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ORIGINAL RESEARCH

PEDIATRIC CARDIOLOGY

Severe Maternal Morbidity in Pregnancies Complicated by Fetal Congenital Heart Disease

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ABSTRACT

BACKGROUND Maternal risk factors for fetal congenital heart disease (CHD) may also be associated with delivery complications in the mother.

OBJECTIVES This study aimed to determine the prevalence of and risk factors for severe maternal morbidity (SMM) and maternal hospital transfer in pregnancies complicated by fetal CHD.

METHODS A population-based retrospective cohort study utilizing linked Ohio birth certificates and birth defect data for all live births from 2011 to 2015 was performed. The primary outcome was composite SMM. Secondary outcome was maternal hospital transfer prior to delivery. Pregnancies with isolated fetal CHD were compared to pregnancies with no fetal anomalies and isolated fetal cleft lip/palate (CLP).

RESULTS A total of 682,929 mothers with live births were included. Of these, 5,844 (0.85%) mothers had fetal CHD, and 963 (0.14%) had fetal CLP. SMM in pregnancies with fetal CHD was higher than that in those with no anomalies (3.6% vs 1.9%, $P < 0.001$) or CLP (3.6% vs 1.9%, $P = 0.006$). After adjusting for known risk factors, fetal CHD remained independently associated with SMM when compared to no fetal anomalies (adjusted relative risk [adjRR]: 1.81, 95% CI: 1.58-2.08) and CLP (adjRR: 1.81, 95% CI: 1.12-2.92). Maternal hospital transfer occurred more frequently in fetal CHD cases vs for those without fetal anomalies with an increased adjusted risk (adjRR: 3.65, 95% CI: 3.14-4.25).

CONCLUSIONS Pregnancies with isolated fetal CHD have increased risk of SMM and maternal hospital transfer after adjusting for known risk factors. This may inform delivery planning for mothers with fetal CHD. Understanding the biological mechanisms may provide insight into other adverse perinatal outcomes in this population. (JACC Adv 2022;1:100125)
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ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

CLP = cleft lip/palate

ICU = intensive care unit

RR = relative risk

SMM = severe maternal morbidity

VSD = ventricular septal defect

Severe maternal morbidity (SMM) is broadly defined as unintended complications to labor and delivery that result in both short- and long-term consequences to maternal health.[1,2] SMM encompasses a variety of diagnoses and outcomes, including the need for blood transfusion or additional surgical procedures, measures of end organ dysfunction, and sepsis.[1,3,4] The rate of severe complications during delivery and postpartum hospitalizations has been steadily increasing in the United States and occurs in approximately 0.3% to 3% of pregnancies.[3,5-8] SMM is approximately 50 times more common than maternal mortality.[9] Postpartum hemorrhage and hypertensive disorders of pregnancies account for more than two-thirds of the primary underlying causes of SMM.[5] Changes in maternal health over the past few decades may also contribute to delivery complications, as the presence of maternal comorbidities, such as obesity and chronic hypertension, and increasing maternal age have been associated with SMM and mortality.[6,8,10-14] Additional risk factors include preterm delivery, cigarette use, and prior cesarean delivery.[5,6] The identification of risk factors to SMM may guide delivery planning and perinatal management.

Many of the risk factors for SMM are shared with fetal congenital heart disease (CHD). Maternal comorbidities such as diabetes, obesity, smoking, and hypertensive disorders of pregnancy have all been associated with fetal CHD.[15-17] Furthermore, pregnancies with fetal CHD are known to have adverse perinatal outcomes, most of which have been documented in the fetus or neonate. This includes preterm delivery, small-for-gestational age, and fetal intolerance of labor.[18,19] Pregnancies complicated by fetal CHD also have increased risk of obstetrical outcomes such as cesarean and instrumental delivery.[19-21] However, the rate of maternal morbidity has not been well characterized in these pregnancies.

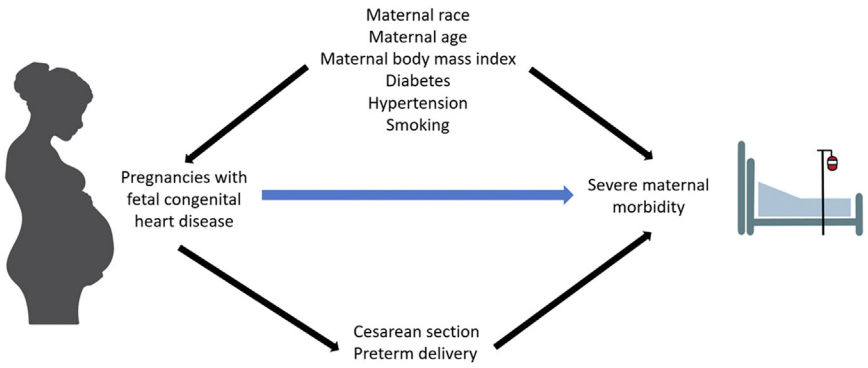
Given the overlap of risk factors between fetal CHD and adverse delivery outcomes, we hypothesized that SMM could be increased in pregnancies complicated by fetal CHD. The risk of SMM in this population is not known, and whether fetal CHD affects this risk is unclear. This information could aid clinicians attempting to balance the competing risks of both patients in the mother-baby dyad. The aim of this study was to determine the risk of SMM in pregnancies complicated by fetal CHD. The secondary aim was to determine the prevalence and risk of maternal hospital transfer prior to delivery in fetal CHD.

METHODS

A population-based retrospective cohort study utilizing linked Ohio birth certificates and birth defect surveillance data of all live births in Ohio (2011-2015) was performed. Mandated by state law, the Ohio Connections for Children with Special Needs system collects birth defect information on children from birth to age 5 years from all hospitals, physicians, and freestanding birthing centers. The birth defect registry includes all diagnoses made up to 5 years of age but does not identify whether the initial diagnoses were made prenatally or postnatally. The protocol for this study was approved, and a data set was provided by the human subjects institutional review board of the Ohio Department of Health. This study was exempt from review by the institutional review board at Cincinnati Children's Hospital Medical Center.

The exposure group comprised pregnancies complicated by isolated fetal CHD compared to the referent group of pregnancies with no fetal anomalies. Using the Ohio birth defect registry,[22] isolated fetal CHD was defined as live births having a CHD diagnosis only and no known extracardiac or genetic anomaly. Fetal CHD included common arterial trunk, transposition of the great arteries, tetralogy of Fallot, ventricular septal defect (VSD), endocardial cushion defect, pulmonary valve atresia and stenosis, tricuspid valve atresia and stenosis, Ebstein anomaly, aortic valve stenosis, hypoplastic left heart syndrome, coarctation of the aorta, interrupted aortic arch, total anomalous pulmonary venous connection, and double outlet right ventricle. The diagnoses of atrial septal defect and patent ductus arteriosus were excluded for this analysis to reduce the potential bias of prematurity. A subgroup of complex CHD was defined by the Centers for Disease Control and Prevention definition of critical CHD and included the following diagnoses: coarctation of the aorta, double outlet right ventricle, transposition of the great arteries, Ebstein anomaly, hypoplastic left heart syndrome, interrupted aortic arch, pulmonary atresia (intact septum), single ventricle, total anomalous pulmonary venous connection, tetralogy of Fallot, tricuspid atresia, and truncus arteriosus (common arterial trunk). The remaining diagnoses were considered simple CHD. Additionally, an alternate comparison group of isolated cleft lip and palate (CLP) was included to estimate whether risk was unique to CHD or shared with another common birth defect. The CLP group included infants with an isolated cleft lip with or without a cleft palate and isolated cleft palate.

FIGURE 1 Directed Acyclic Graph of the Severe Maternal Morbidity Model



The model illustrates the relationship between variables and severe maternal morbidity. Confounding variables include maternal race, maternal age, maternal body mass index, diabetes, hypertension, and smoking status. Mediators include cesarean section and preterm delivery.

The primary outcome of this study was composite SMM based on maternal delivery morbidities identified on the birth certificate.[23] These included maternal intensive care unit (ICU) admission during delivery hospitalization, uterine rupture, unplanned hysterectomy or operative procedure after delivery, or need of blood transfusion. Each individual variable of SMM was also assessed as an outcome. The secondary outcome was maternal hospital transfer for maternal medical or fetal indications prior to delivery. Gestational hypertension included cases of pregnancy-induced hypertension and/or preeclampsia. Prenatal care was defined as limited (1-5 visits), early (initiated in <12 weeks of gestation), and late (initiated at >20 weeks gestation). Social determinants of health were assessed by Medicaid status, participation in the Special Supplemental Nutrition Program for Women, Infants, and Children, educational attainment (low defined as less than a high school degree), and number and timing of prenatal care visits. Prior poor pregnancy outcome was defined as a prior pregnancy associated with perinatal death, small-for-gestational age birthweight, or intrauterine growth restriction. All live births and above outcome variables were recorded in the U.S. birth certificate by standardized methods.[24]

Statistical analyses were performed using STATA 16.1 (StataCorp LLC). The analysis counted multiple gestation pregnancies as 1 event so that maternal outcomes for these pregnancies were counted only once. Statistical comparisons of maternal, obstetric, and delivery characteristics were performed using chi-square analysis and Student's *t*-test for categorical and continuous data, respectively. Frequencies of SMM and maternal hospital transfer among women with pregnancies complicated by isolated fetal CHD were compared to those of women without fetal anomalies and those with fetal CLP. Additional group comparisons were performed between complex and simple CHD groups.

To quantify the effect of fetal CHD on dichotomous outcomes of SMM and maternal transfer, we used a log-binomial, generalized linear model, with log link. This linear model approach for estimating relative risk (RR) is well suited for dichotomous outcomes. Adjusted RR values and associated 95% CIs were calculated to estimate the risk of SMM and maternal transfer in pregnancies complicated by fetal CHD. Multivariable modeling was performed with a backward elimination approach. Variables with significant differences with a P value <0.05 on bivariate comparisons were initially included in the full model, and variables with the least significance were then subsequently removed from the model one at a time via a backward elimination approach until a final parsimonious model was determined that included significant and clinically important variables. Backward elimination was used so that the final model would include the most important variables and assess joint predictability of the variables.[25]

The final model for SMM and unplanned operations included adjustment for the confounding influences of maternal race, maternal age category, smoking status, body mass index category, pre-pregnancy and gestational diabetes, and chronic hypertension (**Figure 1**). The adjusted model for maternal blood transfusion included covariates of maternal race, pre-pregnancy and gestational diabetes, and chronic hypertension. The model for ICU

TABLE 1 Characteristics of Mothers With Live Births in Ohio From 2011 to 2015 (N = 682,929)

	Fetal Congenital Heart Disease (n = 5,844, 0.85%)	No Fetal Anomalies (n = 644,101, 94.03%)	*P* Value	Fetal Cleft Lip and/or Cleft Palate (n = 963, 0.14%)	*P* Value[a]
Maternal age (y)	27.6 ± 5.8 27 (23-32)	27.6 ± 5.7 28 (23-32)	0.999	27.8 ± 5.7 28 (23-32)	0.481
Maternal age category (y)			0.611		0.512
<18	124 (2.1)	12,874 (2.0)		20 (2.1)	
18-34	4,997 (85.5)	551,488 (85.6)		819 (85.1)	
35-39	585 (10.0)	65,842 (10.2)		107 (11.1)	
>40	138 (2.4)	13,897 (2.2)		17 (1.8)	
Pre-pregnancy diabetes	164 (2.8)	5,554 (0.9)	<0.001	10 (1.0)	0.001
Chronic hypertension	218 (3.8)	15,171 (2.4)	<0.001	23 (2.4)	0.036
Gestational diabetes	450 (7.7)	42,545 (6.6)	0.001	75 (7.8)	0.931
Gestational hypertension or pre-eclampsia	430 (7.4)	39,812 (6.2)	<0.001	72 (7.5)	0.902
BMI (kg/m^2) (pre-pregnancy)	27.0 ± 7.2	26.6 ± 6.8	<0.001	26.9 ± 6.7	0.789
BMI category (kg/m^2) (pre-pregnancy)			0.002		0.041
<18.5	234 (4.2)	24,678 (4.0)		38 (4.0)	
18.5-24.9	2,509 (44.8)	287,877 (46.3)		399 (42.4)	
25.0-29.9	1,320 (23.6)	151,740 (24.4)		254 (27.0)	
≥30	1,539 (27.5)	157,469 (25.3)		250 (26.6)	
Race			<0.001		<0.001
Non-Hispanic White	4,141 (71.0)	476,912 (74.2)		794 (82.5)	
Non-Hispanic Black	1,167 (20.0)	108,396 (16.9)		90 (9.4)	
Hispanic	100 (1.7)	9,942 (1.6)		18 (1.9)	
Other	423 (7.3)	47,390 (7.4)		60 (6.2)	
Prenatal factors					
Assisted reproductive technology (Y)	35 (1.4)	2,326 (1.0)	0.055	N/A	N/A
Fertility enhancing drugs (Y)	86 (2.9)	9,157 (3.0)	0.736	19 (4.2)	0.116
Smoking during pregnancy (Y)	978 (16.8)	105,526 (16.5)	0.425	170 (17.8)	0.464
Cigarette use duration			0.005		0.396
Never used	4,495 (78.0)	500,739 (78.6)		738 (77.8)	
Pre only	334 (5.8)	35,143 (5.5)		47 (5.0)	
Pre through 1st trimester	126 (2.2)	14,160 (2.2)		16 (1.7)	
Pre through 2nd trimester	78 (1.4)	5,660 (0.9)		11 (1.2)	
Pre through 3rd trimester	733 (12.7)	81,503 (12.8)		137 (14.4)	
Prenatal care					
None	94 (1.7)	8,451 (1.4)	0.024	13 (1.4)	0.482
Limited (1-5 visits)	558 (10.5)	41,353 (6.9)	<0.001	64 (7.1)	0.001
Early (<12 wks)	2,957 (50.7)	351,462 (54.7)	<0.001	550 (57.2)	<0.001
Late (>20 wks)	1,755 (30.0)	165,816 (25.7)	<0.001	246 (25.6)	0.005
Social factors					
Married	3,175 (54.3)	367,306 (57.0)	<0.001	542 (56.3)	0.259
Low educational attainment	794 (13.7)	90,359 (14.1)	0.337	148 (15.6)	0.124
Medicaid	2,377 (41.1)	246,792 (38.8)	<0.001	399 (41.9)	0.648
WIC	2,517 (43.4)	256,010 (40.0)	<0.001	404 (42.3)	0.519

Values are mean ± SD, median (25th-75th percentile), or n (%) unless otherwise specified. Missing or incomplete congenital anomaly data, N = 10,869 (1.6%). [a]*P* value for comparison between fetal congenital heart disease and fetal cleft lip and/or cleft palate cohorts.

BMI = body mass index (kg/m^2); N/A = nonapplicable; Pre = prenatal; WIC = Women, Infants, and Children Program; Y = yes.

admission included adjustment for maternal race and pre-pregnancy diabetes. For the secondary outcome of maternal hospital transfer, adjustment was made for maternal race, maternal age category, Medicaid, late prenatal care, smoking status, pre-pregnancy and gestational diabetes, and chronic hypertension. Adjusted RR was calculated to estimate risk of fetal CHD on composite SMM compared to CLP after adjustment for maternal race, maternal age category, pre-pregnancy and gestation diabetes, and chronic hypertension. The adjusted model for unplanned operations and maternal hospital transfer in fetal CHD compared to CLP included the covariate of maternal race. Sensitivity analyses were performed to estimate adjusted RR by including cesarean delivery or preterm delivery as mediators in 2 separate

models. Race was included in all final models of the analysis as it is a known biologically important risk factor for adverse maternal outcomes. An additional sensitivity analysis was performed to assess unplanned cesarean deliveries as a mediator for SMM. The impact of CHD severity was assessed by repeating the composite SMM model with CHD categorized as complex or simple. In addition, a model with isolated VSD compared to no fetal anomalies was used. Significant differences were defined as a *P* value of <0.05 and 95% CI excluding the null value of 1.0.

RESULTS

From 2011 to 2015, 682,929 mothers delivered live born neonates in Ohio. Of these, 5,844 pregnancies had isolated fetal CHD, 644,101 pregnancies had no fetal anomaly, and 963 pregnancies had isolated fetal CLP. Maternal demographic characteristics are presented in Table 1. When compared to the no-fetal-anomalies cohort, the fetal CHD cohort had higher rates of pre-pregnancy diabetes (2.8% vs 0.9%, $P < 0.001$), gestational diabetes (7.7% vs 6.6%, $P = 0.001$), chronic hypertension (3.8% vs 2.4%, $P < 0.001$), and gestational hypertension (7.4% vs 6.2%, $P < 0.001$). Compared to mothers with fetal CLP, those with fetal CHD had higher rates of pre-pregnancy diabetes (2.8% vs 1.0%, $P = 0.001$) and chronic hypertension (3.8% vs 2.4%, $P = 0.04$).

Obstetrical and delivery characteristics of mothers with fetal CHD and non-CHD pregnancies are presented in Table 2. Mothers with fetal CHD were more likely to have a prior history of cesarean delivery, poor pregnancy outcome, and preterm birth. Additionally, there were higher rates of cesarean delivery (40.8% vs 29.7%, $P < 0.001$), premature rupture of membranes (7.5% vs 4.1%, $P < 0.001$), and fetal intolerance of labor (12.0% vs 9.1%, $P < 0.001$) in the fetal CHD cohort. Planned cesarean was determined if there was a cesarean delivery and no trial of labor. Among cesarean deliveries, there was a higher prevalence of planned cesarean deliveries in fetal CHD cases than in those with no fetal anomalies (72.2% vs 67.6%, $P < 0.001$).

The overall rate of SMM in fetal CHD cases was higher than that in those with no fetal anomalies (3.6% vs 1.9%, $P < 0.001$) (Table 3). Fetal CHD carried higher rates of the individual subcomponents of SMM, including maternal ICU admission, maternal transfusion, and unplanned operative procedure after delivery (Central Illustration). The risk of SMM was higher in fetal CHD cases (unadjusted RR: 1.93, 95% CI: 1.68-2.20) and remained high accounting for available maternal characteristics, pregnancy history, and obstetrical care variables (adjusted RR: 1.81, 95% CI: 1.58-2.08). The adjusted RR for each subcomponent of SMM remained increased for births complicated by fetal CHD (Table 3). Sensitivity analyses considering the mediating variables of cesarean delivery or preterm delivery as confounders and adjusting for them demonstrated an attenuated risk of SMM, but the risk remained increased (cesarean delivery adjusted RR: 1.44, 95% CI: 1.25-1.66; preterm delivery adjusted RR: 1.38, 95% CI: 1.11-1.73). Further adjustment for unplanned cesarean delivery resulted in a decreased risk of SMM (adjusted RR: 1.26, 95% CI: 1.03-1.55). Maternal hospital transfer prior to delivery occurred more frequently in fetal CHD cases (3.0% vs 0.7%, $P < 0.001$) with an adjusted RR of 3.65 (95% CI: 3.14-4.25).

To assess the impact of CHD severity on outcomes, complex CHD was compared with simple CHD (Supplemental Table 1). There were few differences in the maternal demographics or obstetrical outcomes. Interestingly, gestational age was higher in the complex CHD group (37.6 vs 37.1 weeks, $P < 0.001$) as well as birthweight (3,087 vs 3,024 g, $P = 0.013$). An additional analysis of pregnancies with isolated fetal

TABLE 2 Obstetric and Delivery Characteristics in Mothers With Live Births in Ohio From 2011 to 2015 (N = 682,929)

	Fetal Congenital Heart Disease (n = 5,844, 0.85%)	No Fetal Anomalies (n = 644,101, 94.03%)	*P* Value
Obstetric characteristic			
Parity	2 (1-3)	2 (1-3)	0.183
Primiparous	2,365 (40.5)	250,504 (38.9)	0.014
Prior cesarean birth	1,025 (17.6)	91,811 (14.3)	<0.001
Prior poor pregnancy outcome	368 (6.3)	31,992 (5.0)	<0.001
Prior preterm birth	404 (7.0)	30,945 (4.8)	<0.001
Antenatal corticosteroids	669 (11.5)	22,807 (3.5)	<0.001
Malpresentation	284 (4.9)	15,506 (2.4)	<0.001
Singleton	5,652 (96.7)	632,450 (98.2)	<0.001
Multifetal gestation	192 (3.3)	11,651 (1.8)	<0.001
Cerclage	38 (0.7)	2,192 (0.3)	<0.001
Delivery characteristic			
Gestational age at delivery (wks)	37.3 ± 3.7	38.6 ± 2.0	<0.001
Birthweight (g)	3,042 ± 868	3,297 ± 574	<0.001
Cesarean delivery	2,384 (40.8)	191,164 (29.7)	<0.001
Primary cesarean	1,474 (25.2)	111,461 (17.3)	<0.001
Induction of labor	1,632 (28.0)	201,200 (31.3)	<0.001
Assisted delivery (forceps/vacuum)	250 (4.3)	31,936 (5.0)	0.017
Epidural anesthesia	4,722 (80.9)	503,344 (78.2)	<0.001
Premature rupture of membranes	438 (7.5)	26,350 (4.1)	<0.001
Prolonged labor	97 (1.7)	11,459 (1.8)	0.492
Chorioamnionitis	137 (2.4)	9,590 (1.5)	<0.001
Meconium	397 (6.8)	42,740 (6.6)	0.635
Fetal intolerance of labor	700 (12.0)	58,764 (9.1)	<0.001

Values are median (25th-75th percentile), n (%), or mean ± SD.

TABLE 3 Severe Maternal Morbidity and Maternal Transfer Outcomes Among Live Births in Ohio From 2011 to 2015 (N = 682,929)

Maternal Outcome	Fetal Congenital Heart Disease (n = 5,844, 0.85%)	No Fetal Anomalies (n = 644,101, 94.03%)	*P* Value	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Composite SMM	210 (3.6)	12,019 (1.9)	<0.001	1.93 (1.68-2.20)	1.81 (1.58-2.08)[a]
Maternal transfusion	44 (0.8)	2,469 (0.4)	<0.001	1.96 (1.46-2.64)	1.86 (1.38-2.51)[b]
ICU admission	26 (0.5)	908 (0.1)	<0.001	3.16 (2.14-4.66)	2.95 (2.00-4.36)[c]
Unplanned operative procedure after delivery	151 (2.6)	9,319 (1.5)	<0.001	1.79 (1.52-2.09)	1.71 (1.46-2.01)[a]
Maternal transfer	172 (3.0)	4,599 (0.7)	<0.001	4.12 (3.54-4.79)	3.65 (3.14-4.25)[d]
		Fetal Cleft Lip and/or Cleft Palate (n = 963, 0.14%)			
Composite SMM	210 (3.6)	18 (1.9)	0.006	1.92 (1.19-3.10)	1.81 (1.12-2.92)[e]
Unplanned operative procedure after delivery	151 (2.6)	15 (1.6)	0.055	1.66 (0.98-2.81)	1.67 (0.98-2.82)[f]
Maternal transfer	172 (3.0)	13 (1.4)	0.005	2.18 (1.25-3.82)	2.26 (1.29-3.96)[f]

Values are n (%) unless otherwise indicated. [a]Adjusted for maternal race, maternal age category, smoking status, body mass index category, pre-pregnancy and gestational diabetes, and chronic hypertension. [b]Adjusted for maternal race, pre-pregnancy or gestational diabetes, and chronic hypertension. [c]Adjusted for maternal race and pre-pregnancy diabetes. [d]Adjusted for maternal race, maternal age category, Medicaid, late prenatal care, smoking status, pre-pregnancy and gestational diabetes, and chronic hypertension. [e]Adjusted for maternal race, maternal age category, pre-pregnancy and gestational diabetes, and chronic hypertension. [f]Adjusted for maternal race.

ICU = intensive care unit; RR = relative risk; SMM = severe maternal morbidity.

VSD compared to no fetal anomalies was performed (Supplemental Table 2). Mothers with fetal VSD demonstrated higher rates of pre-pregnancy diabetes and gestational hypertension than those with no fetal anomalies. Multiple obstetrical characteristic differences were observed: Mothers with fetal VSD were more likely to have a prior history of cesarean section and poor pregnancy outcome. For pregnancies complicated by fetal VSD, there were higher rates of antenatal corticosteroid use (5.1% vs 3.5%, $P = 0.001$) and cesarean delivery (36.2% vs 29.7%, $P < 0.001$). Gestational age in the fetal VSD group was lower than that among those without anomalies (38.2 vs 38.5 weeks, $P < 0.001$). Further analyses of maternal outcomes between these group comparisons were performed (Supplemental Table 3). There was no difference in rate of composite SMM or adjusted RR between complex and simple CHD. There was also no difference in maternal transfer rates between types of CHD. However, the presence of VSD in the fetus was associated with an increased rate of SMM compared to no fetal anomalies (2.9% vs 1.9%, $P = 0.002$), along with higher rates of unplanned operations and maternal transfusions. Fetal VSD was associated with increased risk of composite SMM (unadjusted RR: 1.56, 95% CI: 1.17-2.08; adjusted RR: 1.54, 95% CI: 1.15-2.05). There was no difference in maternal transfer rate between fetal VSD and no fetal anomalies.

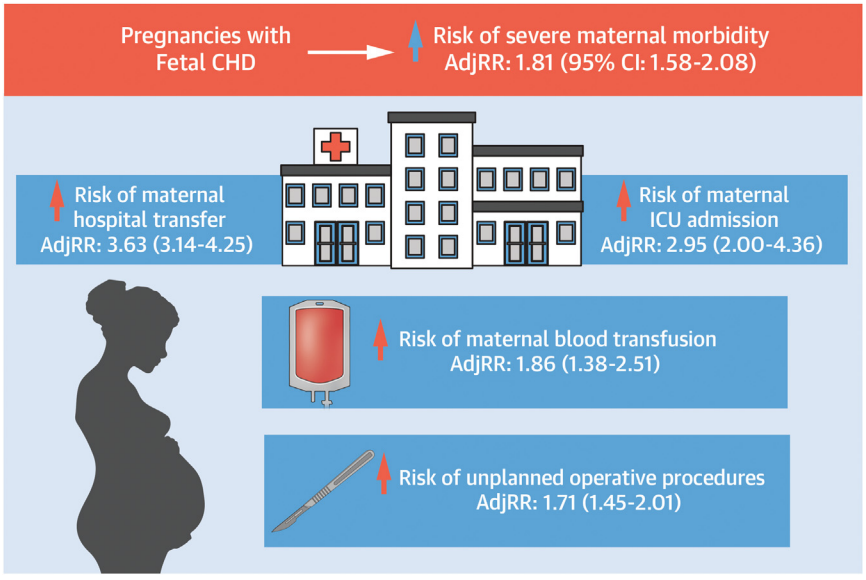
In comparisons to pregnancies with CLP, those with fetal CHD demonstrated increased risk of SMM (**Table 3**). Unplanned operative procedures after delivery were more common among fetal CHD cases, and there was no difference in RR. Pregnancies complicated by fetal CHD were 81% more likely to experience an SMM event after adjustment (adjusted RR: 1.81, 95% CI: 1.12-2.92) than CLP. In addition, mothers with fetal CHD were more likely to undergo hospital transfer prior to delivery with an adjusted RR of 2.26 (95% CI: 1.29-3.96).

DISCUSSION

We identified more than 80% increased risk of SMM in pregnancies complicated with fetal CHD. This includes the need for maternal ICU admission during delivery, maternal blood transfusions, and unplanned operative procedures after delivery. With approximately 40,000 women delivering infants with CHD annually, this suggests that SMM could complicate nearly 1,440 CHD-associated births per year.[26,27] Furthermore, the risk is independent of maternal demographic and social risk factors, medical comorbidities, pregnancy history, and prenatal care characteristics. These findings have not been previously reported and have important implications on maternal health in this population. Moreover, the findings represent a novel SMM risk factor and may serve as the basis for further investigation aimed at optimizing outcomes in pregnancies complicated by fetal CHD.[3,28,29]

Risk factors for the occurrence of CHD in the fetus have overlapped with risk factors for SMM in the general population. Maternal diabetes, obesity, and hypertensive disorders of pregnancy have all been identified as risk factors for CHD causation[15,16,30,31]

CENTRAL ILLUSTRATION **Severe Maternal Morbidity Outcomes in Pregnancies With Fetal CHD**



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Pregnant mothers with a fetus with congenital heart disease (CHD) are at risk for severe maternal morbidity (SMM) with an adjusted relative risk (AdjRR) of 1.81 (95% CI: 1.58-2.08). These mothers are specifically at increased risk of maternal intensive care unit (ICU) admission, maternal blood transfusion, unplanned operative procedures, and maternal hospital transfers.

and, as expected, were more common in the CHD cohort of this study. These same factors have also been associated with SMM in the general population and contribute a portion of the attributable risk in this study.[5,8] Additionally, significant differences in socioeconomic status and health disparities exist between pregnancies with fetal CHD and those without fetal anomalies leading to live births. Such differences may play a role in adverse maternal outcomes.[32-35] The observed history of adverse pregnancy outcomes may be explained by this clustering of risk. Yet adjustment for such factors had only modest influence on SMM risk estimates in this analysis, suggesting that fetal CHD is independently associated with SMM. Furthermore, there was no difference in SMM rate between complex and simple CHD lesions, indicating that CHD severity did not appear to affect SMM. This study demonstrated an increase in SMM among cases of a simple and common type of CHD, an isolated VSD, suggesting that even mothers with simple fetal CHD lesions are not exempt from maternal risk. These findings contribute to the evolving understanding of SMM while potentially impacting prenatal care and delivery planning following the identification of fetal CHD.

The causal mechanism for this observation is unknown. One potential explanation is the impact of placental maldevelopment in the setting of fetal CHD. Findings of low placental weight, thrombosis and infarction, abnormal villous development, and fetal growth disturbances have been identified in pregnancies complicated by fetal CHD.[36-39] The fetal heart and the placenta develop concurrently and share common genetic and molecular pathways.[40] The placenta is extraembryonic fetal tissue, and vascular developmental abnormalities that co-occur in the fetal heart and the placenta could contribute to the observed risk of SMM. Placental abruption appears to occur more frequently in the setting of fetal CHD, providing further clinical support for placental pathology.[41,42] We also observed that unplanned cesarean deliveries contribute to a portion of the SMM risk in fetal CHD cases. This finding suggests the presence of an unknown factor contributing to such deliveries which may be in the causal path between fetal CHD and SMM. Additionally, there was no difference in SMM risk between complex and simple fetal CHD in our study, which also supports the hypothesis that an underlying biologic mechanism, shared across various forms of CHD in these pregnancies, increases

the risk of SMM. Further research is needed to understand what factors may necessitate an unplanned cesarean delivery and how it affects adverse maternal outcomes in this population.

Alternatively, shared genetic variants could manifest as different phenotypes in the mother and fetus. Specifically, angiogenic pathways have been associated with maternal cardiovascular disease as well as fetal CHD, but other pathways could also be considered.[16,43] The relationship between fetal CHD and maternal health and nutrition is another potential explanation. Vitamin B12 and folate deficiencies in pregnancy are associated with increased risk of fetal CHD as well as adverse pregnancy outcomes such as gestational diabetes and lower birth weight.[44,45] It is plausible that nutritional deficiencies may also play a role in maternal morbidity. Finally, fetal CHD could represent an unmeasured confounding effect in this complex interaction between the mother and baby. Understanding why SMM occurs more frequently in the setting of fetal CHD may also provide mechanistic insights into the observed increase in prevalence of long-term cardiovascular disease among women who deliver infants with heart defects.[46]

The rate of maternal hospital transfer in pregnancies complicated by fetal CHD was also higher than that of the general population, even after adjustment for risk factors of adverse maternal outcomes. While it is unclear if the indication for transfer was maternal or fetal, the finding very likely reflects transfer to a higher level of care during the delivery hospitalization. Such transfers may suggest an opportunity to improve prenatal delivery planning for both patients in the maternal-fetal dyad—the mother with the risk of SMM and the fetus with the need for specialized postnatal cardiac care.[47,48] Prenatal diagnosis of CHD, whether critical or noncritical, provides such an opportunity for delivery planning.[49] Further research will be needed to understand the complex interaction between prenatal diagnosis of CHD and pregnancy outcomes for both the mother and fetus. For example, mothers with prenatally diagnosed fetal CHD have been found to have increased cesarean delivery, which may contribute to the maternal morbidity. The mother's health and risk factors should be carefully examined in the prenatal assessment and consideration of delivery planning after a diagnosis of fetal CHD.

STUDY LIMITATIONS. While birth certificate and birth defect registry allow for a large population-based cohort study, there are a few limitations with using this data source. Due to data collection and recording processes for both the birth certificate and the birth defect registry, variables are subject to possible underreporting, misclassification, or missing data including the diagnosis codes for CHD. However, the 0.85% prevalence of CHD is similar to that in other studies and suggests relatively accurate case ascertainment.[26] Unfortunately, given the nature of the data source, we are unable to determine whether CHD diagnoses were a prenatal or postnatal diagnosis. This analysis was limited to live births, and the effect of fetal demise or elective terminations is unknown in this analysis. Additionally, the data set reports only a subset of delivery-related diagnoses that are considered SMM. The Centers for Disease Control and Prevention describes 21 indicators of SMM, many of which are not recorded in the birth certificate and thus does not capture the full picture or incidence of SMM.[1] Lastly, although the rate of maternal transfer prior to delivery is known, the reason for transfer is unknown, whether it was due to a maternal or fetal indication or if it was a planned or unplanned transfer. Despite these limitations, we believe that these observations represent a novel insight that deserves further investigation given implications for both the mother and infant.

CONCLUSIONS

Mothers with pregnancies complicated by fetal CHD are at an increased risk of SMM, and this risk is unique to these pregnancies. SMM is associated with a multitude of maternal and obstetrical factors; however, fetal CHD is demonstrated to also be an independent predictor of SMM. Understanding these risk factors and biological etiologies for SMM in this population will allow for improvements in the perinatal management and delivery planning of mothers with fetal CHD with the goal to optimize maternal health outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Pregnancies complicated by fetal CHD are at risk of adverse obstetrical outcomes and severe maternal morbidity. The presence of a fetus with CHD contributes to an independent increased risk of severe maternal morbidity compared to pregnancies without fetal CHD.

TRANSLATIONAL OUTLOOK 1: The mechanism by which fetal CHD increases risk of severe maternal morbidity requires further investigation.

TRANSLATIONAL OUTLOOK 2: Additional research is needed to understand how to improve management of these patients prenatally to optimize outcomes in the mother-fetal dyad.

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