Women with peripartum cardiomyopathy have normal ejection fraction, but abnormal systolic strain, during pregnancy

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Abstract

We report a case series of six women with peripartum cardiomyopathy (PPCM) who incidentally underwent echocardiography prior to the clinical presentation of PPCM. For comparison, we identified controls, matched 2:1 on age, race, body mass index, gestational age, and hypertensive disorder. Among the six cases, all were diagnosed with PPCM during the post-partum period. Pre-PPCM echocardiograms were performed between 17.7 weeks of gestation and 13 days post-partum. Baseline left ventricular ejection fraction and size were normal and similar to the 12 matched controls (60% ± 6.6% vs. 61.4% ± 6.3%, $P = 0.63$) or left ventricular end-diastolic dimension (4.6 cm ± 0.2 cm vs. 4.5 cm ± 0.4 cm, $P = 0.689$). There was a trend towards a less negative (more abnormal) mean global longitudinal strain in cases compared with controls ($-14\% \pm 4\%$ vs. $-18.3\% \pm 4.5\%$, $P = 0.0658$). Mean global circumferential strain was significantly less negative (more abnormal) in cases compared with controls ($-21.5\% \pm 5\%$ vs. $-29.3\% \pm 7.6\%$, $P = 0.0329$). We conclude that women who develop PPCM have normal left ventricular ejection fraction during gestation preceding PPCM, indicating that the disease develops acutely in the peripartum period. Abnormal strain can be detected, however, suggesting that strain imaging could represent a screening method in populations at high risk for PPCM if confirmed in future studies.

Introduction

Peripartum cardiomyopathy (PPCM) is a form of systolic heart failure diagnosed towards the end of pregnancy or in the months following delivery in women without pre-existing cardiac disease.[1] Contemporary cohorts in the USA demonstrate that 65% to 72% have recovery of left ventricular (LV) function; however, recovery rates vary by population, and many women experience adverse outcomes, including persistent heart failure, arrhythmias, thromboembolic complications, or death.[1–5] Whether women have normal LV ejection fraction (LVEF) and LV size during pregnancy and prior to development of PPCM has been disputed and has been difficult to study given the low incidence of PPCM and the infrequent use of echocardiograms during pregnancy. In addition, LV

strain has emerged as a powerful tool to detect subclinical LV dysfunction in the setting of cardiotoxic chemotherapy, prior to a subsequent decrease in LVEF.[6] Whether changes in LV strain indices precede the drop in LVEF in PPCM has not been studied and may hold predictive ability to identify women at risk. Our aims are to describe baseline LV function, including LVEF and strain indices, of peripartum women prior to their development of PPCM and to compare these measures to peripartum women without PPCM.

Case report

We identified six cases of pregnant women with echocardiograms performed during pregnancy or post-partum period

and prior to the development of PPCM. We identified cases from a previously established and updated retrospective cohort of women with PPCM treated within the University of Pennsylvania Health System, as previously described.[3] We included women who had also had an echocardiogram performed during pregnancy/post-partum period prior to the diagnosis of PPCM (pre-PPCM echocardiogram). We also compared baseline echocardiographic parameters of peripartum women who subsequently developed PPCM (cases) to peripartum women without PPCM (controls). Controls without known cardiac disease were matched 2:1 on maternal age (±5 years), race, body mass index, gestational age (±4 weeks), and hypertensive disorder. Control echocardiograms were selected from women who had enrolled in prior clinical research studies at our health system evaluating echocardiographic differences between women with hypertensive disorders of pregnancy and normotensive pregnancies. The primary outcomes were LVEF, LV end-diastolic dimension, global longitudinal strain (GLS), and global circumferential strain (GCS). LVEF was measured using modified Simpson biplane method. Strain was measured using speckle tracking (TomTec Imaging Systems, Unterschleissheim, Germany), as described previously.[7,8] All echocardiograms were analysed by study staff (R.T. and Y.K.). Continuous variables were presented as means and standard deviations and assessed using the Student's t-test given normality of the data. Categorical variables were assessed using Fisher's exact test. We used univariate exact conditional regression to analyse outcomes to account for matched data.

The timing of pre-PPCM echocardiograms ranged from 17.7 weeks of gestation to 13 days post-partum. Indications for the pre-PPCM echocardiograms are presented in *Table 1*. For Cases 1, 2, and 3, indications for echocardiogram were first degree atrioventricular block, palpitations, and chronic hypertension, respectively. Case 4 had a known small, restrictive ventricular septal defect (VSD), and an echocardiogram was performed during pregnancy for routine screening. Of note, at the time of her subsequent PPCM diagnosis, it was thought that the drop in LVEF was not related to her known prior VSD. Case 5 had an echocardiogram performed as part of a workup for hypoxia and tachycardia, and she was ultimately diagnosed with a pulmonary embolism. Case 6 had an echocardiogram performed due to chest pain, and she was ultimately diagnosed with and treated for pericarditis.

Peripartum cardiomyopathy was diagnosed post-partum in all cases, ranging from 6 to 100 days after delivery. The timing between the pre-PPCM echocardiograms and PPCM diagnosis echocardiograms ranged from 19 to 222 days. At the time of PPCM diagnosis, LVEF ranged from 24% to 45%. The majority of the cases (5/6) ultimately had LVEF recovery (LVEF ≥ 50%). Genetic results were available for 4/6 cases, and none had a titin-truncating mutation.

The mean age was 32.8 years, and the majority (4/6) were black. There were no significant differences in baseline

Table 1 Cases of peripartum cardiomyopathy with echocardiograms performed prior to diagnosis

| Case | Medical history | Pre-PPCM echocardiogram[a] | | | At time of PPCM diagnosis | | | Recovery | |
		GA or days post-partum	Clinical indication	LVEF	Days post-partum	LVEF	Days between echocardiograms	Recovery to LVEF ≥ 50%	TTN mutation
1	T2 IDDM	17.7 weeks	First degree AVB on ECG	52%	73 days	33%	222	Yes	No
2	Crohn's disease	19.7 weeks	Palpitations	68%	9 days	37%	121	Yes	N/A
3	T1DM, chronic HTN	20.1 weeks	Screening given chronic HTN	54%	93 days	36%	153	No	No
4	Small restrictive VSD	32.9 weeks	Screening given known VSD	67%	6 days	45%	42	Yes	No
5	Asthma, rheumatoid arthritis	Post-partum 1 day	Shortness of breath due to PE	61%	20 days	29%	19	Yes	N/A
6	Asthma, hyperlipidaemia	Post-partum 13 days	Chest pain, diagnosed with pericarditis	58%	100 days	24%	87	Yes	No

AVB, atrioventricular block; ECG, electrocardiogram; GA, gestational age; HTN, hypertension; LVEF, left ventricular ejection fraction; N/A, not available; PE, pulmonary embolism; PPCM, peripartum cardiomyopathy; T1DM, type 1 diabetes mellitus; T2 IDDM, type 2 insulin-dependent diabetes mellitus; TTN, titin; VSD, ventricular septal defect.
[a]Echocardiogram performed prior to diagnosis of PPCM.

characteristics between the matched cases and controls (*Table 2*). There was no significant difference in pre-PPCM LVEF (60% ± 6.6% vs. 61.4% ± 6.3%, *P* = 0.63) or LV end-diastolic dimension (4.6 cm ± 0.2 cm vs. 4.5 cm ± 0.4 cm, *P* = 0.689) between cases and controls. Strain analysis was technically able to be performed in 5/6 cases and all controls. There was a trend towards a less negative (more abnormal) mean GLS in cases compared with controls (−14% ± 4% vs. −18.3% ± 4.5%, *P* = 0.0658). Mean GCS was significantly less negative (more abnormal) in cases compared with controls (−21.5% ± 5% vs. −29.3% ± 7.6%, *P* = 0.0329) (*Table 2*).

Discussion

While it has been often assumed that women have normal LVEF and LV dimensions during pregnancy and prior to development of PPCM, this has not been previously confirmed with serial echocardiograms. Our findings support the conclusion that LVEF and LV dimensions are largely normal during pregnancy and early post-partum period in women who go on to develop PPCM and that changes in LVEF and LV dimensions occur acutely at the time of or shortly before the diagnosis of PPCM. Our study suggests that subclinical dysfunction, as measured by GLS and GCS, may be present prior to the development of symptomatic heart failure and LV dysfunction in women with PPCM. Therefore, subclinical strain abnormalities identified during pregnancy may help to identify women at increased risk of developing PPCM. Current thinking on the pathophysiology of PPCM suggests that hormones of late gestation, including those increased by pre-eclampsia, cause microvascular damage to the heart, leading to

PPCM.[1,9] This abnormal hormonal milieu may manifest its cardiotoxic effect as subclinical dysfunction prior to causing an overt drop in LVEF, analogous to the cardiotoxic effect of chemotherapy.[6] If our results are confirmed in larger cohorts, strain imaging could serve as a screening target in populations at increased risk for developing PPCM.

Cardiovascular disease, including PPCM, is a leading cause of maternal morbidity and mortality, disproportionately impacts women of African ancestry, and contributes to significant racial disparities in maternal outcomes observed in the USA.[10] A limited echocardiogram during pregnancy to identify clinical or subclinical abnormalities in women with risk factors for PPCM, such as African ancestry, advanced maternal age, multi-gestational pregnancies, or hypertensive disorders, may identify women who need closer follow-up during pregnancy and the post-partum period to monitor for early signs or symptoms of heart disease. This is especially important for women who experience barriers to accessing care and may mistake cardiac symptoms for normal pregnancy symptoms.[11] Further research should examine the feasibility of obtaining limited maternal cardiac views during routine pregnancy care, such as the second trimester foetal ultrasound scan.

Our study has limitations to consider. First, normative values for strain during pregnancy have not been established, although some studies suggest that strain worsens during the third trimester.[12,13] Average strain rates in our control cohort are similar to those reported in the literature. We aimed to account for pregnancy-related changes in strain by matching on gestational age and other clinical factors, although it was not possible to match on all relevant factors. Second, our sample size is small, and therefore, our results need to be confirmed in a larger

Table 2 Clinical and echocardiographic characteristics of peripartum women who subsequently develop peripartum cardiomyopathy and matched controls

	Cases (*n* = 6)	Controls (*n* = 12)	*P*-value
Baseline characteristics[a]			
Age at delivery, mean (SD)	32.8 (8.3)	30.0 (8.3)	0.505
Race, *n* (%)			1.000
White	2 (33.3)	4 (33.3)	
Black	4 (66.7)	8 (66.7)	
BMI, mean (SD)	31.1 (4.9)	30.0 (4.7)	0.645
GA or days PP at time of echocardiogram	17.7 weeks to 13 days PP	19.1 weeks to 2 days PP	
Hypertensive disorder at time of echocardiogram, *n* (%)	2 (33.3)	3 (25.0)	1.000
GA at delivery, mean (SD)	35.5 (4.5)	36.6 (4.2)	0.619
Echocardiographic parameters, mean (SD)[b]			
LV ejection fraction (%)	60.0 (6.6)	61.4 (6.3)	0.630
LV end-diastolic dimension (cm)	4.6 (0.2)	4.5 (0.4)	0.689
Global longitudinal strain (%)	−14.0 (4.0)	−18.3 (4.5)	0.066
Global circumferential strain (%)	−21.5 (5.0)	−29.3 (7.6)	0.033

BMI, body mass index; GA, gestational age; LV, left ventricular; PP, post-partum.
[a]Analysed using the Student's *t*-test for continuous variables and Fisher's exact test for binary variables.
[b]Analysed using univariate conditional exact regression.

study. Third, we do not have longitudinal strain data to determine whether these changes in strain persist or resolve over time in women with subsequent LV recovery. Finally, echocardiograms are not standard of care during pregnancy, and our cases and controls may represent selection bias. Pre-eclampsia and hypertension can impact strain values and are associated with PPCM, for which we aimed to control through matching. To our knowledge, the other indications for pre-PPCM echocardiograms (e.g. restrictive VSD and pulmonary embolism) do not significantly affect LV strain values.[14–16]

Peripartum cardiomyopathy is a leading cause of maternal mortality in the post-partum period, especially among black women, and delayed diagnosis leads to worse clinical outcomes. Therefore, efforts focused on closer monitoring and earlier treatment of those at risk have the potential to improve maternal cardiovascular health and lessen racial disparities.

Acknowledgement

Conflict of interest

None declared.

Funding

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