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ORIGINAL RESEARCH

Impact of Maternal–Fetal Environment on Mortality in Children With Single Ventricle Heart Disease

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BACKGROUND: Children with single ventricle heart disease have significant morbidity and mortality. The maternal–fetal environment (MFE) may adversely impact outcomes after neonatal cardiac surgery. We hypothesized that impaired MFE would be associated with an increased risk of death after stage 1 Norwood reconstruction.

METHODS AND RESULTS: We performed a retrospective cohort study of children with hypoplastic left heart syndrome (and anatomic variants) who underwent stage 1 Norwood reconstruction between 2008 and 2018. Impaired MFE was defined as maternal gestational hypertension, preeclampsia, gestational diabetes, and/or smoking during pregnancy. Cox proportional hazards regression models were used to investigate the association between impaired MFE and death while adjusting for confounders. Hospital length of stay was assessed with the competing risk of in-hospital death. In 273 children, the median age at stage 1 Norwood reconstruction was 4 days (interquartile range [IQR], 3–6 days). A total of 72 children (26%) were exposed to an impaired MFE; they had more preterm births (18% versus 7%) and a greater percentage with low birth weights <2.5 kg (18% versus 4%) than those without impaired MFE. Impaired MFE was associated with a higher risk of death (hazard ratio [HR], 6.05; 95% CI, 3.59–10.21; $P<0.001$) after adjusting for age at surgery, Hispanic ethnicity, genetic syndrome, cardiac diagnosis, surgeon, and birth era. Children with impaired MFE had almost double the risk of prolonged hospital stay (HR, 1.95; 95% CI, 1.41–2.70; $P<0.001$).

CONCLUSIONS: Children exposed to an impaired MFE had a higher risk of death following stage 1 Norwood reconstruction. Prenatal exposures are potentially modifiable factors that can be targeted to improve outcomes after pediatric cardiac surgery.

Key Words: hypoplastic left heart syndrome ■ congenital heart disease ■ preeclampsia/pregnancy ■ fetal programming ■ fetal development ■ Stage 1 Norwood procedure ■ prenatal exposures

See Editorial by Limperopoulos et al.

Cardiovascular programming suggests that prenatal exposures can influence postnatal cardiac health.[1–3] Prenatally, the maternal–fetal environment (MFE) is defined by the mother's medical history, health and behavior during pregnancy, and environmental exposures. These maternal factors are thought to influence the development of the fetal cardiovascular system and fetal myocardium through placental pathways and angiogenic imbalances.[4–7] For example, population health studies suggest a relationship between maternal diabetes, hypertension, and preeclampsia and the risk of developing congenital heart disease (CHD).[8–11]

For children with confirmed CHD, prenatal characteristics can impact postoperative survival after congenital heart surgery.[12] Placental abnormalities and

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CLINICAL PERSPECTIVE

What Is New?

- For patients with single ventricle heart disease, important prenatal exposures include maternal characteristics such as gestational hypertension, preeclampsia, gestational diabetes, and/or smoking during pregnancy.
- Impaired maternal–fetal environment is associated with a substantially increased risk of mortality after stage 1 Norwood reconstruction surgery.

What Are the Clinical Implications?

- Prenatal exposures are important clinical factors that should be incorporated into prenatal patient/family counseling and preoperative risk stratification for this vulnerable population with single ventricle congenital heart disease.
- These potentially modifiable factors should be targeted in future quality improvement projects and research studies to improve outcomes after congenital heart surgery.

Nonstandard Abbreviations and Acronyms

CHOP	Children's Hospital of Philadelphia
HLHS	hypoplastic left heart syndrome
MFE	maternal–fetal environment
RMST	restricted mean survival times
S1R	stage 1 Norwood reconstruction

perturbations in the MFE can lead to poor growth and preterm birth.[13,14] Recent studies have demonstrated a relationship between the sequelae of an inhospitable MFE (ie, prematurity and growth restriction) and worse early outcomes after CHD surgery.[15–17] However, the associations between maternal prenatal risk factors and longer term pediatric postoperative outcomes are not well understood.

Hypoplastic left heart syndrome (HLHS) is a complex form of CHD in which the left ventricle is inadequate to provide systemic perfusion. Several anatomic variants of single ventricle heart disease with aortic arch obstruction have similar treatments to HLHS and are often grouped together. The management involves the following 3 surgeries: stage 1 Norwood reconstruction (S1R) followed by stage 2 superior cavopulmonary connection (Glenn or Hemi-Fontan), and stage 3 total cavopulmonary connection (Fontan). Although overall survival in children with CHD has improved in recent years, children with HLHS (and anatomic variants) still have a 35% chance of death by 6 years after S1R.[18] Efforts to improve these outcomes have largely focused on surgical technique and postoperative care, whereas prenatal characteristics have been less studied.[19] We hypothesized that exposure to an impaired MFE would be associated with an increased risk of death after S1R.

METHODS

The data, analytical methods, and study materials will not be made publicly available to other researchers. Institutional review board approval was obtained before initiating this study, and informed consent was waived. We performed a retrospective cohort study of children with single ventricle heart disease with aortic arch obstruction (ie, HLHS and anatomic variants) who underwent surgical intervention with S1R as a newborn at Children's Hospital of Philadelphia (CHOP). We included children who were followed prenatally by the CHOP Fetal Heart Program and born between June 2008 and June 2018 in either the CHOP Special Delivery Unit or Hospital of University of Pennsylvania Labor and Delivery Unit. A subset of patients (N=43) in this study was previously described.[12]

Exposures, Covariates, and Outcomes

The primary exposure of "impaired MFE" was defined by the presence of ≥1 of the following: gestational hypertension, preeclampsia, gestational diabetes, and/or maternal smoking during pregnancy.[20–22] This composite variable was defined a priori. The components were not analyzed individually because they were not mutually exclusive and to minimize multiple comparisons. Each of these conditions was routinely queried on clinical intake forms. Exposure status was defined by documentation in the mother's medical record by the CHOP Fetal Heart Program and Center for Fetal Diagnosis and Treatment, which relied on clinical definitions used by the mothers' treating physicians during the pregnancy. The presence of maternal prenatal smoking was based on patient self-report of cigarette smoking anytime during the affected pregnancy.

Several covariates were considered potential confounders based on their past associations with outcomes and clinical importance.[23,24] Maternal covariates included age, race and ethnicity, chronic hypertension, and pregestational diabetes. Fetal covariates included mode of conception, multiple gestation, and mode of delivery. Neonatal variables included sex, genetic syndrome, major extracardiac anomaly, cardiac diagnosis, age at surgery, and surgeon as a dichotomous variable. Birth era (2008–2013 versus 2013–2018) was included to account for improvements in postoperative outcomes over time. We did not consider postoperative

complications, such as cardiac arrest or extracorporeal membrane oxygenation, because these may be in the causal pathway. Potential mediators of interest included gestational age at birth, birth weight, and birth weight percentile. Birth weight percentile for full-term infants (≥37 weeks gestation) was calculated using the World Health Organization child growth standards, and birth weight percentile for preterm infants (<37 weeks gestation) was corrected for gestational age at birth using the Fenton growth chart.[25,26]

The primary outcome was overall survival from S1R surgery to death with censoring at April 2019 or the date of last known follow-up. We focused on overall survival instead of transplant-free survival because heart transplantation can be an important therapeutic option in this complex patient population. Secondary outcomes included 30-day survival, 1-year survival, and risk of prolonged length of hospital stay after S1R.

Data Collection

The maternal obstetrical records included outpatient visits in the maternal–fetal medicine clinic and inpatient hospital admissions for delivery. Our research coordinators collected exposure data from the maternal prenatal record by chart review while blinded to the child's postnatal course. Similarly, pediatric postnatal data were collected by the primary investigator while blinded to the maternal prenatal record. Postoperative outcomes were provided by the CHOP Cardiac Center Long-Term Follow-Up Program.[27] These clinical data were acquired through telephone and email surveys with families at predetermined postoperative intervals.

Statistical Analysis

Variables were compared between those with and without impaired MFE using the chi-squared test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. We first fit univariable Cox proportional hazards regression models to evaluate the association of impaired MFE with the risk of death. For the multivariable Cox model, covariates associated with a P value <0.20 in univariable analyses were initially included. We used stepwise variable selection with backward elimination to determine which covariates remained in the model; birth era and surgeon were forced into the final multivariable Cox regression model. The output of the final model was reported as an adjusted hazard ratio (HR) for impaired versus nonimpaired MFE with 95% CI and adjusted survival curves.

We repeated this analysis conditional on surviving for at least 30 days after surgery. In addition, we analyzed the difference in restricted mean survival times (RMST) between both groups at 30 days, 1 year, and 5 years.[28,29] The RMST difference was reported as a gain or loss in event-free survival time caused by the presence of impaired MFE.

Because postoperative deaths by 30 days and 1 year after S1R were not rare events, we calculated the adjusted risk ratios for these outcomes instead of using odds ratios from logistic regression models.[30] First, we set the follow-up time for the entire cohort to 1. Then, we fit Cox proportional hazards models using a robust variance estimator while adjusting for the same covariates.[31]

To assess differences in the length of initial hospital stay after S1R, we performed a time-to-event analysis for the risk of discharge and accounted for in-hospital death as a competing risk.[32,33] We used the Fine and Gray method to determine the subdistribution hazard function and reported the inverse of the HR, both with and without adjustments for the covariates included in the final multivariable Cox model.[34,35]

Causal mediation methods assessed the potential role of explanatory factors and underlying mechanisms. Mediators are variables that are considered to be an intermediate step (ie, causal pathway) between the exposure and outcome (Figure 1). Indirect effects were considered those mediated by the following 3 intermediate birth factors: gestational age at birth, birth weight, and birth weight percentile.[36–38] We used single mediator models and accounted for the same confounders that were included in the final multivariable Cox model.[39,40] The proportion of mediation was estimated by the ratio of indirect effect to total effect.

Analyses were conducted using Stata (version 14.2; StataCorp, College Station, TX) and R (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria). Tests were 2-sided, and α was 0.05.

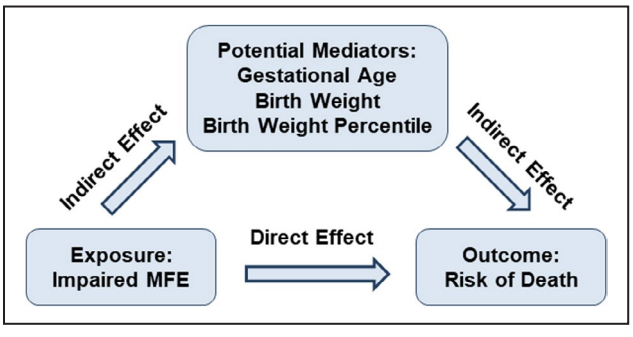

Figure 1. Framework for causal mediation analysis.
This schematic diagram demonstrates the causal mediation analysis that was performed to estimate the direct and indirect effects of impaired maternal–fetal environment (MFE) on the risk of death after Stage 1 Norwood reconstruction surgery. Indirect effects were considered those mediated by the following 3 intermediate birth factors: gestational age at birth, birth weight, and birth weight percentile.

RESULTS

A total of 273 children with HLHS (and anatomic variants) who underwent S1R surgery comprised the study sample (Table 1). The majority of children were boys and born full term (≥37 weeks gestation). Of the mothers, 10% had gestational hypertension, 7% had preeclampsia, 7% had gestational diabetes, and 11% smoked during pregnancy. Based on these components, 72 children (26%; 95% CI, 21%–32%) were prenatally exposed to an impaired MFE. The group with impaired MFE had lower gestational ages at birth (ie, more preterm births <37 weeks, 18% versus 7%; *P*=0.007) and lower birth weights (ie, greater percentage with low birth weight <2.5 kg, 18% versus 4%; *P*=0.003) than those without impaired MFE. The 2 groups were similar in cardiac diagnosis, genetic syndromes, age at S1R (median 4 days; interquartile range [IQR], 3–6 days), and birth era.

Postoperative details are reported in Table 2. In the 235 (86%) children who survived to hospital discharge, the median length of postoperative hospital stay was 20 days (IQR, 14–37 days). By group, the median length of hospital stay was 19 days (IQR, 13–32 days) for those without impaired MFE and 28 days (IQR, 17–46 days) for those with impaired MFE (*P*=0.03). The overall median follow-up time was 3.7 years (IQR, 1.1–7.0 years). A total of 6 (2%) children were lost to follow-up before completing 1 year of routine postoperative surveillance. Based on the final model, the estimated 1-year survival probability was 89% (95% CI, 84%–93%) for those without impaired MFE and 50% (95% CI, 38%–61%) for those with impaired MFE. Only 7 children underwent heart transplantation, 4 (2%) without impaired MFE and 3 (4%) with impaired MFE. The causes of death and indications for heart transplantation were relatively similar between both groups (Table S1).

In the total cohort, the unadjusted HR for death after S1R for those with versus without impaired MFE was 6.16 (95% CI, 3.76–10.10; *P*<0.001; Table 3). The results of the univariable Cox models for maternal, fetal, and neonatal characteristics with the risk of death are presented in Table S2. After adjusting for age at surgery, Hispanic or Latino ethnicity, genetic syndrome or chromosomal anomaly, cardiac diagnosis of unbalanced common atrioventricular canal, surgeon, and birth era, children who were prenatally exposed to an impaired MFE had a 6-fold greater risk of death than children without an impaired MFE (HR, 6.05; 95% CI, 3.59–10.21; *P*<0.001; Figure 2, Table 3).

The risk of death did not only reflect perioperative mortality. The effect estimate was similar (HR, 6.41; 95% CI, 3.42–12.00; *P*<0.001) in those who survived for at least 30 days after the initial S1R surgery, after adjustment for the same covariates. Children with impaired MFE had significantly lower mean survival time at 30 days (RMST, −3.6 days; 95% CI, −5.7 to −1.5; *P*<0.001), 1 year (RMST, −3.7 months; 95% CI, −5.0 to −2.5; *P*<0.001), and 5 years (RMST, −1.9 years; 95% CI, −2.4 to −1.3; *P*<0.001) after S1R.

Adjusted risk ratios were calculated to assess 30-day and 1-year postoperative mortality (Table 3). Children with impaired MFE were 5.5 times (95% CI, 2.2–13.8; *P*<0.001) more likely to die by 30 days after S1R than children without impaired MFE after adjustment for the same covariates. Children with impaired MFE were 4.1 times (95% CI, 2.6–6.6; *P*<0.001) more likely to die by 1 year after surgery after adjusting for covariates.

A time-to-discharge analysis was performed with the competing risk of in-hospital death. Children who were prenatally exposed to an impaired MFE had a greater risk of prolonged hospital stay after S1R with an unadjusted HR of 2.30 (95% CI, 1.67–3.15; *P*<0.001; Table 3). After taking covariates into account (age at surgery, Hispanic ethnicity, genetic syndrome, unbalanced common atrioventricular canal, surgeon, and birth era), the adjusted HR for prolonged initial hospital stay was 1.95 (95% CI, 1.41–2.70; *P*<0.001) in children with versus without impaired MFE (Figure 3).

Table 4 shows the analysis of potential mediators: gestational age at birth and birthweight (expressed as both an absolute value and a percentile). In single mediator models, they accounted for only 16.4% to 19.3% of the total effect of impaired MFE. For example, the indirect effect of impaired MFE mediated through gestational age was HR 1.23 compared with a direct effect of HR 5.13. Thus, gestational age and birth weight were not strong mediators of the association, suggesting other mechanisms for the effect of impaired MFE on postoperative mortality.

DISCUSSION

In children with HLHS (and anatomic variants), impaired MFE (defined by maternal gestational hypertension, preeclampsia, gestational diabetes, and/or smoking during pregnancy) was associated with a substantially increased risk of mortality after S1R surgery. This finding was independent of potential confounders, including other maternal prenatal characteristics and neonatal risk factors. Children prenatally exposed to an impaired MFE also had a greater risk of prolonged hospital stay after their initial surgery. This impact of impaired MFE on outcomes extended beyond the immediate postoperative period. Among those who survived for at least 1 month after S1R, impaired MFE still conferred a dramatically increased risk of death. These findings may have major clinical implications for prenatal counseling and preoperative risk stratification.

Table 1. Baseline Characteristics in Total Cohort and Group Comparisons

	Total cohort, N=273	Without impaired MFE, N=201	With impaired MFE, N=72	*P* value
Maternal characteristics				
Age at delivery, y	30 (25–34)	30 (25–34)	31 (25–34)	0.65
Advanced maternal age ≥35 y	57 (21)	40 (20)	17 (24)	0.51
Race and ethnicity				
White, non-Hispanic	171 (63)	132 (66)	39 (54)	0.25
Black, non-Hispanic	41 (15)	28 (14)	13 (18)	
Hispanic or Latino	44 (16)	28 (14)	16 (22)	
Other[†]	17 (6)	13 (7)	4 (6)	
Private insurance	182 (67)	141 (70)	41 (57)	0.053
Medicaid insurance	91 (33)	60 (30)	31 (43)	
Chronic hypertension	13 (5)	9 (4)	4 (6)	0.75
Gestational hypertension[*]	27 (10)	0	27 (38)	<0.001
Preeclampsia[*]	19 (7)	0	19 (26)	<0.001
Pregestational diabetes	7 (3)	2 (1)	5 (7)	0.02
Gestational diabetes[*]	19 (7)	0	19 (26)	<0.001
Cigarette smoking				
Current, anytime during pregnancy[*]	30 (11)	0	30 (42)	<0.001
Past, quit before pregnancy	24 (9)	19 (9)	5 (7)	
Marijuana use during pregnancy	10 (4)	5 (2)	5 (7)	0.14
Opioid use during pregnancy	5 (2)	2 (1)	3 (4)	0.04
Fetal characteristics				
Natural/spontaneous conception	259 (95)	193 (96)	66 (92)	0.15
In vitro fertilization	14 (5)	8 (4)	6 (8)	
Singleton gestation	262 (96)	196 (98)	66 (92)	0.04
Twins gestation	11 (4)	5 (2)	6 (8)	
Oligohydramnios	23 (8)	19 (9)	4 (6)	0.46
Polyhydramnios	10 (4)	7 (3)	3 (4)	0.73
Fetal hydrops	2 (1)	2 (1)	0	1.0
Location of delivery				
Children's Hospital of Philadelphia	248 (91)	182 (91)	66 (92)	0.78
Hospital of the University of Pennsylvania	25 (9)	19 (9)	6 (8)	
Vaginal delivery	147 (54)	111 (55)	36 (50)	0.45
Cesarean section	126 (46)	90 (45)	36 (50)	
Neonatal characteristics				
Birth era, June 2008 to May 2013	140 (51)	102 (51)	38 (53)	0.77
Birth era, June 2013 to June 2018	133 (49)	99 (49)	34 (47)	
Male sex	166 (61)	124 (62)	42 (58)	0.62
Gestational age at birth, wk	39.0 (38.3–39.3)	39.0 (38.7–39.4)	38.3 (37.1–39.0)	<0.001
Preterm birth <37 wk gestation	27 (10)	14 (7)	13 (18)	0.007
Birth weight, kg	3.2 (2.9–3.5)	3.2 (2.9–3.6)	3.1 (2.6–3.4)	0.002
Low birth weight, <2.5 kg	22 (8)	9 (4)	13 (18)	<0.001
Birth weight, percentile	44 (23–72)	47 (26–74)	36 (13–58)	0.01
Small for gestational age, birth weight <10th percentile	35 (13)	21 (10)	14 (19)	0.050
Large for gestational age, birth weight >10th percentile	22 (8)	16 (8)	6 (8)	0.92
Genetic syndrome or chromosomal anomaly	32 (12)	22 (11)	10 (14)	0.51
Major extracardiac anomaly	43 (16)	28 (14)	15 (21)	0.17

(*Continued*)

Table 1. Continued

	Total cohort, N=273	Without impaired MFE, N=201	With impaired MFE, N=72	*P* value
Cardiac diagnosis				
Hypoplastic left heart syndrome	215 (79)	158 (79)	57 (79)	0.98
Unbalanced common atrioventricular canal	23 (8)	16 (8)	7 (10)	
Double outlet right ventricle, mitral atresia	14 (5)	11 (5)	3 (4)	
Double inlet left ventricle	10 (4)	8 (4)	2 (3)	
Tricuspid atresia, aortic arch hypoplasia	8 (3)	6 (3)	2 (3)	
Other†	3 (1)	2 (1)	1 (1)	
Restrictive atrial septum	41 (15)	29 (14)	12 (17)	0.65
Severe preoperative AV valve regurgitation	18 (7)	12 (6)	6 (8)	0.34
Age at initial surgery, d	4 (3–6)	4 (3–6)	4 (3–6)	0.21
Blalock-Taussig shunt	158 (58)	116 (58)	42 (58)	0.86
Sano right ventricle to pulmonary artery shunt	112 (41)	82 (41)	30 (42)	

All values are reported as number (percentage) or median (interquartile range). AV indicates atrioventricular; and MFE, maternal–fetal environment.
* The 4 components of the composite exposure variable for impaired MFE are indicated.
†Other (includes Asian, Pacific Islander, and mixed race)

Our study hypothesis was predicated on the cumulative impact of maternal medical conditions and exposures on the fetus with long-term consequences that may impact postnatal postoperative outcomes. Recent studies suggest a shared developmental pathway between the placenta and fetal heart.[41–43] Placentas from pregnancies carrying fetuses with CHD often have adverse changes, such as vascular malperfusion or low placental/birth weight ratio.[44,45] A recent study by Rychik et al found that placental thrombosis, abnormal chorangiosis, and infarction were common in newborns with CHD.[46] Umbilical artery pulsatility index reflects placental vascular resistance and predicts intrauterine growth restriction.[47–49] Gaynor et al showed that the umbilical artery pulsatility index was higher and placental weight was lower for those with an impaired MFE.[12]

Imaging modalities and laboratory criteria are not yet able to consistently detect or quantify placental insufficiency and dysfunction in utero; however, a pregnancy resulting in preterm birth or low birth weight may reflect poor placental health. In this study, we explored gestational age and birth weight as intermediate (indirect) pathways of the association between impaired MFE and mortality. We found that these potential mediators did not account for a large proportion of the total effect, suggesting other mechanisms to explain the adverse impact of impaired MFE on survival. The underlying pathophysiologic connection between this maternal-placental-fetal axis of interaction may be related to shared molecular signaling and regulatory pathways.[50] For example, Llurba et al found that biomarkers of chronic hypoxia, antioxidant activity, and angiogenic factor expression of VEGF (vascular endothelial growth factor) were significantly increased in heart tissue from fetuses with CHD compared with controls.[5] Furthermore, PGF (placental growth factor) in maternal plasma was significantly decreased in pregnancies with CHD. They speculated that placental

Table 2. Postoperative Details and Additional Surgeries

	Total cohort, N=273	Without impaired MFE, N=201	With impaired MFE, N=72	*P* value
Stage 1 Norwood procedure				
Survived to initial hospital discharge	235 (86)	187 (93)	48 (67)	<0.001
Length of postoperative hospital stay from surgery to discharge home, d	20 (14–37)	19 (13–32)	28 (17–46)	0.03
Additional planned surgeries				
Stage 2 procedure, bidirectional Glenn, Hemi-Fontan, Kawashima	218 (80)	182 (91)	36 (50)	<0.001
Age at Stage 2 procedure, mo	4.5 (4.1–5.1)	4.5 (4.1–5.1)	4.6 (4.3–5.3)	0.33
Stage 3 procedure, extracardiac Fontan, lateral tunnel Fontan, hepatic vein inclusion*	146 (53)	126 (63)	20 (28)	<0.001
Age at stage 3 procedure, y*	2.9 (2.5–3.3)	2.9 (2.6–3.3)	2.7 (2.4–3.6)	0.69

All values are reported as number (percentage) or median (interquartile range). MFE indicates maternal–fetal environment.
*Patients born from 2016 to 2018 may still be alive with Glenn physiology and have not yet reached the appropriate age range (2–4 years old) for Fontan completion.

Table 3. Effect of Impaired Maternal–Fetal Environment After Stage 1 Norwood Procedure

Postoperative outcome	HR or RR	95% CI	*P* value
Mortality, overall risk of death			
Unadjusted HR	6.16	3.76–10.10	<0.001
Adjusted HR	6.05	3.59–10.21	<0.001
30-d mortality			
Unadjusted RR	6.98	2.81–17.33	<0.001
Adjusted RR	5.48	2.17–13.82	<0.001
1-y mortality			
Unadjusted RR	4.57	2.89–7.22	<0.001
Adjusted RR	4.10	2.56–6.56	<0.001
Risk of prolonged hospital stay after stage 1 Norwood reconstruction			
Unadjusted HR	2.30	1.67–3.15	<0.001
Adjusted HR	1.95	1.41–2.70	<0.001

Statistical models were adjusted for age at surgery, Hispanic or Latino ethnicity, genetic syndrome or chromosomal anomaly, cardiac diagnosis of unbalanced common atrioventricular canal, surgeon, and birth era. HR indicates hazard ratio; and RR, risk ratio.

hypoxia attributed to abnormal angiogenesis may have led to abnormal cardiac development. We hypothesize that placental insufficiency and these angiogenic/antiangiogenic imbalances may be exacerbated in the setting of an impaired MFE and could potentially be precursors to increased mortality.

The design of this study differed from a recent analysis of 43 children with HLHS from our center.[12] The composite exposure in the prior study included preterm birth and small for gestational age, which we conceptualized as consequences of an impaired MFE in this study. The design of our study also differed from a recent population-based study that examined a heterogeneous CHD cohort from an administrative database and combined small for gestational age status at birth with prenatal exposures.[51] In our current study, we refined the definition of an impaired MFE (by focusing on maternal prenatal characteristics), added exposure data on gestational diabetes and maternal smoking (potentially modifiable), and considered both intermediate birth factors (prematurity and birth weight) as possible causal mediators.

The association of Hispanic ethnicity with increased mortality after cardiac surgery for CHD has previously been described in the literature and is potentially a surrogate for other risk factors.[52] Peyvandi et al explored the socioeconomic mediators of racial and ethnic disparities in CHD outcomes.[53] In their analysis cohort of 1315 patients, Hispanic ethnicity was associated with a poor outcome (crude odds ratio, 1.72). In their causal

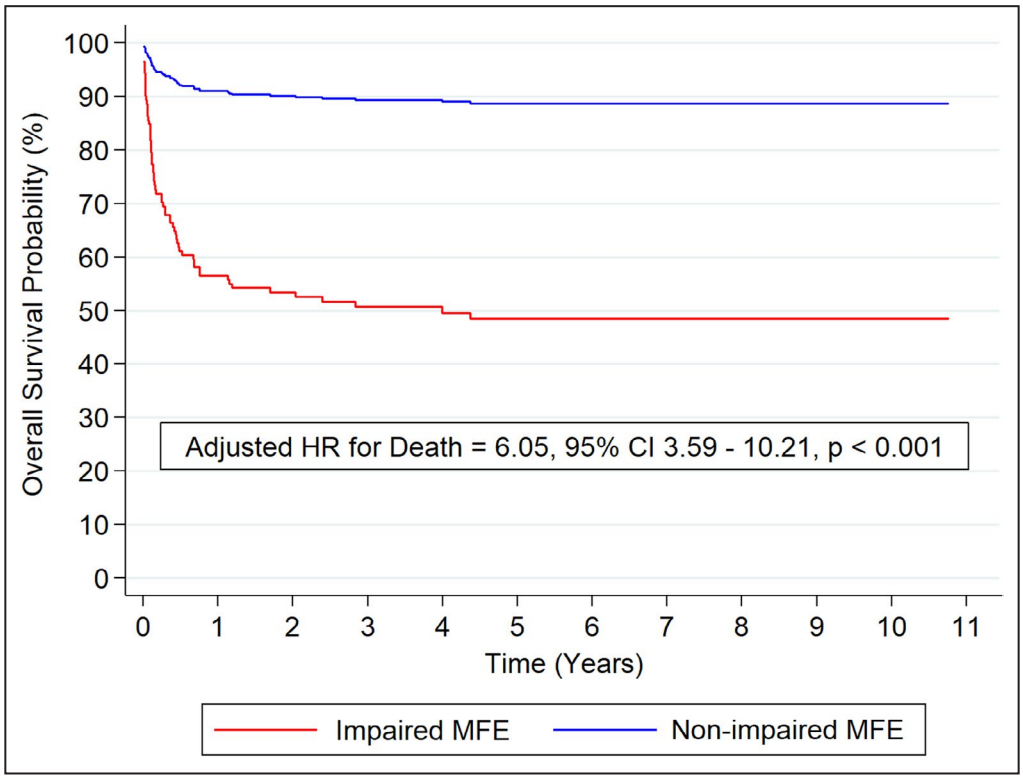

Figure 2. Adjusted survival curves for postoperative mortality after stage 1 Norwood procedure. These adjusted survival curves consider the median age at initial surgery (4 days old), non-Hispanic ethnicity, no genetic syndrome, no unbalanced common atrioventricular canal, the most common surgeon, and birth era (June 2008–May 2013). HR indicates hazard ratio; and MFE, maternal–fetal environment.

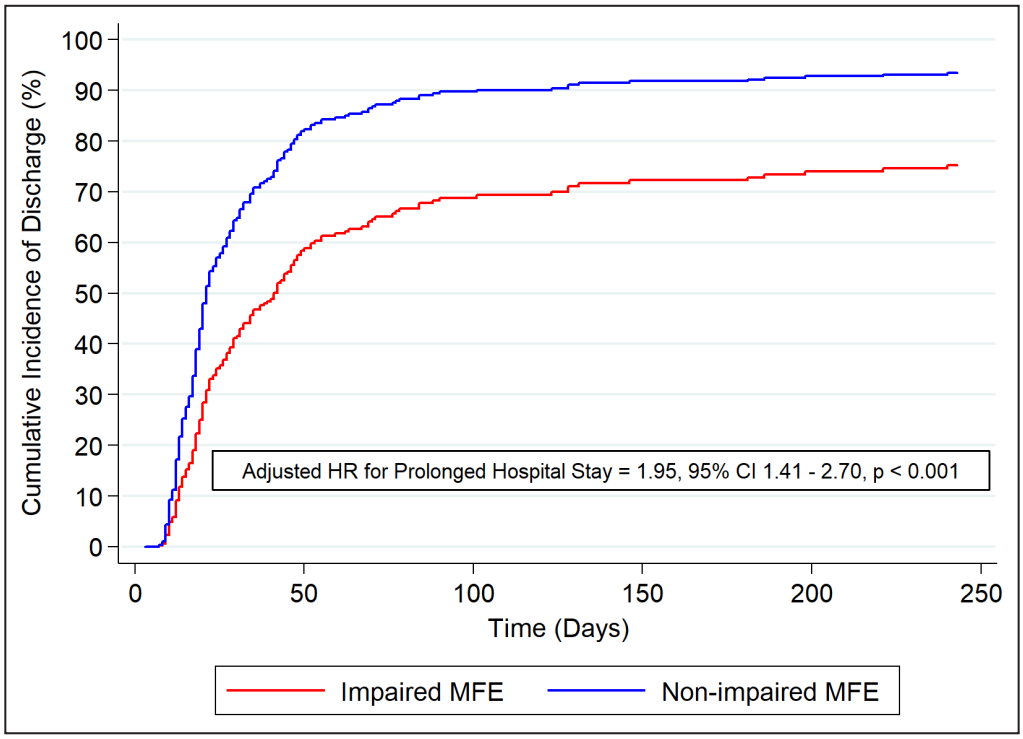

Figure 3. Adjusted competing risk model for time to discharge after stage 1 Norwood reconstruction.
These adjusted cumulative incidence curves consider the median age at initial surgery (4 days old), non-Hispanic ethnicity, no genetic syndrome, no unbalanced common atrioventricular canal, the most common surgeon, and birth era (June 2008–May 2013). HR indicates hazard ratio; and MFE, maternal–fetal environment.

mediation analysis, lower maternal education level and public insurance status explained 33% and 28% of the association, respectively. These potential mediators (maternal education level and public insurance status) may impact patient/family resources, reliable access to care, and health literacy (such as the ability to understand medication administration instructions at home), which may then influence patient outcomes. Further exploration of the social determinants of health, racial and ethnic disparities, and the relationship between socioeconomic status and impaired MFE could lead to a more comprehensive and holistic understanding of the prenatal environment.

The objective of this research was to identify maternal–fetal dyads at increased risk of postoperative morbidity and mortality. Current methods of preoperative risk stratification do not fully account for the patient-level variability that exists in CHD outcomes.[54] The earlier identification of maternal and fetal characteristics linked to adverse outcomes could lead to individualized counseling and the development of novel therapies for this high-risk population.

Table 4. Results of Causal Mediation Analysis

Mediator	Total effect of impaired MFE on mortality	Direct effect of impaired MFE on mortality	Indirect effect of impaired MFE (through mediator)	Percent mediation (indirect/total)
Gestational age, wk	HR, 6.36 95% CI, 3.82–10.54 *P*<0.001	HR, 5.13 95% CI, 3.01–8.73 *P*<0.001	HR, 1.23 95% CI, 1.06–1.50 *P*=0.03	19.3
Birth weight, kg	HR, 6.36 95% CI, 4.00–9.96 *P*<0.001	HR, 5.94 95% CI, 3.51–10.03 *P*<0.001	HR, 1.07 95% CI, 0.99–1.21 *P*=0.22	16.8
Birth weight percentile	HR, 6.15 95% CI, 3.63–10.43 *P*<0.001	HR, 6.07 95% CI, 3.60–10.24 *P*<0.001	HR, 1.01 95% CI, 0.94–1.11 *P*=0.64	16.4

HR indicates hazard ratio; and MFE, maternal–fetal environment.

The strengths of this study are the cohort size, data completeness, and long-term follow-up. The potential limitations of this study include selection bias, misclassification bias, and unmeasured confounding. To be included, patients had to be referred to our center prenatally and undergo S1R surgery. We did not include patients with in utero fetal demise, termination of pregnancy, or neonatal comfort care. Of note, children with a prenatal diagnosis of HLHS and planned surgical intervention rarely died before surgery. If present, this selection bias would likely have skewed our results toward the null. Misclassification bias was possible because our exposure was based on clinical diagnoses made by the mother's physicians. Given the retrospective nature of this study, quantitative data were not always available via chart review. If present, misclassification would likely have been nondifferential (biasing toward the null) because prenatal documentation in the mother's medical record was completed before neonatal cardiac surgery was performed and likely did not vary based on the outcome. Furthermore, the mother's prenatal and child's postnatal data collection were conducted by different members of the research team while blinded to other clinical data, thus reducing the chance of bias.

There are possible limitations inherent to causal mediation analyses involving perinatal epidemiology and birth weight.[55,56] The specific biological mechanisms by which these mediators exert their impact has not yet been delineated. Although gestational age and birth weight are still considered important, there are additional unexplained factors that also contribute to the association of interest. Therefore, causal mediation estimates may potentially be biased because of unmeasured confounding.[57,58] However, the alternative method of including these mediators as covariates in a multivariable model would "adjust away" their potentially meaningful relationship. Our study results are generalizable to other centers because most patients with HLHS (and anatomic variants) are treated in a similar fashion at specialized centers. Nevertheless, unique center-specific effects and different patient populations may have affected the results. Finally, we examined a composite exposure variable for impaired MFE that was defined a priori based on factors previously demonstrated to exert influence on placental and fetal health. We intentionally did not focus on individual components because they do not exert their influence in isolation.

Future research endeavors should provide a more detailed characterization of the postoperative recovery period and focus on specific organ systems that may be disproportionately impacted by an impaired MFE. In addition, multicenter studies should be conducted to develop a more comprehensive understanding of the MFE.

CONCLUSIONS

Children with HLHS (and anatomic variants) with impaired MFE had a higher risk of death following S1R surgery after adjustment for potential confounders. The influence of impaired MFE on mortality extended beyond the immediate postoperative period. This association was not substantially mediated by gestational age or birth weight. Maternal characteristics are an important prenatal exposure and need to be taken into account when risk stratifying this vulnerable patient population. Focusing on potentially modifiable factors could shift prenatal counseling toward a personalized medicine approach of treating the maternal–fetal dyad before delivery to optimize pediatric cardiac surgery outcomes.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Death or Transplantation

Primary Cause of Death or Indication for Heart Transplantation	Total Cohort	Without Impaired MFE	With Impaired MFE
Overall Deaths	N=67	N=26	N=41
Acute Cardiac Arrest	21 (31)	7 (27)	14 (34)
Multiple Organ Dysfunction Syndrome (MODS)	13 (19)	8 (31)	5 (12)
Coagulopathy/Bleeding	7 (10)	2 (8)	5 (12)
Thrombosis (Confirmed BT Shunt Occlusion)	6 (9)	2 (8)	4 (10)
Respiratory Failure	4 (6)	2 (8)	2 (5)
Infection	3 (4)	1 (4)	2 (5)
Stroke	2 (3)	0 (0)	2 (5)
Genetic or Non-Cardiac Congenital Anomaly	1 (1)	0 (0)	1 (2)
Unknown (Death at Home or Outside Hospital)	10 (15)	4 (15)	6 (15)
Heart Transplantations	N=7	N=4	N=3
Severe Ventricular Dysfunction	4	2	2
Severe Atrioventricular (AV) Valve Regurgitation	1	1	
Pulmonary Vein Stenosis and Pulmonary Hypertension	1		1
Plastic Bronchitis	1	1	

Notes: All values are reported as numbers of subjects (percentage).

Abbreviations: Maternal-Fetal Environment (MFE); Blalock-Taussig (BT)

Table S2. Univariable Survival Analysis.

	Hazard Ratio for Risk of Death	95% Confidence Interval	P-Value
Maternal Characteristics			
Age at Delivery (Years)	0.99	0.95 - 1.03	0.66
Advanced Maternal Age ≥ 35 Years	1.12	0.63 - 1.99	0.70
Race/Ethnicity			
White, Non-Hispanic White	---Reference---	---Reference---	---
Black, Non-Hispanic Black	1.38	0.70 - 2.72	0.36
Hispanic or Latino	2.39	1.35 - 4.24	0.003
Other	1.30	0.46 - 3.66	0.62
Hispanic vs. Non-Hispanic Ethnicity	2.20	1.28 - 3.78	0.004
Medicaid vs. Private Insurance	1.31	0.80 - 2.14	0.28
Chronic Hypertension	0.96	0.30 - 3.07	0.95
Gestational Hypertension*	3.49	1.96 - 6.21	< 0.001
Preeclampsia*	4.92	2.68 - 9.06	< 0.001
Pre-Gestational Diabetes	2.36	0.74 - 7.51	0.15
Gestational Diabetes*	5.84	3.23 - 10.56	< 0.001
Marijuana Use During Pregnancy	1.80	0.65 - 4.94	0.26
Opioid Use During Pregnancy	0.86	0.12 - 6.19	0.88
Cigarette Smoking During Pregnancy*	2.94	1.67 - 5.16	0.001
Fetal Characteristics			
In-Vitro Fertilization vs. Natural Conception	1.18	0.43 - 3.24	0.75
Twin vs. Singleton Gestation	1.79	0.65 - 4.93	0.26
Oligohydramnios	1.34	0.61 - 2.92	0.47
Polyhydramnios	2.06	0.75 - 5.66	0.16
Delivery at CHOP vs. HUP	0.85	0.39 - 1.87	0.69
Cesarean vs. Vaginal Delivery	1.09	0.67 - 1.76	0.73
Neonatal Characteristics			
Birth Era (2008-2013 vs. 2013-2018)	1.34	0.82 - 2.19	0.24
Male vs. Female Sex	0.75	0.47 - 1.22	0.25
Gestational Age at Birth (Weeks)	0.69	0.59 - 0.79	< 0.001
Preterm Birth < 37 Weeks Gestation	2.14	1.12 - 4.08	0.02
Birth Weight (BW in Kilograms)	0.51	0.32 - 0.82	0.006
Low Birth Weight < 2.5 Kilograms	2.45	1.25 - 4.79	0.009
Birth Weight Percentile (%)	0.99	0.99 - 1.00	0.20
Small for Gestational Age with BW < 10th %	1.82	0.99 - 3.34	0.053
Large for Gestational Age with BW > 10th %	1.11	0.48 - 2.56	0.82
Genetic Syndrome or Chromosomal Anomaly	2.39	1.32 - 4.30	0.004
Major Extracardiac Anomaly	2.48	1.45 - 4.21	0.001
Cardiac Diagnosis			
Hypoplastic Left Heart Syndrome	---Reference---	---Reference---	---
Unbalanced Common Atrioventricular Canal (CAVC)	1.99	1.02 - 3.92	0.045
Double Outlet Right Ventricle, Mitral Atresia	0.54	0.13 - 2.23	0.40
Other	0.28	0.04 - 2.06	0.21
Unbalanced CAVC vs. All Other Cardiac Diagnoses	2.22	1.14 – 4.36	0.02
Restrictive Atrial Septum	1.56	0.49 – 4.96	0.45
Severe Preoperative Valve Regurgitation	1.56	0.49 – 4.96	0.45
Age at Initial Surgery (Days)	1.07	1.02 - 1.13	0.01
Sano vs. Blalock-Taussig Shunt	0.93	0.59 - 1.49	0.77

Notes: *Indicates the 4 components of the composite exposure variable for impaired maternal-fetal environment
Abbreviations: Children's Hospital of Philadelphia (CHOP); Hospital of the University of Pennsylvania (HUP)