

Comparative analysis of cerebrovascular resistance in fetuses with single-ventricle congenital heart disease

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ABSTRACT

Objective We sought to determine whether the presence or absence of aortic obstruction impacts cerebrovascular resistance in fetuses with single-ventricle (SV) congenital heart disease (CHD).

Methods Pulsatility indices (PIs) were recorded for the middle cerebral artery (MCA) and the umbilical artery (UA) from 18 to 40 weeks' gestation in 59 fetuses (163 examinations) with SV-CHD with unobstructed aortic flow, yet decreased pulmonary flow, in 72 fetuses (170 examinations) with obstructed aortic flow and hypoplastic left heart syndrome (HLHS) and in 92 normal fetuses (92 examinations). The cerebral-to-placental resistance (CPR) was calculated as the MCA-PI/UA-PI. Z-scores were generated for the MCA-PI and the UA-PI in order to make comparisons independent of gestational age. Statistical analyses were performed using one-way ANOVA with post-hoc testing. Trends in these variables over the course of gestation were assessed using linear regression and univariate ANOVA.

Results The MCA-PI and the CPR were significantly lower in SV fetuses with aortic obstruction compared with SV fetuses with pulmonary obstruction and with normal fetuses. Moreover, the MCA-PI decreased significantly for SV fetuses with aortic obstruction over the course of gestation. In contrast, the MCA-PI was higher over the course of gestation in SV fetuses with pulmonary obstruction compared with normal fetuses.

Conclusion In fetuses with SV-CHD, cerebrovascular resistance varies substantially between fetuses with and without aortic obstruction. Compared with normal fetuses, cerebrovascular resistance is decreased in SV fetuses with aortic obstruction, yet increased in SV fetuses with pulmonary obstruction. In fetuses with SV

physiology, inherent differences in cerebral blood flow may underlie postnatal neurodevelopmental outcomes. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Children with congenital heart disease (CHD) have structural and functional brain abnormalities, even at birth before initial surgical palliation^{1–3}. Such abnormalities probably have their origins in fetal life and altered cerebral blood-flow patterns may be responsible. Delivery of blood flow to the brain *in utero* can be variable and may depend upon the type of CHD present^{4–6}. The number of ventricles (one or two), systemic ventricular morphology (right or left) and the nature of flow into the aorta (obstructed or unobstructed) theoretically may all influence the pathways and the patterns of blood-flow delivery to the aorta, hence potentially altering the cerebral circulation. In hypoplastic left heart syndrome (HLHS), anatomic constraints limit aortic blood flow. Utilizing Doppler techniques, investigators have demonstrated decreased cerebrovascular resistance in fetuses with HLHS compared with normal fetuses^{5,6}. A lower cerebrovascular resistance reflects an autoregulatory attempt to increase cerebral blood flow under conditions where blood-flow delivery is inherently diminished, a phenomenon known as 'brain sparing'.

Linkage between fetal blood-flow patterns and childhood neurodevelopmental outcomes in CHD has not yet been established; however, variability in neurodevelopmental outcomes based upon CHD type is evident. In particular, children with HLHS, a form of single-ventricle (SV) CHD, appear to exhibit the greatest degree of deficits, with a substantial number manifesting learning difficulties, lower intelligence quotient (IQ), impaired executive

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function and increased incidence of hyperactivity attention deficit disorder^{7–13}. In contrast, children with non-HLHS forms of SV-CHD perform comparatively well, having IQ scores no different from normal¹⁰. We hypothesize that the presence or absence of aortic obstruction may contribute to this difference in neurodevelopmental outcome in children with SV-CHD.

The purpose of our study was twofold: first, to investigate for differences in cerebral blood-flow patterns between SV fetuses with aortic obstruction *vs* pulmonary obstruction in comparison with normal fetuses; and, second, to explore the changes in these cerebral blood-flow patterns over gestation. By investigating cerebral blood-flow patterns in a large cohort of fetuses with SV-CHD, we may be able to gain a better understanding of some of the earliest developmental factors that might influence childhood neurodevelopmental outcome.

METHODS

Study population

This study was a retrospective, single institutional, observational investigation. Institutional Review Board approval was obtained (IRB 10-007793). Our fetal echocardiographic database from 1 January 2005 until 1 September 2010 was reviewed and fetuses with normal cardiovascular structure and function, SV fetuses with aortic obstruction (HLHS) and SV fetuses with pulmonary obstruction were eligible for enrollment. All fetuses with HLHS had either no, or only minimal, antegrade flow in the ascending aorta, with the transverse aorta perfused in a retrograde manner by the ductus arteriosus. All SV fetuses with pulmonary obstruction had either a normal or an enlarged aorta with complete antegrade flow throughout the aortic arch, and all had some degree of pulmonary stenosis or atresia. Only singleton fetuses were considered for enrollment. Any fetus diagnosed prenatally with functional SV-CHD who underwent a biventricular repair after birth was excluded from the final analysis. Fetuses with CHD underwent one or more echocardiograms over the course of gestation, while fetuses with normal cardiovascular function underwent only one fetal echocardiogram.

Fetal echocardiography

Fetal echocardiograms were performed using the standardized American Society of Echocardiography protocol¹⁴ on a Siemens Acuson Sequoia (Mountain View, CA, USA) ultrasound system, coupled with a 6C2 or an 8V3 transducer. Doppler flow patterns for the middle cerebral artery (MCA) and the umbilical artery (UA) were acquired during fetal apnea, according to previously published methods^{15,16}. For each examination of each subject, estimated fetal weight, gestational age (GA) and pulsatility index (PI) for the MCA and the UA, defined as the (peak systolic velocity – end-diastolic velocity)/time-averaged mean velocity, were recorded. Three consecutive

MCA and UA Doppler flow patterns were traced by the principal investigator using the Syngo Dynamics version 9 Cardiovascular Software package (Siemens Medical Solutions, Ann Arbor, MI, USA). The echocardiographic results for each parameter were averaged for the purpose of statistical analysis. A comparative measure of the cerebral-to-placental resistance (CPR) was calculated as the MCA-PI/UA-PI.

Statistical analysis

In order to make comparisons between groups independently of GA, Z-scores were generated for the MCA-PI and the UA-PI using a previously published dataset of normal fetuses from 20 to 42 weeks' gestation¹⁶. Only the first scan of each subject after 20 weeks' gestation was included in this analysis. Statistical analysis was performed using one-way ANOVA with post-hoc Scheffé testing. Univariate ANOVA was then used to assess for changes in the MCA-PI, UA-PI and CPR over the course of gestation among the three study groups. Models were generated for each study cohort and estimated marginal means were calculated. Adjustments for multiple comparisons were made with the Bonferroni correction. To describe the changes in these variables over the course of gestation for each study group, regression analysis was performed using all scans over the course of gestation for each subject. Statistical analysis was performed using SPSS version 17 software (SPSS Inc., Chicago, IL, USA) and Intercooled Stata 9 (StataCorp, College Station, TX, USA). Significance was set at $P < 0.05$.

RESULTS

The study population consisted of 59 SV fetuses with pulmonary obstruction (163 serial examinations), 72 SV fetuses with aortic obstruction (HLHS) (170 serial examinations) and 92 fetuses with normal cardiovascular anatomy and function (92 examinations). Anatomic characteristics for the SV cohort with pulmonary obstruction are shown in Table 1. The mean GA and Z-score for the study parameters for each group are presented in Table 2. The mean GA of the SV cohort with pulmonary obstruction was lower than the mean GA of the normal cohort and of the SV cohort with aortic obstruction. SV fetuses with aortic obstruction had significantly lower Z-scores for the MCA-PI compared with the normal cohort and the SV cohort with pulmonary obstruction. Conversely, SV fetuses with pulmonary obstruction had slightly higher Z-scores for the MCA-PI compared with the normal cohort, although this was not statistically significant ($P = 0.08$). The CPR was also lower in the SV cohort with aortic obstruction compared with the SV cohort with pulmonary obstruction and with the normal cohort. However, the Z-scores for the UA-PI were not significantly different among the three groups ($P = 0.10$).

Table 1 Anatomic characteristics of the single-ventricle (SV) cohort with pulmonary obstruction ($n = 59$)

Anatomic characteristics	n	%
PA/IVS	20	33.90
TA, VSD, PS	10	16.95
Heterotaxy, R-UAVC, DORV, PS	10	16.95
Heterotaxy, R-UAVC, RV-Ao, PA	7	11.86
Heterotaxy, RV-Ao, PA, MA	2	3.38
DILV, PA	2	3.38
DILV, PS	2	3.38
RV-Ao, PA, MA	2	3.38
DORV, MA, PS	1	1.69
TS, critical PS, RV hypoplasia	1	1.69
R-UAVC, DORV, PS	1	1.69
Heterotaxy, DORV, PS, MA	1	1.69

DILV, double-inlet left ventricle; DORV, double-outlet right ventricle; IVS, intact ventricular septum; MA, mitral atresia; PA, pulmonary atresia; PS, pulmonary stenosis; R-UAVC, right dominant unbalanced atrioventricular canal; RV, right ventricle; RV-Ao, right ventricle to aorta; TA, tricuspid atresia; TS, tricuspid stenosis; VSD, ventricular septal defect.

Univariate ANOVA was then performed to assess between-group changes during gestation in the MCA-PI, UA-PI and CPR. During gestation, the MCA-PI and the CPR were lower in the SV cohort with aortic obstruction than in the SV cohort with pulmonary obstruction and in the normal cohort. As shown in Table 3, the parameter estimates for the MCA-PI at a mean GA of 26.8 weeks were 2.16 for the SV cohort with pulmonary obstruction, 1.79 for the SV cohort with aortic obstruction and 1.97 for the normal cohort. Post-hoc analysis with adjustments for multiple comparisons made by the Bonferroni correction revealed $P < 0.001$ for SV fetuses with pulmonary obstruction *vs* SV fetuses with aortic obstruction, $P = 0.018$ for SV fetuses with pulmonary obstruction *vs* normal fetuses and $P = 0.010$ for SV fetuses with aortic obstruction *vs* normal fetuses. The model was highly significant ($F = 9.84$, $P < 0.001$, $R^2 = 0.12$). As shown in Table 4, the parameter estimates for the CPR at a mean GA of 26.8 weeks were 1.75 for the SV cohort with pulmonary obstruction, 1.43 for the SV cohort with aortic obstruction and 1.67 for the normal cohort. Post-hoc analysis with adjustments for multiple comparisons by the Bonferroni

correction revealed $P < 0.001$ for the SV cohort with pulmonary obstruction *vs* the SV cohort with aortic obstruction and $P < 0.001$ for the SV cohort with aortic obstruction *vs* the normal cohort. However, there was no significant difference in CPR between the SV cohort with pulmonary obstruction and the normal cohort. The model was highly significant ($F = 40.0$, $P < 0.001$, $R^2 = 0.36$). Finally, univariate analysis demonstrated no significant differences over the course of gestation in the UA-PI among the three groups.

To determine whether there were any significant changes over the course of gestation in the MCA-PI, UA-PI and CPR for each study group, linear regression analysis was performed and all studies for each subject were utilized. Figure 1 demonstrates the mean and 95% CI for the MCA-PI over the course of gestation for each group. Linear regression analysis showed that the MCA-PI decreased significantly over the course of gestation in the SV cohort with aortic obstruction, yet increased slightly in the normal cohort. There was no significant change in the MCA-PI for the SV cohort with pulmonary obstruction. The UA-PI decreased over the course of gestation in all three groups, but there were no differences between groups (Figure 2). Figure 3 demonstrates changes in the CPR over the course of gestation for all three study groups. CPR increased significantly over the course of gestation in the SV cohort with pulmonary obstruction and in the normal cohort. There was a very slight increase in CPR over the course of gestation in the SV cohort with aortic obstruction.

DISCUSSION

In our study, we found lower cerebrovascular resistance and lower CPR in SV fetuses with aortic obstruction compared with normal fetuses and with SV fetuses with pulmonary obstruction. As demonstrated in Figure 1, cerebrovascular resistance for SV fetuses with aortic obstruction was similar to that of normal fetuses at 20 weeks' gestation, but dropped below the expected normal values at approximately 27 weeks' gestation. In contrast, SV fetuses with pulmonary obstruction demonstrated elevated cerebrovascular resistance over the course of gestation compared with normal fetuses. Placental resistance, as assessed by the UA-PI, decreased in

Table 2 Comparison between groups using ANOVA of gestational age at examination (GA), middle cerebral artery pulsatility index (MCA-PI) Z-score, umbilical artery pulsatility index (UA-PI) Z-score and cerebral-to-placental resistance (CPR)

	SV with pulmonary obstruction ($n = 59$)	SV with aortic obstruction ($n = 72$)	Normal ($n = 92$)	P
GA (weeks)	24.36 \pm 4.04*†	27.99 \pm 5.38*	27.37 \pm 5.65†	< 0.001
MCA-PI Z-score	0.92 \pm 2.00*	-0.47 \pm 1.43*‡	0.31 \pm 1.47‡	< 0.001
UA-PI Z-score	0.15 \pm 1.13	0.28 \pm 0.65	-0.02 \pm 0.82	0.097
CPR	1.63 \pm 0.53	1.49 \pm 0.37‡	1.71 \pm 0.43‡	0.008

Results are given as mean \pm SD. Significant differences (all $P < 0.05$) in the following groups were identified by post-hoc Scheffe analysis:

*single-ventricle (SV) cohort with pulmonary obstruction *vs* SV cohort with aortic obstruction; †SV cohort with aortic obstruction *vs* normal; and ‡SV cohort with aortic obstruction *vs* normal.

Table 3 Parameter estimates by univariate ANOVA for predicting the middle cerebral artery pulsatility index (MCA-PI)

Parameter	B	SE	t	P	Estimated marginal mean at 26.8 weeks
Intercept	1.591	0.145	10.991	0.000	
GA	0.014	0.005	2.804	0.005	
SV: pulmonary obstruction	0.185	0.067	2.766	0.006	2.16†‡
SV: aortic obstruction	-0.183	0.061	-2.976	0.004	1.79†§
Normal	0*				1.97‡§

*Parameter set to zero because it is redundant. The model was highly significant ($F = 9.84$, $P < 0.001$, $R^2 = 0.12$). †Single-ventricle (SV) with pulmonary obstruction *vs* SV with aortic obstruction ($P < 0.001$). ‡SV with pulmonary obstruction *vs* normal ($P = 0.018$). §SV with aortic obstruction *vs* normal ($P = 0.01$). GA, gestational age; SE, standard error.

Table 4 Parameter estimates by univariate ANOVA for predicting cerebral-to-placental resistance (CPR)

Parameter	B	SE	t	P	Estimated marginal mean at 26.8 weeks
Intercept	0.523	0.178	2.943	0.004	
GA	0.044	0.006	7.572	0.000	
SV: pulmonary obstruction	0.089	0.080	1.114	0.267	1.753†
SV: aortic obstruction	-0.266	0.068	-3.914	0.000	1.430†‡
Normal	0*				1.673‡

*Parameter set to zero because it is redundant. The model was highly significant ($F = 40.0$, $P < 0.001$, $R^2 = 0.36$). †Single ventricle (SV) with pulmonary obstruction *vs* SV with aortic obstruction ($P < 0.001$). ‡SV with aortic obstruction *vs* normal ($P < 0.001$). GA, gestational age; SE, standard error.

all three study groups over gestation, as expected^{15–17}, yet there were no differences between groups. Over the course of gestation, CPR increased significantly in SV fetuses with pulmonary obstruction and in normal fetuses, but there was no significant difference between these groups. SV fetuses with aortic obstruction, on the other hand, demonstrated only a very slight increase in CPR over the course of gestation, which was markedly lower than found for the other two groups.

Variability in cardiac anatomy and in the pathway of delivery of blood to the aorta in fetuses with SV-CHD may explain our findings. In SV fetuses with aortic obstruction, namely HLHS, the presence of aortic hypoplasia and the need for support of aortic perfusion by retrograde flow from the ductus arteriosus indicates an inherently diminished quantity of blood flow delivered to the cerebral circulation. The size of the ascending aorta in HLHS has been associated with the degree of microcephaly, suggesting a link between brain growth and aortic morphometry¹⁸. A decrease in cerebrovascular resistance, as reflected by our findings of a low MCA-PI and a low CPR, represents the brain's attempt to increase blood flow in the face of an insufficient source of flow. Conversely, in SV fetuses with pulmonary obstruction, the entire cardiac output traverses the sole functional ventricle, with the vast majority of blood volume exiting into the unobstructed aorta. The cerebral circulation therefore receives a substantially increased fraction of overall cardiac output relative to normal, and autoregulates by increasing cerebrovascular resistance in order to limit blood flow and prevent hyperperfusion. This is supported

by our findings of a higher MCA-PI Z-score in the SV cohort with pulmonary obstruction relative to the SV cohort with aortic obstruction, with a trend toward significance compared with normal fetuses.

Diminished cerebral blood flow has been demonstrated in prenatal and early postnatal magnetic resonance imaging (MRI) studies in fetuses with CHD^{19,20}. Compensatory mechanisms to maintain adequate cerebral perfusion in fetuses with aortic obstruction may become overwhelmed in fetuses with HLHS as they grow, leading to delayed brain development and structural abnormalities of the brain, as documented in prenatal²⁰ and postnatal^{1–3,21} MRI studies. Myocardial mechanics and ventricular performance may change during the course of gestation in fetuses with HLHS, leading to a point in time when there is a mismatch between cerebral blood-flow delivery and the perfusion needs of the developing brain. In fetuses with HLHS, overall cardiac output is diminished by 20% relative to normal and the workload of right ventricular ejection progressively increases during the third trimester of gestation²². Demands for cerebral blood flow may increase in the third trimester, when key brain-maturational processes, such as cortical folding and gyration, occur²³. HLHS fetuses may attempt to augment cerebral blood flow by lowering cerebrovascular resistance in the third trimester, as evidenced by a lower MCA-PI in HLHS fetuses after 27 weeks compared with normal fetuses (Figure 1); yet, the absolute amount of increased flow to the brain may still be inadequate to ensure normal growth and development.

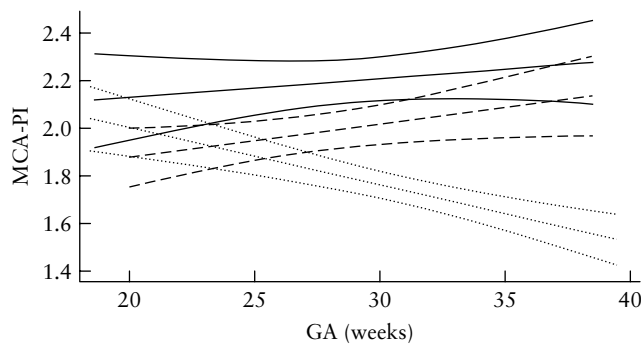


Figure 1 Linear regression and 95% CIs for middle cerebral artery pulsatility index (MCA-PI) vs gestational age (GA). Single-ventricle (SV) cohort with aortic obstruction (.....): $\text{MCA-PI} = -0.024 (\text{GA}) + 2.487$ ($F = 21.73$, $R^2 = 0.12$, $P < 0.001$). Cohort of normal fetuses (---): $\text{MCA-PI} = 0.014 (\text{GA}) + 1.599$ ($F = 4.254$, $R^2 = 0.05$, $P = 0.04$). SV cohort with pulmonary obstruction (—): regression equation was not significant.

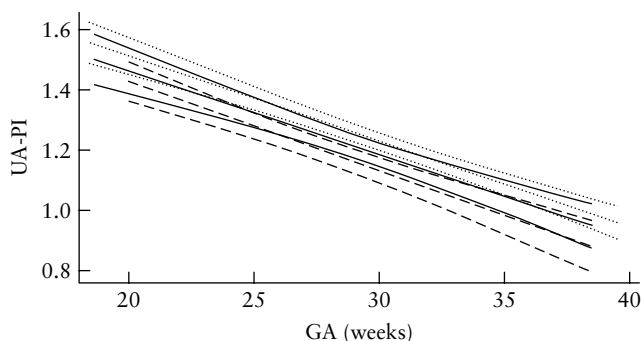


Figure 2 Linear regression and 95% CIs for umbilical artery pulsatility index (UA-PI) vs gestational age (GA). Single-ventricle (SV) cohort with pulmonary obstruction (—): $\text{UA-PI} = -0.028 (\text{GA}) + 2.018$ ($F = 63.44$, $R^2 = 0.28$, $P < 0.001$). SV cohort with aortic obstruction (.....): $\text{UA-PI} = -0.028 (\text{GA}) + 2.08$ ($F = 117.96$, $R^2 = 0.42$, $P < 0.001$). Cohort of normal fetuses (---): $\text{UA-PI} = -0.030 (\text{GA}) + 2.019$ ($F = 71.79$, $R^2 = 0.45$, $P < 0.001$).

In contrast to HLHS fetuses, we hypothesize that SV fetuses with pulmonary obstruction have adequate, or even increased, cerebral blood flow, which may underlie differences in postnatal neurodevelopmental outcomes. Goldberg *et al.* demonstrated near-normal IQ scores in non-HLHS SV subjects, while IQ scores were approximately 10 points lower in HLHS subjects¹⁰. Our data suggest that aortic obstruction is the key anatomic feature dictating cerebrovascular resistance, and not the presence of an SV.

In contrast to previous studies^{6,24}, placental resistance was not significantly elevated in SV fetuses with either aortic or pulmonary obstruction, compared with normal fetuses. Only five subjects in the SV cohort with aortic obstruction and seven subjects in the SV cohort with pulmonary obstruction had elevated placental resistance, defined as a Z-score of > 2 for UA-PI, in at least one study, while one subject in the normal cohort had a Z-score of > 2 . Elevated placental resistance is an important factor contributing to late gestational growth restriction in fetuses without CHD²⁵. Although many fetuses

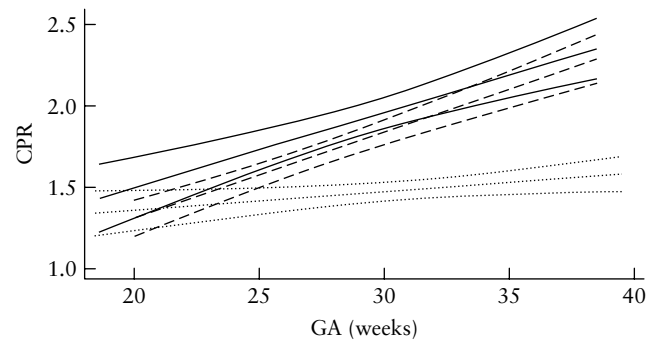


Figure 3 Linear regression and 95% CIs for cerebral-to-placental resistance (CPR) vs gestational age (GA). Single-ventricle (SV) cohort with pulmonary obstruction (—): $\text{CPR} = 0.046 (\text{GA}) + 0.582$ ($F = 27.71$, $R^2 = 0.15$, $P < 0.001$). SV cohort with aortic obstruction (.....): $\text{CPR} = 0.011 (\text{GA}) + 1.128$ ($F = 4.86$, $R^2 = 0.03$, $P = 0.03$). Cohort of normal fetuses (---): $\text{CPR} = 0.053 (\text{GA}) + 0.253$ ($F = 75.36$, $R^2 = 0.46$, $P < 0.001$).

with SV-CHD are small-for-gestational-age at birth^{26,27}, this may be secondary to an overall diminished cardiac output, leading to a diminished rate of growth, rather than inadequate placental blood flow. Unfortunately, many fetuses with SV-CHD continue to be delivered prematurely on account of being small-for-gestational age, despite a reassuring UA Doppler.

An important limitation to the interpretation of our study findings must be stated. Measurement of cerebrovascular resistance through MCA-PI provides for an assessment of the autoregulatory state of the cerebral circulatory bed as being of normal, high or low vascular tone; it does not provide for a measure of the absolute quantity of blood flow. Cerebral vasodilation in response to inherently poor blood-flow delivery may adequately compensate in some cases, resulting in normalization of blood-flow volume. In our study, we interpret the presence of an abnormally low cerebrovascular resistance as a marker for the need of the brain to increase blood flow, which itself is an indicator of a pathological state. This argument will need to be revisited when correlative studies are performed to look at the relationship between fetal MCA-PI findings and later childhood neurocognitive outcomes.

We have described a pattern of change in cerebrovascular resistance over the course of gestation in SV fetuses with either aortic or pulmonary obstruction compared with normal fetuses. Although further research is needed to correlate fetal MCA Doppler flow patterns with neurodevelopmental outcomes, there appear to be profound differences in cerebral flow patterns in fetuses with SV-CHD based upon the presence or absence of aortic obstruction. These differences may lay the foundation for the findings regarding brain structure in the newborn and later neurocognitive function in the child. Further understanding of cerebral blood-flow patterns in CHD will allow improved counseling of expectant parents and will also provide an opportunity to identify fetuses who may benefit from prenatal therapy to improve cerebral perfusion. In fetuses with critical aortic stenosis and evolving

HLHS, fetal aortic valvuloplasty improves hemodynamics and generates antegrade aortic flow, but has not yet been demonstrated to alter cerebrovascular resistance²⁸. Relief of *in-utero* aortic stenosis in fetuses with evolving HLHS, augmentation of fetal cardiac output by pharmacological means or improvement in cerebral oxygen delivery through administration of supplemental maternal oxygen, are examples of strategies that may improve cerebral maturation and development, and may be worthy of further study through assessment of the cerebrovascular resistance.

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