Brain Volume and Metabolism in Fetuses With Congenital Heart Disease
Evaluation With Quantitative Magnetic Resonance Imaging and Spectroscopy

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Background—Adverse neurodevelopmental outcome is an important source of morbidity in children with congenital heart disease (CHD). A significant proportion of newborns with complex CHD have abnormalities of brain size, structure, or function, which suggests that antenatal factors may contribute to childhood neurodevelopmental morbidity.

Methods and Results—Brain volume and metabolism were compared prospectively between 55 fetuses with CHD and 50 normal fetuses with the use of 3-dimensional volumetric magnetic resonance imaging and proton magnetic resonance spectroscopy. Fetal intracranial cavity volume, cerebrospinal fluid volume, and total brain volume were measured by manual segmentation. Proton magnetic resonance spectroscopy was used to measure the cerebral N-acetyl aspartate:choline ratio (NAA:choline) and identify cerebral lactate. Complete fetal echocardiograms were performed. Gestational age at magnetic resonance imaging ranged from 25 1/7 to 37 1/7 weeks (median, 30 weeks). During the third trimester, there were progressive and significant declines in gestational age–adjusted total brain volume and intracranial cavity volume in CHD fetuses relative to controls. NAA:choline increased progressively over the third trimester in normal fetuses, but the rate of rise was significantly slower (P<0.001) in CHD fetuses. On multivariable analysis adjusted for gestational age and weight percentile, cardiac diagnosis and percentage of combined ventricular output through the aortic valve were independently associated with total brain volume. Independent predictors of lower NAA:choline included diagnosis, absence of antegrade aortic arch flow, and evidence of cerebral lactate (P<0.001).

Conclusions—Third-trimester fetuses with some forms of CHD have smaller gestational age– and weight-adjusted total brain volumes than normal fetuses and evidence of impaired neuroaxonal development and metabolism. Hemodynamic factors may play an important role in this abnormal development. (Circulation. 2010;121:26-33.)

Key Words: brain ■ congenital ■ fetal ■ magnetic resonance imaging ■ pediatrics

Neurological and developmental dysfunction are among the most common extracardiac complications in children with complex congenital heart disease (CHD).1–4 Cerebral perfusion abnormalities that occur during intraoperative cardiopulmonary support may cause neurological injury, and extensive research has been performed on the impact of perioperative management on neurodevelopmental outcomes.5–8 Increasing evidence indicates that adverse neurodevelopmental outcomes in children with complex CHD are due not only to perioperative insult but to inborn factors as well. Reports from a number of investigators have documented a high prevalence of anatomic and functional neurological abnormalities before surgery in newborns with CHD9–17 and an association of such abnormalities with childhood developmental status.11,13,18,19 These findings support the hypothesis that abnormal brain development and growth in utero contribute to adverse neurodevelopmental outcomes in children with CHD.

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The underlying causes of abnormal prenatal brain development in fetuses with CHD are not known and may include...
both genetic and epigenetic factors. Several studies have documented abnormal cerebral blood flow in fetuses and newborns with complex anomalies such as hypoplastic left heart syndrome (HLHS).\textsuperscript{12,20,21} Whether these hemodynamic abnormalities are primary or secondary, it is possible that one of the factors contributing to impaired brain development in fetuses with CHD is inability of the abnormal fetal cardiovascular system to meet the metabolic demands of accelerated third-trimester brain growth and maturation.

The aim of the present study was to compare brain growth and metabolism between normal fetuses and those with CHD with the use of 3-dimensional volumetric magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (\textsuperscript{1}H-MRS). We hypothesized that, relative to normal controls, brain volume would be smaller and metabolic indices would be indicative of immaturity in third-trimester fetuses with some forms of CHD.

Methods

Subjects

Subjects were recruited prospectively into a longitudinal case-control study in which volumetric MRI and \textsuperscript{1}H-MRS were performed at a single prenatal time point, in the neonatal period before any cardiac surgery, and at 1 year of age. This report includes data from the prenatal evaluation.

The inception cohort included pregnant women undergoing fetal echocardiography at Children’s Hospital Boston between September 2007 and April 2008. Mothers of fetuses with confirmed CHD were recruited as cases. Normal controls were recruited from healthy pregnant volunteers and from pregnancies with a normal fetal echocardiogram performed for a family history of CHD or for suspected CHD in the current pregnancy. The decision to approach a mother about participation was left to the discretion of the attending fetal echocardiographer. Exclusion criteria for both cases and controls included gestational age (GA) >36 completed weeks; multiple-gestation pregnancy; congenital infection; gestational diabetes; maternal contraindication to MRI; fetal ultrasound findings of dysmorphic features, dysgenetic brain lesions, or anomalies of other organ systems; prenatally documented chromosomal abnormalities; or inadequate MRI data quality due to excessive fetal motion. If structural brain anomalies were identified on fetal or neonatal MRI, the anomalies were reported, but these fetuses were not included in the analysis.

In cases, the MRI was typically scheduled on the same day as a follow-up fetal echocardiogram, usually several weeks after enrollment. In most control fetuses, the MRI was also performed several weeks after enrollment, but the echocardiogram was not repeated. Thus, the duration between the study echocardiogram and MRI was variable and tended to be longer in controls than cases.

Written informed consent from mothers was obtained according to a protocol approved by the Children’s Hospital Committee for Clinical Investigation.

Fetal Echocardiography

Complete anthropometric ultrasound and anatomic and Doppler echocardiographic studies were performed in all fetuses and reviewed by 2 attending fetal echocardiographers (W.T., D.W.B.). Aortic and pulmonary arterial flows were calculated with the use of pulsed-wave Doppler as follows: flow= valve area (computed from valve diameter) \times velocity-time integral (area under the curve of the Doppler signal) \times heart rate. Combined ventricular output was computed as the sum of aortic and pulmonary flow and indexed to estimated fetal weight. Middle cerebral and umbilical arterial flow velocities (systolic, diastolic, and mean) were measured with the use of pulsed-wave Doppler, and pulsatility and resistance indices were calculated. Patients were categorized by diagnosis as having HLHS or variants thereof, d-transposition of the great arteries (TGA), pulmonary atresia, or other cardiac diagnosis, or were categorized as normal.

Estimated GA was based on maternal dates or first-trimester ultrasound measurement, if available. Fetal weight was estimated by Hadlock’s formula,\textsuperscript{22} and fetal weight percentile was calculated from equations reported by Doubilet et al.\textsuperscript{23}

Fetal Brain MRI

MRI scans were performed with the use of a 1.5-T scanner (Achieva, Philips Medical System, the Netherlands) and a 5-channel phased-array cardiac coil. Multiplanar single-shot turbo spin echo imaging was performed (echo time$_{eff}$= 120 ms, repetition time= 1250 ms, 0.625 signal averages, 330-mm field of view, 2-mm slice thickness, no interslice gap, 256\times204 acquisition matrix, acquisition time 30 to 60 seconds). \textsuperscript{1}H-MRS was performed with a single-voxel technique, and the spectra were acquired with a point-resolved echo spectroscopic sequence (echo time= 144 ms, repetition time= 1500 ms, 64 signal averages, scan time \sim 3 minutes). Maternal sedation was not administered. The 4.5-cm$^3$ (20\times15\times15-mm$^3$) volume of interest was placed within the cerebral hemisphere at the level of the centrum ovale, as described by Girard et al.,\textsuperscript{24} to obtain metabolic information about the normal developing white matter (Figure 1).

Conventional MRI

Fetal MRI studies were analyzed by an attending neuroradiologist (R.L.R.) who was blinded to all clinical data. Abnormal patterns of brain development and maturation and the presence and distribution of abnormal white matter were documented.

Quantitative Volumetric MRI Analysis

Postacquisition processing was undertaken on a Linux workstation. MR images of the fetal intracranial cavity were masked manually to extract the fetal brain from the intracranial tissue. Each image was corrected for nonuniformity intensities induced by radiofrequency and shading artifacts with the use of the nonparametric, nonuniform intensity, normalization tool.\textsuperscript{25} To minimize the effects of image degradation secondary to fetal motion, an iterative slice-by-slice registration was used, which normalized the intensity of each slice.\textsuperscript{26} The middle brain slice, defined as the slice at the midpoint of the brain, was used as a reference, and the global median intensity of each subsequent slice was normalized to the reference with the use of a single-scale intensity normalization with a nonlinear registration approach. A Gauss-Seidel iterative schema was then applied to register the slices to a weighted average of the considered slice and the 2 neighboring slices. The rigid-body registration of the slices

Figure 1. Fetal MR image reconstruction. Raw fetal MRI images (A), fetal intracranial cavity extraction (B), and fetal MRI images after intensity correction and slice alignment (C).
reached a steady point when it was identical to the previous registration (Figure 2).

After correction for fetal motion, coronal slices were segmented manually with the use of MINC software (www.bic.mni.mcgill.ca/software/minc) to measure intracranial cavity volume (ICV), total brain volume (TBV), and cerebrospinal fluid (CSF) volume. ICV included CSF and cerebral, cerebellar, and brain stem parenchymal volumes. TBV included cerebral, cerebellar, and brain stem parenchymal volumes but excluded intraventricular and extraventricular CSF volume (Figure 3). CSF volume was derived by subtracting TBV from ICV. Volumes were determined by counting the number of voxels in the segmentation and multiplying by the volume of each voxel (ie, the volume of each slice equaled the product of slice thickness and the measured coronal area). Total ICV, TBV, and CSF volume were computed as the sum of volumes measured on each coronal slice.

All measurements were made by a single operator (C.L.) who was blinded to clinical data. Each coronal area was traced twice, and the average of the 2 measurements was used for volume calculations.

Intraobserver correlation coefficients were determined for measurements of ICV (n=481), TBV (n=458), and CSF volume (n=481) on all individual slices from 10 MRI studies and were ≥0.997 in all cases. Intraobserver correlation coefficients were also determined for the summed volumes of ICV, TBV, and CSF from 15 MRI scans and were 0.98 for ICV, 0.96 for TBV, and 0.95 for CSF volume.

**MR Spectroscopy Analysis**

Four metabolites were assessed by 1H-MRS: N-acetyl aspartate (NAA), choline, creatine, and lactate. Specifically, NAA, choline, and creatine peaks were identified and measured, and the presence or absence of lactate (identified by an inverted doublet peak around −1.33 ppm) was recorded. Choline:creatine and NAA:choline ratios were calculated when MR spectra satisfied a reliable fit with SD <20% for each metabolite.23

**Statistical Analysis**

The primary hypothesis was that GA- and weight-adjusted TBV in late gestation would be smaller in CHD fetuses than in controls. A secondary hypothesis was that GA- and weight-adjusted measures of cerebral metabolism would be abnormal in CHD fetuses relative to controls. Comparison of demographic and baseline characteristics between cases and controls was performed with χ² analysis or Wilcoxon rank sum test. To assess for differences in volumetric and 1H-MRS measures between groups, linear regression was performed, and models were fit with the appropriate interaction terms and type III sum of squares testing. The equality of regressions was tested between groups with the use of a single F test; comparison of y intercepts (25-week GA for GA-adjusted analyses) was also performed. Multivariable models were built after consecutive analysis of individual independent variables adjusted for GA and weight percentile. For analysis of each of the volumetric outcomes, independent variables included presence of CHD, CHD diagnostic category (HLHS, TGA, pulmonary atresia, other CHD, or control), presence or absence of antegrade flow in the aortic arch, percentage of combined ventricular output through the aortic valve, and cerebral artery flow indices. For analysis of quantitative metabolic outcomes, the presence of lactate was also included as an independent variable, and models were adjusted for GA along with TBV rather than weight percentile. All statistically significant associations are noted. Outcome variables were presented graphically with linear or quadratic curve fitting. In regression models, coefficients of determination (R² values) reported in the text reflect the goodness of fit for each independent variable included in the model or for the complete model if no independent variables were included other than GA and weight percentile (or TBV for metabolic outcomes). Scatterplots are presented with linear or quadratic curve fitting for the groups depicted; R² values shown in the figures reflect the goodness of fit for the fitted curve and not for the adjusted linear regression model. Because MRI studies in control fetuses were typically obtained later in gestation than echocardiograms, echocardiographic data were not included as predictor variables in analyses that included control fetuses, although adjustment was performed with the use of weight percentiles derived from ultrasound estimates of fetal weight.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Subjects**

A total of 116 fetuses were enrolled, but 11 were excluded because of excessive fetal motion resulting in inadequate...
MRI data (n=8), brain dysgenesis (inferior vermian hypoplasia) detected by fetal MRI (n=2, both with CHD), and maternal claustrophobia preventing completion of the MRI (n=1). In the remaining 105 fetuses (50 CHD, 55 controls), MRI was performed at a median GA of 30 weeks (25\(\frac{1}{7}\) to 37\(\frac{1}{7}\) weeks). Demographic and diagnostic details are summarized in the Table.

### Fetal Echocardiography
Diagnostic data for fetuses with CHD are summarized in the Table.

### Fetal Brain MRI

#### Conventional MRI Analysis
Six fetuses (all with CHD) had mildly abnormal anatomic findings on MRI: 4 with mild (10 to 13 mm), isolated, unilateral cerebral ventriculomegaly and 2 with small bilateral subependymal cysts. Data from these fetuses were included in the following analyses.

#### Quantitative Volumetric MRI Analysis
Complete volumetric MRI analysis was possible in all 105 fetuses. In control fetuses, there were strong linear relationships between TBV and GA \((R^2=0.98, P<0.001)\) and ICV and GA \((R^2=0.96, P<0.001)\), with progressive increases in TBV and ICV over the third trimester (Figure 4). CSF volume \((R^2=0.80, P<0.001)\) and the proportion of ICV occupied by CSF volume \((R^2=0.93, P<0.001)\) decreased with increasing GA (Figure 4).

At 25 weeks of gestation, TBV and ICV were similar in CHD fetuses and controls (ie, the 25-week y intercept of the control and CHD regression equations did not differ). Over the third trimester, however, TBV and ICV were progressively smaller in CHD fetuses relative to controls \((P<0.001)\) for both TBV and ICV; Figure 4). Similar to controls, CSF volume decreased over the early third trimester in CHD fetuses, but beyond 30 weeks there was considerable variation. The CSF:ICV ratio, which normally decreases from \(\frac{1}{4}\) at 25 weeks to \(\frac{1}{15}\) at term, was progressively higher in CHD fetuses through the third trimester \((P<0.001)\) compared with controls (Figure 4). There was no clear difference in TBV between the 6 CHD fetuses with mild abnormalities on conventional MRI and those without.

In a multivariable model adjusted for GA and weight percentile, a lower percentage of combined ventricular output from the aorta \((P=0.001)\) and diagnostic category \((P<0.001)\) were independently associated with smaller TBV (model \(R^2=0.94)\).

Similarly, on adjusted multivariable analysis, CHD category was independently associated with the CSF:ICV ratio, with the highest ratios in HLHS and the lowest in fetuses with no CHD or other CHD \((P<0.001)\), model \(R^2=0.85)\).

### MR Spectroscopy Analysis
\(^1\)H-MRS spectra were successfully obtained in 75 fetuses: 36 with CHD (72\%) and 39 controls (71\%). The NAA:choline

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<th>Table. Characteristics of the Cohort (n=105)</th>
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<td>Characteristic</td>
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<td>Weight percentile at echocardiography</td>
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<td>GA at MRI, median (range), wk</td>
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<td>n (%) of subjects within 1 day</td>
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<td>Type of CHD, n (%)</td>
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<td>TGA</td>
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<td>Pulmonary atresia with intact ventricular septum</td>
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<td>Other</td>
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<tr>
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<td>Percentage of combined ventricular output through the aortic valve</td>
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*By \(\chi^2\) analysis or Wilcoxon rank sum test.
ratio increased progressively over the third trimester in controls, from ~0.1 at 25 weeks to ~0.8 at 36 weeks ($R^2=0.94$, $P<0.001$) (Figure 5). Compared with controls, NAA:choline in CHD fetuses was significantly and progressively lower with advancing GA ($P<0.001$) (Figure 5).

On multivariable analysis adjusted for both GA and TBV (a stronger correlate of NAA:choline than GA), independent predictors of lower NAA:choline included diagnostic category (HLHS, TGA, pulmonary atresia, other CHD, or control; $P<0.001$), absence of antegrade flow in the aortic arch ($P=0.01$), and the presence of lactate ($P<0.001$) (model $R^2=0.90$).

Choline:creatine generally declined over gestation in control (quadratic $R^2=0.47$) and CHD ($R^2=0.23$) fetuses, with weak correlation with GA in both groups. There was no difference in choline:creatine between cases and controls, and no predictors of choline:creatine were identified.

Cerebral lactate was detected in 7 of 36 fetuses (20%) with CHD (5 with HLHS, 2 with TGA) between 29 3/7 and 35 5/7 weeks of GA. Overall, fetuses with cerebral lactate had the lowest GA- and TBV-adjusted NAA:choline. No control fetuses had detectable cerebral lactate.

**Discussion**

**Brain Growth and Development in Fetuses With CHD**

In this study, we present the first in vivo MRI evidence of abnormal brain volume and metabolism in fetuses with CHD. Compared with normal controls, fetuses with CHD had progressively smaller GA- and weight-adjusted TBV and progressively lower NAA:choline during the third trimester, a
critical developmental period during which there is usually acceleration of energy-demanding brain growth. In addition, we detected cerebral lactate in a subset of fetuses with HLHS and TGA and the lowest adjusted NAA:choline. Although MRI and 1H-MRS evaluations in this study were cross-sectional, the widening difference between cases and controls in later gestation suggests that there may be progressive impairment of brain growth and maturation in fetuses with CHD, especially in light of the high coefficients of determination for the GA-TBV and GA-NAA:choline relationships in controls.

These findings add to a growing body of literature detailing antenatal and preoperative neonatal abnormalities of brain size, structure, and function in individuals with CHD.9–19 Although it is becoming well established that prenatal factors may contribute to the neurodevelopmental morbidity associated with CHD, the specific prenatal causes and mechanisms of insult are largely unknown. Potential mechanisms of abnormal neurodevelopmental development in fetuses with CHD include primary genetic and dysgenetic conditions,28,29 secondary disruptions of brain development, and encephaloclastic injury due to acute or chronic oxygen/glucose deprivation.14,30 Although many critical steps in brain development are completed earlier, major events occur during the second half of gestation, including neuronal migration and arborization, synaptogenesis, programmed cell death, oligodendrocyte maturation, and extensive reorganization of synaptic connections. During the third trimester, there is a surge in synapse formation and activity, with increasing demand for oxygen and metabolic substrate to maintain Na+/K+ -ATPase-generated neuronal membrane gradients. Cerebral myelination also accelerates in the third trimester.31,32 These critical processes in brain development place an escalating demand on the cardiovascular system for delivery of oxygen and energy substrate.

At the outset of this project, one of our underlying hypotheses was that major circulatory disturbances, such as those that occur in complex defects such as HLHS, TGA, and pulmonary atresia, may contribute to abnormal brain development. The basis for this hypothesis was the assumption that circulatory abnormalities in fetuses with these anomalies would place them at risk for inadequate delivery of oxygen and metabolic substrate to the developing brain, slowing normal brain growth and impairing cortical organization and myelination. In the normal fetus, relatively oxygenated umbilical venous return is preferentially directed through the foramen ovale, into the left heart, and out the aortic valve to supply the myocardium and brain.33 The majority of deoxygenated blood returning from the systemic circulation streams into the right ventricle, through the ductus arteriosus into the descending aorta, and to the placenta (and lower body). In complex CHD, this efficient network may be perturbed, either because of loss or major reduction of outflow from the left or right heart (eg, HLHS, pulmonary atresia) or because of a short circuit that reverses or eliminates flow streaming (eg, TGA). Thus, in theory, the content of oxygen and glucose in cerebral arterial blood is likely to be abnormal in fetuses with some forms of complex CHD, although we are aware of no data that support this speculation.

It is not currently feasible to measure oxygen or glucose in human fetal blood. Thus, there is no way to test the proposal that reduced cerebral oxygen and/or glucose delivery contributes to abnormal brain development in fetuses with CHD. Nevertheless, multivariable analysis of factors associated with smaller adjusted TBV and lower NAA:choline is consistent with the hypothesis that circulatory features contribute to impaired brain development. Specifically, abnormalities of TBV and NAA:choline were most pronounced in fetuses with HLHS and TGA and those with a lower percentage of combined ventricular output through the aortic valve or absence of antegrade flow in the aortic arch, and cerebral lactate was found exclusively in the same fetuses. Previous studies have shown cerebral blood flow to be reduced or otherwise abnormal in fetuses or neonates with these anomalies.12,20,21 Further studies will be necessary to substantiate and elucidate the contribution of cerebral hemodynamics and substrate delivery to abnormal brain development in fetuses with CHD.

Quantitative MRI and MRS in the Evaluation of Brain Development
Quantitative MRI is emerging as a powerful tool for the investigation of early brain development. Three-dimensional MRI in premature infants demonstrated a 4- to 5-fold increase in the volumes of cerebral cortical gray and myelinated white matter between 28 and 40 weeks after conception, as well as an association between volumetric abnormalities and adverse neurodevelopmental outcome.34,35 Similarly, 1H-MRS may offer insight into brain development in high-risk neonates and fetuses. NAA increases with GA and decreases with brain injury24 and reflects not only the development of dendrites and synapses but also oligodendrocyte proliferation and differentiation.36 Both NAA and lactate reflect neuronal mitochondrial function and may be valuable measures of brain metabolism.37,38 Cerebral lactate, a marker of anaerobic metabolism in the newborn and fetus,38,39 has been found in up to 50% of preoperative infants with CHD14,15 and is associated with adverse outcome in other high-risk infants.40 Although lactate has been identified with 1H-MRS in stable premature infants, it has not been reported in normal fetuses.24,41 Longitudinal evaluation of the fetuses in this study should help to elucidate the clinical significance of cerebral NAA:choline and lactate in fetuses with complex CHD.

Limitations
Recently reported multislice snapshot image techniques may provide higher-resolution imaging of the fetal brain than the acquisitions used in this study.42 These acquisitions were not available at the beginning of this study and were not incorporated into our fetal MRI protocol. Although we attempted to exclude fetuses with genetic or cerebral dysgenetic conditions, undiagnosed or as yet unknown genetic conditions may have been missed. Such anomalies may be more common in subjects with CHD than in controls, potentially introducing bias. The temporal relationship between fetal MRI and echocardiograms differed between control and CHD groups; therefore, comparison of cardiovascular parameters was not possible between these groups. Finally, we did not measure...
serial fetal brain volumes and therefore could not truly assess growth. Follow-up MRI studies are under way in this cohort to measure neonatal brain volume and metabolism before cardiac surgery.

Conclusions

Brain volume and metabolism are abnormal in third-trimester fetuses with some forms of complex CHD, particularly those with HLHS or TGA and reduced flow through the systemic ventricle or antegrade around the aortic arch. Quantitative MRI may provide deeper insight into the timing of insults that might disrupt normal fetal brain development. Although further studies are needed to confirm and elucidate these findings, the data presented in this report offer promise that quantitative MRI will advance our understanding of the neurodevelopmental implications of circulatory pathophysiology, extend our ability to provide informed parental counseling, and aid in evaluating the neurodevelopmental impact of prenatal intervention.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Neurological impairment in children with complex congenital heart disease may originate in the fetal period, before postnatal medical or surgical intervention. This hypothesis is supported by the present study, in which we compared third-trimester fetuses with complex congenital heart defects with normal control fetuses by using quantitative magnetic resonance imaging. Fetuses with heart disease had smaller brain volume and spectroscopic evidence of abnormal cerebral metabolism, with the most pronounced abnormalities in fetuses with lesions that predispose to reduced cerebral substrate supply.
Brain Volume and Metabolism in Fetuses With Congenital Heart Disease: Evaluation With Quantitative Magnetic Resonance Imaging and Spectroscopy

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