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ORIGINAL RESEARCH

Impaired Maternal-Fetal Environment and Risk for Preoperative Focal White Matter Injury in Neonates With Complex Congenital Heart Disease

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BACKGROUND: Infants with congenital heart disease (CHD) are at risk for white matter injury (WMI) before neonatal heart surgery. Better knowledge of the causes of preoperative WMI may provide insights into interventions that improve neurodevelopmental outcomes in these patients.

METHODS AND RESULTS: A prospective single-center study of preoperative WMI in neonates with CHD recorded data on primary cardiac diagnosis, maternal-fetal environment (MFE), delivery type, subject anthropometrics, and preoperative care. Total maturation score and WMI were assessed, and stepwise logistic regression modeling selected risk factors for WMI. Among subjects with severe CHD (n=183) who received a preoperative brain magnetic resonance imaging, WMI occurred in 40 (21.9%) patients. WMI prevalence (21.4%–22.1%) and mean volumes (119.7–160.4 mm^3) were similar across CHD diagnoses. Stepwise logistic regression selected impaired MFE (odds ratio [OR], 2.85 [95% CI, 1.29–6.30]), male sex (OR, 2.27 [95% CI, 1.03–5.36]), and older age at surgery/magnetic resonance imaging (OR, 1.20 per day [95% CI, 1.03–1.41]) as risk factors for preoperative WMI and higher total maturation score values (OR, 0.65 per unit increase [95% CI, 0.43–0.95]) as protective. A quarter (24.6%; n=45) of subjects had ≥1 components of impaired MFE (gestational diabetes [n=12; 6.6%], gestational hypertension [n=11; 6.0%], preeclampsia [n=2; 1.1%], tobacco use [n=9; 4.9%], hypothyroidism [n=6; 3.3%], and other [n=16; 8.7%]). In a subset of 138 subjects, an exploratory analysis of additional MFE-related factors disclosed other potential risk factors for WMI.

CONCLUSIONS: This study is the first to identify impaired MFE as an important risk factor for preoperative WMI. Vulnerability to preoperative WMI was shared across CHD diagnoses.

Key Words: congenital brain injuries ■ heart defects ■ maternal fetal environment ■ placenta ■ risk factors ■ white matter injury

In the era of improving survival, adults with complex congenital heart disease (CHD) now outnumber the pediatric CHD population.[1] However, many survivors experience long-term functional morbidity, particularly with neurodevelopmental outcomes. In several studies, over half of school-aged children with CHD experienced neurodevelopmental and behavioral problems, even in the absence of an underlying genetic syndrome.[1,2] White matter injury (WMI) may contribute to these adverse neurobehavioral outcomes.[3] In preterm infants,

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CLINICAL PERSPECTIVE

What Is New?

- Impairments to the maternal-fetal environment (ie, gestational diabetes and gestational hypertension) can impact risk for postnatal presurgical white matter brain injury.
- The prevalence of preoperative white matter injury was remarkably similar across cardiac diagnoses.
- Time to surgery remains an important risk factor for postnatal, presurgical white matter injury.

What Are the Clinical Implications?

- This study demonstrates that gestational diabetes and gestational hypertension also impact the risk for fetal brain injury before surgery.
- The similar prevalence of white matter injury across cardiac diagnoses suggests that strategies to mitigate preoperative white matter injury do not need tailoring to specific forms of congenital heart disease.
- Time to surgery (magnetic resonance imaging) is one of the only potentially modifiable risks for white matter injury.

Nonstandard Abbreviations and Acronyms

HLHS	hypoplastic left heart syndrome
MCA	middle cerebral artery
MFE	maternal-fetal environment
PIs	pulsatility indices
TGA	transposition of the great arteries
TMS	total maturation score
WMI	white matter injury

WMI seen on brain magnetic resonance imaging (MRI) is associated with worse long-term (2-year) neurodevelopmental outcomes.[4-6] The WMI seen on MRI in infants born prematurely and those with CHD has similar distribution and signal characteristics.[7] Similar to infants born prematurely, infants with CHD have delayed fetal brain growth,[8] delayed white matter development as measured by alterations in postnatal brain biochemistry and microstructure,[9] and gross delays in structural brain maturation.[10] Thus, in infants with CHD who require surgery in the first weeks of life, WMI seen on perioperative brain MRIs may be an important biomarker of impaired long-term neurodevelopment.[3,9,10,11,12,13] For this reason, understanding risk factors for WMI in these subjects is important. Early identification of patients with CHD at high risk of poor neurodevelopmental outcomes has the potential for early intervention, mitigation, and improved quality of life.

This article attempts to broaden our understanding of risk factors for preoperative WMI. Notably, our previous work identified male sex, brain maturation at time of surgery, and increasing time to surgery as risk factors for preoperative as well as postoperative WMI.[10,14,15,16] Other factors, including cardiac anatomy and the maternal-fetal environment (MFE), were identified a priori as possible risk factors for preoperative WMI. Cardiac anatomy was identified as being of interest because the anatomy of the lesion may have differential impacts on the developing fetal brain. It has thus been postulated that neonates with CHD experience the delay in brain maturation attributable to adverse in utero hemodynamics, including impaired oxygen delivery and deficient nutrients.[17,18] Transposition of the great arteries (TGA) and hypoplastic left heart syndrome (HLHS) are the most prevalent pathologies, but roughly one-third of subjects in our center have other diagnoses, including other types of uni- and biventricular anatomies (Table 1). Earlier work found similar prevalence of preoperative WMI in individuals with TGA (21%) and HLHS (19%)/single-ventricle pathology (26%),[15,19] but there is little published work on the prevalence of preoperative WMI in these other diagnoses. Determining whether there are differences in prevalence could be important for targeting early interventions.

The MFE is defined as the shared maternal, placental, and fetal physiology. The MFE may be impaired because of maternal smoking, gestational diabetes, or gestational hypertension or preeclampsia, as well as other maternal behaviors or conditions. At birth, placentas in pregnancies affected by CHD are abnormal, a possible reason for reduced blood flow and injury to the brain of the developing fetus.[20] An initial study by Gaynor et al found a pronounced association of a composite indicator of impaired MFE and risk of death at 36 months of life.[21] This study defined impaired MFE as the presence of gestational hypertension or preeclampsia but also included small for gestational age or preterm birth as presumed indicators of an impaired MFE. Maternal smoking history and pregestational and gestational diabetes were not included. A subsequent study of subjects with HLHS confirmed that impaired MFE dramatically increased the length of hospital stay, risk for prematurity, small for gestational age, and death.[22] This study defined impaired MFE as ≥1 of the following: self-reported maternal smoking, gestational diabetes, gestational hypertension, or preeclampsia. While other studies have shown associations between specific conditions possibly related to MFE and WMI, this is the first to comprehensively examine placental,

Table 1. Details of Cardiac Diagnoses

Analytic group	Primary cardiac diagnosis	N=183, n (%)
TGA	Transposition of the great arteries	59 (32.2)
	Intact ventricular septum	42
	Ventricular septal defect	17
HLHS	Hypoplastic left heart syndrome	68 (37.2)
	Mitral atresia/aortic atresia	39
	Mitral stenosis/aortic atresia	18
	Mitral stenosis/aortic stenosis	11
Other	Univentricular	19 (10.4)
	Unbalanced atrioventricular canal	7
	Double-inlet left ventricle	3
	Double-outlet right ventricle	7
	Pulmonary atresia/right ventricular aorta	1
	Tricuspid atresia	1
	Biventricular	37 (20.2)
	Interrupted aortic arch	8
	Coarctation of the aortic arch*	17
	Tetralogy of Fallot/pulmonary atresia	9
	Truncus arteriosus	2
	Epstein anomaly	1

*Intact ventricular septum (n=8) and ventricular septal defect (n=9).

maternal, and postnatal factors that contribute to the prevalence of WMI.

Taking advantage of a large clinical research database and prospectively acquired pre- and postoperative brain MRIs, this study reports on the association of prenatal factors with the risk of perioperative WMI. We explore previously described and hypothesized risk factors, including cardiac anatomy and the impaired MFE, using both univariable and multivariable analyses. These analyses pointed to the MFE as an important risk factor for WMI, and we followed up with exploratory analyses of a subset of the data to generate hypotheses related to the MFE and WMI.

METHODS

Design and Study Population

This single-center, prospective study recruited a cohort of neonates with a variety of complex CHD lesions requiring neonatal cardiac surgery at the Children's Hospital of Philadelphia between October 2008 and October 2017. Children's Hospital of Philadelphia's institutional review board approved the study, and all participating families provided informed consent. All data that support the findings of this study are available from the corresponding author upon reasonable request. Inclusion criteria included "otherwise healthy" infants who were full term (gestational age >37 weeks) with severe CHD requiring surgery in the first weeks of life. Exclusion criteria included factors that could independently affect brain maturity, injury, or other MRI findings, including intrauterine growth retardation, a history of perinatal depression (APGAR score <5 at 5 minutes or pH <7.0), evidence of end-organ injury (liver function tests >23 upper limit normal, creatinine >2 mg/dL, encephalopathy, or seizures), or evidence of intracranial hemorrhage on head ultrasound. Optical imaging data from a subset of patients from this cohort have been published previously.[14,23] Patient characteristics as well as surgical and medical data were collected during the neonatal hospitalization in a REDCap (Research Electronic Data Capture, Nashville, TN) research database.[24] Variables included prenatal (CHD type, MFE data, delivery type), demographic (sex, anthropometrics), and presurgical (time to surgery/MRI, preoperative interventions) risk factors. Initially, a composite impaired MFE variable, which was based on information in the database regarding the pregnancy. This predefined impaired MFE included the presence of ≥1 of the following variables: gestational diabetes, gestational hypertension, preeclampsia, self-reported in utero exposure to tobacco, hypothyroidism, or "other" complications of pregnancy (including maternal trauma, maternal medications, maternal suicide attempt, obesity, and hepatitis B). These "other" conditions were included as possibly detrimental to the in utero environment conditions. In a sensitivity analysis, we used the impaired MFE definition previously used by Savla et al, dropping hypothyroidism and the "other" categories. Anthropometric measures (birth weight and head circumference) were normalized *Z* scores based on the Centers for Disease Control and Prevention's calculator.[25] Complete data on all covariates were available for 183 of 192 subjects (95%). Six subjects had missing preoperative MRI data because of unavailability of the scanner on the morning of scheduled surgery.

After the initial model identified impaired MFE as a strong predictor of WMI (see Results), additional variables, including chromosomal disorders, placental weight, birth weight to placental weight ratio, placental pathology, and pulsatility indices (PIs; middle cerebral artery and umbilical artery), were added in a second exploratory analysis. PIs are reported as raw values, not *Z* scores.

Neuroimaging

All neonates underwent a preoperative brain MRI scan under general anesthesia immediately before neonatal cardiac surgery. MRIs were reviewed immediately, and surgery was delayed for 7 days for findings of parenchymal hemorrhage. MRI scanning and brain total maturation score (TMS) were performed and evaluated as described previously.[10] Two independent investigators

(A.V., D.J.L.) evaluated the brain TMS. Methods for WMI and whole brain volume segmentations are available in Data S1.

Other imaging abnormalities (ischemia, hemorrhages) were identified by their appearance, signal intensity on standard anatomic sequences, and susceptibility-weighted imaging. Acuity of injury was judged by the presence or absence of water movement restriction on diffusion-weighted sequences.

Statistical Analysis and Power

For a 2-sided type 1 error rate of 0.05, an anticipated sample size of 190 and a binary risk factor with a prevalence of 50% (equal-sized groups), the study has 80% power to detect a fairly large risk difference in the proportion of preoperative WMI of 0.16, equivalently an odds ratio (OR) of 2.3. The calculation assumes a rate of preoperative WMI of 0.12 in the group with lower risk, for an overall prevalence of WMI in the population of 0.20, similar to previous studies.[11,12,13,15] For factors with lower or higher prevalence (unequal-sized groups), the power to detect these effect sizes will be somewhat reduced, holding other conditions constant. For a 2-sample *t* test using a continuous variable, the detectable effect size (mean difference divided by the SD) for this scenario was 0.40.

We summarized the data using proportions for categorical variables or means±SD and medians (interquartile range [IQR]) for continuous variables. In univariate analyses, chi-square tests of proportions for categorical variables and either the Wilcoxon rank-sum (2-group) or Kruskal-Wallis test (3-group) were used to assess differences. For multivariable analyses, we used a stepwise logistic regression model with backward and forward elimination based on the Akaike information criterion (details available in Data S2) to select variables for the final model. For the final model selected by the stepwise algorithm, Wald tests were used as tests of significance and the area under the receiver operating curve reported. After the initial analysis, we were able to assess chromosomal disorders, and sensitivity analyses were conducted by including this variable in the analysis. We subsequently explored associations of TMS, divided into quartiles, with WMI, and created a model to determine associations between TMS and other variables in the data set.

Following the initial analysis, a second data set with information on weights, PIs, and placental pathology was obtained on a subset of the subjects. The analysis was repeated, including these variables as candidate predictors.

All tests were 2-sided, with a type I error rate of 0.05; 95% CIs were similarly 2-sided. These analyses were carried out in R version 4.05 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the Overall Cohort and by Cardiac Diagnosis

Of the 192 patients who gave informed consent, 183 (95.3%) received a preoperative brain MRI. Reasons for not receiving an MRI included rescinded consent (n=2), medical instability (n=1), and MRI unavailable on the morning of surgery (n=6). Table 1 describes the distribution of cardiac diagnoses. For the statistical analysis, specific diagnoses were grouped on the basis of the 2 most common diagnoses (TGA, HLHS), with "Other" representing a more heterogenous cohort of less common diagnoses. The diagnostic categories were relatively evenly split among the cohort; 59 subjects (32.2%) had TGA, 68 had HLHS (37.2%), and the remaining 56 (30.6%) had Other diagnoses, including single-ventricle (n=19, 10.4%) and 2-ventricle (n=37, 20.2%) physiologies (for details see Table 1).

Table 2 describes the cohort overall and by cardiac diagnosis. The prevalence of WMI preoperatively was 21.9% (n=40), a rate remarkably constant across diagnostic groups (21.4%–22.1%, *P*=0.996) and without any preference for location of WMI lesions (Figure 1). Among those with WMI, lesion volumes averaged 134.0±209.1 mm^3, and Quarter Point System scores[26] ranged from mild (Quarter Point System=1, n=17; 42.5%) to moderate (Quarter Point System=2 or 3, n=20; 50%) to severe WMI (Quarter Point System=4, n=3; 7.5%; Table S1).Impaired MFE occurred in 45 subjects (24.6%; Table 2, *P*=0.506 across diagnostic groups). Vaginal delivery was most frequent (57.9%), but type of delivery differed somewhat by diagnosis (*P*=0.026). Male sex was more frequent (57.9%). The majority of subjects were non-Hispanic (92.9%); White (75.4%) race was most prevalent. Normalized birth weights (*Z* scores) differed among diagnoses (*P*=0.031), with TGA having higher (0.29 ±0.87) and Other (–0.12±0.95) having lower than expected values. The median TMS score was 10.00 and almost identical across cardiac diagnoses. Mean age at MRI differed among cardiac diagnoses, with HLHS and Other trending toward longer times (*P*=0.004). Notably, at Children's Hospital of Philadelphia, protocols for infants with TGA, but not those with HLHS or Other diagnoses, recommend surgery within 4 days of birth. Details on the distribution of age at MRI are available in Table S2. Age at MRI and age at surgery were identical for all but 3 (1.6%) subjects following diagnosis of parenchymal (subpial) hemorrhages on the preoperative brain MRI (days 1–10 of life) and concern for worsening hemorrhage on cardiopulmonary bypass. Presurgical cardiac catheterizations occurred in 40 subjects (21.9%); the majority were balloon atrial septostomies in patients with TGA (n=33/40; 82.5%).

Table 2. Description of Cohort by Cardiac Diagnosis

Variable	Overall (N=183)	TGA (N=59)	HLHS (N=68)	Other (N=56)	*P* value*
Preoperative WMI, n (%)					
No	143 (78.1)	46 (78.0)	53 (77.9)	44 (78.6)	
Yes	40 (21.9)	13 (22.0)	15 (22.1)	12 (21.4)	0.996
Impaired MFE, n (%)					
No	138 (75.4)	46 (78.0)	48 (70.6)	44 (78.6)	
Yes	45 (24.6)	13 (22.0)	20 (29.4)	12 (21.4)	0.506
Type of birth,† n (%)					
Vaginal	106 (57.9)	32 (54.2)	40 (58.8)	34 (60.7)	
Cesarean section elective	44 (24.0)	17 (28.8)	21 (30.9)	6 (10.7)	
Cesarean section nonelective	32 (17.5)	10 (16.9)	7 (10.3)	15 (26.8)	0.026
Sex, n (%)					
Female	77 (42.1)	21 (35.6)	28 (41.2)	28 (50.0)	
Male	106 (57.9)	38 (64.4)	40 (58.8)	28 (50.0)	0.289
Ethnicity, n (%)					
Not Hispanic	170 (92.9)	53 (89.8)	65 (95.6)	52 (92.9)	
Hispanic	13 (7.1)	6 (10.2)	3 (4.4)	4 (7.1)	0.452
Race, n (%)					
White	138 (75.4)	47 (79.7)	51 (75.0)	40 (71.4)	
Black/African American	21 (11.5)	2 (3.4)	12 (17.6)	7 (12.5)	
Mixed, other, unknown	24 (13.1)	10 (16.9)	5 (7.4)	9 (16.1)	0.069
Postmenstrual age, wk					
Mean (SD)	38.94 (0.88)	38.89 (0.85)	38.98 (0.78)	38.95 (1.01)	
Median (IQR)	39.00 (38.29, 39.57)	39.00 (38.14, 39.29)	39.00 (38.57, 39.32)	38.93 (38.29, 39.71)	0.786
Weight					
Z-score, mean (SD)	0.04 (0.94)	0.29 (0.87)	−0.04 (0.95)	−0.12 (0.95)	
Z-score, median (IQR)	−0.07 (−0.57, 0.71)	0.21 (−0.18, 0.95)	−0.14 (−0.69, 0.48)	−0.25 (−0.67, 0.58)	0.031
Raw value, kg, mean (SD)	3.33 (0.49)	3.45 (0.47)	3.31 (0.51)	3.24 (0.47)	
Head circumference					
Z score, mean (SD)	−0.18 (0.80)	−0.22 (0.78)	−0.14 (0.72)	−0.19 (0.92)	
Z score, median (IQR)	−0.17 (−0.72, 0.37)	−0.17 (−0.70, 0.25)	−0.21 (−0.65, 0.24)	0.04 (−0.83, 0.48)	0.880
Raw value, cm, mean (SD)	34.06 (1.31)	34.00 (1.23)	34.14 (1.26)	34.03 (1.45)	
Preoperative TMS‡					
Mean (SD)	10.14 (1.01)	10.15 (0.91)	10.13 (1.04)	10.14 (1.09)	
Median (IQR)	10.00 (9.33, 10.67)	10.00 (9.58, 10.50)	10.08 (9.33, 10.83)	10.00 (9.33, 10.67)	0.986
Age at MRI, d§					
Mean (SD)	4.27 (2.33)	3.47 (1.18)	4.35 (2.09)	5.00 (3.16)	
Median (IQR)	4.00 (3.00, 5.00)	3.00 (3.00, 4.00)	4.00 (3.00, 6.00)	4.00 (3.00, 6.00)	0.004
By category,§ n (%)					
<5 d	117 (63.9)	50 (84.7)	38 (55.9)	29 (51.8)	
5–7 d	55 (30.1)	9 (15.3)	25 (36.8)	21 (37.5)	
>7 d	11 (6.0)	0 (0)	5 (7.4)	6 (10.7)	0.001
Age at surgery by category§					
<5 d	115 (62.8)	49 (83.1)	37 (54.4)	29 (51.8)	
5–7 d	56 (30.6)	10 (16.9)	25 (36.8)	21 (37.5)	
>7 d	12 (6.6)	0 (0)	6 (8.8)	6 (10.7)	0.002
Cardiac catheter,‖ n (%)					
No	143 (78.1)	26 (44.1)	64 (94.1)	53 (94.6)	

(*Continued*)

Table 2. Continued

Variable	Overall (N=183)	TGA (N=59)	HLHS (N=68)	Other (N=56)	*P* value*
Yes	40 (21.9)	33 (55.9)	4 (5.9)	3 (5.4)	<0.001
Chromosomal disorder,# n (%)					
No	135 (73.8)	51 (86.4)	58 (85.3)	26 (46.4)	
Yes	10 (5.5)	0 (0)	0 (0)	10 (17.9)	
Suspected	38 (20.8)	8 (13.6)	10 (14.7)	20 (35.7)	<0.001

HLHS indicates hypoplastic left heart syndrome; IQR, interquartile range (25th, 75th percentile); MFE, maternal-fetal environment; MRI, magnetic resonance imaging; TGA, transposition of the great arteries; TMS, total maturation score; and WMI, white matter injury.

*Kruskal-Wallis test for continuous and chi-square for categorical variables.

†Unknown delivery type for n=1 in Other category.

‡Total Maturation Score on preoperative MRI.

§Age at MRI and Age at surgery identical except for 3 subjects.

‖Cardiac catheter intervention.

#Chromosomal disorder added to database after initial analysis.

Table 3 describes the cohort by the MFE. Subjects with impaired MFE had a higher prevalence of WMI (35.6%) compared with those without impaired MFE (17.4%; *P*=0.019) and were of lower postmenstrual age at birth (median=38.71 [IQR, 38.29–39.29] versus median 39.0 [IQR, 38.6–39.7]; *P*=0.008). In other ways, the 2 groups were comparable.

Further details of preoperative MRI findings appear in Table S1. Most subjects (n=167; 91.3%) had a lesion (WMI, stroke, hemorrhage, or microhemorrhage) on the preoperative scan. Common preoperative findings related to the birthing process included subdural hemorrhages (n=75; 41%) and choroid plexus hypointensities (n=150; 82%), which account for the bulk of lesions. Choroid plexus hypointensities are not commonly reported. Cerebral microhemorrhages were also common before surgery (n=45, 25%). Stroke (n=3; 1.6%) and parenchymal hemorrhage (n=4; 2.2%) occurred infrequently.

Risk Factors for Preoperative WMI

Table 4 describes the same characteristics as Tables 2 and 3 but by preoperative WMI. Impaired MFE was present in 20.3% of subjects without and 40.0% of subjects with preoperative WMI (*P*=0.019; Table 3). Differences in the distribution of individual covariates by WMI status did not reach statistical significance; we note that for binary variables the a priori power calculation suggested good power to detect only large differences between groups.

As shown in Figure 2, the final stepwise model built using the variables described in Tables 2 through 4 included impaired MFE (OR, 2.85 [95% CI, 1.29–6.30]; *P*=0.009), older age at MRI (OR, 1.20 per day [95% CI, 1.03–1.41]; *P*=0.019), and male sex (OR, 2.27 [95% CI, 1.03–5.36]; *P*=0.049) as risk factors, while higher preoperative TMS (OR, 0.65 per unit increase [95% CI, 0.43–0.95]; *P*=0.032) was a protective factor for WMI. The final model's area under the receiver operating curve of 0.71(95% CI, 0.62–0.80), was modest, suggesting overall limited accuracy of prediction. A division into 2 epochs comparing <5 days to 5 to 7 days of life and <5 days to >7 days of life better represented the nonlinear risk of older age at MRI.

Exploratory Analyses Subsequent to Initial Analyses

We obtained data on chromosomal disorders. Table 2 shows that chromosomal disorders tended to occur most frequently in the Other CHD category (n=20/56; 35.7%); this variable showed little evidence of association with WMI, either in univariate (*P*=0.361; Table 4) or multivariable analyses. In the multivariable model, compared with those without chromosomal disorder, the odds of WMI for individuals with chromosomal disorder was 0.37 (95% CI, 0.02–2.44; *P*=0.38) and for those with suspected chromosomal disorder was 1.28 (95% CI, 0.54–3.10; *P*=0.58).

We explored the association between impaired MFE and TMS, hypothesizing that an impaired MFE might delay brain maturation, leading to reduced TMS. Surprisingly, the distribution of TMS was similar for individuals with (median, 10.0 [IQR, 9.5–10.8]) and without (median, 10.0 [IQR, (9.3–10.7]) impaired MFE (Wilcoxon rank-sum test *P*=0.6). Table S3 divides the cohort into similarly sized groups on the basis of quartiles of TMS and reports summary statistics for the 3 other predictors in the logistic regression model (impaired MFE, sex, and age at preoperative MRI) and the outcome variable (WMI). No association between MFE and TMS was evident in this exploratory analysis. Finally, in a multivariable model with TMS as the outcome, postmenstrual age at birth and time from birth to MRI were associated with higher TMS scores, and suspected chromosomal anomalies were associated with worse scores, but chromosomal disorders were not selected by the stepwise algorithm (Table S4).

In advance of the analysis, our study defined a subject to have impaired MFE if they had ≥1 of the following: gestational diabetes (n=12; 6.6%), gestational

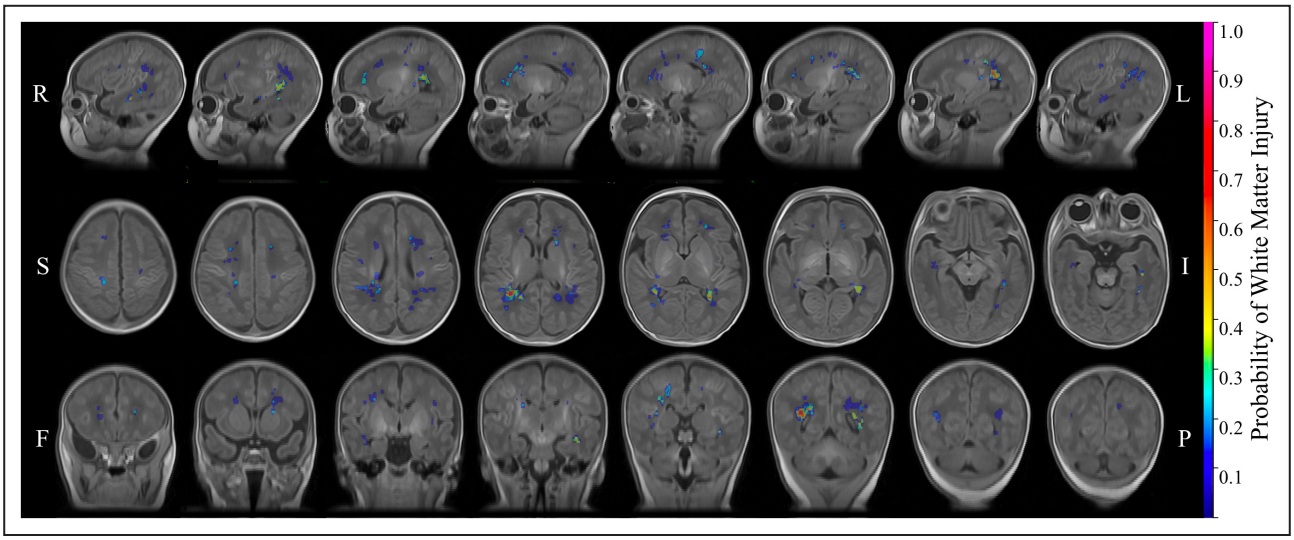

Figure 1. Probabilistic maps of preoperative WMI volumes in 40 patients.
WMI lesions were manually traced and overlayed on a study subject template. F indicates frontal; I, inferior; L, left; P, posterior; R, right; S, superior; and WMI, white matter injury.

hypertension (n=11; 6.0%), preeclampsia (n=2; 1.1%), self-reported in utero exposure to tobacco (n=9; 4.9%), and "other" complications of pregnancy (n=22; 12%). Hypothyroidism was the most common complication in the "other" category (n=6; 3.3). Thus, while impaired MFE was reasonably common (24.6% of the cohort), specific conditions were relatively rare and the power to test meaningful hypotheses presumably small.[27] Given this limitation, we focus on describing effect sizes, rather than *P* values, with the goal of informing future studies. For variables used in the earlier definition of impaired MFE, the OR for all but tobacco use was at least 1.8, albeit with wide CIs (Table 5).[21] In contrast, the OR for tobacco use was 0.43 (95% CI, 0.01–3.41). In addition, 6 infants had mothers with hypothyroidism; of these, 5 (83%) had preoperative WMI, yielding a strong association (OR, 19.85 [95% CI, 2.13–9.60]; *P*=0.002). We explored other risk factors for WMI among the individuals with hypothyroidism (Table S5). Three were male individuals, and among them, 1 had 2 other risk factors, including a low TMS score of 8.5 (1.6 SD below the mean), as well as gestational hypertension in the mother. Two individuals (1 male and 1 female) had slightly longer time to surgery (5–6 days). A formal assessment of confounding was not possible, given the small number of subjects with specific components of the MFE.

Finally, the "other" component of the impaired MFE group, composed of a heterogeneous group of problems including maternal trauma, maternal medications, maternal suicide attempt, obesity, and hepatitis B, yielded an OR near 1.0 (OR, 1.21 [95% CI, 0.27–4.32]; *P*=0.75; Table 5).

Considering the novel finding of the association of impaired MFE with preoperative WMI, we defined additional variables potentially related to MFE. The variables included placental weight, birth weight (absolute scale), and birth weight : placental weight ratio. PIs included middle cerebral artery (MCA) and umbilical artery. Except for chromosomal disorders (see Results above), these additional variables were acquired as standard of care for subjects recruited later in the study. Placentas were collected for 144 subjects (78.6% of the original cohort), with placental weights reported in 105 (73%). MFE variables were consistently available in 138 of the 183 subjects. Placental weight, birth weight, and the birth weight : placental weight ratio and umbilical artery were similar across diagnoses. The MCA PI and the MCA : umbilical PI ratio differed across diagnostic categories (*P*=0.037, *P*=0.039), with the HLHS group tending toward higher values. Of the 144 placentas with histological pathology reports, placental infarction was common, occurring in 11.8% (n=17/144; *P*=0.46 across diagnostic groups). Univariate comparisons of these variables by preoperative WMI status appear in Table S6. Among the postmodeling variables, the birth weight : placental weight ratio tended to be higher among subjects with (median, 8.0 [IQR, 7.3–8.9]) versus without WMI (median, 7.4 [IQR, 6.6–8.3]; *P*=0.029). Descriptive data of postmodeling variables are available by cardiac diagnosis (Table S7) and by MFE status (Table S8).

We added more variables to the original data set and refit the stepwise model using the 138 subjects with complete data. The stepwise algorithm comprised all 4 variables included originally (Figure 2). Additionally, the final model included birth by cesarean section (OR, 0.52 [95% CI, 0.20–1.26]; *P*=0.153) and increasing placental weight (OR, 0.94 per 10 g increase [95%

Table 3. Description of Cohort by Impaired MFE

Variable	Not impaired MFE (N=138)	Impaired MFE (N=45)	Overall (N=183)	*P* value
Preoperative WMI, n (%)				
No	114 (82.6)	29 (64.4)	143 (78.1)	
Yes	24 (17.4)	16 (35.6)	40 (21.9)	0.019
Type of birth, n (%)				
Vaginal	84 (60.9)	22 (48.9)	106 (57.9)	
Cesarean section (elective)	33 (23.9)	11 (24.4)	44 (24.0)	
Cesarean section (nonelective)	20 (14.5)	12 (26.7)	32 (17.5)	0.157
Sex, n (%)				
Female	58 (42.0)	19 (42.2)	77 (42.1)	
Male	80 (58.0)	26 (57.8)	106 (57.9)	1.00
Ethnicity, n (%)				
Not Hispanic/Latino	128 (92.8)	42 (93.3)	170 (92.9)	
Hispanic/Latino	10 (7.2)	3 (6.7)	13 (7.1)	1.00
Race, n (%)				
White	102 (73.9)	36 (80.0)	138 (75.4)	
Black	15 (10.9)	6 (13.3)	21 (11.5)	
Asian	4 (2.9)	0 (0)	4 (2.2)	
Mixed	2 (1.4)	0 (0)	2 (1.1)	
Other	14 (10.1)	2 (4.4)	16 (8.7)	
Unknown	1 (0.7)	1 (2.2)	2 (1.1)	0.533
Gestational age				
Mean (SD)	39.06 (0.87)	38.59 (0.82)	38.94 (0.88)	
Median (IQR)	39.00 (38.57, 39.71)	38.71 (38.29, 39.29)	39.00 (38.29, 39.57)	
(Min, max)	(37.00, 41.43)	(36.29, 40.29)	(36.29, 41.43)	
IQR	(1.14)	(1.00)	(1.29)	0.008
Head circumference (*Z* score)				
Mean (SD)	−0.14 (0.75)	−0.31 (0.93)	−0.18 (0.80)	
Median (IQR)	−0.11 (−0.71, 0.38)	−0.25 (−0.73, 0.19)	−0.17 (−0.72, 0.37)	
(Min, max)	(−2.08, 1.78)	(−2.45, 1.55)	(−2.45, 1.78)	
IQR	(1.09)	(0.92)	(1.09)	0.326
Birth weight (*Z* score)				
Mean (SD)	0.06 (0.91)	−0.01 (1.03)	0.04 (0.94)	
Median (IQR)	−0.07 (−0.52, 0.63)	−0.13 (−0.86, 0.75)	−0.07 (−0.57, 0.71)	
(Min, max)	(−2.20, 2.19)	(−2.20, 2.36)	(−2.20, 2.36)	
IQR	(1.15)	(1.61)	(1.29)	0.652
TMS (preoperative)				
Mean (SD)	10.11 (1.00)	10.21 (1.04)	10.14 (1.01)	
Median (IQR)	10.00 (9.33, 10.67)	10.00 (9.50, 10.83)	10.00 (9.33, 10.67)	
(Min, max)	(8.00, 13.50)	(8.50, 13.17)	(8.00, 13.50)	
IQR	(1.33)	(1.33)	(1.34)	0.628
Age at preoperative MRI				
Mean (SD)	4.20 (2.33)	4.47 (2.35)	4.27 (2.33)	
Median (IQR)	4.00 (3.00, 5.00)	4.00 (3.00, 6.00)	4.00 (3.00, 5.00)	
(Min, max)	(1.00, 19.00)	(1.00, 16.00)	(1.00, 19.00)	
IQR	(2.00)	(3.00)	(2.00)	0.280
Age at surgery				
Mean (SD)	4.33 (2.53)	4.47 (2.35)	4.37 (2.48)	
Median (IQR)	4.00 (3.00, 5.00)	4.00 (3.00, 6.00)	4.00 (3.00, 5.00)	
(Min, max)	(1.00, 19.00)	(1.00, 16.00)	(1.00, 19.00)	
IQR	(2.00)	(3.00)	(2.00)	0.390

(*Continued*)

Table 3. Continued

Variable	Not impaired MFE (N=138)	Impaired MFE (N=45)	Overall (N=183)	*P* value
Age at surgery (categorical), n (%)				
<5 d	90 (65.2)	25 (55.6)	115 (62.8)	
5–7 d	38 (27.5)	18 (40.0)	56 (30.6)	
>7 d	10 (7.2)	2 (4.4)	12 (6.6)	0.268
Intervention cardiac catheter, n (%)				
No	108 (78.3)	35 (77.8)	143 (78.1)	
Yes	30 (21.7)	10 (22.2)	40 (21.9)	1.00
Chromosomal disorder,* n (%)				
Yes	5 (3.6)	5 (11.1)	10 (5.5)	
No	104 (75.4)	31 (68.9)	135 (73.8)	
Suspected	29 (21.0)	9 (20.0)	38 (20.8)	0.158

IQR indicates interquartile range (25th, 75th percentile); MFE, maternal-fetal environment; MRI, magnetic resonance imaging; TMS, total maturation score; and WMI, white matter injury.

*Chromosomal disorder added to database after initial analysis.

CI, 0.88–1.00]; *P*=0.057) as protective variables, while increasing birth weight (OR, 1.09 per 100 g increase [95% CI, 0.97–1.23]; *P*=0.165) and MCA PI (1.10 per 0.1 increase [95% CI, 0.99–1.23]; *P*=0.082) were selected as risk factors (Table 6).

DISCUSSION

Our study has 2 key findings. First, the prevalence of preoperative WMI was remarkably similar across cardiac diagnoses, suggesting that strategies to mitigate preoperative WMI do not need tailoring to specific forms of CHD. Second, this is the first study to implicate impaired MFE as a substantial risk for preoperative WMI in infants with severe CHD.

An impaired MFE, defined here as a composite of maternal pregnancy comorbidities and thought to represent the shared maternal, placental, and fetal physiology, was associated with more than twice the odds of preoperative WMI, a risk comparable with that of male sex. Gestational hypertension and gestational diabetes may result from abnormal placentation with consequent poor gas and nutrient/waste exchange between the fetus and mother. While these maternal adaptations may maximize fetal growth and viability at birth,[20] they may also affect the development of individual fetal tissues, with pathophysiological consequences long after birth.[28]

While the causes of impaired MFE remain under investigation, the negative influences of an impaired MFE (using slightly different definition criteria) on the developing fetus have been previously reported in populations without CHD.[29] Other studies have similarly shown an elevated risk for WMI in infants born to pregnancies affected by factors related to the MFE, including maternal obesity,[30] preeclampsia,[31] and intrauterine growth restriction.[32] Our definition of impaired MFE was similar to that used by Savla et al[22] in a study linking impaired MFE with elevated risk of death before 36 months of age. However, with limited understanding of the mechanisms by which an impaired MFE might impact fetal brain development, we used a broader definition of MFE in this early-stage investigation of the links between the MFE and brain development in infants with CHD. We thus include maternal hypothyroidism and a collection of other complications of pregnancy.

We included maternal hypothyroidism as a component of MFE. Thyroid hormone is essential for metabolic homeostasis and temperature control and is also essential for the development of the fetus during pregnancy. Hypothyroidism affects up to 4% of all pregnancies and, if untreated, can result in gestational hypertension, preeclampsia, low birth weight, postpartum hemorrhage, congenital malformations, premature birth, placental abruption, and impaired neuropsychological development, specifically expressive language deficits.[33-35] The 6 mothers in our study were prescribed thyroid replacement hormone before study entry, and we did not have records about their adherence to medication or any thyroid levels determined during the pregnancy. Thyroid testing is not routinely performed during pregnancy at our center, as testing would find mostly subclinical hypothyroidism, and treatment of subclinical hypothyroidism did not improve neurological outcomes in a clinical trial in normal pregnancies.[34-36] Thyroid testing is done routinely in infertility clinics. However, only 1 of the 6 was treated for infertility (Clomid), suggesting that our results are not reflective of treatment for infertility.[37]

Because fetuses with CHD have abnormal vascular physiology that has been associated with delayed brain development, there has been a growing interest in investigating the role of an impaired

Table 4. Description of Cohort by Preoperative WMI Status

Feature	WMI		*P* value*
	None (n=143)	Present (n=40)	
Primary diagnosis, n (%)			
TGA	46 (32.2)	13 (32.5)	
HLHS	53 (37.1)	15 (37.5)	
Other	44 (30.8)	12 (30.0)	0.996
Impaired MFE, n (%)			
No	114 (79.7)	24 (60.0)	
Yes	29 (20.3)	16 (40.0)	0.019
Type of birth,† n (%)			
Vaginal	80 (55.9)	26 (65.0)	
Cesarean section elective	36 (25.2)	8 (20.0)	
Cesarean section nonelective	26 (18.2)	6 (15.0)	0.617
Sex, n (%)			
Female	65 (45.5)	12 (30.0)	
Male	78 (54.5)	28 (70.0)	0.117
Ethnicity, n (%)			
Not Hispanic	131 (91.6)	39 (97.5)	
Hispanic	12 (8.4)	1 (2.5)	0.350
Race, n (%)			
White	104 (72.7)	34 (85.0)	
Black	19 (13.3)	2 (5.0)	
Other, mixed, unknown	20 (14.0)	4 (10.0)	0.238
Postmenstrual age, wk			
Mean (SD)	38.94 (0.89)	38.96 (0.84)	
Median (IQR)	39.00 (38.29, 39.50)	39.00 (38.54, 39.57)	0.930
Head circumference (*Z* score)			
Mean (SD)	−0.21 (0.78)	−0.09 (0.86)	
Median (IQR)	−0.17 (−0.72, 0.32)	−0.04 (−0.69, 0.51)	0.440
Birthweight (*Z* score)			
Mean (SD)	0.01 (0.94)	0.15 (0.93)	
Median (IQR)	−0.08 (−0.62, 0.62)	−0.07 (−0.45, 0.93)	0.413
Preoperative TMS‡			
Mean (SD)	10.21 (1.05)	9.87 (0.83)	
Median (IQR)	10.0 (9.42, 10.83)	9.83 (9.33, 10.50)	0.130
Age at MRI, d§			
Mean (SD)	4.10 (2.02)	4.85 (3.17)	
Median (IQR)	4.00 (3.00, 5.00)	4.00 (3.00, 5.25)	0.258
By category,§ n (%)			
<5 d	92 (64.3)	25 (62.5)	
5–7 d	45 (31.5)	10 (25.0)	
>7 d	6 (4.2)	5 (12.5)	0.133
Cardiac catheter,‖ n (%)			
No	113 (79.0)	30 (75.0)	
Yes	30 (21.0)	10 (25.0)	0.743
Chromosomal disorder,# n (%)			
No	107 (74.8)	28 (70.0)	
Yes	9 (6.3)	1 (2.5)	

(*Continued*)

Table 4. Continued

Feature	WMI		*P* value*
	None (n=143)	Present (n=40)	
Suspected	27 (18.9)	11 (27.5)	0.361

HLHS indicates hypoplastic left heart syndrome; IQR, interquartile range (25th, 75th percentile); MFE, maternal-fetal environment; MRI, magnetic resonance imaging; TGA, transposition of the great arteries; TMS, total maturation score; and WMI, white matter injury.

*Kruskal-Wallis test for continuous and chi-square for categorical variables.

†Unknown delivery type for n=1 in Other category.

‡Total maturation score on preoperative MRI.

§Age at MRI and age at surgery identical except for 3 subjects.

‖Cardiac catheter intervention.

#Chromosomal disorder added to database after initial analysis.

MFE.[21,22] Rychik et al[38] recently demonstrated that placentas in pregnancies affected by CHD are abnormal. In that study, the placentas of fetuses with CHD tend to be smaller than those of infants without CHD, the placenta-to-birth weight ratios were very low, and abnormalities such as chorangiosis, hypomature villi, thrombosis, and infarction were common. The finding of chorangiosis in 20% of CHD placentas is pertinent, as chorangiosis is seen in pregnancy complications such as maternal diabetes and preeclampsia. New research suggests that genetic variants may contribute to reduced placental growth.[39]

Based on both biological plausibility and our empirical results, we hypothesize that an impaired MFE combined with altered fetal oxygen delivery to the brain increases white matter vulnerability in fetuses with CHD. Interventions for improving fetal oxygen delivery being studied and drug trials aimed at impacting placentation are underway.[40] Sadhwani et al found that fetal brain volumes were strongly correlated with neurodevelopmental testing at 2 years[41]; thus, there may be fetal markers that can be monitored. Enhanced monitoring of pregnancies affected by CHD and more aggressive management of MFE may also reduce the risks for WMI.

We were surprised that the cohorts with and without an impaired MFE had similar levels of brain immaturity (lower TMS). Further exploratory analyses suggested little evidence of an association between brain immaturity (lower TMS) and increased prevalence of impaired MFE, either for the cohort as a whole or when stratified by sex (Table 4). With few individuals in any 1 category of impaired MFE, it seemed unwise to delve further, but it remains possible that some components of the composite impaired MFE variable are individually associated with brain maturation. Interestingly, the post hoc analysis suggested that the inverse association between brain maturation and preoperative WMI could be stronger in male than in female individuals, a topic for further research. In a similar population of infants with CHD, sex differences in cortical folding have been previously demonstrated.[42]

The association of impaired MFE and risk of WMI prompted us to expand the analysis to include multiple variables related to fetal morphometry and physiology. We had complete data on a number of fetal variables on 138 subjects, 75% of the original sample, with most of the missing data in subjects without WMI (Table S6). The stepwise model for this subcohort again selected the 4 variables from the model for the full cohort (male sex, time to preoperative MRI, TMS, and impaired MFE) in addition to type of birth by cesarean section, birth weight, placental weight, and MCA PI. With only 34 cases of WMI, this model is limited to hypothesis generating.

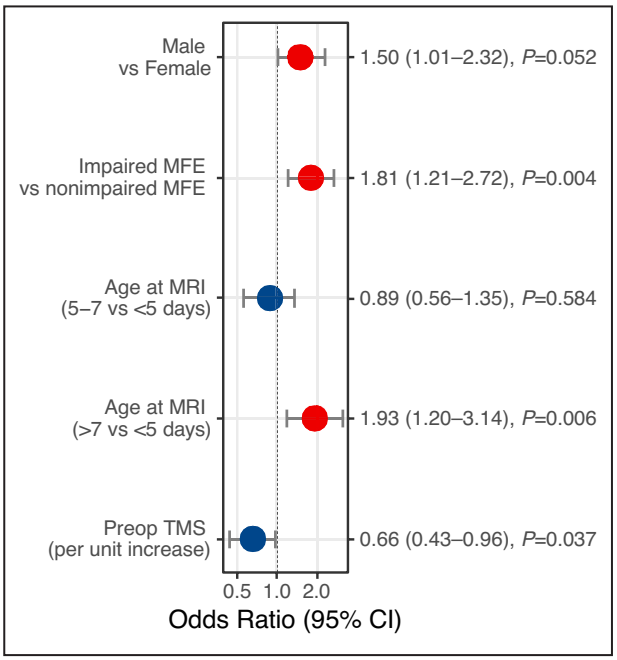

Figure 2. Odds ratios of WMI for the 4 features remaining in the final stepwise model.
Red indicates risk factors, and blue indicates a protective factor. An odds ratio of 1.0 indicates no association. Horizontal lines are 95% CI. The final model had an area under the receiver operating curve of 0.71 (95% CI, 0.62, 0.80). All 183 subjects were included in the analysis. MFE indicates maternal-fetal environment; MRI, magnetic resonance imaging; TMS, total maturation score; and WMI, white matter injury.

Table 5. Distribution of Specific Contributors to Impaired MFE for Subjects With and Without Preoperative WMI

	Overall (n=183)	WMI No (n=143)	WMI Yes (n=40)	OR (95% CI)	*P* value*
Impaired MFE (this study),† n (%)					
No	138 (75.4)	114 (79.7)	24 (60.0)		
Yes	45 (24.6)	29 (20.3)	16 (40.0)	2.60 (1.14, 5.90)	0.013
Gestational diabetes,‡ n (%)					
No	171 (93.4)	135 (94.4)	36 (90.0)		
Yes	12 (6.6)	8 (5.6)	4 (10.0)	1.87 (0.39, 7.46)	0.299
Gestational hypertension,‡ n (%)					
No	172 (94.0)	136 (95.1)	36 (90.0)		
Yes	11 (6.0)	7 (4.9)	4 (10.0)	2.15 (0.44, 9.01)	0.260
Preeclampsia,‡ n (%)					
No	181 (98.9)	142 (99.3)	39 (97.5)		
Yes	2 (1.1)	1 (0.7)	1 (2.5)	3.61 (0.05, 287)	0.390
Tobacco use,‡ n (%)					
No	174 (95.1)	135 (94.4)	39 (97.5)		
Yes	9 (4.9)	8 (5.6)	1 (2.5)	0.43 (<0.01, 3.41)	0.686
Hypothyroidism,§ n (%)					
No	177 (96.7)	142 (99.3)	35 (87.5.0)		
Yes	6 (3.3)	1 (0.7)	5 (12.5)	19.8 (2.13, 960)	0.002
Other,§,‖ n (%)					
No	167 (91.3)	131 (93.7)	36 (92.5)		
Yes	16 (8.7)	12 (6.3)	4 (7.5)	1.21 (0.27, 4.32)	0.754
Impaired MFE#, (Savla et al), n (%)					
No	153 (83.6)	123 (86.0)	30 (75.0)		
Yes	30 (16.4)	20 (14.0)	10 (25.0)	2.04 (0.77, 5.16)	0.144

MFE indicates maternal-fetal environment; OR, odds ratio; and WMI white matter injury.

**P* values based on Fisher exact test.

†Predefined impaired MFE for this study includes ≥1 of gestational diabetes, gestational hypertension, preeclampsia, tobacco use, hypothyroidism, and "other" complications of pregnancy that possibly impact the in utero environment.

‡Component of impaired MFE used in both this study and the earlier definition of impaired MFE from Savla et al.[22]

§Component of definition of impaired MFE from this but not Savla et al.[22]

‖Other complications of pregnancy with possible impact on the in utero environment conditions, including maternal trauma, maternal medications, maternal suicide attempt, obesity, and hepatitis B.

#As previously defined by and does not include hypothyroidism or "other" complications of pregnancy.

Even without impaired MFE, the congenital heart defect influences brain development. Brains of infants with CHD tend to be small as well as biochemically and structurally immature.[10,43] Brain maturation, as measured by TMS, is a consistent risk factor for WMI across many centers.[10,12,13] Average TMS at preoperative brain MRI was 10.1 ±1.01, the equivalent of an average brain maturity of late 35-week gestation in healthy norms.[44] Brain maturation may be slowed by the lower oxygen delivery that results from abnormal fetal vascular physiology.[17]

In multiple studies at our institution, increasing age at preoperative MRI (or time to surgery) is consistently associated with elevated risk of preoperative WMI.[14,16,45] In neonates with complex CHD, our work suggests that longer time to MRI may invoke a mismatch between increased cerebral metabolic demand and impaired oxygen delivery.[14,23] At Children's Hospital of Philadelphia, a protocol for surgery within 4 days of birth is in place for infants with TGA and, subsequent to this, the incidence of WMI has dropped from 38% to the presently reported 22%.[16] While our inclusion criteria strategy was to include CHD infants who were "otherwise well" at birth, a few children may have had delayed MRIs because of underlying conditions that were independently associated with WMI. Future studies in larger populations could look more closely at this possible source of confounding and explore possible modification of the association between time to MRI and WMI by key clinical risk factors.

While there are sound clinical reasons to believe that shorter times to surgery protect infants from preoperative WMI, our study design is observational, and we cannot rule out unmeasured confounding between time to surgery and innate risk of WMI as contributing to the association between time to MRI and WMI.

Table 6. WMI Logistic Regression Model With Postmodeling MFE Variables. (n=138)

Variable	OR (95% CI)	*P* value*
Male sex	3.07 (1.07–10.09)	0.047
Impaired MFE	2.78 (1.07–7.42)	0.037
Age at MRI	1.32 (1.02–1.74)	0.039
Preoperative TMS	0.60 (0.36–0.95)	0.035
Birth by cesarean section	0.52 (0.20–1.26)	0.153
Birthweight (per 100-g increase)	1.09 (0.97–1.23)	0.165
Placental weight (per 10-g increase)	0.94 (0.88–1.00)	0.057
MCA PI (per 0.1 increase)	1.10 (0.99–1.23)	0.082

MCA PI indicates middle cerebral artery pulsatility indices; MFE, maternal-fetal environment; MRI, magnetic resonance imaging; OR, odds ratio; TMS, total maturation score; and WMI, white matter injury.

*Based on Wald test for logistic regression.

Limitations

This single-center prospective cohort study of infants with severe CHD has inherent limitations with respect to generalizability to other centers with differences in practice and study populations. However, because this study looked only at preoperative risk factors and findings were primarily birth and prenatal variables, the influence of surgical and postoperative medical management practice variations is limited. We cannot exclude unmeasured confounders as contributing to the associations described here. Notably, TMS may be on the causal pathway between impaired MFE and WMI. Unmeasured confounding variables can yield paradoxical associations in these situations and potentially invalidate causal interpretation.[46] In addition, the overall power to detect associations between WMI and categorical variables was limited to reasonably larger ORs, and the numbers of subjects in some analyses, particularly the secondary analysis involving components of the composite impaired MFE variable, were small and our findings limited to hypothesis generation.

Even within our own cohort, a training set, the area under the receiver operating curve for our model was a modest 0.71 (95% CI, 0.62–0.80), suggesting limited utility as a diagnostic tool. If our model was assessed using an external cohort, we anticipate worse performance. It is possible that variables, such as placental size, MCA PIs, and umbilical artery PIs, as well as other environmental exposures (ie, maternal medications), could improve the model.[38] Additionally, our exploratory analysis suggested that effect modification by biological sex should be explored in future studies. Larger sample sizes, possibly from a multicenter study, are needed to tune the model and validate our findings.

CONCLUSIONS

Our study identified impaired MFE as an important risk factor for WMI (OR, 2.85 [95% CI, 1.29–6.30]), discovered that WMI occurs in a similar prevalence across all CHD diagnoses, and confirmed previous findings of risks associated with male sex, lower TMS, and longer time to MRI. Individual components of the MFE, including gestational hypertension, preeclampsia, gestational diabetes, and maternal hypothyroidism, may be individually associated with elevated risk for WMI, but definitive conclusions require studies with a larger sample size. The incidence of WMI was consistent across diagnoses.

While the fetal environment is a subject of intense research, there are currently no established interventions to improve the maternal-fetal environment. Time to MRI is, however, completely modifiable, and the care of infants with severe forms of CHD may benefit from clinical protocols that mandate earlier surgeries.

The predictive power of the current model is modest. Future studies might improve this model through incorporating additional prenatal factors, such as fetal resistivity, fetal pulsatility trends, additional maternal factors (ie, socioeconomic status), and other potential fetal environmental exposures, and by exploring male/female differences in risk factors.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Data S2
Tables S1–S8
References [47-49]

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SUPPLEMENTAL MATERIAL

Data S1. MRI Methods

All scanning was done on a single 1.5T Avanto MRI system (Siemens Medical Systems, Malvern, PA) with a 12-channel head coil. Brain MRI sequences included T1-weighted magnetization- prepared rapid acquisition gradient echo (T1-MPRAGE TR/TE/inversion time=1980/2.65/1100 milliseconds, flip angle=15°, voxel size=0.4x0.4x1.5 mm, matrix=256×256), T2- weighted sampling perfection with application-optimized contrasts using different flip angle evolution (T2- SPACE, TR/TE=3200/453 milliseconds, voxel size = 0.9x0.9x2 mm, matrix=256×254), susceptibility- weighted imaging (SWI; TR/TE=49/40 milliseconds, slice thickness=2 mm, matrix=256×177), and diffusion- weighted imaging (DTI; TR/TE=2903/86 milliseconds; slice thickness=4 mm; b values=0, 1000mm/s2; 20 directions; matrix 128×128). Sequences were acquired in the axial plane and reformatted off-line in the sagittal and coronal planes.

WMI and Whole Brain Volume Segmentations

WMI in the periventricular white matter was identified as T1 hyperintensity and conventionally rated using the previously validated quadrant scoring system (QPS) with increasing scale indicating increasing severity in WMI: 0 signifies no WMI, 1 mild WMI, 2 to 3 moderate WMI, and 4 severe WMI[27]. Volumetric measurements of WMI were performed by manual segmentation using ITK-SNAP[48]. Total intracranial and whole brain volumes were derived with the semi- automated FMRIB Software Library-based (FSL) Neonatal Brain Structure Segmentation (NEBSS) pipeline and the ratio of WMI volume to total brain volume was calculated[49]. For regional mapping of WMI, a template of preoperative T2-weighted images was constructed using Advanced Neuroimaging Tools (ANTs)[50]. T1- MPR images were registered to the template using ANTs and the derived registration matrix was then applied to the WMI volume masks (**Figure 1**). WMI masks for all CHD diagnoses were added and then overlaid on the template. Data sets were analyzed on a Mac (ITK-SNAP) and Linux workstation (NEBSS, ANTs).

Data S2. Description of AIC Stepwise Algorithm

The AIC stepwise algorithm is described in detail in the classic text by Venables and Ripley (Venables W N, Ripley B D. *Modern Applied Statistics with S.* 4th ed. New York, NY, 1999). Briefly:

- The algorithm starts with an assessment of the AIC for the 'full model' containing all candidate variables.
- StepAIC drops each variable from the full model in (1) and recomputes the AIC for this 'reduced model'. The AIC from the reduced model is compared to the full model. The variable associated with the largest decrease in AIC compared to the full model is dropped and this 'reduced by one-variable' model becomes the new 'full model' in Step 1.
- The algorithm is repeated from Step 1, but in addition to dropping a variable, each of the previously dropped variables (Step 2) is added. If a previously dropped variable decreases AIC, it is included back in the new model; if the previously dropped variable does not decrease AIC, it remains deleted.

The output from our stepwise procedure appears below. The initial model included cardiac diagnosis, sex, gestational age, pregnancy complications, age at MRI (3 categories), TMS score, birthweight (Z-score), head circumference at birth (Z-score), type of birth (C-section elective or emergent, Vaginal), cardiac catheter intervention and had an AIC of 194.8. Six variables were dropped and none re-entered for an AIC of 184.1 for the model shown in **Figure 2**.

>step4_3cat$anova Stepwise
Model Path nalysis of Deviance
Table

Initial Model:

preop_mri_pvl_y_bin ~ primary_cardiac_dx_3cat + sex_bin + gest_age + preg_comp_y_bin + preop_mri_age3cat + preop_tms_score + WZ + HCZ + tob_bin + cardiac_cath_interv

Final Model:

preop_mri_pvl_y_bin ~ sex_bin + preg_comp_y_bin + preop_mri_age3cat + preop_tms_score

	Step	Df	Deviance	Resid. Df	Resid. Dev	AIC
1				170	168.8	194.8
2	- primary_cardiac_dx_3cat	2	0.06824	172	168.8	190.8
3	- HCZ	1	0.01785	173	168.8	188.8
4	- cardiac_cath_interv	1	0.25140	174	169.1	187.1
5	- gest_age	1	0.53053	175	169.6	185.6
6	- WZ	1	0.96992	176	170.6	184.6
7	- tob_bin	1	1.48867	177	172.1	184.1

Table S1. Preoperative MRI features by CHD diagnosis

Features	Overall (N=183)	TGA (N=59)	HLHS (N=68)	Other (N=56)
Volume among those with WMI (mm^3)*				
Mean (SD)	133.96 (209.09)	126.04 (233.30)	119.71 (138.05)	160.36 (265.05)
WMI Quartered Point System (QPS)				
0	143 (78.1%)	46 (78.0%)	53 (77.9%)	44 (78.6%)
1	17 (9.3%)	6 (10.2%)	4 (5.9%)	7 (12.5%)
2	18 (9.8%)	5 (8.5%)	11 (16.2%)	2 (3.6%)
3	2 (1.1%)	1 (1.7%)	0 (0%)	1 (1.8%)
4	3 (1.6%)	1 (1.7%)	0 (0%)	2 (3.6%)
Any Lesion (WMI, stroke, hemorrhage or microhemorrhage)				
No	16 (8.7%)	5 (8.5%)	3 (4.4%)	8 (14.3%)
Yes	167 (91.3)	54 (91.5%)	65 (95.6%)	48 (85.7)
Stroke				
No	180 (98.4%)	58 (98.3%)	67 (98.5%)	55 (98.2%)
Yes	3 (1.6%)	1 (1.7%)	1 (1.5%)	1 (1.8%)
Microhemorrhage				
No	138 (75.4%)	47 (79.7%)	50 (73.5%)	41 (73.2%)
Yes	45 (24.6%)	12 (20.3%)	18 (26.5%)	15 (26.8%)
Parenchymal Hemorrhage				
No	179 (97.8%)	58 (98.3%)	66 (97.1%)	55 (98.2%)
Yes	4 (2.2%)	1 (1.7%)	2 (2.9%)	1 (1.8%)
Germinal Matrix Hemorrhage				
No	175 (95.6%)	59 (100%)	64 (94.1%)	52 (92.9%)
Yes	8 (4.4%)	0 (0%)	4 (5.9%)	4 (7.1%)
Choroid Plexus Hypointensities				
No	33 (18.0%)	11 (18.6%)	8 (11.8%)	14 (25.0%)
Yes	150 (82.0%)	48 (81.4%)	60 (88.2%)	42 (75.0%)
Subdural Hemorrhage				
No	108 (59.0%)	40 (67.8%)	31 (45.6%)	37 (66.1%)
Yes	75 (41.0%)	19 (32.2%)	37 (54.4%)	19 (33.9%)

*Mean values exclude 0's for those without WMI; CHD congenital heart disease; WMI white matter injury; SD standard deviation

Table S2. WMI as a function of age at MRI stratified by primary cardiac diagnosis. At CHOP, surgery for subjects with TGA, but not other diagnoses, typically occurs before 5 days. Values shown are number of subjects and columnwise percentages.

	TGA (N=59)			HLHS (N=68)				OTHER (N=56)			
Age at MRI (days)	**(0,3] (N=31)**	**(3,5] (N=24)**	**(5,7] (N=4)**	**(0,3] (N=26)**	**(3,5] (N=24)**	**(5,7] (N=13)**	**(8,19] (N=5)**	**(0,3] (N=18)**	**(3,5] (N=22)**	**(5,7] (N=10)**	**(8,19] (N=6)**
WMI											
No	25 80.6%	18 75.0%	3 75.0%	23 88.5%	18 75.0%	9 69.2%	3 60.0%	14 77.8%	17 77.3%	10 90.9%	3 50.0%
Yes	6 19.4%	6 25.0%	1 25.0%	3 11.5%	6 25.0%	4 30.8%	2 40.0%	4 22.2%	5 22.7%	0 0%	3 50.0%

WMI white matter injury; TMS total maturation score; MFE maternal-fetal environment; MCA middle cerebral artery; PI pulsatility indices; Unbal AVCanal Unbalanced Atrio-ventricular Canal

Table S3. Summary statistics for variables in the logistic regression model by quartile of preoperative Total Maturation Score (TMS). Values are percentages for binary variables and medians for preoperative age.

TMS Quartile*	n	Impaired MFE (%)	Male (%)	Preoperative MRI Age in days (Median)	WMI (%)
All Subjects (n=183)					
8-9.3	48	22.9	62.5	4.0	25.0
9.4-10.0	46	26.1	63.0	3.5	21.7
10.1-10.7	45	20.0	55.6	4.0	24.4
10.8-14	44	29.6	50.0	4.0	15.9
Males (n=106)					
8-9.3	30	23.3	100	4.0	36.7
9.4-10.0	29	34.5	100	3.0	24.1
10.1-10.7	25	8.0	100	4.0	24.0
10.8-14	22	31.8	100	4.0	18.2
Females (n=77)					
8-9.3	18	22.2	0	4.0	5.6
9.4-10.0	17	11.8	0	4.0	17.6
10.1-10.7	20	35.0	0	4.0	25.0
10.8-14	22	27.3	0	4.5	13.6

*Based on quartiles of TMS in overall sample with values showing the range in each quartile; WMI white matter injury; MFE maternal-fetal environment

Table S4. Model selected by stepwise regression for TMS outcome using all data and no placental variables (n=183)

Variables	Estimate	SE	P-value	Lower-95%	Upper-95%
(Intercept)	3.4015	3.2418	0.2955	-2.9523	9.7553
Postmenstrual Age (per week increase)	0.1678	0.0835	0.0460	0.0041	0.3316
Age at Preop MRI (per day increase)	0.0640	0.0316	0.0443	0.0021	0.1259
Chromosomal disorder (Yes)	0.3116	0.3224	0.3351	-0.3203	0.9435
Chromosomal disorder (Suspected)	-0.4373	0.1812	0.0169	-0.7925	-0.0820

Reference is no chromosomal disorder

SE standard error, L95 lower bound of 95 % confidence intervaI; U95 upper bound of 95% confidence interval

Table S5. Characteristics of subjects with mothers with hypothyroidism

Characteristic						
Subject ID	112	6	45	51	53	134
Preoperative WMI	No	Yes	Yes	Yes	Yes	Yes
Pre-specified Variables						
Cardiac Diagnosis	TGA	Unbal AVCanal	HLHS	TGA	TGA	HLHS
Sex	Female	Male	Male	Male	Female	Female
TMS Score	10.2	8.5	9.3	11	10.5	10.8
MRI/Surgery Age (Days)	4	4	5	3	4	6
Gestational Diabetes	No	No	No	No	No	No
Gestational Hypertension	No	**Yes**	No	No	No	No
Pre-eclampsia	No	No	No	No	No	No
Tobacco Use	No	No	No	No	No	No
Other Complications of Pregnancy	No	No	No	No	**Yes**	No
Post-modeling Variables						
Placental Weight (g)	364	484	438	406	NA	358
Birthweight (Kg)	2.61	4.10	3.73	3.60	4.05	3.07
Birthweight: Placental Weight	7.2	8.5	8.5	8.9	NA	8.6
MCA PI	1.09	1.43	1.12	1.80	NA	2.18
MCA:Umbilical PI	1.20	1.62	1.16	2.65	NA	2.12

Table S6. Description of cohort by preoperative WMI status with post-modeling variables*

Feature	Preoperative WMI		P-value†
	None (n=143)	**Present** (n=40)	
Chromosomal Abnormality			
Yes	9 (6.3%)	1 (2.5%)	
No	107 (74.8%)	28 (70.0%)	
Suspected	27 (18.9%)	11 (27.5%)	0.361
Placental Weight (g)			
Mean (SD)	453.9 (110.14)	425.7 (81.87)	
Median (IQR)	448.0 [382.0, 516.0]	406.0 [369.0, 471.0]	0.169
Missing	34 (23.8%)	5 (12.5%)	
Birthweight(kg)			
Mean(SD)	3.31 (0.50)	3.40 (0.46)	
Median(IQR)	3.30 [2.99, 3.61]	3.37 [3.08, 3.68]	0.252
Birthweight: Placental Weight			
Mean (SD)	7.60 (1.48)	8.14 (1.26)	
Median (IQR)	7.39 [6.63, 8.30]	8.01 [7.31, 8.90]	0.029
Missing	34 (23.8%)	5 (12.5%)	
Umbilical Artery PI			
Mean (SD)	1.03 (0.23)	1.00 (0.26)	
Median (IQR)	1.01 [0.87, 1.18]	0.98 [0.88, 1.06]	0.303
Missing	31 (21.7%)	4 (10.0%)	
Uterine Artery PI			
Mean (SD)	0.78 (0.28)	0.82 (0.28)	
Median (IQR)	0.73 [0.64, 0.83]	0.81 [0.62, 0.97]	0.530
Missing	58 (40.6%)	15 (37.5%)	
Middle Cerebral Artery PI			
Mean (SD)	1.54 (0.41)	1.63 (0.43)	
Median (IQR)	1.53 (1.23, 1.81)	1.54 (1.24, 1.85)	0.388
Missing	31 (21.7%)	4 (10.0%)	
MCA:Umbilical			
Mean (SD)	1.55 (0.52)	1.73 (0.62)	
Median (IQR)	1.47 (1.25, 1.89)	1.61 (1.33, 2.10)	0.151
Missing	31 (21.7%)	4 (10.0%)	
Placental Pathology			
No	33 (23.1%)	5 (12.5%)	
Yes	109 (76.2%)	35 (87.5%)	0.209
Missing	1 (0.7%)	0 (0%)	
Placental Infarction			
No	95 (66.4%)	32 (80.0%)	
Yes	14 (9.8%)	3 (7.5%)	0.704
Missing	34 (23.8%)	5 (12.5%)	

*Variables added for exploratory purposes after the initial analysis added based on importance of maternal- fetal environment (MFE) in prospective study; †Wilcoxon Rank Sum test for continuous and Chi-square for categorical variables; WMI white matter injury; SD standard deviation; IQR interquartile range 25th and 75th percentile; PI pulsatility indices; MCA middle cerebral

Table S7. Description of cohort by diagnosis with post-modeling variables potentially related to MFE*

	Overall (N=183)	TGA (N=59)	HLHS (N=68)	Other (N=56)	P-value†
Chromosomal Disorder					
Yes	10 (5.5%)	0 (0%)	0 (0%)	10 (17.9%)	
No	135 (73.8%)	51 (86.4%)	58 (85.3%)	26 (46.4%)	
Suspected	38 (20.8%)	8 (13.6%)	10 (14.7%)	20 (35.7%)	<.001
Placental Weight (g)					
Mean (SD)	447.07 (104.42)	441.30 (91.73)	454.90 (96.48)	441.98 (126.11)	
Median (IQR)	445.00 [378.25, 508.50]	421.50 [373.75, 514.50]	448.00 [382.50, 510.00]	446.00 [374.00, 494.00]	0.703
Missing	39 (21.3%)	17 (28.8%)	9 (13.2%)	13 (23.2%)	
Birthweight (Kg)					
Mean (SD)	3.33 (0.49)	3.45 (0.47)	3.31 (0.51)	3.24 (0.47)	
Median (IQR)	3.33 [3.00, 3.65]	3.44 [3.12, 3.75]	3.33 [2.98, 3.62]	3.20 [2.98, 3.52]	0.078
Birthweight: Placental Weight					
Mean (SD)	7.73 (1.45)	7.83 (1.31)	7.57 (1.41)	7.85 (1.62)	
Median (IQR)	7.53 [6.77, 8.73]	7.55 [6.84, 8.39]	7.32 [6.65, 8.42]	7.82 [7.04, 9.04]	0.413
Missing	39 (21.3%)	17 (28.8%)	9 (13.2%)	13 (23.2%)	
Umbilical Artery PI					
Mean (SD)	1.03 (0.24)	0.99 (0.25)	1.01 (0.20)	1.08 (0.27)	
Median (IQR)	1.01 [0.87, 1.15]	0.97 [0.81, 1.10]	0.99 [0.89, 1.10]	1.07 [0.88, 1.27]	0.206
Missing	35 (19.1%)	18 (30.5%)	8 (11.8%)	9 (16.1%)	
Uterine Artery PI					
Mean (SD)	0.79 (0.28)	0.74 (0.15)	0.80 (0.26)	0.82 (0.36)	
Median (IQR)	0.73 [0.63, 0.87]	0.72 [0.63, 0.87]	0.74 [0.64, 0.92]	0.73 [0.63, 0.83]	0.775
Missing	73 (39.9%)	30 (50.8%)	25 (36.8%)	18 (32.1%)	
Middle Cerebral Artery PI					
Mean (SD)	1.56 (0.42)	1.67 (0.45)	1.44 (0.31)	1.62 (0.47)	
Median (IQR)	1.54 [1.23, 1.81]	1.62 [1.29, 2.03]	1.42 [1.22, 1.66]	1.57 [1.28, 1.96]	0.037
Missing	35 (19.1%)	18 (30.5%)	8 (11.8%)	9 (16.1%)	
MCA:Umbilical					
Mean (SD)	1.59 (0.55)	1.77 (0.60)	1.46 (0.38)	1.61 (0.64)	
Median (IQR)	1.49 [1.25, 1.89]	1.64 [1.34, 2.08]	1.34 [1.25, 1.69]	1.47 [1.08, 2.01]	0.039
Missing	35 (19.1%)	18 (30.5%)	8 (11.8%)	9 (16.1%)	
Placental Pathology					
No	38 (20.8%)	17 (28.8%)	9 (13.2%)	12 (21.4%)	
Yes	144 (78.7%)	42 (71.2%)	59 (86.8%)	43 (76.8%)	0.096
Missing	1 (0.5%)	0 (0%)	0 (0%)	1 (1.8%)	
Placental Infarction					
No	127 (69.4%)	39 (66.1%)	50 (73.5%)	38 (67.9%)	
Yes	17 (9.3%)	3 (5.1%)	9 (13.2%)	5 (8.9%)	0.460
Missing	39 (21.3%)	17 (28.8%)	9 (13.2%)	13 (23.2%)	

*Variables added for exploratory purposes after the initial analysis added based on importance of MFE in prospective study;
†Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables; MFE maternal-fetal environment; SD standard deviation; IQR interquartile range 25th and 75th percentile; PI pulsatility indices; MCA middle cerebral artery

Table S8. Description of cohort by MFE status with post-modeling variables*			
Feature	**Impaired MFE**		**P-value†**
	No (n=138)	**Yes** (n=45)	
Chromosomal Abnormality			
No	104 (75.4%)	31 (68.9%)	
Yes	5 (3.6%)	5 (11.1%)	
Suspected	29 (21.0%)	9 (20.0%)	0.158
Placental Weight (g)			
Mean (SD)	450.88 (108.29)	436.05 (92.79)	
Median (IQR)	446.00 [382.00, 512.00]	430.00 [366.00, 504.00]	0.679
Missing	31 (22.5%)	8 (17.8%)	
Birthweight(kg)			
Mean(SD)	3.36 (0.47)	3.24 (0.54)	
Median(IQR)	3.34 [3.04, 3.65]	3.18 [2.80, 3.60]	0.189
Birthweight: Placental Weight			
Mean (SD)	7.76 (1.47)	7.63 (1.40)	
Median (IQR)	7.52 [6.77, 8.90]	7.54 [6.78, 8.47]	0.857
Missing	31 (22.5%)	8 (17.8%	
Umbilical Artery PI			
Mean (SD)	1.03 (0.23)	1.00 (0.27)	
Median (IQR)	1.02 [0.88, 1.15]	0.96 [0.84, 1.07]	0.242
Missing	30 (21.7%)	5 (11.1%)	
Uterine Artery PI			
Mean (SD)	0.80 (0.30)	0.78 (0.21)	
Median (IQR)	0.71 [0.62, 0.88]	0.74 [0.67, 0.87]	0.537
Missing	58 (42.0%)	15 (33.3%)	
Middle Cerebral Artery PI			
Mean (SD)	1.58 (0.41)	1.51 (0.43)	
Median (IQR)	1.54 [1.30, 1.83]	1.52 [1.16, 1.79]	0.389
Missing	30 (21.7%)	5 (11.1%)	
MCA:Umbilical			
Mean (SD)	1.59 (0.49)	1.61 (0.68)	
Median (IQR)	1.49 [1.27, 1.89]	1.34 [1.18, 1.93]	0.528
Missing	30 (21.7%)	5 (11.1%)	
Placental Pathology			
No	30 (21.7%)	8 (17.8%)	
Yes	107 (77.5%)	37 (82.2%)	0.705
Missing	1 (0.7%)	0 (0%)	
Placental Infarction			
No	95 (68.8%)	32 (71.1%)	
Yes	12 (8.7%)	5 (11.1%)	0.938
Missing	31 (22.5%)	8 (17.8%)	

*Variables added for exploratory purposes after the initial analysis added based on importance of maternal- fetal environment (MFE) in prospective study; †Wilcoxon Rank Sum test for continuous and Chi-square for categorical variables; WMI white

matter injury; SD standard deviation; IQR interquartile range 25th and 75th percentile; PI pulsatility indices; MCA middle cerebral