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ORIGINAL RESEARCH ARTICLE

Electrocardiographic features and their echocardiographic correlates in peripartum cardiomyopathy: results from the ESC EORP PPCM registry

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Abstract

Aims In peripartum cardiomyopathy (PPCM), electrocardiography (ECG) and its relationship to echocardiography have not yet been investigated in large multi-centre and multi-ethnic studies. We aimed to identify ECG abnormalities associated with PPCM, including regional and ethnic differences, and their correlation with echocardiographic features.

Methods and results We studied 411 patients from the EURObservational PPCM registry. Baseline demographic, clinical, and echocardiographic data were collected. ECGs were analysed for rate, rhythm, QRS width and morphology, and QTc interval. The median age was 31 [interquartile range (IQR) 26–35] years. The ECG was abnormal in $>$ 95% of PPCM patients. Sinus tachycardia (heart rate $>$ 100 b.p.m.) was common (51%), but atrial fibrillation was rare (2.27%). Median QRS width was 82 ms [IQR 80–97]. Left bundle branch block (LBBB) was reported in 9.30%. Left ventricular (LV) hypertrophy (LVH), as per ECG criteria, was more prevalent amongst Africans (59.62%) and Asians (23.17%) than Caucasians (7.63%, $P < 0.001$) but did not correlate with LVH on echocardiography. Median LV end-diastolic diameter (LVEDD) was 60 mm [IQR 55–65] and LV ejection fraction (LVEF) 32.5% [IQR 25–39], with no significant regional or ethnic differences. Sinus tachycardia was associated with an LVEF $<$ 35% (OR 1.85 [95% CI 1.20–2.85], $P = 0.006$). ECG features that predicted an LVEDD $>$ 55 mm included a QRS complex $>$ 120 ms (OR 11.32 [95% CI 1.52–84.84], $P = 0.018$), LBBB (OR 4.35 [95% CI 1.30–14.53], $P = 0.017$), and LVH (OR 2.03 [95% CI 1.13–3.64], $P = 0.017$).

Conclusions PPCM patients often have ECG abnormalities. Sinus tachycardia predicted poor systolic function, whereas wide QRS, LBBB, and LVH were associated with LV dilatation.

Keywords Peripartum cardiomyopathy; Electrocardiography; Echocardiography; Heart failure

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Introduction

Cardiac disease is a major contributor to maternal morbidity and mortality globally.[1,2] Peripartum cardiomyopathy (PPCM) is an idiopathic form of cardiomyopathy, in which previously healthy women present with heart failure (HF) due to left ventricular (LV) systolic dysfunction (LVSD) towards the end of pregnancy or up to 5 months following delivery.[3]

PPCM occurs worldwide. However, the incidence seems to be higher in women of African descent.[4,5] It was the second most common cardiomyopathy in women recruited to the ROPAC registry.[6] It is a diagnosis of exclusion and can easily be missed because of similarities of features with symptoms of late pregnancy and early puerperium.[7] Many theories exist regarding the pathophysiological mechanism.[8] However, the antiapoptotic effect of the 16 kDa fragment of the nursing hormone, prolactin, has the highest level of evidence.[9]

In its severe form, PPCM can result in cardiogenic shock due to severe LV dysfunction or cardiac arrhythmias leading to sudden cardiac death (SCD).[10] However, owing to the high rate of LV recovery, implantable cardioverter defibrillator implantation (ICD) is only recommended for patients with persistent poor systolic function [LV ejection fraction (LVEF) $<$ 35%] at follow-up. The wearable cardioverter/defibrillator (WCD) has, therefore, been suggested as 'bridging therapy' to protect against life-threatening ventricular arrhythmias until the LV function is reassessed. Indeed, the WCD has been shown to be protective in patients with PPCM with severely impaired systolic function and in whom ventricular arrhythmias have been found in up to 50% of patients.[11]

The cardiac electrical activity of PPCM patients, as well its relationship to the cardiac dysfunction, has only been evaluated in small studies,[12–14] and has not been conclusively interrogated in large studies. Reports from these studies suggest that up to 96% of women with PPCM would have electrocardiographic (ECG) abnormalities at presentation.[12] The most common electrical abnormalities include sinus tachycardia and repolarization abnormalities, such as T-wave inversion and prolongation of the QT interval. It remains uncertain, however, whether the ECG features of PPCM are different to those of other forms of dilated cardiomyopathies and, particularly, those with an inflammatory aetiology.[15] Although ethnic differences have been reported in the ECG patterns amongst healthy subjects,[16,17] it also remains unknown whether ethnicity has an impact on the ECG features of women with PPCM.

This study therefore aimed to identify the ECG abnormalities associated with PPCM in a large cohort of patients with PPCM in the EURObservational registry, recruited from more than 40 countries, and to study the ECG abnormalities' relationship, if any, with structural and functional abnormalities found on echocardiography. Furthermore, we aimed to discern the regional and ethnic differences in ECG features and abnormalities in PPCM.

Methods

The study design, recruitment, and data collection for the registry have been published earlier.[18] Centres were only eligible to participate if they were able to obtain ECGs and perform echocardiography. Women were recruited for the study if the diagnosis of PPCM was made within 6 months prior to enrolment. Patients who had a prior diagnosis of PPCM were only included if there was a relapse of PPCM in the pregnancy that resulted in enrolment. Baseline demographic, clinical, laboratory, ECG, and echocardiographic data were collected. ECGs done at the time of PPCM diagnosis were analysed for rate, rhythm (e.g. sinus rhythm or atrial fibrillation), QRS width, QRS axis, bundle branch blocks, LV hypertrophy (LVH), pathological Q waves, and QTc interval.[12,13] The QT interval was measured from the beginning of the QRS wave to the terminal point of the descending limb of the T wave in the lead with the longest interval and corrected for heart rate (HR) using the Bazett and Fridericia formulae.[19] The Sokolow–Lyon criteria were used to define ECG LVH.[20] These were recorded by the managing physicians at the participating sites and entered into an electronic case report form on the EURObservational PPCM registry (EORP) website (www.eorp.org). Recruiting sites were monitored both in person and remotely. There was no ECG core laboratory, but ECGs were validated by a team of physicians with special interest in ECG, who independently analysed random ECGs from all participating sites. ECG features with $>$ 90% interobserver agreement were included in the analysis.

Statistical analysis

Continuous variables were reported as mean with standard deviation or as median and interquartile range (IQR). Between-group comparisons were made by using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Between-group comparisons were made by using a χ^2 test or a Fisher's exact test if any expected cell count was $<$ 5. The ECG features of the study population were analysed according to country of residence (European vs. non-European), ethnicity (Caucasian vs. African vs. Asian), degree of LVSD (EF $\leq$ 35% vs. EF $>$ 35%), and LV structural abnormality [LV end-diastolic diameter (LVEDD) $\geq$ 55 mm vs. LVEDD $<$ 55 mm]. Similarly, baseline echocardiographic parameters were analysed based on country of residence (European vs. non-European) and the major ethnic groups represented in the study (Caucasian, African, or Asian). Correlation was sought between ECG features and selected echocardiographic parameters. For categorical variables with more than two possible values, exact *P*-values have been estimated according to the Monte Carlo method. A two-sided *P*-value $<$ 0.05 was considered statistically

significant. All analyses were performed using SAS statistical software Version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Analysis was done on data from the first 411 women enrolled into the EORP. Baseline socio-demographic and clinical characteristics are shown in *Table 1*, which was published earlier.[21]

The registry consisted of three major ethnic groups: Caucasian (n = 137, 34.00%), Africans (n = 104, 25.81%), and Asians (n = 88, 21.84%). The median age of women in this cohort was 31 years [IQR 26–35]. Women from the non-European countries were younger (30 [IQR 25–34] vs. 32 [IQR 27–36] years, P = 0.036), had higher parity (3 [IQR 2–4] vs. 2 [IQR 2–4], P = 0.018), and breastfed longer (total of 24.5 [IQR 12–49.5] vs. 9 months [IQR 5–18], $P < 0.001$). More than two-thirds of patients presented with a New York Heart Association (NYHA) functional class III or IV (with no significant regional differences). The most common presenting symptoms were dyspnoea (92.93%), palpitations (49.76%), and dizziness (24.15%). Signs of HF were more often reported amongst women from non-European countries.

Echocardiographic features of the study population

More than half of the study population had a severely reduced systolic function (LVEF $<$ 35%) at baseline. The median LVEF was 32.5% [IQR 25–39]. Considering the median LVEDD of 60 mm [IQR 55–66] and LV end-systolic diameter of 50 [IQR 45–54], 72.63% of the study population fulfilled criteria for LV dilatation (LVEDD $>$ 55 mm). Overall, 8.12% of patients had LVH as defined by an interventricular septal thickness in diastole (IVSd) of $>$12 mm. Right ventricular (RV) systolic dysfunction defined as tricuspid annular plane systolic excursion (TAPSE) $<$ 1.6 cm was present in 46.47% of the study population (*Table 2*).

Echocardiographic differences between European and non-European countries

There were no differences in the mean EF or LV dimensions between women from the European and non-European countries. However, as shown in *Table 2*, women from non-European countries were more frequently found to have severely impaired LV systolic function (80.10% vs. 70.67%, P = 0.042).

Echocardiographic differences between different ethnic groups in the study

There were significant differences in the left atrial (LA), LV, and RV structure and function amongst the major ethnic groups in this study. Women of African descent had the largest LA size (median LA diameter of 43 mm [IQR 37–47] in African, 40 mm [IQR 35.5–46] in Caucasian, and 39 mm [IQR 33–44] in Asian women; P = 0.001) and LV dimensions

Table 1 Socio-demographic, obstetric, and clinical parameters of the study population

		All (n = 411)	European (n = 203)	Non-European (n = 208)	P-value
Socio-demographic parameters					
Age (years)	Median (IQR)	31.0 (26.0–35.0)	32.0 (27.0–36.0)	30.0 (25.0–34.0)	0.036
Obstetric history					
Parity	Median (IQR)	3 (2–4)	2 (2–4)	3 (2–4)	0.018
Para 0	n (%)	1/267 (0.37%)	1/118 (0.85%)	0/149 (0.00%)	0.121
Para 1	n (%)	40/267 (14.98%)	22/118 (18.64%)	18/149 (12.08%)	
Para $\geq$ 2	n (%)	226/267 (84.64%)	95/118 (80.51%)	131/149 (87.92%)	
Hypertension in pregnancy	n (%)	120/404 (29.70%)	55/197 (27.92%)	65/207 (31.40%)	0.444
Pre-eclampsia	n (%)	89/391 (22.76%)	42/195 (21.54%)	47/196 (23.98%)	0.565
Breastfeeding (total in months)	Median (IQR)	18 (6–40)	9 (5–18)	24.5 (12–49.5)	$<$0.001
Clinical presentation					
BMI	Median (IQR)	25 (22.4–29.0)	26 (23.2–30.0)	24.2 (21.7–27.4)	$<$0.001
NYHA I–II	n (%)	128/410 (31.22%)	57/202 (28.22%)	71/208 (34.13%)	0.418
NYHA III	n (%)	150/410 (36.59%)	76/202 (37.62%)	74/208 (35.58%)	
NYHA IV	n (%)	132/410 (32.20%)	69/202 (34.16%)	63/208 (30.29%)	
Dyspnoea	n (%)	381/410 (92.93%)	186/202 (92.08%)	195/208 (93.75%)	0.509
Palpitations	n (%)	204/410 (49.76%)	95/202 (47.03%)	109/208 (52.40%)	0.277
Dizziness	n (%)	99/410 (24.15%)	52/202 (25.74%)	47/208 (22.60%)	0.457
Heart rate	Median (IQR)	102 (87–117)	100 (83–119)	104 (90–116.5)	0.182
Systolic BP	Median (IQR)	112 (100–131)	115 (100–131)	110 (100–130)	0.558
Diastolic BP	Median (IQR)	75 (65–90)	72.5 (60–90)	79 (70–90)	0.273
S3	n (%)	200/409 (48.90%)	83/202 (41.09%)	117/207 (56.52%)	0.002
JVP ($>$6 cm)	n (%)	194/408 (47.55%)	81/201 (40.30%)	113/207 (54.59%)	0.004
Pulmonary rales	n (%)	261/410 (63.66%)	111/202 (54.95%)	150/208 (72.12%)	$<$0.001

BP, blood pressure; JVP, jugular venous pressure; NYHA, New York Heart Association.

Table 2 Features of the study population, as categorized by region and ethnicity

		(A) Echocardiographic features							
			Comparison by region (n = 411)			Comparison by ethnicity (n = 329)			
		All (n = 411)	European (n = 203)	Non-European (n = 208)	P-value	Caucasians (n = 137)	African (n = 104)	Asian (n = 88)	P-value
Heart rate (b.p.m.)	Median (IQR)	97 (86–110)	98 (84–110)	96 (86–110)	0.412	100 (85–110)	100 (90–110)	96 (84–101)	0.164
Aortic root diameter	Median (IQR)	27 (24–30)	28.0 (25–31)	26 (24–29)	<0.001	27 (24–30)	27 (25–29)	26 (23–28)	0.004
LA diameter	Median (IQR)	41 (35–45)	41 (36–46)	40 (35–45)	0.423	40 (35.5–46)	43 (37–47)	39 (33–44)	0.001
LA diameter > 40 mm	n (%)	174/347 (50.14%)	76/146 (52.05%)	98/201 (48.76%)	0.544	41/88 (46.59%)	61/102 (59.80%)	36/85 (42.35%)	0.043
LVEDD (mm)	Median (IQR)	60 (55–65)	60.0 (55.0;66.0)	59 (55–64)	0.644	58 (54.5–64)	61 (57–66)	58 (53–63)	0.002
LVEDD > 55 mm	n (%)	276/380 (72.63%)	127/177 (71.75%)	148/203 (73.40%)	0.719	75/116 (64.66%)	83/104 (79.81%)	57/87 (65.52%)	0.028
LVESD (mm)	Median (IQR)	49.5 (45–55)	49 (43–57)	50 (45–54)	0.698	47 (41–55)	51 (47–55)	48 (44–54)	0.021
LVESD > 40 mm	n (%)	292/334 (87.43%)	113/135 (83.70%)	179/199 (89.95%)	0.091	65/84 (77.38%)	91/96 (94.79%)	73/85 (85.88%)	0.003
IVSd (mm)	Median (IQR)	9 (8–10)	9 (8–10)	9 (8–11)	0.184	10 (9–11)	9 (7–10)	9 (8–11)	<0.001
IVSd > 12 mm	n (%)	28/345 (8.12%)	15/153 (9.80%)	13/192 (6.77%)	0.305	12/92 (13.04%)	3/103 (2.91%)	5/79 (6.33%)	0.023
IVSs (mm)	Median (IQR)	10 (8–12)	9 (7–12)	10 (9–12)	0.013	10 (9–13)	10 (8.3–11)	10 (9–12)	0.314
IVSs > 18 mm	n (%)	10/258 (3.88%)	4/87 (4.60%)	6/171 (3.51%)	0.737	3/42 (7.14%)	0/87 (0.00%)	3/72 (4.17%)	0.033
Posterior wall in systole (mm)	Median (IQR)	10 (9–12)	9.9 (9.0;11.0)	10 (8–13)	0.53	10 (9–12)	10 (8–11)	11 (9–14)	0.002
LVEF (Teicholz) (%)	Median (IQR)	32.5 (25–39)	34.0 (25.0;40.0)	32 (25–38)	0.253	30 (25–40)	35 (26–40)	30 (24–35)	0.051
LVEF < 40%	n (%)	263/346 (76.01%)	106/150 (70.67%)	157/196 (80.10%)	0.042	214/275 (77.82%)	68/93 (73.12%)	75/101 (74.26%)	0.039
LVEF < 35%	n (%)	187/346 (54.05%)	79/150 (52.67%)	108/196 (55.10%)	0.652	53/93 (56.99%)	50/101 (49.50%)	52/81 (64.20%)	0.138
Regional wall motion abnormality	n (%)	85/385 (22.08%)	50/184 (27.17%)	35/201 (17.41%)	0.021	33/127 (25.98%)	3/101 (2.97%)	22/85 (25.88%)	<0.001
RV function – mildly abnormal	n (%)	134/368 (36.41%)	60/171 (35.09%)	74/197 (37.56%)	0.623	39/121 (32.23%)	52/101 (51.49%)	22/83 (26.51%)	<0.001
RV function – severely abnormal	n (%)	37/368 (10.05%)	16/171 (9.36%)	21/197 (10.66%)	0.678	10/121 (8.26%)	12/101 (11.88%)	5/83 (6.02%)	0.364
		(B) Electrocardiographic features							
			Comparison by region (n = 411)			Comparison by ethnicity (n = 329)			
		All (n = 411)	European (n = 203)	Non-European (n = 208)	P-value	Asian (n = 88)	African (n = 104)	Caucasian (n = 137)	P-value
Heart rate (b.p.m.)	Median (IQR)	102 (87–117)	100 (83–119)	104 (90–116)	0.182	107 (98–120)	102 (88–114)	100 (81–120)	0.075
Tachycardia (HR ≥ 100)	n (%)	203/397 (51.13%)	90/193 (46.63%)	113 (55.39%)	0.081	51/82 (62.20%)	53 (50.96%)	63/131 (48.09%)	0.122
Sinus rhythm	n (%)	382/397 (96.22%)	182/193 (94.30%)	200 (98.04%)	0.051	80/82 (97.56%)	101/104 (97.12%)	123/131 (93.89%)	0.445
AF/atrial flutter	n (%)	9/397 (2.27%)	7/193 (3.63%)	2/204 (0.98%)	0.097	1/82 (1.22%)	1/104 (0.96%)	5/131 (3.82%)	0.381
QRS width (ms)	Median (IQR)	82 (80–97)	90 (80–100)	80 (80–90)	<0.001	80 (78–83)	84 (80–96)	84 (80–98)	<0.001
Wide QRS > 120 ms	n (%)	30/379 (7.92%)	18/176 (10.23%)	12/203 (5.91%)	0.121	3/82 (3.66%)	8/102 (7.84%)	14/121 (11.57%)	0.129
LBBB	n (%)	37/398 (9.30%)	23/194 (11.86%)	14/204 (6.86%)	0.086	7/82 (8.54%)	8/104 (7.69%)	16/132 (12.12%)	0.477
LVH	n (%)	97/397 (24.43%)	14/193 (7.25%)	83/204 (40.69%)	<0.001	19/82 (23.17%)	62/104 (59.62%)	10/131 (7.63%)	<0.001
Pathological Q waves	n (%)	20/396 (5.05%)	12/192 (6.25%)	8/204 (3.92%)	0.290	7/82 (8.54%)	0/104 (0%)	4/131 (3.05%)	0.006
QT interval (ms)	Median (IQR)	360 (320–400)	380 (345–400)	346 (320–390)	<0.001	344 (300–400)	350 (320–380)	370 (346–400)	0.003
QTc by Bazett (ms)	Median (IQR)	457 (409–491)	461 (391–502)	454 (411–485)	0.937	453 (411–506)	458 (427–478)	456(391–489)	0.534
Prolonged QTc by Bazett (> 460 ms)	n (%)	179/380 (47.11%)	90/179 (50.28%)	89/201 (44.28%)	0.242	39/82 (47.56%)	44/101 (43.56%)	57/119 (47.90%)	0.787
QTc by Fridericia (ms)	Median (IQR)	421 (378–450)	426 (367–457)	416 (379–441)	0.487	414 (379–469)	417 (388–434)	425 (368–451)	0.904
Prolonged QTc by Fridericia (> 460 ms)	n (%)	79/380 (20.79%)	43/179 (24.02%)	36/201 (17.91%)	0.143	22/82 (26.83%)	11/101 (10.89%)	20/119 (16.81%)	0.018

AF, atrial fibrillation; LA, left atrial; LVESD, left ventricular end-systolic diameter.

(median LVEDD of 61 mm [IQR 57–66] in African, 58 mm [IQR 54.5–64.44] in Caucasians, and 58 mm [IQR 53–63] in Asian women, $P = 0.002$). There was a significant difference in the interventricular septal thickness. Caucasian women had more LVH (IVSd $>$ 12 mm) than their African and Asian counterparts (13.04%, vs. 2.91% in Africans and 6.33% in Asians, $P = 0.028$), although there was no significant difference in LVEF between the ethnic groups. Impaired RV function (measured by TAPSE $<$ 1.6 cm) was more frequent amongst Africans (63.37%) than their Caucasian (40.5%) and Asian (32.53%) counterparts.

Electrocardiographic features of the study population

As shown in *Table 2*, the median QRS rate was 102 b.p.m. [IQR 90–118]. More than half of the cohort presented with sinus tachycardia (QRS rate $>$ 100 b.p.m.), whereas atrial fibrillation was rare (2.27%). The median QRS width was 82 ms [IQR 82–97]. Left bundle branch block (LBBB) was reported in 9.30% of the cohort. LVH was present in about a quarter of the cohort. The median QTc by Bazett was 457 ms [IQR 409–491] with almost half the cohort (47.11%) having a prolonged QTcB ($>$ 460 ms).

Electrocardiographic differences between European and non-European countries

There was no difference in HR or rhythm between patients from European and non-European countries (*Table 2*). However, the patients from European countries had a wider QRS complex (90 ms [IQR 80–100] vs. non-European 80 ms [IQR 80–90], $P < 0.001$) and a tendency to have more LBBB (11.86% vs. 6.86%, $P = 0.086$). Patients from non-European countries were more often reported to have LVH (40.69% vs. 7.25%, $P < 0.001$) (*Figure S1*).

Electrocardiographic differences between different ethnic groups in the study

The median QRS duration was different amongst the ethnic groups (80 ms [IQR 78–83] in Asians, 84 ms [IQR 80–96] in Africans, and 84 ms [IQR 80–98] in Caucasians, $P < 0.001$). Pathological Q waves were more common in Asian women than Caucasian and African patients. African women had the highest frequency of LVH (59.62% vs. 7.63% in Caucasians and 23.17% in Asians, $P < 0.001$). When corrected by the Bazett and Fridericia formulae, there was no significant difference in QTc interval between the ethnic groups (*Figure S2*).

Electrocardiographic differences between those with LVEF $\leq$ 35% and LVEF $>$ 35%

As shown in *Table 3*, patients with an LVEF $\leq$ 35% were more commonly found to have tachycardia (59.02% vs. 43.79% in those with LVEF $>$ 35%, $P = 0.005$). Sinus tachycardia predicted poor systolic function (OR 1.85 [95% CI 1.20–2.85], $P = 0.006$) (*Table 4*).

Electrocardiographic differences between normal and dilated left ventricle (left ventricular end-diastolic diameter $<$ 55 mm vs. $\geq$55 mm)

The median QRS width was significantly longer in women with dilated LV (84 [IQR 80–100] vs. 80[IQR 80–90] ms, $P = 0.003$). These patients also had a higher frequency of wide QRS complex $>$ 120 ms [27/255 (10.55%) vs. 1/97 (1.03%), $P = 0.003$] and more frequently LBBB [2/270 (11.85%) vs. 3/100 (3.00%), $P = 0.010$]. The frequency of ECG LVH was also higher in the women with the dilated LV (79/269 [29.37%] vs. 17/100 [17.00%], $P = 0.016$). ECG features that predicted an LVEDD $>$ 55 mm included a wide QRS complex ($>$ 120 ms) (OR 11.32 [95% CI 1.52–84.84], $P = 0.018$), LBBB (OR 4.35 [95% CI 1.30–14.53], $P = 0.017$), and LVH (OR 2.03 [95% CI 1.13–3.64], $P = 0.017$) (*Table 4*).

Correlations between electrocardiography and echocardiography

There was a weak but significant negative correlation between LVEF and HR (-0.153, $P = 0.005$), as well as with LVEF and the presence of LBBB (-0.147, $P = 0.007$). Although the correlation was not strong, there was a statistically significant correlation between LVEDD and some ECG features including QRS duration, LBBB, LVH, and QTc (by Bazett and Fridericia's formulae). However, there was no correlation between LA size and any of the ECG features measured in this study (*Table S1*). Sinus tachycardia was associated with LVEF $\leq$ 35% and poor systolic function (OR 1.85 [95% CI 1.20–2.85], $P = 0.006$) (*Table 4*). LVH on the ECG did not predict LVH defined as IVSd $>$ 12 mm on echocardiography in the overall study population, and the different ethnicities were evaluated in this study.

Discussion

In this large global cohort of women with PPCM, we evaluated the prevalence of ECG abnormalities at the time of diagnosis, as well as the ECG differences between ethnicities and geographical location. We also investigated correlations

Table 3 Comparison of electrocardiographic features between patient with ejection fraction < 35% and ejection fraction > 35% and left ventricular end-diastolic diameter > 55 or <55 mm at presentation

			Categorization by left ventricular ejection fraction (EF)			Categorization by left ventricular end-diastolic diameter (LVEDD)		
		All (n = 346)	LVEF ≤35% (n = 187)	LVEF > 35% (n = 159)	*P*-value	LVEDD > 55 mm (n = 286)	LVEDD ≤55 mm (n = 104)	*P*-value
Heart rate (b.p.m.)	Median (IQR)	102 (89.5–118)	107 (95–120)	98 (83–115)	0.002	102.0 (90–117)	100.0 (80.0–102.0)	0.197
Tachycardia (HR ≥ 100)	*n* (%)	175/336 (52.08%)	108/183 (59.02%)	67/153 (43.79%)	0.005	141/269 (52.42%)	48/101 (47.52%)	0.461
Sinus rhythm	*n* (%)	324/335 (96.72%)	177/183 (96.72%)	147/152 (96.71%)	1.000	259/269 (95.72%)	95/100 (95%)	1.000
Atrial fibrillation / flutter	*n* (%)	8/335 (2.39%)	4/183 (2.19%)	4/152 (2.63%)	1.000	7/269 (2.60%)	2/100 (2.00%)	1.0
QRS width (ms)	Median (IQR)	81 (80–96)	82 (80–96)	80 (80–96)	0.888	84 (80–100)	80 (80–90)	0.003
Wide QRS > 120 ms	*n* (%)	25/322 (7.76%)	16/177 (9.04%)	9/145 (6.21%)	0.345	27/256 (10.55%)	1/97 (1.03%)	0.003
LBBB	*n* (%)	29/335 (8.66%)	20/183 (10.93%)	9/152 (5.92%)	0.105	32/270 (11.85%)	3/100 (3%)	0.010
LVH	*n* (%)	94/335 (28.06%)	51/183 (27.87%)	43/152 (28.29%)	0.932	79/269 (29.37%)	17/100 (17%)	0.016
Pathological Q waves	*n* (%)	14/335 (4.18%)	8/183 (4.37%)	6/152 (3.95%)	0.847	14/266 (5.22%)	5/100 (5%)	0.937
QT interval (ms)	Median (IQR)	359 (320–398)	350 (320–398)	360 (320–399)	0.149	360 (320–395)	368 (334–406)	0.202
QTc by Bazett (ms)	Median (IQR)	457 (406–490)	456 (400–490)	457 (410–490)	0.575	457.7 (402.5–490.8)	452.6 (421.3–490.5)	0.875
Prolonged QTc by Bazett (> 460 ms)	*n* (%)	150/320 (46.88%)	86/179 (48.04%)	64/141 (45.39%)	0.637	125/261 (47.89%)	41/94 (43.62%)	0.476
QTc by Fridericia (ms)	Median (IQR)	419 (371–448)	418 (365–445)	421 (381–456)	0.264	420 (371.7–44)7	421 (387.9–457.8)	0.497
Prolonged QTc by Fridericia (> 460 ms)	*n* (%)	66/320 (20.63%)	33/179 (18.44%)	33/141 (23.40%)	0.275	54/261 (20.69%)	21/94 (22.34%)	0.737

between these ECG features with the structural and functional abnormalities found on echocardiography in this population.

Only a few studies have systematically studied the role of the 12-lead ECG in PPCM, and most of these studies were conducted at single centres with a limited number of patients. In our multi-centre study comprising 411 patients, we could show that more than 95% of women with PPCM had ECG abnormalities at presentation. Our findings are in keeping with the literature suggesting that an abnormal ECG is highly sensitive and moderately specific for LVSD.[22,23] In 1999, Davie *et al*. found abnormalities on the ECG tracings of 94% of their study population with LVSD.[24] However, the diagnostic accuracy depends on the ECG competence of health care professionals. Johnson *et al*. demonstrated in 2015 that advanced ECG analysis improved both sensitivity and specificity for identifying LVSD in patients with non-ischaemic dilated cardiomyopathy (DCM).[25] We therefore suggest that a woman who presents with fatigue and dyspnoea in the puerperal period should have an ECG, which if abnormal warrants further work-up.

The most commonly described ECG abnormalities were sinus tachycardia, seen in about half of the study population; prolonged QTc is seen in in almost half and LVH in about a quarter. This is similar to what has been documented by smaller studies evaluating the ECG abnormalities in women with PPCM.[12,13,26] Tibazarwa *et al*. in 2012 showed that ECG abnormalities were present in about 96% of the study population and about half of them had major ECG abnormalities. However, the most significant ECG abnormality found in that study was the abnormal T wave, which was not evaluated in our study.

A wide QRS complex is common in HF and has previously been shown to be independently associated with age, male gender, DCM, impaired systolic function, and the duration of HF.[27] In our study, a wider QRS, and the presence of LBBB in particular, predicted LV dilatation; however, the majority of our patients with PPCM had a normal QRS complex width. In their recent review paper, Finocchiaro *et al*. suggested a 'cardiomyopathy-oriented' approach to ECG interpretation in patients with LV or biventricular dysfunction as these may reveal red flags for particular DCM phenotypes. The authors suggested that ECG analysis should particularly focus on the identification of atrioventricular blocks and/or atrial fibrillation, low QRS voltages, and T wave inversion in the lateral leads. These features in addition to presence of LBBB were found to predict ventricular arrhythmias and SCD.[28]

There were regional differences in the ECG features of patients with PPCM. The QRS complex was wider, and the QT interval was longer in women residing in European countries. This may be related to the differences in ECG parameters seen in different ethnic groups, as documented by earlier studies.[29,30] This is corroborated by the significantly wider QRS duration and QT interval, and frequency of prolonged

Table 4 Electrocardiographic features

ECG parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR	95% CI	*P*-value
(A) As predictors of very poor systolic function (LVEF < 35%)							
Tachycardia	59.02	56.21	61.71	53.42	1.848	[1.197; 2.854]	0.006
Atrial fibrillation	2.19	97.37	50.00	45.26	0.826	[0.203; 3.359]	0.789
Wide QRS (>120 ms)	9.04	93.79	64.00	45.79	1.502	[0.643; 3.506]	0.347
LBBB	10.93	94.08	68.97	46.73	1.949	[0.860; 4.417]	0.110
LVH	27.87	71.71	54.26	45.23	0.979	[0.607; 1.580]	0.932
Pathological Q waves	4.37	96.05	57.14	45.48	1.112	[0.377; 3.277]	0.848
Prolonged QTc by Bazett (> 460 ms)	48.04	54.61	57.33	45.29	1.113	[0.715; 1.732]	0.637
Prolonged QTc by Fridericia (> 460 ms)	18.44	76.60	50.00	42.52	0.740	[0.430; 1.273]	0.276
(B) As predictors of dilated LV (LVEDD > 55 mm)							
Tachycardia	52.42	52.48	74.60	29.28	1.216	[0.769; 1.923]	0.402
Atrial fibrillation	2.60	98.00	77.78	27.22	1.309	[0.267; 6.410]	0.740
Wide QRS (>120 ms)	10.55	98.97	96.43	29.54	11.319	[1.516; 84.484]	0.018
LBBB	11.85	97.00	91.43	28.96	4.347	[1.301; 14.532]	0.017
LVH	29.37	83.00	82.29	30.40	2.030	[1.132; 3.640]	0.017
Pathological Q waves	5.22	95.00	73.68	27.22	1.047	[0.367; 2.985]	0.932
Prolonged QTc by Bazett (> 460 ms)	47.89	56.38	75.30	28.04	1.188	[0.739; 1.910]	0.476
Prolonged QTc by Fridericia (> 460 ms)	20.69	77.66	72.00	26.07	0.907	[0.513; 1.604]	0.737

CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

QTc in the Caucasian women compared with the African and Asian women. QTc prolongation has been documented as a major finding in other studies of women with PPCM.[12,13] QTc prolongation in the setting of HF is thought to be related to both systolic dysfunction and LV dilatation.[26]

The frequency of LVH on ECG was higher in the women from non-European countries compared with European countries. LVH on the ECG was particularly prevalent amongst the African women in this cohort. The observed differences in frequency of LVH could either be due to the ethnic ECG differences that have been documented between Africans and Caucasians. Young Africans, especially men, tend to have tall precordial LV voltages in the absence of true LVH.[31] This is further buttressed by a lower mean IVSd in the African women and lower frequency of IVSd > 12 mm seen in the African women. We are not aware of any other studies on PPCM that have evaluated ECG or echocardiographic parameters of the women based on region of residence and ethnicity.

Sinus tachycardia was more prevalent in patients with a severely impaired systolic function (LVEF < 35%). This is in agreement with prior studies of HF and DCM, which have shown that sinus tachycardia is a common ECG abnormality, especially in the presence of severe LV dysfunction. Indeed, sinus tachycardia is a surrogate marker of neurohormonal activation in the setting of HF with severe LV dysfunction. Higher resting HR in HF is also a predictor of worse outcomes even in stable HF without atrial fibrillation[32] and has recently been shown to be an independent predictor of poor outcome in PPCM.[13]

It is also important to note that tachycardia is deemed a reliable warning sign to reduce maternal mortality. The Modified Early Obstetric Warning System (MEOWS) considers an HR that exceeds 100 b.p.m. to be prognostic[33] and an HR of >110 b.p.m. is a risk factor that forms part of the assessment by the Maternal Early Warning Trigger tool.[34] Our position is that the presence of tachycardia with other complaints of fatigue and exercise intolerance (which could easily be dismissed as puerperal symptoms) should prompt cardiac evaluation for PPCM.

As shown in previous studies on DCM,[35] women with a wide QRS or LBBB on the ECG were more likely to have a dilated LV. Although the QRS complex was marginally wider than that of a healthy population, most patients in this PPCM cohort had QRS duration within the normal range. LBBB was also uncommon in this population, as opposed to other forms of DCM where bundle branch blocks are encountered in up to 25–30% of patients.[35]

There were differences in some of the evaluated echocardiographic parameters between the groups. In this study, women from non-European countries had significantly higher frequency of severe LVSD than women from European countries. They also had a higher frequency of abnormal RV function. Contributing factors to these differences could include late presentation to health care facilities, which is common in low- and middle-income countries due to poor access to health care.[36] Other factors that were not investigated in this study, which may contribute to this difference, include the effect of the Human Immunodeficiency Virus (HIV), chronic infections, and malnutrition. Sliwa *et al*. had earlier alluded to the impact of HIV infection amongst patients with cardiac disease in South Africa.[37] HIV seropositivity was reported in eight patients in this study, and they were all African women.

Major differences in echocardiographic parameters were also noted when the women were categorized based on ethnicity. African women tended to have a larger left atrium and ventricle than the other ethnic groups, and a higher proportion of the African women had severe LVSD. However, they had much thinner LV walls than the other groups. This may reflect the burden of disease or premorbid confounding

issues like infection and malnutrition on the heart before the onset of PPCM. This may also portend a poorer prognosis for these women than their counterparts, as increased thickness of the posterior wall has been shown to be related to better outcomes in cardiomyopathy. African women in this study had the lowest frequency of regional wall motion abnormality, although they had a higher frequency of mild RV systolic dysfunction.

In the present study, a few ECG parameters correlated with echocardiographic parameters of LV structural abnormality and dysfunction. HR, presence of LBBB, and prolonged QTc interval correlated negatively with the LVEF, but parameters of depolarization and repolarization (QRS duration and QTc intervals) and LVH correlated positively with LV dimension (LVEDD). Worsening LV systolic function with the accompanying neurohormonal compensatory mechanisms will cause an increase in HR and could also affect cardiac electrical activity. Alteration in the myocardial architecture with LV dilatation could affect both impulse generation and propagation. Surprisingly, no relationship was found between the LA size and the assessed ECG abnormalities. The recognition of sinus tachycardia is important in the risk stratification of patients with PPCM, as sinus tachycardia has previously been shown to be associated with worse outcome in PPCM.[13] Furthermore, the addition of the I_f-channel inhibitor, ivabradine, to standard HF therapy has been shown to suggest clinical benefit by reducing HR in the setting of PPCM.[38]

The only ECG parameter in this study with a significant prediction of severe LV dysfunction was sinus tachycardia (OR 1.848). Although the positive predictive value was 62%, presence of tachycardia during the postpartum period when symptoms of HF may be masked should prompt a more thorough cardiovascular evaluation. LBBB was associated with LV dilatation. The presence of these abnormal ECG parameters could serve as useful criteria in decision making during the assessment of a breathless or easily fatigued women in the postpartum period. In their paper on predictive ECG features for PPCM, Karaye *et al*. recommended a criterion to include HR and QTc.[31] Hoevelmann *et al*. found that tachycardia and prolonged QTc predicted a poor outcome at 6 months for women with PPCM.

Limitations

This cohort was recruited via the EURObservational online registry, and, as such, the accuracy of all the ECG measurements could not be ascertained. We tried to mitigate this by personal and remote monitoring of high recruiting centres that had all their ECG tracings and echocardiography reports reviewed by independent experts for adjudication. This study lacks an age-matched healthy control group, as well as patients with DCM other than PPCM, as comparators. This should be the focus of future research in this area. We acknowledge the limitation of using the Sokolow–Lyon criteria for the ECG diagnosis of LVH, as these criteria are not validated for a young population such as patients with PPCM. However, there is no well-established standard for younger individuals, and the diagnosis of LVH in this age group is known to have low accuracy.[39] The Sokolow–Lyon diagnostic criteria for LVH are commonly applied in clinical practice. Data on LV mass were not collected in this study, and a direct comparison of LVH diagnosed by ECG and echocardiography could, therefore, not be made. Contemporary cardiac imaging, including speckle-trace echocardiography and cardiac magnetic resonance, would have added further information about the correlation between ECG and structural and functional abnormalities found in PPCM. These novel imaging modalities were unfortunately not available at all participant sites but should be evaluated in future studies. We acknowledge that only a limited number of ECG features were considered for the analyses of this study. The features considered were those that are commonly encountered in the PPCM population.[12] However, this limitation did not detract from the core message of this study that 95% of patients with PPCM have an abnormal ECG and that these common features are different amongst various ethnic groups.

Conclusions

In this large global, multi-ethnic cohort of women with PPCM, common ECG patterns in the setting of PPCM have emerged. These include sinus tachycardia, prolonged QTc, and LVH. Sinus tachycardia and LBBB were associated with LVSD and LV dilation, respectively, and would be useful in triaging the breathless and easily fatigued postpartum women who may have PPCM but may be missed because of similar features seen during the puerperium.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. The Peripartum Cardiomyopathy Investigators Group.
Table S1: Correlation between ECG and echocardiographic variables.
Figure S1: The prevalence of major ECG abnormalities according to region in PPCM.
Figure S2: The prevalence of major ECG abnormalities according to ethnicity in PPCM.

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