Discordant Congenital Heart Defects in Monochorionic Twins: Risk Factors and Proposed Pathophysiology

David Geffen School of Medicine

Helia Imany-Shakibai[1], Ophelia Yin, MD[1,2], Matthew R. Russell, MD[3], Mark Sklansky, MD[1,4], Gary Satou, MD[1,4], Yalda Afshar, MD, PhD[1,2]

[1]David Geffen School of Medicine, UCLA, [2]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, UCLA Medical Center, [3]Department of Pediatrics, Kaiser Permanente Southern California, [4]Division of Pediatric Cardiology, UCLA Mattel Children's Hospital

Society for Maternal-Fetal Medicine

Background

- Rates of congenital heart defects (CHD) are six-fold higher among monochorionic (MC) twins compared to singleton or dichorionic twin pregnancies.[1]
- Discordant phenotypes related to CHD and other malformations have been described in MC twins, despite identical genotype.[2]
- Late diagnosis of critical CHD is associated with increased risk of morbidity and mortality, increased hospital length of stay, and 35% higher inpatient costs during infancy. [3]
- Factors including epigenetics and placental hemodynamics have been linked to CHD, but there is still an incomplete understanding of the pathophysiology and associated risk factors.[2,4]

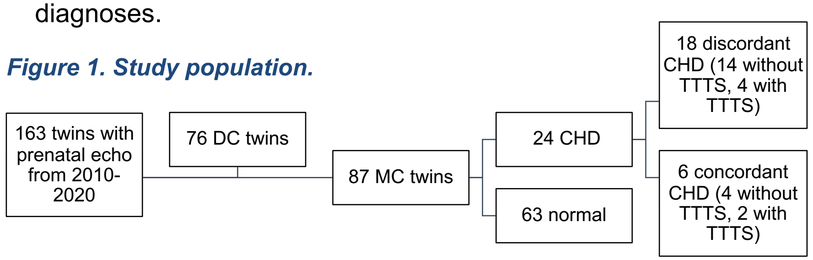
Objectives

- Characterize the frequency and spectrum of concordant and discordant CHD in monochorionic twins in the context of genetic results and clinical demographics in a modern cohort.
- Provide insight into the risk factors and pathophysiology of discordant CHD in MC twins.

Methods

- Inclusion criteria: maternal age ≥ 18 years, date of delivery from January 2010 – March 2020, MC twin gestation confirmed by ultrasound, prenatal fetal echocardiography confirming CHD in at least one twin fetus.
- Concordant CHD (N=6): twin pairs with identical CHD diagnoses.
- Discordant CHD (N=18): pairs with one affected fetus and one non-affected fetus or twin pairs with fetuses affected by different CHD diagnoses.

Figure 1. Study population.



Results

Table 1. Spectrum of CHD in concordant and discordant MC twins, as diagnosed by prenatal echocardiography.

Diagnosis[1,2]	Concordant CHD Cohort (n=12)	Discordant CHD Cohort (n=22)
Septal defects	6 (50%)	10 (45%)
Systemic venous anomalies	0 (0%)	1 (5%)
Right heart lesions	4 (33%)	4 (18%)
Left heart lesions	0 (0%)	2 (9%)
Transposition of the great arteries	2 (17%)	2 (9%)
Thoracic arteries/veins	0 (0%)	3 (14%)
CHD Severity Category (affected)[3]	1.33 ± 0.49	1.27 ± 0.55[4]
CHD Severity Category (all)[3,5]	1.33 ± 0.49	0.78 ± 0.76[6]

Data are no. (%) or mean ± s.d.
[1]Based on the International Nomenclature for Congenital Heart Surgery; [2]p = 0.63; [3]Category 1 = low risk of hemodynamic instability in the delivery room, Category 2 = minimal risk of hemodynamic stability but requiring postnatal surgical intervention, Category 3 = likely hemodynamic instability requiring immediate specialty care, Category 4 = expected hemodynamic instability requiring immediate surgical intervention; [4]p = 0.75; [5]Concordant n=12, discordant n=36 for affected and non-affected; [6]p < 0.01

Table 2. Maternal demographics in concordant and discordant cohorts.

Variable	Concordant CHD cohort (N=6)	Discordant CHD cohort (N=18)	P-value
Maternal age (years)	30.50 ± 3.33	32.39 ± 7.51	0.407
Race			0.798
American Indian or Alaska Native	0 (0%)	0 (0%)	
Asian	1 (17%)	1 (6%)	
Black or African American	0 (0%)	0 (0%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	
White	5 (83%)	14 (78%)	
Other	0 (0%)	2 (11%)	
Denied	0 (0%)	1 (6%)	
Ethnicity			1.00
Hispanic or Latino	1(17%)	4 (22%)	
Not Hispanic or Latino	5 (83%)	13 (72%)	
Other	0 (0%)	1 (6%)	
Pre-gravid BMI (kg/m^2)	25.70 ± 5.62	24.75 ± 6.26	0.754
Pre-gestational Diabetes Mellitus	0 (0%)	0 (0%)	
Gestational Diabetes	0 (0%)	4 (22%)	0.539
Chronic Hypertension	0 (0%)	1 (6%)	1.00
Hypertensive Disease of Pregnancy	2 (33%)	4 (22%)	0.407
Urinary tract infection	1 (17%)	0 (0%)	0.250
Family History of CHD	0 (0%)	2 (11%)	1.00
IVF pregnancy	0 (0%)	5 (28%)	0.280
Maternal length of stay (L&D)	4.67 ± 1.75	10.61 ± 13.05	0.075
1st trimester exposure to SSRI	1 (17%)	1 (6%)	0.446
Illicit drug use in pregnancy	0 (0%)	0 (0%)	
Diagnostic genetic testing	4 (67%)	9 (50%)	0.650
Abnormal genetic results	1 (17%)	1 (6%)	0.450

BMI = body mass index, IVF = in-vitro fertilization, SSRI = selective serotonin reuptake inhibitor. Data are mean ± s.d. or no. (%)

Results, Cont'd

Table 3. Neonatal outcomes and clinical details in concordant and discordant cohorts.

Variable	Concordant CHD cohort (N=12)	Discordant CHD cohort (N=36)	P-value
Sex			1.00
Female	6 (50%)	18 (50%)	
Male	6 (50%)	18 (50%)	
Gestational age at birth (days)	233.67 ± 8.54	236.17 ± 23.28	0.589
Birthweight (g)	2090.58 ± 549.32	1959.92 ± 677.32	0.509
Mode of Delivery			1.00
Vaginal	2 (17%)	6 (17%)	
Cesarean delivery	10 (83%)	30 (83%)	
APGAR 1 minute	6.75 ± 2.90	7.20 ± 2.46	0.639
APGAR 5 minute	7.50 ± 2.65	8.20 ± 1.51	0.403
NICU Admission	12 (100%)	31 (86%)	0.312
NICU LOS	26.83 ± 24.17	34.44 ± 42.97	0.451
Number of surgeries in first year	0.33 ± 0.78	0.53 ± 1.36	0.547
Outcome			0.114
Live Birth	10 (83%)	34 (94%)	
Neonatal Death (<28 days)	2 (17%)	0 (0%)	
Infant Death (>28 days)	0 (0%)	2 (6%)	

NICU = neonatal intensive care unit, LOS = length of stay, Data are mean ± s.d. or no. (%)

Discussion

- Environmental influences play a greater role than genetic factors in the development of discordant CHD, as supported by higher rates of discordant versus concordant MC twin pairs, low incidence of family history of CHD, and low incidence of genetic abnormalities in MC twins with CHD.
- Placental hemodynamics may contribute to the development of discordant CHD, given the high frequency of twin-to-twin transfusion syndrome (TTTS) in this population.
- Limitations include small sample size and lack of genetic test results for every patient.
- Future directions include analysis of both prenatal and postnatal echocardiography records of twins who did not receive a prenatal diagnosis.

References

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