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3-D volumetric MRI evaluation of the placenta in fetuses with complex congenital heart disease

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Each author contributed to this work in the following capacity:

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Abstract

Introduction—Placental insufficiency remains a common cause of perinatal mortality and neurodevelopmental morbidity. Congenital heart disease (CHD) in the fetus and its relationship to placental function is unknown. This study explores placental health and its relationship to neonatal outcomes by comparing placental volumes in healthy pregnancies and pregnancies complicated by CHD using in vivo three-dimensional MRI studies.

Methods—In a prospective observational study, pregnant women greater than 18 weeks gestation with normal pregnancies or pregnancies complicated by CHD were recruited and underwent fetal MR imaging. The placenta was manually outlined and the volume was calculated in cm³. Brain volume was also calculated and clinical data were also collected. Relationships, including interactive effects, between placental and fetal growth, including brain growth, were evaluated using longitudinal multiple linear regression analysis.

Results—135 women underwent fetal MRI between 18 and 39 weeks gestation (mean 31.6 ± 4.4). Placental volume increased exponentially with gestational age ($p=0.041$). Placental volume was positively associated with birth weight ($p<0.001$) and increased more steeply with birth weight in CHD-affected fetuses ($p=0.046$). Total brain and cerebral volumes were smaller in the CHD group ($p<0.001$), but brainstem volume ($p<0.001$) was larger. Placental volumes were not associated with brain volumes.

Discussion—Impaired placental growth in CHD is associated with gestational age and birth weight at delivery. Abnormalities in placental development may contribute to the significant morbidity in this high-risk population. Assessment of placental volume by MRI allows for in vivo assessments of placental development.

Keywords

placenta; congenital heart disease; volumetric assessment; fetal MRI

Introduction

Placental function and a well-controlled intrauterine environment are critical for normal neurodevelopment of the fetus (1, 2). Placental insufficiency can compromise the developing fetus by limiting essential nutrient transfer from the mother, allowing for the transfer of toxic substrates to the fetus or diminishing the neuroendocrine function of the placenta (1, 3–5). Despite its critical function, placental insufficiency remains difficult to

identify until after the fetus has been compromised by growth restriction or abnormalities have developed in the umbilical or fetal vascular network. While it is known that placental insufficiency is a complication of maternal vascular disease that impairs uterine blood flow (6–9) as well as a complication of abnormal placental implantation and vascular development (10–12), the relationship between fetal vascular disease and placental health is unknown. Fetal vascular disease, as in congenital heart disease (CHD), can result in alterations in oxygen delivery and blood flow in the fetal and placental circulation (13). Much less is known about the effect of fetal vascular abnormalities associated with CHD on placental growth and function.

As mortality rates continue to decrease dramatically in newborns diagnosed with complex CHD, long-term neurodevelopmental impairments are recognized with increased frequency in surviving infants. Motor and cognitive disabilities, as well as neurosensory and psychosocial impairments are frequently described in children with complex CHD (14). In addition to the genetic predisposition for structural brain anomalies in the patient with CHD, there is a growing body of evidence that supports acquired brain injury in this population. It is now well established that brain injury is multi-factorial and includes several periods of risks including intraoperative events and postoperative complications, in addition to postnatal pre-operative vulnerability for neonatal brain injury (14, 15). Advances in fetal imaging, and particularly magnetic resonance imaging (MRI) have recently provided important insights into abnormal intrauterine neurodevelopment in the fetus with CHD. Abnormalities in the fetal circulation due to CHD disrupt oxygen and substrate delivery to the cerebral circulation, which further disrupt cerebral perfusion (14). In addition, alterations in the fetal circulation due to CHD have also been associated with blood flow abnormalities of the umbilical vessels (16–18). Evaluation of the cerebral-placental vascular bed in CHD using Doppler measures of the middle cerebral arteries, umbilical arteries and cerebro-placental ratio has revealed decreased resistance of blood flow in the cerebral arteries as well as significant abnormalities of the cerebro-placental ratio (19). These changes are similar to those reported in placental insufficiency and intrauterine growth restriction, another population that has high perinatal mortality and neurodevelopmental morbidity (20). Though the placenta has been studied in growth restriction, to date no study has examined placental growth in fetuses diagnosed with complex CHD in utero.

The objective of this investigation was to compare placental volumes in healthy pregnancies and those complicated by complex CHD using in vivo three-dimensional MRI studies, and to delineate clinical and hemodynamic effects associated with impaired placental growth. We hypothesized that (1) placental growth in the fetus with CHD would be diminished in the second and third trimesters compared to healthy controls, (2) impaired placental growth in CHD will be associated with impaired fetal brain growth and (3) impaired placental growth in CHD will be associated with known adverse neonatal outcomes of placental insufficiency.

Methods

Subjects

Subjects were recruited prospectively into a longitudinal, observational study in which MRI was performed up to two time points in the fetal period, and in the immediate neonatal period. This report includes data from the fetal evaluation(s).

Pregnant women carrying fetuses with confirmed CHD were recruited from the Fetal Heart Program at Children's National Medical Center. Normal controls were recruited from healthy volunteers with a normal prenatal history that included normal screening laboratory and ultrasound studies. Exclusion criteria for both CHD and control fetuses were multiple-gestation pregnancy, known or suspected congenital infection, dysmorphic features or dysgenetic lesions of the fetus, or documented chromosomal abnormalities. We also excluded patients with any maternal contraindication to MRI. Enrolled subjects found to have structural brain abnormalities on fetal MRI, postnatal confirmation of a genetic syndrome or significant extra-cardiac anomalies were subsequently excluded from the analysis.

Study Protocol

The initial research protocol included performance of a single fetal MRI at any time point after 18 weeks gestations. In 2013, the protocol was amended to include two serial fetal MR imaging studies. For the subset of fetuses that underwent 2 fetal imaging scans, both studies were included in the analysis. The study was approved by the institutional review board of Children's National Medical Center and written informed consent was obtained from every woman who participated.

Demographic and Clinical Data

Gestational age was calculated based on last menstrual period or first-trimester ultrasound measurement. Clinical and demographic data were collected for each subject through medical chart review and/or subject questionnaire, including maternal parity, maternal health conditions and medications, fetal gender, gestational age at delivery, birth weight, and fetal or neonatal demise. Birth weight was corrected for gestational age at birth using the Fenton growth chart calculations (21).

Fetal Echocardiography

All CHD fetuses underwent complete fetal echocardiographic assessment of both anatomy and Doppler evaluation as part of the study protocol. For the majority of cases, the echocardiographic studies were completed within 48 hours of MR imaging, and for 5 CHD cases, the duration between echocardiogram and MRI was up to two weeks. All echocardiographic studies were reviewed by a single attending cardiologist (M.D.). Fetal CHD diagnoses were categorized based on lesion, and as cyanotic vs. acyanotic, single vs. two ventricle physiology, and aortic obstruction vs. no aortic obstruction. Flow at the aortic isthmus was categorized as forward, reversed or bi-directional, based on Doppler signal. Middle cerebral and umbilical arterial flow velocities were measured with the use of pulse-wave Doppler, and pulsatility and resistance indices were calculated. The cerebroplacental

ratio was calculated by dividing the middle cerebral artery pulsatility index by the umbilical artery pulsatility index (22).

Fetal MRI

MRI scans were performed on a 1.5T Discovery MR450 scanner (GE Healthcare, Milwaukee, Wisconsin) using an 8-channel surface receive coil (USAI, Aurora, OH). Single shot fast spin echo (SSFSE) T2-weighted images were performed as follows: for the placenta, fat suppressed with TE 160ms, TR 1100ms, FOV 420 × 420mm, 4mm slice thickness and 40 to 60 consecutive slices for full placental coverage in the axial plane. For the fetal brain, TE 160ms, TR 1100ms, FOV 320 × 320 mm, 2mm slice thickness and 40 to 60 consecutive slices for full brain coverage in all 3 orthogonal plans (axial, coronal, sagittal). No contrast or sedation was used for any of the imaging studies. Fetal MRI studies were reviewed by an attending pediatric neuroradiologist who was blinded to CHD case versus control status. Any abnormalities of brain development, maturation or the presence of dysgenetic or acquired brain lesions were documented.

Volumetric MRI Analysis

The placenta was manually outlined in all three planes using ITK-SNAP software (23) and the volume was calculated in cm³ (Figure 1). The fetal brain was reconstructed into 3D high resolution images and segmented into parcellated brain volumes using an atlas-based approach (24, 25). Each automated segmentation was visually inspected and manually corrected by a trained expert using ITK-SNAP software (23) and cerebral, cerebellar and brainstem volumes were calculated in cm³, with total brain volume defined as the sum of the previous three volumes (Figure 2).

Statistical Analysis

Comparison of demographic and clinical characteristics between cases and controls were performed with chi-square analysis. Longitudinal multiple linear regression models were used to derive volumetric estimates by study group controlling for GA and to evaluate relationships between placental volume and demographic and clinical characteristics by group. Models corrected variance estimates for the correlation between multiple assessments on the same participant. Models evaluated evidence of both additive and multiplicative effects, especially interactive effects, e.g. synergistic effect of study group and birth weight percent. Scatterplots are presented with superimposed linear regressions curves for the two groups. All analyses were performed using Stata 13 (26).

Results

Characteristics of our cohort

A total of 135 pregnant women were enrolled, 94 healthy controls and 41 with pregnancies complicated by CHD. Twenty-five women had two fetal MRI studies, for a total of 160 scans (112 controls and 48 cases of CHD). Of these, 5 scans from the CHD group were excluded because the fetuses were subsequently diagnosed with significant extra-cardiac anomaly (2 DiGeorge syndrome, 1 chromosomal anomaly and 2 with pulmonary agenesis) and 1 CHD scan had incomplete MRI data. In the remaining 155 studies (112 controls, 43

CHD), MRI was performed at a median GA of 30 weeks (range: 18 1/7 to 39 2/7 weeks). Demographic and diagnostic comparisons are presented by group in Table 1. Anatomic data for all CHD fetuses is presented in Table 1. The most common structural lesion was double outlet right ventricle (23%), followed by hypoplastic left heart syndrome (18.6%). Subsequent categorization revealed 79% of lesions as cyanotic, 49% as single ventricle physiology, and 30% had abnormal flow at the aortic isthmus.

Conventional MRI review and interpretation

Healthy control fetuses were free of any placental or structural brain anomalies detected on conventional MRI. CHD cases also had no placental anomalies detected on conventional MRI. The majority of CHD fetuses had structurally normal fetal brains (n=38), while 4 (9%) fetuses had the following findings: two with mild maturational delay, one with mild bilateral ventriculomegaly, and one with a left-sided sub-ependymal cyst.

Comparison of placental volume in CHD versus healthy fetuses during gestation

Volumetric data from the placenta were available for 155 fetal MRI studies. Placental volume increased with gestational age for both control and CHD fetuses (Figure 3). Controlling for gestational age, the difference in placental volume during gestation between CHD and control fetuses did not reach statistical significance ($p=0.134$). Within the CHD group, there was no significant difference in placental volume based on lesion type, cyanotic or acyanotic heart disease, single vs. two-ventricle disease or reversed/bi-directional flow at the ductus or aortic isthmus.

Relationship between placental volume and clinical characteristics at birth

There was a statistically significant relationship between placental volume and gestational age at birth in which fetuses with smaller placental volumes were born at a younger gestational age ($p=0.041$), even when controlling for GA at the time of MRI. Similarly, CHD fetuses with smaller placental volumes had significantly lower birth weights ($p<0.001$). This relationship held true even when birth weight was corrected for gestational age at birth (Table 2). Placental volume increased more steeply with birth weight in CHD fetuses than controls ($p=0.046$) (Figure 4). In addition, primiparous women had smaller placental volumes compared to multiparous women ($p=0.049$) and female fetuses had smaller placental volumes compared to males ($p=0.025$) (Table 3).

Relationship between placental and fetal brain volumes

At comparable gestational ages, CHD fetuses had smaller total brain volume ($p<0.001$) and cerebral volume ($p<0.001$) but larger brainstem volumes ($p<0.001$) than control fetuses, but not cerebellar volume ($p=0.529$). There was little evidence that placental volumes were not associated with the differences in brain volumes between in the CHD or control groups. All four brain volume measures showed borderline associations ($p=0.076 - 0.840$) with Doppler measures of the umbilical arteries and the cerebro-placental ratio in CHD fetuses (Table 4).

Discussion

In this prospective study, we investigated the relationship between altered fetal hemodynamics and placental growth by evaluating placental volume in the fetus with CHD. Using MRI to assess placental growth in the fetus with CHD, we found little evidence that placental volume differs between CHD and healthy fetuses during gestation. As expected, placental volume increased with gestational age at birth and birth weight; not expected was that the growth in placental volume in relation to birth weight was greatest in the CHD group (Figure 4). We did not find evidence show that placental volume in CHD fetuses was not associated with brain volumes, despite significantly smaller total brain volume and cerebral brain volumes in the CHD fetus compared to controls. Finally, brain volumes were not clearly associated with dynamic measures of umbilical artery and middle cerebral artery flow in fetuses with CHD.

Placental insufficiency is a known, independent risk factor for impaired growth and neurodevelopment of the fetus (20) and is a known complication of maternal vascular disease and placental vascular disease (10, 27). Vascular development of the placenta is influenced by regional oxygen tension that modulates local growth factors and placental microstructure (28). Normal endovascular invasion of the placenta is disrupted in maternal vascular disease such as diabetes or preeclampsia, in part through alterations in perfusion, oxygen delivery, and oxidative stress (10, 27, 29). Changes in systemic oxygen delivery and perfusion of the fetus, however, and the role of fetal vascular disease, as modeled by CHD, and its relation to placental insufficiency however, has not been well studied. Fetal thrombotic vasculopathy, a placental lesion characterized by avascular villi and thrombosis of placental vessels, has been associated with a 6-fold increase in CHD (10). However, the mechanisms of altered placental growth and placental vasculature in CHD are not well understood. Mice knockout models suggest that placental and cardiovascular development is closely intertwined, where hormones produced by the placenta affect maternal and fetal cardiovascular function (30). Additional genetic and molecular signaling pathways are being recognized as critical, common components in the early embryonic development of both the heart and placenta (31). Specifically, the PPAR γ receptor promotes adipogenesis, and in knockouts results in diminished placental vascularization, subsequent myocardial thinning and embryonic death. When knockout mice are rescued with wild-type placenta the cardiac defects are corrected, suggesting that early alterations in nutrient supply from the placenta influence cardiac development (32). Our study did not assess first trimester or embryonic placental development, but evaluated placental development in the latter half of pregnancy. Though placental volume trended smaller in fetuses with CHD, these differences did not reach statistical significance.

In addition to the embryonic origin hypothesis that suggests an early placenta-heart developmental axis, we hypothesized that placental dysfunction resulting from early abnormal implantation can in turn restrict nutrient and oxygen transfer to the developing fetus. Ongoing hypoxia and altered fetal blood flow in the fetus with CHD could further impair both placental and brain growth in the second and third trimesters. While we were unable to demonstrate differences between ongoing hypoxia (cyanotic heart disease vs. acyanotic heart disease) and altered fetal blood flow (single vs. two ventricle physiology or

aortic obstruction vs. no aortic obstruction), it may be that our study was underpowered to detect differences in placental growth for these sub-group analyses. Despite these limitations, we were able to demonstrate impaired fetal growth and perinatal outcomes; in our study, over 25% of infants with CHD were born at a weight below the 20% for gestational age and over 20% were born prematurely, each of which is an independent risk factor for perinatal morbidity.

Unfortunately, there are few clinical biomarkers of in vivo placental function, and in fact, placental dysfunction is only recognized after the onset of fetal growth restriction or abnormal Doppler interrogation of the umbilical and fetal vessels. These Doppler measures are indirect assessments of placental function thought to occur as impaired hemodynamics within the placenta result in increased resistance to blood flow (33). Elevations in the umbilical artery resistive index (UA RI) and umbilical artery pulsatility index (UA PI) that lead to absent or reversed flow during diastole are late findings of placental failure and associated with increased risk of stillbirth and neonatal demise (33). As placental dysfunction results in decreased nutrient and oxygen supply to the fetus, there is a compensatory response of the middle cerebral artery (MCA) that is meant to promote oxygen delivery to the brain as represented by a decrease in the pulsatility index of the MCA (33). Relative changes between flow velocity in the middle cerebral and umbilical arteries are captured using the cerebro-placental ratio, and when abnormal, is associated with adverse perinatal outcomes (34). Anomalies in MCA, UA and CPR measures have been associated with complex CHD with severe left heart obstruction and reversed aortic arch flow (18), however in our study, we found that placental volume was not associated with UA RI or UA PI. We did find that CPR and its relation to brain volume revealed interesting trends between altered hemodynamics and impaired brain growth, but did not reach statistical significance. While again this may reflect the heterogeneity in CHD lesions and pathophysiology, it is also likely that the relationship between placental function and fetal brain development is highly complex, and should take into consideration placental size, structure and function.

Identification of intrauterine growth failure remains a clinical necessity in that growth restriction adds significant morbidity and mortality to the fetus and newborn. Low birth weight infants with CHD have a higher risk of mortality and morbidity than CHD infants with appropriate birth weight for gestational age – both during perinatal transition and in the immediate perioperative period (35).

With improved survival for the fetus with complex CHD, emphasis has transitioned to improving neurologic outcomes in survivors. Our group has previously shown that neurodevelopmental impairments and brain injury in CHD has its origins in the fetal period, where impaired brain growth and delayed maturation can be detected by advanced MRI (36–39). Alterations in the fetal circulation caused by CHD have been associated with changes in cerebral blood flow and oxygen delivery to the brain, and in turn may contribute to disrupted fetal brain development and long term neurodevelopmental impairments (38).

In the fetus with CHD, placental insufficiency and subsequent growth restriction may contribute to the multi-factorial causes of neurodevelopmental morbidity that is currently

seen. Given that placental impairment, and its consequences of growth restriction, can occur with or without Doppler changes, we propose that in vivo assessment of placental volume in CHD can help identify the high-risk fetus, so that additional care is given in the delivery and neonatal management of the growth-restricted fetus with CHD.

Limitations

Our study is powered to detect moderate differences in placental volume between the CHD and control groups, but is less likely to detect smaller differences, which may still be clinically meaningful. Furthermore, our study cohort of fetuses with CHD represent a heterogeneous group that include cardiac lesions of varying severity in regards to blood flow and oxygen delivery. These differences may have diverse effects on placental growth that we were not able to capture in this group; particularly as a sub-group analysis aimed at distinguishing such differences was not sufficiently powered. Differences in placental volume have not been correlated with placental changes detected by pathology which may provide insight into the degree of intrinsic versus acquired injury of the placenta. Prospective studies of placental imaging and placental pathology are ongoing.

Conclusions

We report that decreased placental growth in the CHD fetus may be associated with impaired fetal growth and premature delivery, each outcome an independent risk factor for neonatal mortality and morbidity. The relationship between placental growth, function and fetal brain size was less pronounced. Further studies are needed to confirm these findings and help elucidate the mechanisms behind intrauterine placental and cardiac dysfunction and the effects on neurodevelopment.

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Highlights

- We examine placental volume in congenital heart disease using magnetic resonance imaging.
- Placental volume increases with advancing gestational age.
- Placental volume is positively associated with birth weight.
- Placental volume is positively associated with gestational age at birth.
- Placental volume is not associated with fetal brain volume.

Figure 1.
A: T2-weighted image of the placenta in the axial plane; B: placenta outlined; C/D: 3D reconstructions of the placenta.

Figure 2.

High resolution fetal brain reconstruction of 24 week fetus in the sagittal (A,D), axial (B,E) and coronal (C, F) planes. The T2W reconstructions are shown in A, B, C and the corresponding parcellations are immediately below (D, E, F). Light blue: cerebrospinal fluid, Dark blue: cerebrum, Red: cerebellum and Green: brainstem.

Placental volume in CHD vs. healthy controls

Figure 3. Placental volume (in cm³) versus gestational age (in weeks) for CHD fetuses and healthy controls.

Figure 4.

The association of placental volume with birth weight, expressed as percentile to correct for gestational age, is greater in fetuses with CHD than in healthy fetuses.

Table 1

Demographics and clinical characteristics of our cohort

	Control (n=112)	CHD (n=43)
Gestational Age at MRI (weeks)	29±6	31±4
Maternal Age (years)	27.4±5.9	32.3±7.6
Gender, n (%)		
Male	55 (49.1%)	29 (67%)
Female	57 (50.9%)	14 (33%)
Race or Ethnicity, n (%)		
Black	67 (60%)	3(7%)
White	23 (20%)	23 (53%)
Hispanic	12 (11%)	8 (19%)
Other or Unknown	10 (9%)	9 (21%)
Cardiac Lesion		
Hypoplastic Left Heart Syndrome	n/a	8 (18.6%)
Transposition of the Great Arteries	n/a	7 (16.3%)
Double Outlet Right Ventricle	n/a	10 (23%)
Tetralogy of Fallot	n/a	7 (16.3%)
Complex Single Ventricle (TA, PA)	n/a	5 (11.6%)
Coarctation of the Aorta	n/a	3 (7%)
Other (AVC, VSD, ASD)	n/a	3 (7%)

AVC=atrioventricular canal defect, ASD=atrial septal defect, PA=pulmonary atresia, TA=tricuspid atresia, VSD=ventricular septal defect

Table 2

Effect size of placental volume and neonatal clinical characteristics in CHD fetuses

Clinical Factor	CHD	Control	Effect Size*	P-value
GA age at birth in weeks, mean ($\pm$ SD)	37.8 ($\pm$ 1.5)	39.0 ($\pm$ 1.5)	2.11	P=0.041
Birth weight in kg, mean ($\pm$ SD)	3.141 ($\pm$ 0.70)	3.345($\pm$ 0.46)	5.01	P<0.001
Fenton z-score for birth weight, mean ($\pm$ SD)	-0.05 ($\pm$ 1.00)	-0.02 ($\pm$ 0.07)	4.85	P<0.001

* Effect size reflects the effect on outcome (clinical factor) for every 1 SD in placental volume.

Table 3

Relationship between placental volume and clinical characteristics in CHD fetuses

Clinical Factor	CHD			Control			P-value
	Result	Mean Volume (cm ³)	Result	Mean Volume (cm ³)	Result	Mean Volume (cm ³)	
Maternal Parity, n (%)							
Primiparous	18 (42%)	585	46 (41%)	578			P=0.049
Multiparous	25 (58%)	676	66 (59%)	607			
Gender, n (%)							
Male	29 (67%)	680	49 (44%)	558			P=0.025
Female	14 (33%)	564	63 (56%)	623			
Cyanotic heart disease, n (%)							
Yes	33 (77%)	640	n/a	n/a			P=0.727
No	10 (23%)	620					
Single ventricle heart disease, n (%)							
Yes	20 (46%)	643	n/a	n/a			P=0.761
No	23 (54%)	628					
Abnormal ductal flow, n (%)							
Yes	9 (21%)	641	n/a	n/a			P=0.901
No	34 (79%)	634					
Abnormal isthmus flow, n (%)							
Yes	13 (30%)	656	n/a	n/a			P=0.561
No	30 (70%)	626					

Table 4

Relationship between brain volume and Doppler evaluation in CHD fetuses

Association	N (%)	Mean Volume (cm ³)	P-value
Total brain volume			
UA PI > 95%	10 (23%)	186.989	P=0.619
UA PI ≤ 95%	33 (77%)	182.739	
Total brain volume			
CPR > 1	27 (63%)	179.816	P=0.156
CPR ≤ 1	16 (37%)	191.053	
Cerebral volume			
UA PI > 95%	10 (23%)	173.898	P=0.587
UA PI ≤ 95%	33 (77%)	169.615	
Cerebral volume			
CPR > 1	27 (63%)	167.220	P=0.181
CPR ≤ 1	16 (37%)	176.993	
Cerebellar volume			
UA PI > 95%	10 (23%)	9.434	P=0.840
UA PI ≤ 95%	33 (77%)	9.589	
Cerebellar volume			
CPR > 1	27 (63%)	9.107	P=0.076
CPR ≤ 1	16 (37%)	10.356	
Brainstem volume			
UA PI > 95%	10 (23%)	3.656	P=0.361
UA PI ≤ 95%	33 (77%)	3.535	
Brainstem volume			
CPR > 1	27 (63%)	3.489	P=0.081
CPR ≤ 1	16 (37%)	3.703	

CPR=cerebroplacental ratio; UA PI= umbilical artery pulsatility index