ORIGINAL RESEARCH

Impaired Fetal Environment and Gestational Age: What Is Driving Mortality in Neonates With Critical Congenital Heart Disease?

Martina A. Steurer, MD, MAS; Shabnam Peyvandi, MD, MAS; Rebecca J. Baer, MPH; Scott P. Oltman, MS; Christina D. Chambers, PhD; Mary E. Norton, MD; Kelli K. Ryckman, PhD; Anita J. Moon-Grady, MD; Roberta L. Keller, MD; Stephen C. Shiboski, PhD; Laura L. Jelliffe-Pawlowski, PhD

***Background*—**Infants with critical congenital heart disease (CCHD) are more likely to be small for gestational age (SGA) or born to mothers with maternal placental syndrome. The objective of this study was to investigate the relationship between maternal placental syndrome, SGA, and gestational age (GA) on 1-year mortality in infants with CCHD.

***Methods and Results*—**In a population-based administrative database of all live-born infants in California (2007–2012) we identified all infants with CCHD without chromosomal anomalies. Our primary predictor was an impaired fetal environment (IFE), defined as presence of maternal placental syndrome or SGA. We calculated hazard ratios to quantify the association between different components of IFE and 1-year mortality and conducted a causal mediation analysis to assess GA at birth as a mediator. We identified 6863 infants with CCHD. IFE was present in 25.1%. Infants with IFE were more likely to die than infants without IFE (16.6% versus 11.1%; hazard ratios 1.55, 95% CI 1.34–1.78). Only SGA (hazard ratios 1.76, 95% CI 1.50–2.05) and placental abruption (hazard ratios 1.70, 95% CI 1.17–2.48) were significantly associated with mortality; preeclampsia and gestational hypertension had no significant association with mortality. The mediation analysis showed that 32.8% (95% CI 24.9–47.0%) of the relationship between IFE and mortality is mediated through GA.

***Conclusions*—**IFE is a significant contributor to outcomes in the CCHD population. SGA and placental abruption are the main drivers of postnatal mortality while other maternal placental syndrome components had much less of an impact. Only one third of the effect between IFE and mortality is mediated through GA. **(*J Am Heart Assoc*. 2019;8:e013194. DOI: 10.1161/JAHA.119.013194.)**

Key Words: congenital heart disease • fetal environment • maternal placental syndrome • small for gestational age

Traditionally, outcomes research in critical congenital heart disease (CCHD) has focused on specific anatomical details, surgical techniques, and postnatal complications.[1] More recently, literature has emerged showing that other infant factors impact mortality and morbidity in this population.[2–5] For example, gestational age (GA) independently affects mortality, postoperative complications, and neonatal morbidity after adjusting for severity of CHD. Even early-term infants (GA 37–38 weeks) are at higher risk for poor outcomes compared with full-term infants (GA ≥39 weeks).[2,3] Our group and others have shown that fetal growth impacts mortality in infants with CCHD,[4,5] suggesting that the fetal period is a critical contributor to outcomes in this population. To this point, Gaynor et al found that an impaired fetal environment (IFE) was a strong risk factor for early- and intermediate-term outcomes in neonates undergoing cardiac surgery.[6] The definition of IFE included maternal characteristics such as preeclampsia or gestational hypertension—markers of placental function, as well as infant characteristics such as prematurity or small for gestational age (SGA).

The placenta plays a crucial role in maternal–fetal health. Maternal placental syndrome (MPS) is defined as maternal preeclampsia, gestational hypertension, or placental abruption[7] and signifies impaired placental function. It occurs as a consequence of abnormal placental vessel formation.[7–9] MPS,

From the Departments of Pediatrics (M.A.S., S.P., A.J.M.-G., R.L.K.), Epidemiology and Biostatistics (M.A.S., S.P., S.P.O., S.C.S., L.L.J.-P.), and Obstetrics, Gynecology, and Reproductive Sciences (R.J.B., M.E.N.), University of California San Francisco, San Francisco, CA; Department of Pediatrics, University of California San Diego, La Jolla, CA (R.J.B., C.D.C.); Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA (K.K.R.).

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Correspondence to: Martina A. Steurer, MD, MAS, UCSF Department of Pediatrics, 550 16th St, 5th Floor, San Francisco, CA 94143. E-mail: martina.steurermuller@ucsf.edu

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Clinical Perspective

What Is New?

- An impaired fetal environment consisting of small for gestational age or maternal placental syndrome consisting of placental abruption, maternal diabetes mellitus, or maternal hypertensive disorders are significant contributors to mortality in neonates with critical congenital heart disease.
- Only one third of this effect between impaired fetal environment and mortality is mediated through gestational age.

What Are the Clinical Implications?

- This information enhances the understanding of the complicated interplay between maternal factors and mortality in neonates with critical congenital heart disease and helps to identify infants at high risk for mortality.

and more specifically preeclampsia, is hypothesized to affect the developing fetus via poor fetal growth[7] and increased risk of congenital heart disease.[10] Not surprisingly, both MPS and poor fetal growth are risk factors for prematurity.[11] Thus, a complex relationship exists between placental factors, fetal growth and development, perinatal factors (ie, length of gestation), and long-term outcomes in offspring, particularly as it relates to CCHD.

While we previously showed that fetal growth restriction was associated with mortality in infants with CCHD, the current study's objective is to investigate the interplay between MPS, SGA (as a surrogate marker for fetal growth restriction), and the intersection with length of gestation on 1-year mortality in infants with CCHD.

Methods

The data use agreement with the California Office of Statewide Health Planning and Development prohibits distribution of any patient-level data; thus, the data used for this study are not made publicly available. Data can be requested from Office of Statewide Health Planning and Development (https://www.oshpd.ca.gov/HID/HIRC/index.html) by qualified researchers for a fee. All other analytic methods and study materials are available upon reasonable request from the corresponding author. All California licensed hospitals report to Office of Statewide Health Planning and Development and the office maintains a database including detailed information on infant characteristics derived from hospital discharge records (birth hospitalization and readmissions), birth and death certificates, from birth to 1 year of age. This information is linked by Office of Statewide Health Planning and Development to maternal characteristics derived from hospital discharge records from up to 9 months before birth of the infant. Details about the linkage process can be found here (https://oshpd.ca.gov/data-and-reports/request-data/tools-resources). The database contains 3 160 268 linked live births from the years 2007 to 2012. The file provides diagnosis and procedure codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*).[12] We previously used the same database and study cohort to investigate the effect of GA and fetal growth on mortality and severe neonatal morbidity in infants with CCHD.[3,4]

We included all live-born infants with GA 22 to 42 completed weeks and excluded newborns with known chromosomal abnormalities (defined as presence of *ICD-9* codes 758.0–758.9). Infants with CCHD were identified by *ICD-9-CM* diagnostic and procedure codes present in the birth, transfer, or readmission records. CCHD was defined as 1 or a combination of the following lesions: hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, transposition of the great arteries (TGA), tricuspid atresia, truncus arteriosus (TA), total anomalous venous return, coarctation of the aorta, double-outlet right ventricle, Ebstein anomaly, and single ventricle.[13,14] Additionally, we included pulmonary and aortic stenosis requiring intervention during the first year of life.[14] Two investigators (MAS and AMG) reviewed all cases according to a proposed framework based on morphogenetically similar developmental mechanisms[13,15] to ensure correct classifications of infants with multiple *ICD-9-CM* codes. Final diagnosis was reached by consensus. Infants with multiple CCHD codes consistent with heterotaxy were also classified as CCHD.

The outcome assessed was 1-year mortality. The method of death ascertainment was death certificate or hospital discharge status of death for the years 2007 to 2011 and hospital discharge status of death for 2012. The primary predictor was presence of IFE defined as maternal preeclampsia or eclampsia (*ICD-9* code 642.4–642.7), pre-existing or gestational hypertension (*ICD-9* code 401–405, 642.1–3), placental abruption (*ICD-9* code 641.2) in the maternal record of the birth hospitalization or small for GA offspring (birth weight $\leq$10th percentile for GA) based on birth weight and GA on the birth certificate.

Incidences of different maternal and fetal conditions were compared between infants with and without CCHD using χ^2 tests for categorical variables. We used Cox proportional-hazards regression methods to estimate unadjusted (marginal) and adjusted hazard ratios (HR) with 95% CI for our primary outcome by IFE and by each of its components. We adjusted for severity of CCHD by modified risk adjustment in congenital heart surgery (RACHS) because it was not possible

to use in its original form because of the lack of specific surgical details needed for classification. In brief, we used 6 severity groups modified from RACHS[16] as further detailed in Steurer et al.[3] We also performed analyses for selected types of CCHD (ie, single ventricle, TGA, and truncus arteriosus [TA]).

To understand the complex interplay between IFE, GA at birth, and mortality, a causal mediation analysis was performed. The conceptual model is demonstrated in Figure 1 and proposes that the effects of IFE on mortality are mediated by GA. We considered GA as a continuous measure (in weeks). Valid conclusions about both the direct effect of IFE on mortality (ie, the effect not mediated by GA) as well as the indirect effect via the GA pathway require that relevant variables that potentially confound both pathways are accounted for in the analysis. We considered CCHD severity measured by modified RACHS score as a potential confounder of the relationship between preterm birth/GA and mortality, as illustrated in Figure 1. Furthermore, valid estimates of the estimated proportion of the overall effect that is accounted for by mediation via GA must be based on an estimation approach appropriate for survival outcomes. Our analysis was conducted using the Mediation package in Stata® (Stata Version 14.2; StataCorp LLC, College Station, TX) and the Mediation package in R® (R Version R 3.5.3, R Core Team 2019), which both require separate models for the relationship between the primary predictor and both the mediator and the outcome.[17,18] These were specified as linear regression for the relationship between IFE and GA, and Weibull survival regression for the relationship between IFA, GA, and the mortality outcome. The latter also controlled for the modified RACHS score as a possible confounder (Figure 1B). In addition, we performed an additional analysis to examine the sensitivity of the estimated mediated effect based on the continuous GA measure to varying degrees of possible uncontrolled confounding. Because the latter analysis is not available for censored survival outcomes, the relationship between mortality, IFA, and GA was represented by a probit regression model.

As a final step in our investigation of the interplay between IFE and GA, we stratified by GA group (preterm <37 weeks, early term 37–38 weeks, and term >38 weeks) and calculated GA specific crude and adjusted HR.

A P value of <0.05 was considered significant for all analyses. All analyses other than the mediation analysis were performed by using Stata version 14.2 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The study was approved by the Committee for the Protection of

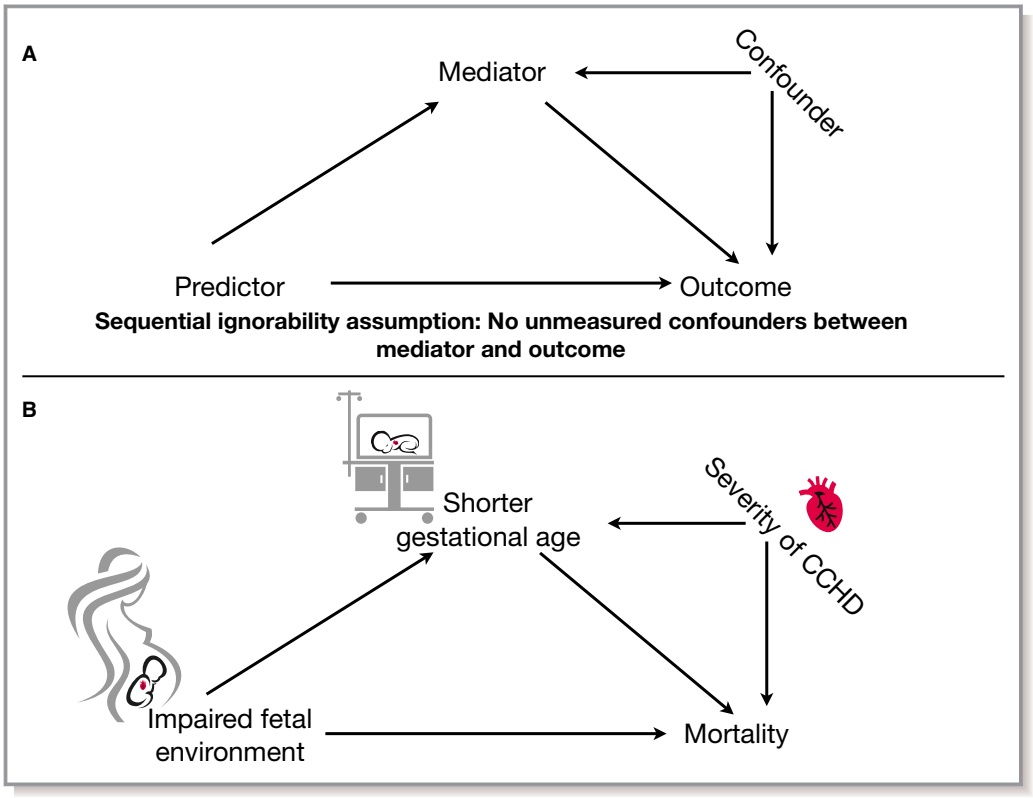

Figure 1. Directed acyclic graph illustrates the relationship between different variables and mortality. **A**, Generic definition of a mediator. **B**, Adapted to current study. CCHD indicates critical congenital heart disease.

Table 1. Incidence of Indicators of IFE in Infants With and Without CCHD

	CCHD (n=6863)	No CCHD* (n=2 974 681)
IFE, %	25.1	14.8
MPS, %	11.7	7.8
Maternal pre- or eclampsia, %	5.8	3.7
Hypertension, %	4.1	3.3
Placental abruption, %	2.0	1.0
SGA, %	16.3	8.1
SGA+MPS, %	2.9	1.2
Preterm birth, %	17.9	8.3

CCHD indicates critical congenital heart disease; IFE, impaired fetal environment defined as MPS or SGA; MPS, maternal placental syndrome defined as 1 or more of the following: maternal preeclampsia, eclampsia, gestational or pre-existing hypertension or placental abruption; SGA, small for gestational age.
*All differences between CCHD and no CCHD are significant with $P<0001$.

Human Subjects within the California Health and Human Services Agency, thus the informed consent requirement was waived.

Results

In our cohort of 6863 infants with CCHD, 25.1% had IFE compared with 14.8% in infants without CCHD (n=2 974 681, $P<0.0001$). Both MPS and SGA (components of IFE) were individually significantly higher in the CCHD group than in newborns without CCHD (11.7 versus 7.8% for MPS and 16.3 versus 8.1% for SGA, $P<0.0001$) (Table 1). The incidence of IFE was highest in newborns with TA (n=180, 30%) and lowest in the TGA group (n=844, 21.9%) (Table 2). 16.3% of infants with CCHD were born SGA, only 2.9% were SGA and had a mother with MPS (Table 1). We performed the same analysis and restricted maternal data to information during the delivery hospitalization (and not the information available from the previous 9 months), which showed very similar results (data not shown).

The overall 1-year mortality rate in infants with CCHD was 12.5%. The probability of death was 16.6% in infants with IFE compared with 11.1% in infants with CCHD without IFE; this difference remained statistically significant after adjusting for severity of CCHD (adjusted HR 1.61, 95% CI 1.40–1.86). When investigating the association of each individual component of IFE with mortality, only placental abruption (adjusted HR 1.94, 95% CI 1.33–2.83) and SGA (adjusted HR 1.77, 95% CI 1.52–2.07) were significantly associated with death within the first year of life while maternal pre- or eclampsia or maternal hypertension did not have a significantly higher 1-year mortality (Table 3). Mortality did not differ between infants who were SGA and had a mother with MPS (SGA+MPS, mortality 18%) versus infants who were SGA without a diagnosis of MPS (SGA-MPS, mortality 19%, adjusted HR 0.92, 95% CI 0.64–1.32) (Table 3).

While each group of selected types of CCHD (single ventricle, TGA, and TA) had a higher mortality when IFE was present, the strongest association between IFE and mortality was found in the TA group: infants with TA and IFE had a mortality of 24.1% compared with infants with TA without IFE of 9.5% (HR 2.7, 95% CI 1.23–5.92) (Table 4, Figure 2). The mortality difference for infants with IFE was driven in each cardiac group by the SGA component with a HR of 1.54 in the larger single ventricle group (95% CI 1.19–2.0), 1.96 (95% CI 1.14–3.37) in the TGA group, and 3.89 (95% CI 1.77–8.54) in the TA group. While the point estimate of the HR for placental abruption was >1 for all 3 subgroups, it only reached statistical significance in the single ventricle group (HR 2.05, 95% CI 1.06–3.97) (Table 4). In the TGA and in the TA groups,

Table 2. Incidence of Indicators of IFE in Infants With Selected Types of CCHD

	SV (n=1389) % (95% CI)	TGA (n=844) % (95% CI)	TA (n=180) % (95% CI)
IFE	23.8 (21.6–26.2)	21.9 (19.2–24.9)	30.0 (23.4–37.3)
MPS	10.3 (8.7–12.0)	10.1 (8.1–12.3)	13.3 (8.7–19.2)
Maternal pre- or eclampsia	5.7 (4.5–7.0)	3.9 (2.7–5.4)	5.0 (2.3–9.3)
Hypertension	3.3 (2.4–4.4)	3.8 (2.6–5.3)	6.7 (3.5–11.4)
Placental abruption	1.5 0.9–2.3)	2.7 (1.7–4.1)	2.2 (0.6–5.6)
SGA	16.7 (14.8–18.8)	14.1 (11.8–16.6)	21.1 (15.4–27.8)
SGA+MPS	3.2 (2.3–4.2)	2.3 (1.4–3.5)	4.4 (1.9–8.6)
Preterm birth	16.3 (14.4–18.4)	13.9 (11.6–16.4)	21.7 (15.99–28.4)

CCHD indicates critical congenital heart disease; IFE, impaired fetal environment defined as MPS or SGA; MPS, maternal placental syndrome defined as 1 or more of the following: maternal preeclampsia, eclampsia, gestational or pre-existing hypertension or placental abruption; SGA, small for gestational age; SV, single ventricle; TA, truncus arteriosus; TGA, transposition of the great arteries.

the point estimates for mortality was lower in SGA+MPS infants compared with SGA-MPS infants (TGA: 10.5% versus 15.0%, TA: 25.0% versus 33.3%); however, these differences did not reach statistical significance (TGA: HR 0.72, 95% CI 0.17–3.16, TA HR 0.69, 95% CI 0.15–3.13).

The causal mediation analysis results indicated that 32.8% (95% CI 24.9–47.0%) of the total effect of IFE on mortality is mediated through GA, accounting for RACHS as a confounder of the relationship between prematurity and mortality. The sensitivity analysis procedure to assess plausibility of no unmeasured confounding (also known as sequential ignorability in the context of mediation analysis) for our chosen causal mediation estimation approach is not available for survival regression, so a binary regression model (Model 2, Table 5) was used instead. This approach does not explicitly account for censoring, but the differences in results are minimal. The sensitivity analysis estimates how the average causal mediated effect might vary under varying degrees of unmeasured confounding. The latter is summarized using a parameter ρ, which measures degree of correlation between residuals from the 2 models used in mediation assessment (ie, for the relationship between primary predictor and mediator, and between primary predictor, mediator, and outcome). The key issue addressed is what value of ρ is consistent with an average causal mediated effect equal to zero (ie, indicating no mediation is present). The results indicate that for the average causal mediated effect to exceed zero (ie corresponding to presence of mediation or an indirect effect of GA >0), ρ must >0.2. This suggests that the average causal mediated effect is only moderately sensitive to the presence of uncontrolled confounding of either of the relationships represented in the 2 models used in mediation assessment.

When stratifying the results by GA group, IFE was only associated with increased mortality in early term and term infants (adjusted HR 1.73, 95% CI 1.35–2.23 and 1.68, 95% CI 1.30–2.15, respectively) but not in preterm infants (adjusted HR 0.91, 95% CI 0.72–1.17), (Table 6). In preterm infants, MPS was protective for mortality with an adjusted HR of 0.66 (95% CI 0.49–0.88) and SGA was not significantly associated with mortality (adjusted HR 1.28, 95% CI 0.97–1.70) (Table 6 and Figure 3).

Table 3. Mortality Risk by Components of IFE

	Mortality (%)	Marginal HR* (95% CI)	Adjusted HR† (95% CI)
Overall	12.5		
IFE			
Yes	16.6	1.55 (1.34–1.78)‡	1.61 (1.40–1.86)‡
No	11.1		
MPS			
Yes	13.8	1.13 (0.93–1.38)	1.20 (0.98–1.47)
No	12.3		
Maternal pre- or eclampsia			
Yes	14.0	1.14 (0.87–1.50)	1.18 (0.90–1.54)
No	12.4		
Maternal hypertension			
Yes	12.0	0.95 (0.67–1.34)	1.01 (0.72–1.43)
No	12.5		
Placental abruption			
Yes	20.0	1.70 (1.17–2.48)‡	1.94 (1.33–2.83)‡
No	12.3		
SGA			
Yes	18.8	1.76 (1.50–2.05)‡	1.77 (1.52–2.07)‡
No	11.2		
+ MPS	18.0	0.93 (0.65–1.34)	0.92 (0.64–1.32)
− MPS	19.0		

HR indicates hazard ratio; IFE, impaired fetal environment; MPS, maternal placental syndrome defined as 1 or more of the following: maternal preeclampsia, eclampsia, gestational or pre-existing hypertension or placental abruption; SGA, small for gestational age.
*Marginal HR represents unadjusted estimate.
†Adjusted for severity of critical congenital heart disease using modified risk adjustment in congenital heart surgery.
‡Statistically significant with *P*-value < 0.05.

Discussion

In this population-based cohort study we found IFE to be present in 25% of infants with CCHD and it was associated with an increased 1-year mortality. The 2 main components of IFE, MPS and SGA, were present in 11.7% and 16.3%, respectively. Interestingly, only a small proportion of infants with CCHD had both SGA and MPS (2.9%). Of all the components of IFE, the main driver of mortality was SGA, while preeclampsia and maternal hypertension had no significant effect. Compared with infants with SGA without a diagnosis of MPS, infants with SGA associated with MPS were not at higher risk of mortality. Preterm birth only mediated ≈30% of the relationship between IFE and 1-year mortality.

SGA—1 of the 2 main components in our definition of IFE—is a surrogate marker for poor fetal growth. It is known that infants with CHD are more likely to be SGA; however, the underlying mechanism is elusive.[19–21] MPS is strongly associated with SGA[22,23]; thus the association of SGA and CHD might be at least partially explained by MPS. However, in the present cohort of infants with CCHD, only a small fraction of SGA cases were associated with MPS (2.9% for SGA and MPS versus 13.4% SGA without MPS). While there might be some underascertainment of MPS diagnoses in this administrative database, the increased risk of SGA in infants with CHD does not seem to be solely explained by MPS. Lutin et al

Table 4. One-Year Mortality by Indicators of IFE in Infants With Selected Types of CCHD

	SV		TGA		TA	
	Mortality (%)	Marginal HR* (95% CI)	Mortality (%)	Marginal HR* (95% CI)	Mortality (%)	Marginal HR* (95% CI)
IFE						
Yes	32.0	1.50 (1.19–1.89)†	12.4	1.71 (1.04–2.81)†	24.1	2.70 (1.23–5.92)†
No	22.8		7.4		9.5	
MPS						
Yes	30.3	1.28 (0.91–1.81)	9.7	1.15 (0.53–2.51)	12.4	0.85 (0.26–2.86)
No	24.5		8.4		14.0	
Maternal pre- or eclampsia						
Yes	27.9	1.15 (0.75–1.77)	6.1	0.68 (0.17–2.77)	22.2	1.66 (0.39–7.03)
No	24.8		8.6		13.5	
Maternal hypertension						
Yes	30.4	1.09 (0.49–2.45)	9.4	1.13 (0.35–5.58)	8.3	0.56 (0.08–4.11)
No	24.8		8.5		14.3	
Placental abruption						
Yes	42.9	2.05 (1.06–3.97)†	13.0	1.59 (0.50–5.04)	25.0	1.78 (0.24–13.19)
No	24.7		8.4		13.6	
SGA						
Yes	33.6	1.54 (1.19–2.00)†	14.3	1.96 (1.14–3.37)†	31.6	3.89 (1.77–8.54)†
No	23.3		7.6		9.2	
+ MPS	34.1	1.0 (0.57–1.75)	10.5	0.72 (0.17–3.16)	25.0	0.69 (0.15–3.13)
− MPS	33.5		15.0		33.3	

CCHD indicates critical congenital heart disease; HR, hazard ratio; IFE, impaired fetal environment; MPS, maternal placental syndrome defined as 1 or more of the following: maternal preeclampsia, eclampsia, gestational or pre-existing hypertension or placental abruption; SGA, small for gestational age; SV, single ventricle; TGA, transposition of the great arteries.
*Marginal HR represents unadjusted estimate.
†Statistically significant with P-value < 0.05.

showed that hemodynamic abnormalities in the fetus with congenital heart disease are present before birth and impaired fetal growth might be related to inadequate fetal cardiac output.[24] With regard to postnatal outcomes, our group and others have shown that there is increased mortality in infants with CHD and fetal growth restriction.[4,5] The underlying mechanism is not well studied. In this current investigation, we show that the increased mortality in infants with SGA is not explained by MPS and only partially mediated through prematurity. Lutin et al hypothesized that diminished myocardial reserve related to inadequate fetal cardiac output may put infants with fetal growth restriction at risk postnatally.[24] A group in Denmark found no association between CHD and fetal growth measures in newborns with Down syndrome or 22q11.2 deletion syndrome, indicating that in certain subtypes of CHD, the contribution of genetic factors to prenatal growth impairment may be more important than circulatory disturbances and may be responsible for worse outcomes postnatally.[25]

The other main component in our definition of IFE is MPS. There is a strong association between preeclampsia—1 of the principal components of MPS—and congenital heart disease in the offspring.[10] Recently, an increased long-term risk of cardiovascular disease in women who have had infants with heart defects has been detected,[26] and Ray et al[7] showed that MPS was associated with increased maternal long-term risk of cardiovascular disease potentially because of endothelial dysfunction related to anti-angiogenic factors released by an ischemic placenta.[8] Data suggest that long-term cardiovascular health in infants born to mothers with preeclampsia or hypertension may be altered.[27,28] Contradictory to these previous findings, we did not find an association between MPS and 1-year mortality in infants with CCHD. We were not able to assess the timing of fetal growth restriction or distinguish between early (≤34 weeks of GA) and late-onset preeclampsia. There is literature suggesting that these are 2 different entities[29]; while early-onset preeclampsia is mainly associated with features of impaired maternal uteroplacental perfusion

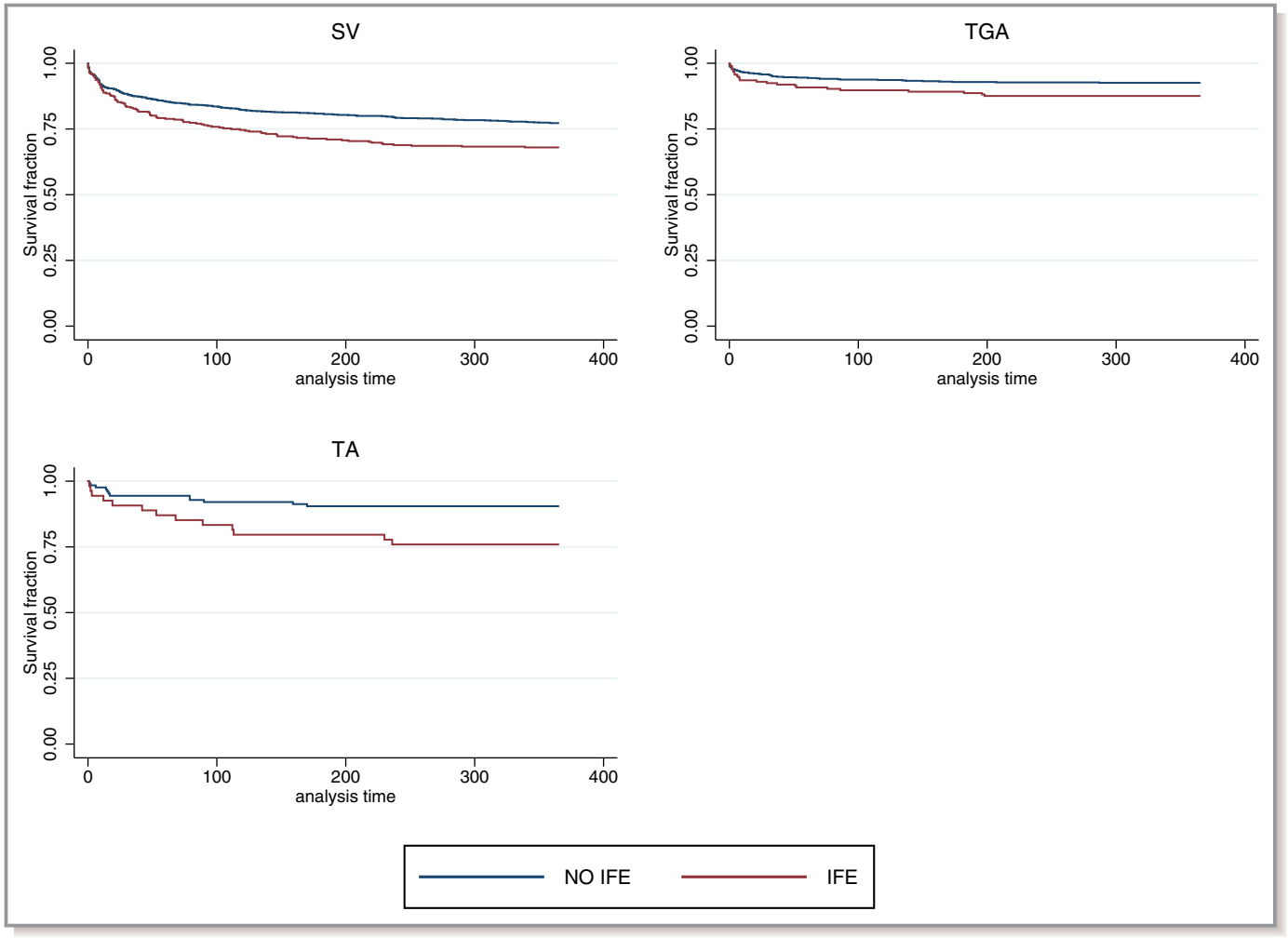

Figure 2. Survival curves for infants with specific types of critical congenital heart disease by impaired fetal environment. IFE indicates impaired fetal environment; SV, single ventricle; TA, truncus arteriosus; TGA, transposition of the great arteries.

secondary to defective extravillous trophoblast invasion, late-onset preeclampsia and fetal growth restriction probably represent a more heterogeneous group with fewer characteristic histological changes.[30] Further studies should focus on outcomes of infants born to mothers with early-onset preeclampsia or long-term follow-up of infants with CHD born to mothers with MPS.

The interplay between IFE, length of gestation, and mortality is complex since MPS and SGA are strongly associated with preterm birth and preterm birth is strongly associated with mortality; thus preterm birth is on the causal pathway between IFE and mortality and qualifies as a mediator. We assessed this intimate relationship by performing a formal mediation analysis and identified that ≈30% of the effect of IFE on mortality is mediated through length of gestation. As such, 70% of the effect of IFE on mortality was independent of gestational age, with the main driver being fetal growth restriction (measured by SGA) and placental abruption. One could argue that SGA is a mediator between MPS and mortality; however, in the present study, MPS alone

Table 5. Alternate Models for the Relationship Between the Primary IFE Predictor (Binary), GA Mediator (Continuous), and Survival Outcome

	Mediator	Outcome	Mediator Model	Outcome Model	Proportion Mediated Based on ACME % (95% CI)
Model 1	Continuous	Survival	Linear regression	Weibull survival regression	32.8% (95% CI 24.9–47.0%)
Model 2	Continuous	Binary	Linear regression model	Binomial GLM model with probit link	32.9% (95% CI 24.5–45.0%)

ACME indicates average causal mediated effect (indirect effect); GLM, Generalized Linear Model; IFE, impaired fetal environment; GA, gestational age.

Table 6. One-Year Mortality by Indicators of IFE in Preterm, Early Term, and Term Infants With CCHD

	Preterm (n=1226)			Early Term (n=2094)			Term (n=3543)		
	Mortality (%)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Mortality (%)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Mortality (%)	Crude HR (95% CI)	Adjusted HR* (95% CI)
IFE									
Yes	20.4	0.80 (0.63–1.02)	0.91 (0.72–1.17)	17.3	1.69 (1.31–2.17)†	1.73 (1.35–2.23)†	12.9	1.68 (1.30–2.15)†	1.65 (1.28–2.13)†
No	24.8			10.7			7.9		
MPS									
Yes	16.6	0.61 (0.46–0.82)†	0.66 (0.49–0.88)†	13.5	1.10 (0.76–1.60)	1.16 (0.80–1.68)	9.5	1.07 (0.68–1.67)	1.06 (0.67–1.67)
No	25.5			12.3			8.9		
Maternal pre- or eclampsia									
Yes	16.3	0.63 (0.44–0.90)†	0.66 (0.46–0.95)†	13.0	1.07 (0.63–1.80)	1.05 (0.62–1.76)	9.3	1.05 (0.49–2.21)	0.99 (0.47–2.10)
No	24.3			12.4			8.8		
Maternal hypertension									
Yes	9.7	0.38 (0.18–0.80)†	0.39 (0.19–0.83)†	14.6	1.17 (0.70–2.0)	1.30 (0.77–2.19)	11.1	1.27 (0.71–2.26)	1.31 (0.73–2.32)
No	23.7			12.4			8.8		
Placental abruption									
Yes	26.4	1.18 (0.77–1.79)	1.32 (0.87–2.01)	10.5	0.85 (0.21–3.40)	1.0 (0.25–4.1)	6.7	0.75 (0.19–3.0)	0.68 (0.17–2.74)
No	22.6			12.5			8.9		
SGA									
Yes	25.1	1.14 (0.87–1.51)	1.28 (0.97–1.70)	19.4	1.88 (1.43–2.46)†	1.88 (1.44–2.48)†	15.0	1.98 (1.52–2.58)†	1.93 (1.48–2.51)†
No	22.3			11.0			7.9		
+ MPS	19.2	0.62 (0.36–1.05)	0.52 (0.30–0.89)†	15.0	0.73 (0.37–1.48)	0.75 (0.37–1.50)	19.5	1.33 (0.64–2.78)	1.18 (0.56–2.48)
− MPS	28.8			20.2			14.6		

Preterm: gestational age at birth <37 wks, early term: gestational age at birth 37 to 38 wks, term: gestational age at birth >38 wks. CCHD indicates critical congenital heart disease; HR, hazard ratio; IFE, impaired fetal environment; MPS, maternal placental syndrome defined as 1 or more of the following: maternal preeclampsia, eclampsia, gestational or pre-existing hypertension or placental abruption; SGA, small for gestational age.

*Adjusted for severity of CCHD by modified risk adjustment in congenital heart surgery.

†Statistically significant with *P*-value < 0.05.

is not associated with mortality, precluding a mediation analysis of this relationship. Our analysis allowed us to separate specific components of IFE and identify their possible causal relationship with prematurity to identify targets for future studies. In this case, further studies should focus on mechanisms that lead to fetal growth restriction in CHD and the underlying mechanisms that put these infants at increased risk of mortality.

When stratifying by GA group, we found that MPS, especially preeclampsia and hypertension, had a protective effect on 1-year mortality in preterm infants. Extremely preterm infants without CHD born because of maternal preeclampsia may have more favorable short-term outcomes than extremely preterm infants born because of spontaneous labor.[31] The most likely explanation of this observation is bias resulting from stratifying on an intermediate factor or mediator. This concept is also known as the "low-birth-weight paradox"[32,33]: Low-birth-weight infants born to smoking mothers have a lower infant mortality rate than the low birth-weight infants of nonsmokers. With smoking, otherwise healthy babies (who would weigh more if it were not for the fact their mother smoked) are born growth restricted.[32,33] However, they still have a lower mortality rate than infants who have another, more severe, medical reason—such as congenital malformations or genetic syndromes—for low birth-weight. Similarly, it is possible that preterm birth related to MPS in the setting of CHD is less detrimental than preterm birth related to other more severe medical reasons such as severe forms of certain congenital heart lesions such as absent pulmonary valve or Epstein anomaly (without MPS) or infectious causes leading to an apparent protective effect of MPS in preterm infants with CHD.

While strengths of the present study include the use of a large population-based data set that allows for a great deal of generalizability as well as the linkage to maternal information, there are several potential limitations to this study that are

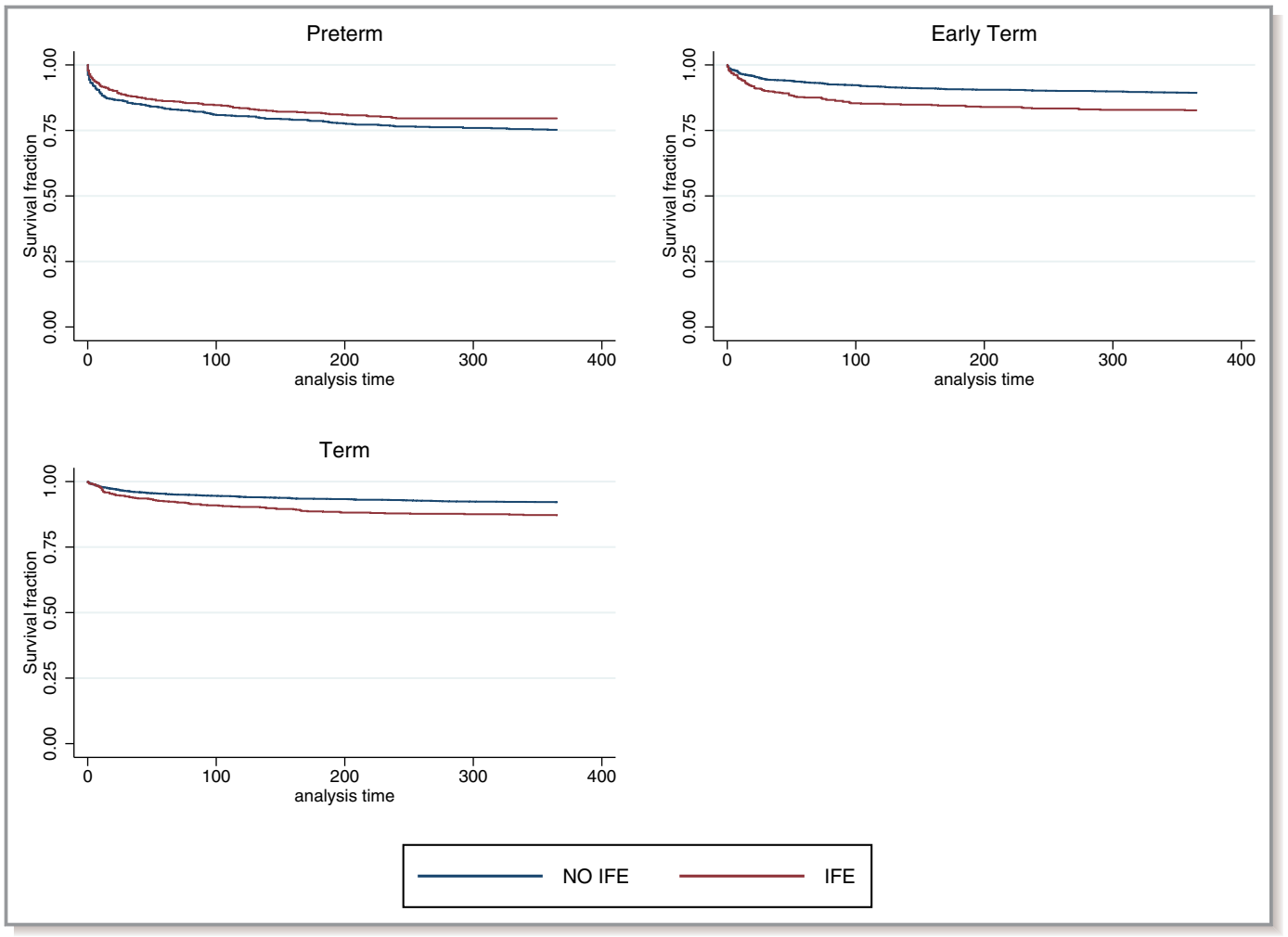

Figure 3. Survival curves for infants with critical congenital heart disease by impaired fetal environment stratified by gestational age groups. Preterm: gestational age <37 wks; early term: gestational age 37 to 38 wks; term: gestational age ≥39 wks. IFE indicates impaired fetal environment.

important to discuss. Most of those are inherent to an administrative database. First, the identification of cases with CCHD depended on *ICD-9* codes. Pasquali et al found that the negative predictive value of the administrative (versus clinical) data was high (98.8–99.9%) while the positive predictive value was lower (56.7–88.0%).[34] However, 2 investigators reviewed all cases according to a proposed framework based on morphogenetically similar developmental mechanisms[13,15] to ensure correct classifications of infants with multiple *ICD-9-CM* codes. Similarly, the ascertainment of maternal conditions depended on *ICD-9* codes, and it is possible that we missed some of these predictors if the *ICD-9* coding was incomplete, which might have occurred, especially if the condition is mild. However, the incidence of preeclampsia in a large Canadian administrative database was identical to ours of 3.7% in the overall population, confirming consistency of *ICD-9* codes across administrative databases.[10] However, we cannot exclude differential ascertainment of the maternal conditions in infants with congenital heart disease versus controls, which would affect the numbers presented in Table 1 only. Given that this is a population-based study, we were able to include all live-born infants, including those who never had surgery, reducing the potential for selection bias. However, we were not able to include fetal demise or those who were stillborn; thus, we might be underestimating the full effect of IFE on infant outcomes.[35,36] Additionally, our cohort might inadvertently include some infants with chromosomal anomalies if the *ICD-9* codes for those anomalies were not sensitive or if testing for chromosomal anomalies was not universally performed. Finally, we acknowledge that our estimated mediation percentage and the accompanying interpretation is limited by both the cross-sectional nature of the measurement of predictors of mortality as well as the possible influence of unmeasured confounding factors.

In conclusion, the maternal–fetal environment is a significant contributor to outcomes in the CCHD population. While

MPS is increased in mothers carrying a fetus with CCHD, it does not account for the increased incidence of SGA in this population nor does it explain the strong association between SGA and mortality in infants with CCHD. Fetal growth (measured by SGA) appears to be the main driver of this association, with prematurity only explaining one third of this effect. Further studies should investigate different causes of growth restriction in infants with CCHD to better understand the complex relationship between IFE, SGA, and prematurity and identify targets for intervention to improve outcomes.

Disclosures

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