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RESEARCH LETTER

Pregnancy Outcomes in Females With Dilated Cardiomyopathy–Associated Rare Genetic Variants

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Genetic testing for familial dilated cardiomyopathy (DCM) is revealing cohorts of asymptomatic women with rare deleterious variants at risk for future disease. Why only some develop DCM is a topic of current interest. The notion of disease-modifying environmental risk factors is gathering ground as possible explanation.[1] Pregnancy increases hemodynamic load and causes depression of cardiac function even in normal hearts.[2] This is particularly problematic for women with preexisting heart disease,[3] and may unmask cardiomyopathy in those with a genetic predisposition. Several cohort studies have supported this hypothesis, with DCM rare variants found in up to 22% of females with peripartum cardiomyopathy.[4,5] However, the risk of pregnancy among asymptomatic women with rare variants, and the extent to which pregnancy modifies DCM onset and progression remains unexplored.

We performed a retrospective cohort study of women with pathogenic or likely pathogenic DCM variants to determine the prevalence of adverse cardiac outcomes during pregnancy. Furthermore, we evaluated whether pregnancy factors, including parity and gestational age, were predictive of DCM development. Women were selected from the Melbourne Health genetic database (2012–2020) and included if they carried a pathogenic or likely pathogenic DCM variant and had ≥1 pregnancy. Interview and file review were conducted. The study was approved by an internal research ethics committee, and participants gave informed consent. The primary outcome was a major cardiac adverse event within six months of pregnancy including confirmed clinical heart failure, sustained ventricular arrhythmias, or death. The secondary outcome was heart failure symptoms or documented left ventricular systolic deterioration (↓ ejection fraction of >10%) within 6 months of pregnancy. The presence or absence of DCM was evaluated for an association with parity and gestational age. Study research data is available from the corresponding author upon reasonable request.

Thirty females from 16 families consented, with 70 total pregnancies. Baseline characteristics were similar between those with and without DCM (Table). Approximately half of the cohort had *TTN* truncating variants (*TTN*tv) (n=15), all of which were located in exons with high (>0.9) percent splice-in scores in the A band (n=5) or I band (n=2) regions. The remainder had rare variants in other genes; *BAG3* (n=2; p.Arg395Glyfs*848), *DES* (n=2; p.Ser13Phe, p.His441Leufs*9), *MYH7* (n=1; p.Gly178Arg), *PLN* (n=2; p.Leu39*), *SCN5A* (n=1; p.Gly1743Arg), *TNNT2* (n=4; p.Arg173Trp), *RBM20* (n=3; p.Arg634Trp, p.Glu913Lys).

All women in this study were asymptomatic leading into their first pregnancy and were stratified into 3 groups based on timing of DCM diagnosis. Group 1 (n=3) diagnosed with DCM during or within 6 months of pregnancy, Group 2 (n=11) diagnosed with DCM >6 months after pregnancy (range, 2–35 years, median 17 years), and group 3 (n=16) no DCM at the time of the study (range, 1–41 years, median 17 years).

All 3 women in group 1 met the primary outcome. One female, previously asymptomatic (likely pathogenic; *TTN*tv p.Ser8552Ter) had cardiac arrest due to ventricular tachycardia at 17 weeks gestation. An echocardiogram confirmed DCM before her death one week later. A second previously asymptomatic female (likely pathogenic; *MYH7* p.Gly178Arg) presented with a stroke and heart failure 4 weeks postpartum and was diagnosed with peripartum cardiomyopathy with left

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Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
TTNtv	TTN truncating variants

ventricular thrombus. A third female (pathogenic; *RBM20* p.Glu913Lys) presented with acute severe heart failure requiring mechanical circulatory support at 36 weeks' gestation. She had been diagnosed with peripartum cardiomyopathy in a pregnancy 7 years earlier with recovery of left ventricular function; however, she had been lost to follow up and had ceased therapy.

None of the individuals in groups 2 or 3 met the primary outcome. Only 1 individual in group 2 met the secondary outcome with symptomatic heart failure during pregnancy that went uninvestigated and settled postpartum. The remaining women in groups 2 and 3 recalled normal pregnancies without symptoms. Only 2 women in group 3 had knowledge of their genetic diagnosis leading into pregnancy, prompting surveillance. No other participants had cardiac assessments or treatments during pregnancy. Pregnancy factors, including parity and gestational age, were not different between those with and without DCM.

The main findings of this study are that (1) most asymptomatic females with rare DCM variants had uneventful pregnancies, however (2) 10% of cases had clinically significant cardiac complications, a rate similar to that seen in women with cardiac disease predating pregnancy.[3] Our data support previous research suggesting that a DCM diagnosis during pregnancy may be the first manifestation of familial DCM with implications for other family members.

Although diagnosis during or shortly after pregnancy was associated with a poor prognosis, those diagnosed with DCM years distant from their last pregnancy, and those without DCM at the time of the study, appeared to have tolerated pregnancy well. Though limited by the retrospective design, these results provide some reassurance that pregnancy in females with DCM rare variants who are confirmed to be clinically unaffected before conception can be well tolerated. However, those with undiagnosed cardiomyopathy are at high risk for adverse events.

The authors advocate for clinical evaluation and echocardiography in women with DCM rare variants as part of preconception workup and pregnancy management. Larger prospective cohort studies are required.

Table. Baseline Characteristics and Outcomes of Groups

	Group 1 (n=3)	Group 2 (n=11)	Group 3 (n=16)	
	DCM		No DCM	*P* value
Baseline characteristics				
Median age (range)	52 (27–79)		51 (28–71)	0.42
Total pregnancies, n	34		37	0.60
Median pregnancies/pt, n	2		2	0.60
Median BMI/BMI>30	28 / 6		25 / 5	0.21/0.41
TTNtv carriers, n	8 (57)		7 (44)	0.46
High alcohol, n	2 (14)		4 (25)	0.41
High exercise, n	1 (7)		0 (0)	0.29
Hypertension	2 (14)		2 (13)	0.941
Outcomes				
Primary outcome	3 (100)[a]	0 (0)[b]	0 (0)[b]	<0.001
Secondary outcome	0 (0)	1 (10)	0 (0)	0.41
DCM predictive variables				
Median age at study*	48	54	51	0.22
Total pregnancies, n	6	31	34	0.72
Median pregnancies per female, n	2	2	2	0.72
Median age at first pregnancy, y	25	29	29	0.19
Median age at last pregnancy, y	27	34	32	0.13

P values reflect significance for overall tests between groups; values within rows that share a superscript are not significantly different from each other for post hoc pairwise comparisons (α=0.05). Group 1: DCM diagnosed within 6 m of pregnancy. Group 2: DCM diagnosed > 6 m from pregnancy. Group 3: no DCM. High alcohol >7 drinks per week, High exercise >12 h training per week. BMI indicates body mass index; DCM, dilated cardiomyopathy; and pt, patient.

*Or age at time of death.

ARTICLE INFORMATION

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Disclosures

None.

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