The Association between Sex and Long-Term Pediatric Cardiovascular Morbidity

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Objective To evaluate the association between sex and long-term pediatric cardiovascular morbidity.

Study design A population-based cohort study was performed that compared the risk of long-term cardiovascular morbidity (up to the age of 18 years) of children according to sex. Deliveries occurred between the years 1991 and 2013 in a tertiary medical center. Multiple pregnancies and fetal congenital malformations were excluded. Kaplan-Meier survival curves were constructed to compare cumulative cardiovascular morbidity incidence. A Cox proportional hazards model was used to control for confounders, including gestational age at birth, birth weight, and maternal factors.

Results During the study period, 240 953 newborns met the inclusion criteria and were included in the long-term analysis. Of them, 51.0% (n = 122 840) were male and 49.0% (n = 118 113) female. Cardiovascular morbidity up to the age of 18 years was significantly more common in male as compared with female newborns (0.3% vs 0.2%, OR 1.33, 95% CI 1.12-1.57, $P = .001$). In the Cox regression model, male sex exhibited an independent association with long-term cardiovascular morbidity with an adjusted hazard ratio of 1.37 (95% CI 1.16-1.63, $P < .001$).

Conclusion Male newborns are at an increased risk for pediatric cardiovascular morbidity independent of gestational age at birth and birth weight. *(J Pediatr 2017;180:68-73).*

The lifelong health of an individual is determined, in part, by the cumulative exposures throughout life. This is particularly true for fetal development, with numerous studies demonstrating that adult disease may be influenced by events that occurred in the womb.[1] The impact of fetal sex and pregnancy course and outcome has been a focus of interest. Sex impact has been explored in several studies,[2-11] leading to a general concept that women carrying a male fetus have greater chances for adverse maternal, fetal, and neonatal outcomes. Pregnancies with male fetuses were shown to be associated with a greater risk of pregnancy complications such as labor dystocia, cord pathologies, fetal distress, and several immediate adverse perinatal outcomes.[2-10] Male fetuses are associated with a greater prevalence of abnormal fetal heart rate patterns, lower 1- and 5-minute Apgar scores, and lower umbilical pH values compared with female fetuses matched for gestational age at delivery.[5,11] Boys grow faster than girls from an early stage of gestation. It has been shown that even before implantation, male karyotype embryos develop earlier than female karyotype embryos.[12,13] This difference makes them more vulnerable in compromised nutritional conditions. More newborn boys than girls have growth restriction and placental pathologies, and more of them die during the perinatal period.[14,15]

Although fetal sex and immediate perinatal outcome has been studied widely, less is known regarding the possible long-term impact of sex on pediatric morbidity. Because male fetuses grow at a faster rate than female fetuses, this accelerated growth makes male fetuses more vulnerable during disturbed pregnancies, with less favorable outcomes occurring throughout the life course of the individual.[16,17] An immediate consequence of fetal undernutrition is reduced growth and low birth weight[18]; a long-term consequence may be vulnerability to cardiovascular disorders later in life.[19] The present study was designed to analyze the link between fetal sex and long-term cardiovascular pediatric morbidity while accounting for gestational age at birth and birth weight.

Methods

A cohort study was performed to compare the risk of long-term cardiovascular morbidity (up to the age of 18 years) according to the offspring's sex. Deliveries occurred between 1991 and 2013. The study was conducted at the Soroka University Medical Center (SUMC), the sole hospital in the Negev (southern Israel), which occupies 60% of the land of Israel, and is serving the entire population of the region (14.4% of Israel's population of about 600,000).[20] Thus, the study is based on nonselective population data. The study was approved by the institutional review board (in accordance with the Declaration of Helsinki, 0438-15-SOR, March 2016).

DOHaD	Developmental origins of health and disease
SUMC	Soroka University Medical Center

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Table I. Different cardiovascular morbidities assessed

	Codes	Diagnosis descriptions
Cardiovascular		
Hypertension	4019	UNSPECIFIED ESSENTIAL HYPERTENSION
Hypertensive kidney disease	40390	UNSP. HYPERTENSIVE KIDNEY DIS. WITH CHRONIC KIDNEY DISEASE STAGE I THROUGH STAGE IV, OR UNSPECIFIED
	40391	UNSP. HYPERTENSIVE KIDNEY DIS. WITH CHRONIC KIDNEY DISEASE
	40391	UNSP. HYPERTENSIVE KIDNEY DIS. WITH CHRONIC KIDNEY DISEASE STAGE V OR END STAGE RENAL DISEASE
	40391	UNSP. HYPERTENSIVE RENAL DIS. + RENAL FAILURE
	40591	UNSPECIFIED RENOVASCULAR HYPERTENSION
Pulmonary heart disease	4160	PRIMARY PULMONARY HYPERTENSION
	4168	OTHER CHRONIC PULMONARY HEART DISEASES
	4169	CHRONIC PULMONARY HEART DISEASE, UNSPECIFIED
Cardiomyopathy	4251	HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY
	4252	OBSCURE CARDIOMYOPATHY OF AFRICA
	4253	ENDOCARDIAL FIBROELASTOSIS
	4254	OTHER PRIMARY CARDIOMYOPATHIES
	4257	NUTRITIONAL AND METABOLIC CARDIOMYOPATHY
	4259	SECONDARY CARDIOMYOPATHY, UNSPECIFIED
Arrhythmia	4260	ATRIOVENTRICULAR BLOCK, COMPLETE
	4263	OTHER LEFT BUNDLE BRANCH BLOCK
	4264	RIGHT BUNDLE BRANCH BLOCK
	4267	ANOMALOUS ATRIOVENTRICULAR EXCITATION
	4270	PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA
	4271	PAROXYSMAL VENTRICULAR TACHYCARDIA
	4272	PAROXYSMAL TACHYCARDIA, UNSPECIFIED
	4273	ATRIAL FIBRILLATION AND FLUTTER
	4275	CARDIAC ARREST
	4279	CARDIAC DYSRHYTHMIA, UNSPECIFIED
	42611	FIRST DEGREE ATRIOVENTRICULAR BLOCK
	42612	MOBITZ (TYPE) II ATRIOVENTRICULAR BLOCK
	42613	OTHER SECOND DEGREE ATRIOVENTRICULAR BLOCK
	42682	LONG QT SYNDROME
	42689	OTHER SPECIFIED CONDUCTION DISORDERS
	42731	ATRIAL FIBRILLATION
	42732	ATRIAL FLUTTER
	42741	VENTRICULAR FIBRILLATION
	42760	PREMATURE BEATS, UNSPECIFIED
	42761	SUPRAVENTRICULAR PREMATURE BEATS
	42769	OTHER PREMATURE BEATS
	42789	OTHER SPECIFIED CARDIAC DYSRHYTHMIAS
	427811	SINUS BRADYCARDIA
	42671	WOLFF-PARKINSON-WHITE SYNDROME
Heart failure	4280	CONGESTIVE HEART FAILURE
	4280	CONGESTIVE HEART FAILURE, UNSPECIFIED
	4281	LEFT HEART FAILURE
	4289	HEART FAILURE, UNSPECIFIED
	4290	MYOCARDITIS, UNSPECIFIED
	4292	CARDIOVASCULAR DISEASE, UNSPECIFIED
	4293	CARDIOMEGALY
	42841	ACUTE COMBINED SYSTOLIC AND DIASTOLIC HEART FAILURE

Exclusion criteria included multiple pregnancies and fetuses with major congenital malformations. Perinatal deaths (intrauterine fetal death, intrapartum death, and postpartum death) were excluded from the long-term follow-up cohort.

A comparison was performed between male and female subjects and included pregnancy characteristics and perinatal outcome. A cardiovascular event was defined as the first hospitalization (following routine neonatal discharge) up to the age of 18 years with any cardiovascular diagnosis. The different cardiovascular morbidities assessed are detailed in **Table I**. Follow-up was terminated if any of the following occurred: first hospitalization for any of the diagnoses listed in **Table I** (ie, an event), hospitalization resulting in death, or when the child reached 18 years of age.

Data were collected from 2 databases that were cross-linked and merged: the computerized hospitalization database of SUMC ("Demog-ICD9") and the computerized perinatal database of the obstetrics and gynecology department. The Demog-ICD9 database includes demographic information and *International Statistical Classification of Diseases and Related Health Problems*, *Ninth Revision*, codes for all medical diagnoses made during encounters with SUMC.

Any encounter of the offspring with SUMC following initial discharge after delivery was included. These encounters include visits to the outpatient clinic located within the hospital, any of the emergency rooms within the hospital (leading to hospitalization), and hospitalization in any department within the hospital.