

DWIs amenable to ADC computation were available for 37/52 (71%) women in the study population, 18/26 (69%) with diabetes and 19/26 (73%) healthy controls. Fetal motion or maternal size prevented interpretable data from being obtained from 9/52 (17%) of the study population. There was no difference in the clinical characteristics of women in whom interpretable data were acquired compared with those in whom they were not (data not shown).

There was no evidence of laterality in the anterior white matter, posterior white matter, or deep gray matter ADC values (all



**FIG 3.** ADC values in the anterior white matter, posterior white matter, and deep gray matter in the fetal brain in women with diabetes and healthy controls. Data are presented as mean  $\pm$  SD.

$P > .05$ ). Data were therefore combined to 3 variables: mean anterior white matter, mean posterior white matter, and mean deep gray matter ADC. There was no difference in mean (SD) ADC values for anterior white matter, posterior white matter, and deep gray matter in women with diabetes mellitus compared with controls (1.16 [0.12] versus 1.16 [0.08],  $P = .96$ ; 1.54 [0.16] versus 1.59 [0.20],  $P = .56$ ; and 1.49 [0.23] versus 1.52 [0.23],  $P = .89$ , respectively) (Fig 3).

There was good interrater agreement between the 2 independent investigators for ADC values. The mean difference and 95% confidence intervals between investigators for anterior white matter, posterior white matter, and deep gray matter measurements are reported in Table 2.

### Brain Volumes

Tissue segmentation data suitable for analysis were used to assess the macrostructure of the fetal brain in 24/52 (46%) of the study population (9/26 [35%] women with diabetes, 15/26 [58%] healthy controls). Fetal motion or data quality prevented interpretable data from being obtained from 28/52 (54%) women of the study population. There was no difference in mean cerebrum volume/milliliter in women with diabetes compared with controls ( $243.0 \pm 22.7 \text{ mL}^3$  versus  $253.8 \pm 31.6 \text{ mL}^3$ ,  $P = .39$ ). There was no difference in mean intracranial volume in fetuses of women with diabetes compared with controls ( $265.0 \pm 22.5 \text{ mL}^3$  versus  $274.5 \pm 32.3 \text{ mL}^3$ ,  $P = .47$ ).

### DISCUSSION

In this study, we demonstrated that it is feasible to recruit pregnant women with diabetes to undergo MR imaging at 3T during the third trimester of pregnancy for measurements of NAA/Cho, NAA/Cr, and Cho/Cr ratios; regional ADC measurements; and cerebrum and intracranial volumes. We chose to acquire  $^1\text{H}$ -MRS, DWI, and sMRI because of their use as markers of tissue injury/altered metabolism in the neonatal period and their relationships with long-term outcome. The values we acquired con-

**Table 2: Bland-Altman statistics for ADC measurements recorded by 2 observers<sup>a</sup>**

|                            | Mean Difference                               | Mean + (1.96 × SD)                           | Mean - (1.96 × SD)                            |
|----------------------------|-----------------------------------------------|----------------------------------------------|-----------------------------------------------|
| Gray matter ADC            | $-0.073 \times 10^{-3} \text{ mm}^2/\text{s}$ | $0.108 \times 10^{-3} \text{ mm}^2/\text{s}$ | $-0.253 \times 10^{-3} \text{ mm}^2/\text{s}$ |
| Anterior white matter ADC  | $-0.033 \times 10^{-3} \text{ mm}^2/\text{s}$ | $0.175 \times 10^{-3} \text{ mm}^2/\text{s}$ | $-0.241 \times 10^{-3} \text{ mm}^2/\text{s}$ |
| Posterior white matter ADC | $-0.028 \times 10^{-3} \text{ mm}^2/\text{s}$ | $0.225 \times 10^{-3} \text{ mm}^2/\text{s}$ | $-0.281 \times 10^{-3} \text{ mm}^2/\text{s}$ |

<sup>a</sup> Data are presented as mean difference  $\pm$  95% confidence intervals  $91.96 \times \text{SD}$ .

tribute useful normative data for future fetal brain studies performed with 3T systems.

Although this feasibility study was not powered to detect group differences, we observed a marginal-but-significant reduction in Cho/Cr in the brains of fetuses of diabetic mothers during the third trimester. The MR spectroscopy choline peak included free choline, phosphocholine, and glycerophosphocholine, so these data raise the possibility that brain metabolism and neuronal membrane phospholipid turn-over are altered in pregnancies with women with diabetes. While this finding requires confirmation in a larger study, alterations in the Cho/Cr ratio in brains of adults with type 2 diabetes have been reported.<sup>44</sup>

A strength of our study is that we recruited a cohort of women with well-characterized diabetes with all participants being scanned within a 4-week time window and gestation matched to our control group. This feature is important because <sup>1</sup>H-MRS spectra and ADC values are dynamic during this period of brain development.<sup>45–47</sup> We also acquired sMRI suitable for conventional clinical reporting, which was possible for all participants. A limitation of our study is that we were unable to acquire data amenable to quantitative analysis on all fetuses scanned. Despite ensuring the comfort of the women in a large-bore scanner, data could not be processed from <sup>1</sup>H-MRS in 21% of cases; DWI in 29% of cases and sMRI in 54% of cases. The low data yield for sMRI was partly because acquisition of <sup>1</sup>H-MRS and DWI was prioritized over sMRI. For future study designs that require fetal brain segmentation, yield may be increased by modifications to the acquisition protocol such as the increasing the number of stacks per plane and accepting the idea that time constraints required for safety may curtail other acquisitions (we capped imaging at 45 minutes). sMRI suitable for conventional clinical reporting was available for all participants.

We chose to recruit a heterogeneous population of women with diabetes to assess the feasibility of dissecting the effect of different in utero exposure to T1DM, T2DM, and GDM in a future study. Recruitment of women with T1DM and GDM was relatively easy; thus, recruitment to a future study assessing the effect of in utero exposure of T1DM and GDM on the fetal brain would be feasible. In contrast, we were able to recruit only 1 woman with T2DM, due to the lower prevalence of this condition. Thus, targeting recruitment of women with T2DM to a future study will not be practical unless recruitment occurs across multiple sites.

Our data were acquired by using a 3T system as opposed to 1.5T. For the advanced imaging techniques used in this study, there are advantages of acquiring data with the higher field strength of 3T.<sup>48</sup> Compared with lower field strengths, imaging at higher field strengths increases the signal-to-noise ratio. This increase improves the spectral quality obtained in <sup>1</sup>H-MRS and the ability to differentiate closely located metabolites, particularly at short TEs. The inability to complete data acquisition within the

time available due to fetal movement is a major limitation of MR imaging in pregnancy. Acquiring data more rapidly by using more advanced imaging methodologies, using methods of motion correction to compensate for fetal movement, and using alternative sampling techniques such as compressed sensing is likely to greatly increase data yield in the future. Finally, one advantage of 3T is the ability to acquire images with higher spatial resolution (depending on the imaging coil used), potentially increasing diagnostic accuracy.<sup>49</sup>

Perinatal image metrics are sensitive to tissue injury and neuroprotective treatment strategies. They are therefore increasingly used to address the “gap in translation” in perinatal neuroscience to assess therapies that show promise in preclinical studies at lower economic and opportunity costs than randomized controlled trials powered on clinical outcomes.<sup>50</sup> The normative data provided here may inform the development of fetal brain biomarkers for use in interventional perinatal neuroprotective outcome studies.

## CONCLUSIONS

The data provide proof-of-concept that comprehensive assessment of the fetal brain using measures derived from images acquired at 3T from women with diabetes and healthy controls is achievable. In addition, they suggest that fetal brain MR spectroscopy may provide a promising image marker of altered brain development in maternal diabetes. Finally, although we studied fetuses of mothers with diabetes, this research pipeline and the normative values obtained could be applied to any paradigm in which fetal origins of brain development are being investigated by using 3T MR imaging.

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