



Electrocardiographic findings in peripartum cardiomyopathy

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Background: There is limited data on electrocardiographic (ECG) abnormalities and their prognostic significance in women with peripartum cardiomyopathy (PPCM). We sought to characterize ECG findings in PPCM and explore the association of ECG findings with myocardial recovery and clinical outcomes.

Hypothesis: We hypothesized that ECG indicators of myocardial remodeling would portend worse systolic function and outcomes.

Methods: Standard 12-lead ECGs were obtained at enrollment in the Investigations of Pregnancy-Associated Cardiomyopathy study and analyzed for 88 women. Left ventricular ejection fraction (LVEF) was measured by echocardiography at baseline, 6 months, and 12 months. Women were followed for clinical events (death, mechanical circulatory support, and/or cardiac transplantation) until 1 year.

Results: Half of women had an "abnormal" ECG, defined as atrial abnormality, ventricular hypertrophy, ST-segment deviation, and/or bundle branch block. Women with left atrial abnormality (LAA) had lower LVEF at 6 months (44% vs 52%, $P = 0.02$) and 12 months (46% vs 54%, $P = 0.03$). LAA also predicted decreased event-free survival at 1 year (76% vs 97%, $P = 0.008$). Neither left ventricular hypertrophy by ECG nor T-wave abnormalities predicted outcomes. A normal ECG was associated with recovery in LVEF to $\geq 50\%$ (84% vs 49%, $P = 0.001$) and event-free survival at 1 year (100% vs 85%, $P = 0.01$).

Conclusions: ECG abnormalities are common in women with PPCM, but a normal ECG does not rule out the presence of PPCM. LAA predicted lower likelihood of myocardial recovery and event-free survival, and a normal ECG predicted favorable event-free survival.

KEYWORDS

electrocardiography, maternal-fetal health, outcomes, peripartum cardiomyopathy

1 | INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a dilated cardiomyopathy marked by systolic dysfunction occurring at the end of pregnancy or, more commonly, in the early postpartum period.^{1,2} Globally, incidence appears to be highest in Nigeria (up to 1 in 100 live births)³ and Haiti (1 in 300 live births).⁴ In the United States, the incidence of PPCM is rising⁵ and is approximately 4-fold higher in black women (1 in

1000-1500 live births) than in Caucasian women (1 in 4000 live births).^{2,6} Other risk factors include older maternal age, multiple gestation, and preeclampsia.^{7,8} The etiology of PPCM remains unclear; proposed mechanisms have included angiogenic factor imbalance, abnormal prolactin cleavage, inflammation, selenium deficiency, and genetic susceptibility.⁹⁻¹⁴

More than half of women recover left ventricular (LV) function after PPCM, but a significant proportion is left with chronic heart

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failure, and some women require ventricular assist device (VAD) implantation or cardiac transplantation. In a recent North American series of 100 women, the Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, 72% of women experienced recovery in LV ejection fraction (LVEF) to >50% by 12 months.¹⁵ Predictors of persistent LV dysfunction included LVEF <30% or LV end-diastolic diameter > 6 cm at diagnosis, black race, and late presentation.¹⁵ Elevation in troponin, B-type natriuretic peptide, and soluble fms-like tyrosine kinase-1 (sFlt-1) may also portend adverse cardiac remodeling and outcomes.^{16–18}

There is limited and conflicting data on ECG abnormalities and their significance in women with PPCM. In a Nigerian series of ECGs for 54 cases of PPCM and 77 postpartum women without PPCM, women with PPCM had faster heart rate, longer QRS and QTc intervals, and a higher frequency of ST-T-wave abnormalities than controls.¹⁹ Of note, the authors did not examine the prognostic significance of ECG findings in this cohort. In a series of 78 South African women, 59% had T-wave abnormalities, 12% had a bundle branch block (BBB), 10% had left atrial abnormality, and 6% had ST-segment changes on baseline ECG.²⁰ Follow-up was available on only 56% of this cohort, but among women with follow-up, T-wave inversions and ST depressions on the presenting ECG were associated with lower LVEF at 6 months.²⁰ In a series of 77 women in Beijing with PPCM, neither QRS nor QTc interval nor the frequency of ST depressions differed between women who did and did not recover LV function.¹⁷ As the phenotypic presentation of PPCM differs across continents,²¹ ECG changes observed in Africa and Asia may not match those seen in North American PPCM patients, for whom there has been no data published on ECG findings to date.

Thus, we sought to characterize ECG findings at PPCM presentation in patients from the United States and Canada in the IPAC cohort and to explore the potential prognostic significance of specific ECG findings in this population. We hypothesized that ECG indicators of myocardial remodeling, such as ventricular hypertrophy and atrial abnormalities, would portend less recovery of systolic function and worse outcomes.

2 | METHODS

Between 2009 and 2012, 100 women at 30 participating sites in North America with newly diagnosed PPCM were enrolled in the IPAC study up to 13 weeks postpartum. Eligible women were 18 years of age or older, lacked underlying cardiac disease, had an LVEF <45% at enrollment, and had been ruled out for alternate etiologies of cardiomyopathy. All women had an echocardiogram at enrollment, 6, and 12 months, and these studies were reviewed by a core laboratory at the University of Pittsburgh for assessment of ventricular volumes and calculation of ejection fraction. Clinical events, including hospitalizations, mechanical circulatory support, cardiac transplantation, and death, were followed to 12 months postpartum. Institutional review boards at all participating centers approved the protocol and all patients signed informed consent.

Standard left-sided 12-lead electrocardiograms (ECGs) were obtained at the time of enrollment and were available for review in

88 of 100 women in the IPAC cohort. For 10 women, a written report of the enrollment ECG was available but not the ECG tracing itself, and two women had tracings of poor quality that were deemed uninterpretable; these 12 subjects were excluded. Features of each ECG tracing (eg, rate, rhythm, intervals, and amplitudes) were systematically analyzed in a blinded fashion by one investigator (M.C.H.), and a second investigator (M.M.G.) validated a random subset of ECG interpretations. The investigators reviewing ECGs were blinded to subject demographics, clinical presentation, echocardiograms, and outcomes.

A normal QRS axis was -30° to $+90^{\circ}$. BBBs were defined per American Heart Association, American College of Cardiology, and Heart Rhythm Society guidelines.²² Left atrial abnormality (LAA) was defined as terminal negative deflection of the P-wave in V_1 > 40 ms wide and > 1 mm deep. Right atrial abnormality was defined as a P-wave >2.5 mm tall in II and/or positive initial deflection of the P-wave in V_1 > 1.5 mm.²³ Left ventricular hypertrophy (LVH) was defined using the Sokolow-Lyon criteria (S in V_1 plus R in V_5 or $V_6 \geq 35$ mm and/or R in aVL ≥ 11 mm) or the Cornell voltage criteria for women (S in V_3 plus R in aVL > 20 mm). Right ventricular hypertrophy (RVH) was defined as R in $V_1 \geq 7$ mm. ST-segments were coded as depressed if ≥ 0.5 mm below baseline and as elevated if ≥ 0.5 mm above baseline. T-waves were recorded as flattened only if the T-wave was completely flat. T-waves were recorded as inverted if they were negatively directed, except for negatively directed T-waves in III, aVR, or V_1 with an associated negative QRS complex, which were recorded as normal. The presence of left atrial enlargement and LVH were also assessed by echocardiography. Left atrial enlargement was defined as left atrial diameter ≥ 40 mm in the parasternal long axis view and LVH as LV posterior wall thickness 12 mm or greater.

Student *t* tests and Fisher exact tests were used to compare continuous and categorical variables between groups, respectively. The Kaplan-Meier log-rank analysis was used to estimate event-free survival, which was defined as survival free from death, mechanical circulatory support, and/or cardiac transplantation. Event-free survival was compared by characteristics of the ECG at entry, including LAA, LVH, ST segment depression, and a “normal” ECG by the exact log-rank test. In addition, the LVEF at 6 and 12 months postpartum was compared by ECG characteristics at entry.

3 | RESULTS

Of the 100 women in the IPAC cohort, 88 had available baseline ECGs. Demographic and clinical characteristics of these women are summarized in Table 1. Mean age was 30 ± 6 years, and 15 (17%) presented with multiple gestation. Diabetes was present in 10 (11%) and hypertension in 38 (43%). At baseline, mean systolic and diastolic blood pressures were 111 ± 17 mm Hg and 70 ± 13 mm Hg, respectively. LVEF at entry was $34\% \pm 10\%$ and LV end-diastolic dimension was 5.6 ± 0.7 cm.¹⁵ By 6 months, LVEF had increased to $51\% \pm 11\%$, and by 12 months to $53 \pm 11\%$. Women with an “abnormal ECG” at study enrollment (defined as presence of BBB, ventricular hypertrophy, atrial abnormality, and/or ST-segment deviation) were more likely to receive inotropes and had a larger LV end-diastolic dimension

TABLE 1 Baseline characteristics of the study population

	All (n = 88)	Normal ECG ^a (n = 43)	Abnormal ECG ^b (n = 45)	P value
Age (years)	30 ± 6	29 ± 6	31 ± 6	0.21
Gravida	2.9 ± 2.0	2.7 ± 1.9	3.0 ± 2.1	0.55
Parity	2.2 ± 1.3	2.0 ± 1.2	2.4 ± 1.4	0.16
Multiple gestation (%)	17	19	16	0.78
Postpartum (days)	32 ± 25	30 ± 22	33 ± 28	0.52
NHYA class (I/II/III/IV)%	11/49/24/16	16/56/21/7	7/42/27/24	0.008
BMI (kg/m ²)	29 ± 8	29 ± 6	29 ± 9	0.87
Black (%)	33	30	36	0.65
Diabetes (%)	11	7	16	0.32
Hypertension (%)	43	40	47	0.53
Smoking (%)	33	33	33	0.94
HR exam (beats/min)	86 ± 17	83 ± 16	90 ± 17	0.045
HR ECG (beats/min)	94 ± 24	86 ± 21	102 ± 24	0.001
SBP (mm Hg)	111 ± 17	111 ± 15	110 ± 19	0.82
DBP (mm Hg)	70 ± 13	70 ± 13	70 ± 14	0.99
Beta-blockers (%)	88	93	82	0.20
ACEIs or ARBs (%)	78	84	73	0.30
Diuretic (%)	68	65	71	0.65
Inotropes (%)	16	5	27	0.007
LVEF at entry (%)	34 ± 10	37 ± 10	32 ± 10	0.02
LVEF at 6 months (%)	51 ± 11	53 ± 8	48 ± 13	0.02
LVEF at 12 months (%)	53 ± 11	55 ± 8	50 ± 13	0.06
LVEDD at entry (cm)	5.6 ± 0.7	5.4 ± 0.5	5.8 ± 0.7	0.002
Recovered ^c (%)	66	84	49	0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; ECG, electrocardiogram; HR, heart rate; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

^a"Normal" ECG defined as absence of atrial abnormality, ventricular hypertrophy, ST-segment deviation, and/or bundle branch block.

^b"Abnormal" ECG defined as presence of atrial abnormality, ventricular hypertrophy, ST-segment deviation, and/or bundle branch block.

^c"Recovered" defined as LVEF ≥50% at 12 months.

(LVEDD) on baseline echocardiogram (58 vs 54 mm, $P = 0.002$). Six women experienced nine major events: four deaths, four LVAD implantations, and one cardiac transplantation. Of women who required an LVAD, two died and one later underwent cardiac transplantation.

3.1 | Electrocardiographic findings

Findings of 12-lead ECGs at study enrollment are summarized in Table 2. One woman was in atrial fibrillation, and all other subjects were in sinus rhythm; 45 (51%) had a normal sinus rhythm, 37 (42%) showed sinus tachycardia, and 5 (6%) showed sinus bradycardia. Ventricular ectopic beats were observed in 3 subjects. QRS axis was normal in 74 (84%). There was no first-, second-, or third-degree atrioventricular block. Two subjects had a QRS duration >120 ms; one met criteria for left BBB, and the other right BBB. LAA was observed in 15 (17%), right atrial abnormality in 5 (6%), and LVH in 8 (9%) ECGs. ST-segment depression was seen in 15 (17%) of women, and ST-segment elevation was seen in 6 (7%). T-wave abnormalities were common, with flattening seen in 62 (71%) and inversions in 56 (64%). A "normal" ECG, defined as absence of atrial abnormality, ventricular

hypertrophy, ST-segment deviation, or BBB, was present in 43 (49%) of women.

3.2 | Prediction of left ventricular recovery and event-free survival

Tables 3 and 4 show the trajectory of LV function for women with and without various ECG and echocardiographic findings. As reported previously,¹⁵ heart rate at enrollment was not correlated with LV recovery ($P = 0.40$ at 6 months and $P = 0.26$ at 12 months).

LAA by ECG was specific (96%) but not sensitive (38%) for left atrial enlargement by echocardiogram. The presence of LAA on ECG was associated with lower LVEF at 6 months (44% vs 52%, $P = 0.02$) and 12 months (46% vs 54%, $P = 0.03$); these findings are almost identical to those comparing women with and without left atrial enlargement by echocardiogram (LVEF 46% vs 54% at 6 months ($P = 0.003$), and 47% vs 56% at 12 months ($P = 0.001$)). As shown in Figure 1A, the presence of LAA by ECG additionally predicted decreased event-free survival at 1 year (76% vs 97%, $P = 0.008$).

LVH was evident by ECG criteria in eight women (9%) and was associated with a lower LVEF at entry (27% vs 35%, $P = 0.03$), but not at 6 months (45% vs 51%, $P = 0.10$) or 12 months (52% vs 53%,

TABLE 2 Features of 12-lead electrocardiograms at enrollment

Category	ECG feature	Mean ± SD (range) or n (%)
Rate	Ventricular rate	94 ± 24 (52-146)
Rhythm	Normal sinus rhythm	45 (51.1%)
	Sinus tachycardia	37 (42.0%)
	Sinus bradycardia	5 (5.7%)
	Atrial fibrillation	1 (1.1%)
	Premature atrial contractions	3 (3.4%)
	Premature ventricular contractions	3 (3.4%)
Axis	Normal	74 (84.1%)
	Left	2 (2.3%)
	Right	11 (12.5%)
	Indeterminate	1 (1.1%)
Intervals	PR	143 ± 19 (88-200)
	QRS	83 ± 14 (60-146)
	QTc	462 ± 39 (376-573)
Conduction	Mobitz II	0 (0%)
	Complete heart block	0 (0%)
	Incomplete right bundle branch block	5 (5.7%)
	Complete right bundle branch block	1 (1.1%)
	Incomplete left bundle branch block	1 (1.1%)
	Complete left bundle branch block	1 (1.1%)
	Left anterior fascicular block	1 (1.1%)
	Left posterior fascicular block	0 (0%)
Chambers	Right atrial abnormality	5 (5.7%)
	Left atrial abnormality	15 (17.0%)
	Right ventricular hypertrophy	0 (0%)
	Left ventricular hypertrophy	8 (9.1%)
Repolarization	ST-segment depression	15 (17.0%)
	ST-segment elevation	6 (6.8%)
	T-wave flattening	62 (70.5%)
	T-wave inversion	56 (63.6%)

$P = 0.74$). Of note, there was no concordance between identification of LVH by ECG and echocardiography (defined as LV posterior wall thickness 12 mm or greater), with only one woman meeting criteria by both

TABLE 3 Left ventricular ejection fraction trajectory for women with and without left atrial abnormality and left ventricular hypertrophy by electrocardiogram and echocardiogram

		Left ventricular ejection fraction (%)						
		Abnormality detected by ECG			Abnormality detected by echocardiogram ^b			
		Enrollment	6 months	12 months	Enrollment	6 months	12 months	
Left atrial abnormality ^a	Yes (n = 15)	31 ± 12	44 ± 14	46 ± 16	Yes (n = 35)	32 ± 11	46 ± 14	47 ± 14
	No (n = 72)	35 ± 9	52 ± 9	54 ± 9	No (n = 52)	36 ± 9	54 ± 7	56 ± 7
	<i>P</i> value	0.185	0.020	0.026	<i>P</i> value	0.045	0.003	0.001
Left ventricular hypertrophy	Yes (n = 8)	27 ± 6	45 ± 10	52 ± 11	Yes (n = 7)	32 ± 11	45 ± 20	47 ± 17
	No (n = 80)	35 ± 10	51 ± 11	53 ± 11	No (n = 79)	35 ± 10	52 ± 9	54 ± 10
	<i>P</i> value	0.029	0.105	0.736	<i>P</i> value	0.553	0.145	0.142

^aExcludes one subject in atrial fibrillation on the enrollment ECG.

^bLeft atrial abnormality by echocardiogram defined as left atrial diameter greater than 40 mm. Left ventricular hypertrophy by echocardiogram defined as posterior wall thickness 12 mm or greater.

TABLE 4 Left ventricular ejection fraction trajectory for women with and without electrocardiographic findings

ECG findings		Left ventricular ejection fraction (%)		
		Enrollment	6 months	12 months
Normal ^a	Yes (n = 43)	37 ± 10	53 ± 8	55 ± 8
	No (n = 45)	32 ± 10	48 ± 13	50 ± 13
	<i>P</i> value	0.020	0.021	0.61
ST-segment depression	Yes (n = 15)	30 ± 8	40 ± 16	45 ± 18
	No (n = 73)	35 ± 10	52 ± 9	54 ± 9
	<i>P</i> value	0.102	0.003	0.025
T-wave inversions	Yes (n = 56)	33 ± 10	51 ± 11	53 ± 11
	No (n = 32)	37 ± 9	50 ± 10	54 ± 9
	<i>P</i> value	0.074	0.708	0.756
T-wave flattening	Yes (n = 62)	34 ± 10	49 ± 12	51 ± 12
	No (n = 26)	35 ± 10	54 ± 7	57 ± 5
	<i>P</i> value	0.702	0.103	0.030

^a“Normal” ECG defined as absence of bundle branch block, ventricular hypertrophy, atrial abnormality, or ST-segment deviation.

modalities. LVH by echocardiogram was seen in seven women and was not predictive of LVEF at entry ($P = 0.55$), 6 months ($P = 0.14$), or 12 months ($P = 0.14$). While there was a trend toward less recovery of EF in women with LVH, the small number of these women provides limited power to detect differences. LVH was not associated with event-free survival at 1 year when assessed by either modality ($P = 0.51$ for LVH by ECG, $P = 0.47$ for LVH by echocardiogram).

The presence of ST-segment depressions correlated with decreased LV recovery at 6 months (LVEF 40% vs 52%, $P = 0.003$) and 12 months (45% vs 54%, $P = 0.025$), but was not predictive of event-free survival ($P = 0.92$). T-wave abnormalities were not predictive of myocardial recovery or event-free survival, except for a small difference in LVEF at 12 months in women with and without T-wave flattening (51% vs 57%, $P = 0.03$).

The presence of a “normal” ECG predicted a significantly higher LVEF at 6 months (53% vs 48%, $P = 0.02$), which was no longer significant at 12 months (55% vs 50%, $P = 0.06$). However, a normal ECG was associated with recovery to an LVEF $\geq 50\%$ by 12 months (84% vs 49%, $P = 0.001$). Event-free survival at 1 year was significantly better (100% vs 85%, $P = 0.013$, Figure 1B), as no events occurred in women with a normal ECG at entry.

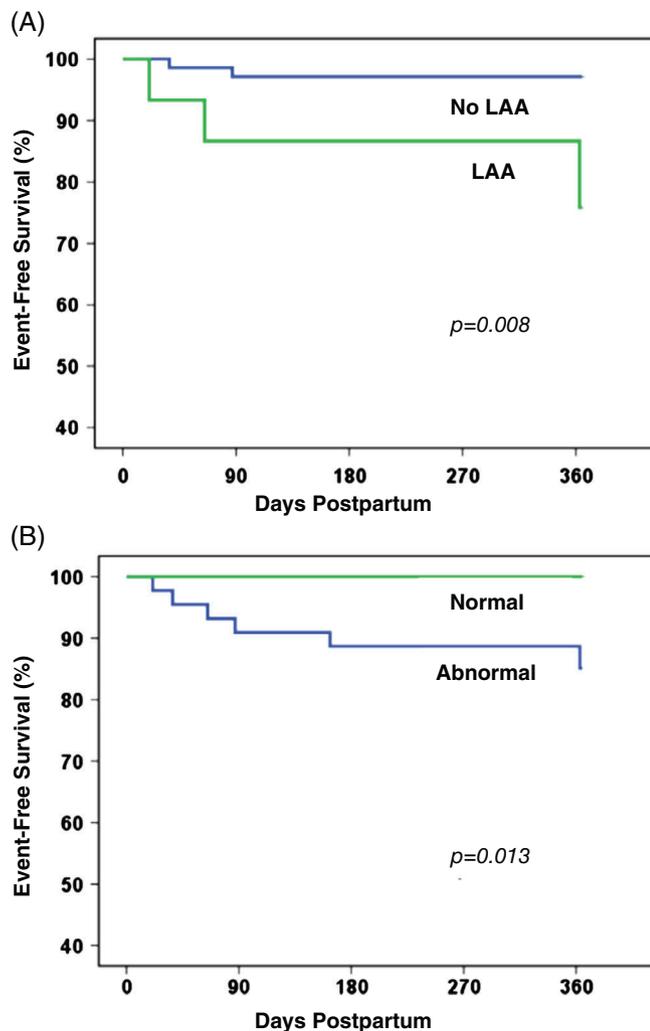


FIGURE 1 (A) Survival free from mechanical circulatory support, cardiac transplantation, and/or death for women with and without left atrial abnormality (LAA) on electrocardiogram (ECG) at study enrollment. (B) Survival free from mechanical circulatory support, cardiac transplantation, and/or death for women with a “normal” ECG (no atrial abnormality, ventricular hypertrophy, ST-segment deviation, or bundle branch block) or “abnormal” ECG at study enrollment

4 | DISCUSSION

We present here electrocardiographic findings in a large, prospective North American cohort of women with PPCM. To the best of our knowledge, this is the largest collection of ECGs in PPCM reported to date, the first report in North America, and the first to explore the association between ECG findings and clinical outcomes (ie, death, mechanical circulatory support, and transplantation). Among prior studies of the ECG in PPCM, Karaye et al¹⁹ did not study prognosis in relation to ECG findings, Tibazarwa et al.²⁰ explored fewer ECG parameters in relation to outcomes with incomplete follow-up, and Li et al¹⁷ examined only QRS and QTc.

In our cohort, the majority of ECGs at study enrollment revealed sinus rhythm, a normal QRS axis, and normal intervals. LAA was seen in 17% of women and predicted both decreased recovery of LV function and decreased event-free survival. This finding is similar to that reported in a study of 468 patients with heart failure after non-ST-elevation myocardial infarction, in which electrocardiographic LAA

was associated with higher risk of recurrent heart failure and mortality.²⁴ As noted, LAA by ECG was only 38% sensitive for left atrial enlargement as assessed by echocardiography. Prior work has suggested modest sensitivity of electrocardiographic LAA for left atrial enlargement measured by echocardiogram, with estimates ranging from 30%-75% when using terminal negative P-wave duration in $V_1 > 40$ ms.^{25,26} It is unclear from the available data whether electrical LAA is associated with adverse events because it indicates more severe left atrial enlargement or whether it is associated with adverse clinical events independent of left atrial size.

Importantly, a “normal” ECG was seen in 49% of women in our series and portended a higher likelihood of recovering LV systolic function and survival free from mechanical circulatory support or transplant at 1 year. Of note, Tibazarwa et al²⁰ reported a normal ECG only in 4% of women in their series. Some, but not all, of this discrepancy arises from the fact that we did not include T-wave abnormalities in our definition of “abnormal.” We made this decision because T-wave abnormalities were present in the majority of our cohort, thus, their inclusion would have diminished the predictive capability of an abnormal ECG, and because such T-wave changes may also be seen in normal pregnancy. Indeed, T-wave abnormalities were the most common noted abnormality but, in contrast to findings reported by Tibazarwa et al, were not predictive of adverse clinical outcomes in our cohort. The association of an abnormal ECG with a larger LVEDD and higher likelihood of requiring inotropic support align with our hypothesis that ECG abnormalities may reflect pathologic remodeling that has already occurred at the time of diagnosis and may therefore indicate more severe cardiomyopathy. The relatively high proportion of women in our series with a normal ECG or only non-specific T-wave abnormalities demonstrates that ECG has poor sensitivity as a screening tool for the detection of PPCM in the North American setting.

One limitation of the current study is the absence of follow-up ECGs to determine the natural history of abnormalities detected on baseline 12-lead ECG. In addition, although a small portion of women with PPCM are diagnosed in the final weeks of pregnancy,²⁷ all women in the IPAC cohort were enrolled postpartum. Pregnancy itself is associated with ECG changes, chiefly increased heart rate, change in QRS axis (most commonly a leftward axis), non-specific ST-segment changes, and change in T-wave axis,^{28,29} although normal pregnancy is not known to be associated with changes in conduction or chamber enlargement. Our analysis thus likely generalizes to women diagnosed with PPCM during pregnancy, but future studies should validate our findings in women who are still pregnant at the time of diagnosis.

5 | CONCLUSIONS

ECG changes are common at the time of presentation with PPCM and can predict likelihood of LV recovery. A normal ECG, however, does not rule out the presence of PPCM. LAA predicted lower likelihood of LV recovery and event-free-survival, and a normal ECG predicted favorable outcomes. Future research should integrate ECG findings with clinical, imaging, and biomarker data to help determine prognosis and guide management of this condition.

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