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Spectrum and Outcome of Primary Cardiomyopathies Diagnosed During Fetal Life

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ABSTRACT

OBJECTIVES The purpose of this study was to determine the phenotypic presentation, causes, and outcome of fetal cardiomyopathy (CM) and to identify early predictors of outcome.

BACKGROUND Although prenatal diagnosis is possible, there is a paucity of information about fetal CM.

METHODS This was a retrospective review of 61 consecutive fetal cases with a diagnosis of CM at a single center between 2000 and 2012.

RESULTS Nonhypertrophic CM (NHCM) was diagnosed in 40 and hypertrophic CM (HCM) in 21 fetuses at 24.7 ± 5.7 gestational weeks. Etiologies included familial (13%), inflammatory (15%), and genetic-metabolic (28%) disorders, whereas 44% were idiopathic. The pregnancy was terminated in 13 of 61 cases (21%). Transplantation-free survival from diagnosis to 1 month and 1 year of life for actively managed patients was better in those with NHCM (n = 31; 58% and 58%, respectively) compared with those with HCM (n = 17; 35% and 18%, respectively; hazard ratio [HR]: 0.44; 95% confidence interval [CI]: 0.12 to 0.72; p = 0.007). Baseline echocardiographic variables associated with mortality in actively managed patients included ventricular septal thickness (HR: 1.21 per *z*-score increment; 95% CI: 1.07 to 1.36; p = 0.002), cardiothoracic area ratio (HR: 1.06 per percent increment; 95% CI: 1.02 to 1.10; p = 0.006), ≥3 abnormal diastolic Doppler flow indexes (HR: 1.44; 95% CI: 1.07 to 1.95; p = 0.02), gestational age at CM diagnosis (HR: 0.91 per week increment; 95% CI: 0.83 to 0.99; p = 0.03), and, for fetuses in sinus rhythm, a lower cardiovascular profile score (HR: 1.45 per point decrease; 95% CI: 1.16 to 1.79; p = 0.001).

CONCLUSIONS Fetal CM originates from a broad spectrum of etiologies and is associated with substantial mortality. Early echocardiographic findings appear useful in predicting adverse perinatal outcomes. (J Am Coll Cardiol HF 2014;2:403–11) © 2014 by the American College of Cardiology Foundation.

Cardiomyopathies (CMs) encompass a spectrum of heart muscle disorders that affect cardiac filling, contraction, or both, in the absence of correctible anatomic and/or hemodynamic abnormalities (1). Most children present with a dilated or hypertrophic phenotype (2–4) without an identifiable genetic, familial, infectious, or metabolic cause (5,6). CM is the most common indication for cardiac transplantation in infants (1,7). The condition is rarely diagnosed prenatally, and there is little knowledge of the disease spectrum and outcome when detected prenatally. In a study that predated this research, Pedra et al. (8) reported 55 fetuses with a hypertrophic (n = 33) or dilated (n = 22) phenotype, diagnosed at The Hospital for Sick Children in Toronto, Ontario, Canada between 1990 and 1999.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CM = cardiomyopathy

CTR = cardiothoracic area ratio

CVPS = cardiovascular profile score

HCM = hypertrophic cardiomyopathy

HR = hazard ratio

LV = left ventricular

MPI = myocardial performance index

NHCM = nonhypertrophic cardiomyopathy

The hypertrophic phenotype was predominantly (76%) related to maternal diabetes and twin-twin transfusion syndrome. Cardiac pathology secondary to these conditions is often reversible (9,10), with a substantially better long-term prognosis compared with primary CM. Accordingly, the purpose of this single-center cohort study was to assess the disease pattern and outcome of disorders in which the primary pathology is the fetal myocardium and to determine epidemiological and hemodynamic markers associated with adverse outcomes.

METHODS

The Research Ethics Board of the Hospital for Sick Children approved this retrospective study.

PATIENTS. The Hospital for Sick Children is the exclusive tertiary perinatal cardiac care provider for a population with 80,000 live births per year. Of 8,506 pregnancy referrals to the Fetal Cardiac Program between January 2000 and June 2012, 2,426 were affected by fetal heart disease. These included 61 fetuses (2.5%) with myocardial disease unrelated to structural heart disease, tachyarrhythmia, abnormal cardiac loading, ischemia, or maternal diabetes. After echocardiographic diagnosis of fetal CM, a comprehensive evaluation by the High-Risk Pregnancy Program and, after birth, by the Heart Failure Program was arranged. The diagnostic workup included genetic counseling, virology (polymerase chain reaction, TORCH [toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex virus] serology), metabolic screening, karyotype, pan-cardiomyopathy gene-panel screening, microarray, and, if applicable, invasive or post-mortem specialized testing. Echocardiograms were offered to first-degree relatives in whom familial CM was a possibility.

MEASUREMENTS. Patient information was systematically reviewed including demographic factors, tests, and outcomes to December 2012. All patients underwent detailed 2-dimensional, M-mode, and Doppler echocardiography to determine cardiovascular anatomy and function. Ventricular dimensions were obtained in the cardiac 4-chamber view from M-mode and 2-dimensional recordings. Offline measurements were made by a single investigator (E.J.) and the mean of 3 consecutive measurements were compared with institutional reference data (11). Findings considered abnormal included ventricular shortening fraction <28%, left ventricular (LV) isovolumic relaxation time >43 ms, LV myocardial performance index (MPI) >0.48, ventricular end-diastolic dimensions >2 *z*-scores, cardiothoracic area ratio (CTR) >35%, and more than mild valvar regurgitation (11–14). For fetuses with normal sinus rhythm, the severity of heart failure was quantified using the cardiovascular profile score (CVPS) (**Table 1**) with 2 modifications to the original scoring system (replacement of "skin edema" with "fetal hydrops" and elimination of "tricuspid valve dP/dt," which had not been routinely measured, as 2-point criteria) (12).

Interrater agreement was assessed on 10 randomly selected fetal studies for the following variables: CVPS, CTR, systolic and diastolic ventricular diameters, ventricular septal wall thickness, isovolumic relaxation time, and MPI. Interrater bias was nonstatistically significant for all parameters. Interrater correlation was statistically significant ($r > 0.8$, $p < 0.01$) for all parameters with the exception of LV MPI ($r = 0.55$, $p > 0.05$). These data confirm that interrater reproducibility was excellent for most parameters.

DEFINITIONS. CM was divided into 2 anatomic phenotypes, depending on the presence or absence of myocardial hypertrophy at final assessment. This approach was selected to allow for phenotypic crossover that can occur during fetal life. *Hypertrophic cardiomyopathy* (HCM) demonstrated inappropriate ventricular hypertrophy and was defined by diastolic ventricular wall thickness >2 *z*-scores at the last echocardiogram or at autopsy (15,16). *Nonhypertrophic cardiomyopathy* (NHCM) was defined by cardiac dysfunction in the absence of myocardial hypertrophy at any stage and included dilated and nondilated phenotypes (17,18). Dilated NHCM was defined by ventricular enlargement >2 *z*-scores of 1 or both ventricles. LV noncompaction was diagnosed on the basis of prominent trabeculations and multiple deep recesses at the ventricular apex (19,20). Fibrosis and calcification were identified as areas of persistently echogenic endomyocardium (8,16,21). *Fetal hydrops* was defined by ≥2 sites of fluid collections. *Diastolic dysfunction* was defined by ≥3 of 5 abnormal echocardiographic markers: monophasic tricuspid flow; monophasic mitral flow; pulmonary venous flow reversal during atrial systole; absent/reversed ductus venosus flow during atrial systole; and umbilical vein pulsations. Umbilical vein pulsation was the only variable used to diagnose diastolic dysfunction in cases of nonsinus rhythm (8).

Each condition was also classified by etiology as follows: 1) *genetic-metabolic* related to chromosomal disorder, inborn error of metabolism, or first-degree family members with CM; 2) *inflammatory* secondary