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RESEARCH ARTICLE

Hypertensive disorders in women with peripartum cardiomyopathy: insights from the ESC EORP PPCM Registry

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Aims Hypertensive disorders occur in women with peripartum cardiomyopathy (PPCM). How often hypertensive disorders co-exist, and to what extent they impact outcomes, is less clear. We describe differences in phenotype and outcomes in women with PPCM with and without hypertensive disorders during pregnancy.

Methods and results The European Society of Cardiology EURObservational Research Programme PPCM Registry enrolled women with PPCM from 2012–2018. Three groups were examined: (i) women without hypertension (PPCM-noHTN); (ii) women with hypertension but without pre-eclampsia (PPCM-HTN); (iii) women with pre-eclampsia (PPCM-PE). Maternal (6-month) and neonatal outcomes were compared. Of 735 women included, 452 (61.5%) had PPCM-noHTN, 99 (13.5%) had PPCM-HTN and 184 (25.0%) had PPCM-PE. Compared to women with PPCM-noHTN, women with PPCM-PE had more severe symptoms (New York Heart Association class IV in 44.4% vs. 29.9%, $P < 0.001$), more frequent signs of heart failure (pulmonary rales in 70.7% vs. 55.4%, $P = 0.002$), a higher baseline left ventricular ejection fraction (LVEF) (32.7% vs. 30.7%, $P = 0.005$) and a smaller left ventricular end-diastolic diameter (57.4 ± 6.7 mm vs. 59.8 ± 8.1 mm, $P = 0.001$). There were no differences in the frequencies of death from any cause, rehospitalization for any cause, stroke, or thromboembolic events. Compared to women with PPCM-noHTN, women with PPCM-PE had a greater likelihood of left ventricular

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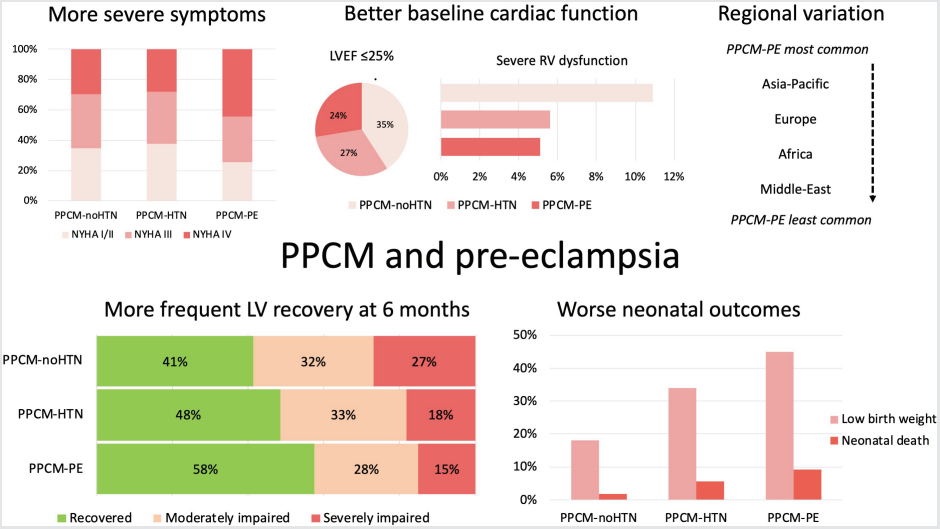
recovery (LVEF ≥ 50%) (adjusted odds ratio 2.08, 95% confidence interval 1.21–3.57) and an adverse neonatal outcome (composite of termination, miscarriage, low birth weight or neonatal death) (adjusted odds ratio 2.84, 95% confidence interval 1.66–4.87).

Conclusion Differences exist in phenotype, recovery of cardiac function and neonatal outcomes according to hypertensive status in women with PPCM.

Graphical Abstract



A summary of the main study findings. LV, left ventricular; PPCM, peripartum cardiomyopathy; PPCM-HTN, women with hypertension but without pre-eclampsia; PPCM-noHTN, women without hypertension; PPCM-PE, women with pre-eclampsia.

Keywords Peripartum cardiomyopathy • Hypertension • Pre-eclampsia • Heart failure • Pregnancy

Introduction

Hypertensive disorders complicate as many as 5–10% of all pregnancies worldwide, with pre-eclampsia in approximately 3%.[1,2] The prevalence of hypertensive disorders in women with peripartum cardiomyopathy (PPCM) is higher; approximately 20–25% of women who develop PPCM have pre-eclampsia during the index pregnancy and 40% have hypertension (with or without pre-eclampsia).[3,4] The relationship between hypertensive disorders of pregnancy and PPCM is not fully understood. Pathophysiological pathways resulting in angiogenic imbalance and endothelial dysfunction have been identified in both conditions, suggesting that there may be an overlap.[5,6] There are several possibilities: that pregnancy-induced hypertensive disorders and PPCM exist on a shared disease spectrum, that pregnancy-induced hypertensive disorders are a risk factor for the development of PPCM, or that they are separate disease processes. Few studies have specifically investigated whether or not outcomes differ for women with PPCM with and without co-existing hypertensive conditions and the results of those which have are conflicting.[7–11] We sought to describe differences in patient characteristics, treatment and maternal and neonatal outcomes according to the presence or absence of co-existing hypertensive disorders in women enrolled into the global European Society of Cardiology (ESC) EURObservational Research Programme (EORP) PPCM Registry – the largest prospective cohort of women with PPCM.

Methods

Registry design

Registry design, patient selection and data collection have been published previously.[4,12] In summary, women within 6 months of a diagnosis of PPCM were prospectively enrolled into a global registry from 2012–2018. By the time this analysis was conducted, data were available for a total of 752 women from 51 countries. Eligibility for the registry included: (i) a peripartum state, (ii) signs and/or symptoms of

heart failure, (iii) a left ventricular ejection fraction (LVEF) ≤45%, and (iv) the exclusion of alternative causes of heart failure. Baseline was defined as the enrolment visit, which was the first visit to the clinician making the diagnosis of PPCM. Pregnancy-induced hypertension and pre-eclampsia were clinician-reported. Right ventricular function was assessed qualitatively, with function recorded by the investigator as normal, mildly impaired, or severely impaired.

Outcomes

Outcomes at 6 months included death due to heart failure, sudden death or any cause; rehospitalization due to heart failure or any cause; thromboembolic events [venous and arterial (including ischaemic stroke)]; stroke; and neonatal outcomes [APGAR scores at 1 and 5 min, low birth weight (defined as weight < 2500 g), termination, miscarriage and death]. An adverse neonatal composite outcome of termination, miscarriage, low birth weight or neonatal death was analysed (expressed as the number of women with at least one component). Left ventricular function at 6 months was defined as: (i) recovered (LVEF ≥50%), (ii) moderate left ventricular dysfunction (LVEF 36–49%), or (iii) severe left ventricular dysfunction (LVEF ≤35%). A composite of severe left ventricular dysfunction or death was also analysed.

Statistical analysis

Women with PPCM with data on hypertensive status during pregnancy were included and were categorized into one of three groups: (i) no hypertension (PPCM-noHTN), (ii) pregnancy-induced hypertension without pre-eclampsia (PPCM-HTN), and (iii) pre-eclampsia (PPCM-PE). Baseline characteristics, treatment and outcomes were compared across the groups using Kruskal–Wallis tests, chi-squared tests and Fisher exact tests. For categorical variables with more than two categories, exact *P*-values were estimated according to the Monte Carlo method. Time-to-first-event outcomes (death from any cause, rehospitalization for any cause and rehospitalization for heart failure) were analysed using Cox proportional hazards regression. Cumulative first events were displayed using Kaplan–Meier curves. Thromboembolic events, stroke, left ventricular recovery and neonatal outcomes were analysed using logistic regression. Models were adjusted for baseline LVEF, region, body mass index and creatinine. Systolic blood pressure was also analysed as a continuous variable. Restricted cubic splines were generated to model the relationship between systolic blood pressure and death from any cause, rehospitalization for any cause, left ventricular recovery and an adverse neonatal outcome, and the continuous hazard/odds ratio (HR/OR) was displayed graphically. Missing values were not imputed; completeness of baseline data is included in online supplementary *Table S1*. A two-sided *P*-value <0.05 was considered statistically significant. Analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA) or Stata version 16 (StataCorp LLC, College Station, TX, USA).

Results

Hypertensive status was available in 735 of 752 (97.7%) women enrolled in the registry at the time this study was performed. Of these, 452 (61.5%) did not have hypertension (PPCM-noHTN), 99 (13.5%) had hypertension without pre-eclampsia (PPCM-HTN) and 184 (25.0%) had pre-eclampsia (PPCM-PE). A total of 596 (81.1%) women had 6-month follow-up, 468 (63.7%) had echocardiographic assessment of left ventricular function at 6 months and neonatal mortality data were available for 574 babies. Other than regional variation (more often performed in Europe, Africa, Asia-Pacific and less often in the Middle East), there were no significant differences in patient characteristics between women with and without assessment of left ventricular function at 6 months.

Baseline characteristics

Systolic blood pressure at baseline was 112.1 (± 19.2) mmHg in women with PPCM-noHTN, 131.2 (± 24.7) mmHg in women with PPCM-HTN and 133.2 mmHg (± 25.0) in women with PPCM-PE ($P < 0.001$) (*Table 1*). There were no differences in age, parity, or in the prevalence of diabetes, smoking, or human immunodeficiency virus across the hypertension groups. Women from Asia-Pacific were more likely to have PPCM-PE, and women from the Middle East less likely. Only 8.0% of women with PPCM-PE developed symptoms prior to the final month of pregnancy, compared with 17.3% with PPCM-HTN and 14.2% with PPCM-noHTN ($P = 0.001$). A family history of dilated cardiomyopathy was reported by 4.0% of women with PPCM-noHTN, by 9.1% of women with PPCM-HTN and by no women with PPCM-PE. A family history of PPCM was only reported by women with PPCM-noHTN (1.8% of this group). No women with PPCM-PE reported either a family history of dilated cardiomyopathy or PPCM. Compared to women with PPCM-noHTN, more women with PPCM-PE had New York Heart Association class III/IV symptoms (74.4% vs. 65.2%, $P = 0.007$) and more frequently with a higher LVEF (*Table 1*, online supplementary *Figure S1*). Peripheral oedema and pulmonary rales were most common in women with PPCM-PE and least common in women with PPCM-noHTN (*Table 1*). There was a stepwise rise in serum creatinine across the groups (lowest in women with PPCM-noHTN and highest in women with PPCM-PE). Body mass index was highest in women with PPCM-HTN. QRS duration was longer in women with PPCM-noHTN than in women with PPCM-PE (90.8 ± 21.4 ms vs. 84.6 ± 18.6 ms, $P = 0.001$) and left bundle branch block occurred least often in women with PPCM-PE. Compared to women with PPCM-noHTN, women with PPCM-PE had a higher baseline LVEF (32.7 ± 8.8% vs. 30.7 ± 10.8%, $P = 0.005$), smaller left ventricular end-diastolic diameter (57.4 ± 6.7 mm vs. 59.8 ± 8.1 mm, $P = 0.001$), and fewer had a LVEF ≤25% (23.7% vs. 35.1%, $P = 0.04$) and severe right ventricular dysfunction (5.1% vs. 10.9%, $P = 0.045$).

Medical therapy

By 6 months, women with PPCM-PE were more often treated with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and less often treated with a mineralocorticoid receptor antagonist and/or digoxin than other women (*Figure 1*). Use of all other medications, including beta-blockers and diuretics, was similar across the hypertension groups.

Table 1 Baseline characteristics according to hypertension group

	PPCM-noHTN (n = 452, 61.5%)	PPCM-HTN (n = 99, 13.5%)	PPCM-PE (n = 184, 25.0%)	P-value
Age, years	30.3 ± 6.4	31.7 ± 5.7	30.7 ± 6.6	0.10
Region, *n* (%)				<0.001
Europe	152 (33.6)	36 (36.4)	57 (31.0)	
Africa	141 (31.2)	25 (25.3)	45 (24.5)	
Asia-Pacific	35 (7.7)	12 (12.1)	47 (25.5)	
Middle East	114 (25.2)	23 (23.2)	30 (16.3)	
The Americas	10 (2.2)	3 (3.0)	5 (2.7)	
Race, *n* (%)				<0.001
White	146 (33.3)	32 (32.7)	56 (30.8)	
Black	128 (29.2)	26 (26.5)	47 (25.8)	
Asian	74 (16.9)	19 (19.4)	55 (30.2)	
Other	91 (20.7)	21 (21.4)	24 (13.2)	
Onset of symptoms, *n* (%)				0.001
Prior to final month prepartum	54 (14.2)	14 (17.3)	13 (8.0)	
Within final month prepartum	65 (17.2)	18 (22.2)	50 (30.7)	
Within 1 month postpartum	168 (44.3)	27 (33.3)	77(47.2)	
Within months 2–3 postpartum	57 (15.0)	17 (21.0)	16 (9.8)	
Within months 4–5 postpartum	27 (7.1)	2 (2.5)	5 (3.1)	
Beyond 5 months postpartum	8 (2.1)	3 (3.7)	2 (1.2)	
Timing of diagnosis, *n* (%)				0.17
Prepartum	61 (14.7)	13 (14.1)	16 (9.1)	
Postpartum	353 (85.3)	79 (85.9)	160 (90.9)	
Parity, *n* (%)				0.10
1	64 (21.8)	12 (17.1)	32 (26.9)	
≥2	223 (75.9)	58 (82.9)	81 (68.1)	
Previous PPCM, *n* (%)	38 (12.9)	4 (5.7)	4 (3.4)	0.006
Diabetes, *n* (%)	14 (3.1)	4 (4.2)	5 (2.7)	0.81
Smoking, *n* (%)	60 (13.7)	15 (15.8)	21 (11.8)	0.64
Human immunodeficiency virus, *n* (%)	16 (5.2)	2 (3.6)	11 (9.7)	0.16
Family history, *n* (%)				
Dilated cardiomyopathy	18 (4.0)	9 (9.1)	0 (0.0)	<0.001
PPCM	8 (1.8)	0 (0.0)	0 (0.0)	0.08
Clinical features				
NYHA functional class, *n* (%)				0.007
I/II	155 (34.8)	36 (37.5)	46 (25.6)	
III	157 (35.3)	33 (34.4)	54 (30.0)	
IV	133 (29.9)	27 (28.1)	80 (44.4)	
Body mass index, kg/m^2	25.7 ± 5.4	28.8 ± 7.5	26.5 ± 6.1	<0.001
Systolic blood pressure, mmHg	112.1 ± 19.2	131.2 ± 24.7	133.2 ± 25.0	<0.001
Diastolic blood pressure, mmHg	73.0 ± 13.7	84.5 ± 15.1	87.5 ± 18.6	<0.001
Heart rate, bpm	98.8 ± 22.3	99.1 ± 20.4	103.4 ± 20.3	0.04
Haemoglobin, g/dL	11.4 ± 2.0	12.0 ± 1.7	11.2 ± 1.9	0.01
Serum creatinine, μmol/L	70.0 (57.0–84.0)	72.0 (61.4–86.7)	79.6 (61.9–95.5)	<0.001
Third heart sound, *n* (%)	203 (47.1)	37 (39.8)	84 (47.7)	0.40
Jugular venous distension, *n* (%)	182 (42.5)	33 (35.9)	79 (44.9)	0.36
Peripheral oedema, *n* (%)	236 (52.7)	51 (53.1)	134 (72.8)	<0.001
Pulmonary rales, *n* (%)	246 (55.4)	56 (58.3)	128 (70.7)	0.002
Electrocardiography				
Atrial fibrillation/flutter, *n* (%)	11 (2.6)	1 (1.1)	2 (1.1)	0.53
QRS duration, ms	90.8 ± 21.4	89.8 ± 23.4	84.6 ± 18.6	0.001
Left bundle branch block, *n* (%)	38 (8.9)	11 (11.6)	6 (3.4)	0.02
QTc duration, ms	363.1 ± 56.0	355.6 ± 51.0	361.5 ± 62.9	0.35
Left ventricular hypertrophy, *n* (%)	83 (19.6)	26 (27.7)	29 (16.3)	0.08

Table 1 (Continued)

	PPCM-noHTN (*n* = 452, 61.5%)	PPCM-HTN (*n* = 99, 13.5%)	PPCM-PE (*n* = 184, 25.0%)	*P*-value
Echocardiography				
Left ventricular ejection fraction, %	30.7 ± 10.8	32.8 ± 9.6	32.7 ± 8.8	0.005
Left ventricular ejection fraction, *n* (%)				0.04
≤25%	155 (35.1)	26 (27.1)	42 (23.7)	
26–35%	153 (34.6)	35 (36.5)	64 (36.2)	
>35%	134 (30.3)	35 (36.5)	71 (40.1)	
Interventricular septal diastolic diameter, mm	9.0 (8.0–10.0)	9.0 (8.0–11.0)	10.0 (9.0–11.0)	0.01
Left ventricular end-diastolic diameter, mm	59.8 ± 8.1	59.1 ± 9.3	57.4 ± 6.7	0.001
Corrected for body surface area, mm/m^2	35.4 ± 5.8	32.8 ± 6.0	33.7 ± 5.4	<0.00
Left ventricular end-systolic diameter, mm	49.8 ± 8.9	49.7 ± 8.2	47.5 ± 7.4	0.008
Corrected for body surface area, mm/m^2	29.5 ± 6.2	27.7 ± 4.9	28.2 ± 5.7	0.02
Left atrial diameter, mm	40.3 ± 8.0	40.6 ± 7.3	39.2 ± 6.6	0.31
Severe right ventricular dysfunction, *n* (%)	44 (10.9)	5 (5.6)	8 (5.1)	0.045
Chest radiography, *n* (%)				
Cardiomegaly	235 (82.5)	43 (71.7)	103 (76.3)	0.10
Congestion	209 (73.1)	44 (73.3)	107 (81.1)	0.20

NYHA, New York Heart Association; PPCM, peripartum cardiomyopathy; PPCM-HTN, women with peripartum cardiomyopathy and hypertension alone; PPCM-noHTN, women with peripartum cardiomyopathy without hypertension; PPCM-PE, women with peripartum cardiomyopathy and pre-eclampsia.

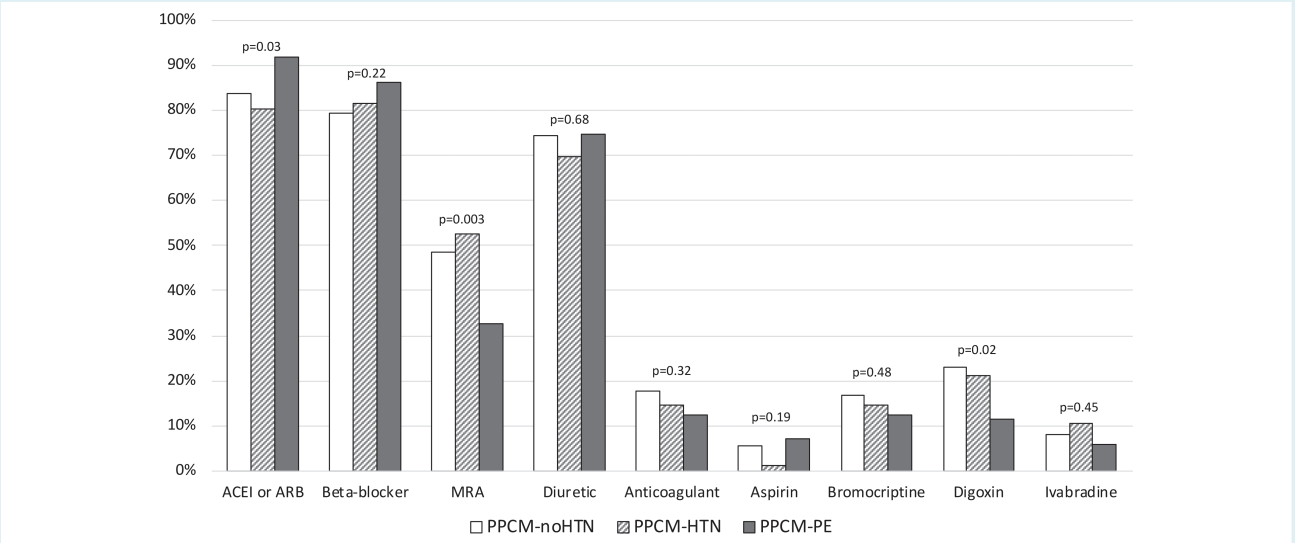


Figure 1 Medical therapy up to 6 months according to hypertension group. Bar chart showing the frequency of medical therapy use in the time up to the 6-month follow-up visit. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; PPCM-HTN, women with peripartum cardiomyopathy and hypertension alone; PPCM-noHTN, women with peripartum cardiomyopathy without hypertension; PPCM-PE, women with peripartum cardiomyopathy and pre-eclampsia.

Outcomes

Obstetric outcomes

Vaginal delivery was less common in women with PPCM-HTN and PPCM-PE than in women with PPCM-noHTN and this was the case whether PPCM was diagnosed pre- or postpartum (*Table 2*). Major postpartum bleeding occurred more than twice as often in women with PPCM-PE than in women with PPCM-noHTN (9.9% vs. 4.5%, $P = 0.03$). Tocolytic therapy was used in 3.7% of women with PPCM-noHTN, in 2.2% of women with PPCM-HTN and in 12.3% of women with PPCM-PE ($P < 0.001$). There was no difference in the frequency of breast feeding across the groups.

Maternal outcomes

Death at 6 months occurred in 6.5% of women with PPCM-noHTN, in 1.2% of women with PPCM-HTN and in 6.9% of women with PPCM-PE ($P = 0.16$) (*Table 2*; *Figure 2*).

Table 2 Obstetric, maternal and neonatal outcomes according to hypertension group

	PPCM-noHTN	PPCM-HTN	PPCM-PE	*P*-value
Obstetric				
Delivery outcome, *n* (%)				
Prepartum diagnosis				0.22
Vaginal	25 (41.0)	2 (15.4)	3 (18.8)	
Caesarean section	30 (49.2)	1 (84.6)	12 (75.0)	
Termination	3 (4.9)	0 (0.0)	0 (0.0)	
Miscarriage	3 (4.9)	0 (0.0)	1 (6.3)	
Postpartum diagnosis				<0.001
Vaginal	212 (60.1)	43 (55.1)	58 (36.3)	
Caesarean section	139 (39.4)	35 (44.9)	102 (63.8)	
Termination	1 (0.3)	0 (0.0)	0 (0.0)	
Miscarriage	1 (0.3)	0 (0.0)	0 (0.0)	
Twin pregnancy, *n* (%)	11 (3.4)	1 (1.4)	10 (6.0)	0.18
Postpartum haemorrhage, *n* (%)	20 (4.5)	5 (5.3)	18 (9.9)	0.03
Tocolytic therapy, *n* (%)	16 (3.7)	2 (2.2)	21 (12.3)	<0.001
Breastfeeding, *n* (%)	223 (49.4)	53 (54.1)	90 (48.9)	0.67
Maternal – baseline				
Mechanical assist device, *n* (%)	13 (3.9)	0 (0.0)	2 (1.7)	0.15
Admission to intensive care, *n* (%)	9 (2.0)	0 (0.0)	2 (1.1)	0.36
Maternal – 6 months				
Death, *n* (%)				
Any cause	24 (6.5)	1 (1.2)	10 (6.9)	0.16
Sudden death[a]	6 (25.0)	0 (0.0)	4 (50.0)	0.35
Heart failure[a]	13 (54.2)	0 (0.0)	2 (25.0)	0.17
Rehospitalization, *n* (%)				
Any cause	40 (11.3)	4 (4.9)	13 (9.2)	0.21
Heart failure[a]	21 (53.8)	2 (50.0)	7 (53.8)	1.00
Other cardiac cause[a]	11 (28.2)	1 (25.0)	1 (7.7)	0.31
Stroke, *n* (%)	8 (2.2)	2 (2.5)	4 (2.8)	0.93
Thromboembolism, *n* (%)	25 (6.9)	6 (7.3)	13 (9.0)	0.72
Left ventricular ejection fraction, %	45.2 ± 13.1	46.5 ± 11.8	49.3 ± 12.0	0.01
Change from baseline to 6 months, %	14.9 ± 13.4	13.2 ± 13.1	17.3 ± 12.3	0.13
Left ventricular end-diastolic diameter, mm	55.0 ± 8.8	54.9 ± 11.0	53.6 ± 7.9	0.16
Change from baseline to 6 months, mm	−4.3 ± 5.8	−4.3 ± 10.5	−4.3 ± 5.8	0.26
Left ventricular end systolic diameter, mm	42.2 ± 10.5	42.3 ± 10.7	40.1 ± 9.2	0.11
Change from baseline to 6 months, mm	−7.2 ± 8.1	−7.8 ± 10.1	−8.1 ± 7.3	0.47
Left ventricular ejection fraction, *n* (%)				
≥50% (recovered)	117 (41.5)	32 (48.5)	69 (57.5)	0.01
36–49% (moderate left ventricular dysfunction)	89 (31.6)	22 (33.3)	33 (27.5)	0.64
≤35% (severe left ventricular dysfunction)	76 (27.0)	12 (18.2)	18 (15.0)	0.02
Severe left ventricular dysfunction or death	100 (32.7)	13 (19.4)	28 (21.5)	0.01
Neonatal				
Female, *n* (%)	152 (47.6)	34 (48.6)	90 (52.9)	0.53
Birth weight, g	3029.9 ± 680.3	2815.5 ± 759.5	2559.8 ± 817.9	<0.001
Low birth weight (<2500 g)	49 (18.0)	21 (33.9)	68 (45.0)	<0.001
APGAR				
1 min	7.9 ± 1.5	7.9 ± 1.9	7.0 ± 2.1	<0.001
5 min	9.2 ± 1.1	9.1 ± 1.7	8.7 ± 1.7	0.007
Death, *n* (%)	6 (1.8)	4 (5.6)	16 (9.1)	<0.001
Termination, miscarriage or death, *n* (%)[b]	14 (4.3)	4 (5.7)	17 (10.2)	0.04
Termination, miscarriage, low birth weight or death, *n* (%)[b]	57 (21.3)	23 (37.1)	74 (49.0)	<0.001

PPCM-HTN, women with peripartum cardiomyopathy and hypertension alone; PPCM-noHTN, women with peripartum cardiomyopathy without hypertension; PPCM-PE, women with peripartum cardiomyopathy and pre-eclampsia.

Data available in $n = 596$ for mortality; $n = 577$ for rehospitalization; $n = 585$ for stroke; $n = 590$ for thromboembolism; $n = 468$ for left ventricular recovery; $n = 503$ for the composite of severe left ventricular dysfunction or death; $n = 480$ for the neonatal composite of termination, miscarriage, low birth weight or death; $n = 574$ (babies) for neonatal mortality.

[a]Expressed as a proportion of any cause.

[b]Expressed as a proportion of women (i.e. the number of women with at least one component of the adverse neonatal outcome).

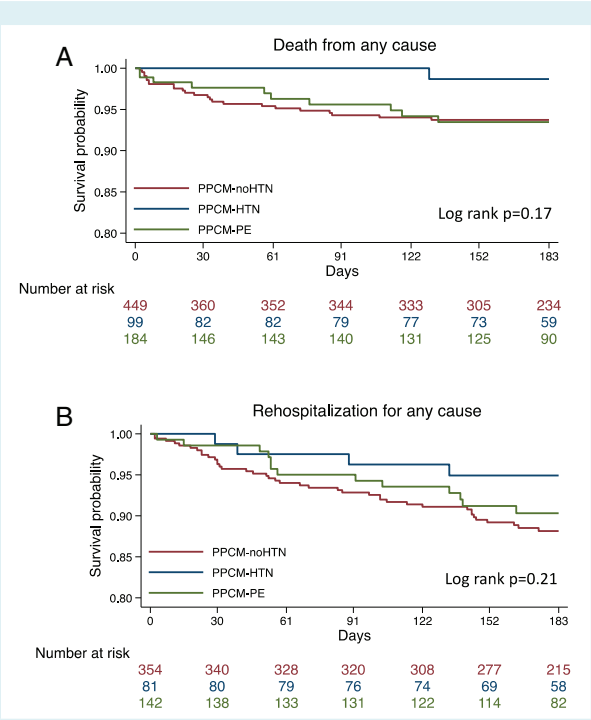


Figure 2 Kaplan–Meier survival curves according to hypertension group: (*A*) death from any cause and (*B*) rehospitalization for any cause. Survival curve showing the probability of being free from the outcome in the first 6 months after enrolment into the registry according to hypertension group. PPCM-HTN, women with peripartum cardiomyopathy and hypertension alone; PPCM-noHTN, women with peripartum cardiomyopathy without hypertension; PPCM-PE, women with peripartum cardiomyopathy and pre-eclampsia.

The risks of death and of rehospitalization, and the likelihood of stroke or thromboembolism were similar for women with PPCM-HTN and those with PPCM-PE, compared to women with PPCM-noHTN (*Table 3*; *Figure 2*, *Figure 3*). A 10 mmHg increase in systolic blood pressure was associated with a lower risk of death from any cause [unadjusted HR 0.76, 95% confidence interval (CI) 0.64–0.90] and lower risk of rehospitalization for any cause (unadjusted HR 0.83, 95% CI 0.73–0.95), but after full adjustment, neither was statistically significant (*Table 3*). Online supplementary *Figure S2* shows the risk of death from any cause and of rehospitalization for any cause across the spectrum of systolic blood pressure, suggesting an inversely linear relationship with the latter outcome (lower risk of rehospitalization with a greater systolic blood pressure).

Recovery of LVEF (≥50%) occurred in 41.5% of women with PPCM-noHTN, in 48.5% of women with PPCM-HTN, and in 57.5% of women with PPCM-PE ($P = 0.01$) (*Table 2*). Compared to women with PPCM-noHTN, the likelihood of left ventricular recovery was 1.9 times higher for women with PPCM-PE (unadjusted OR 1.91, 95% CI 1.24–2.94), but similar for women with PPCM-HTN (unadjusted OR 1.33, 95% CI 0.78–2.27) (*Table 3*, *Figure 3*). As a sensitivity analysis, women who died were categorized as 'unrecovered' and the results were comparable (PPCM-PE vs. PPCM-noHTN: unadjusted OR 1.83, 95% CI 1.21–2.77). Accounting for differences in treatment with an ACE inhibitor or ARB, beta-blocker or mineralocorticoid receptor antagonist did not alter this finding (PPCM-PE vs. PPCM-noHTN: OR 1.85, 95% CI 1.18–2.88; PPCM-HTN vs. PPCM-noHTN: OR 1.28, 95% CI 0.73–2.22). Furthermore, after adjusting for differences in a number of other clinically relevant patient characteristics, including baseline LVEF, body mass index, region and serum creatinine, the association between pre-eclampsia and left ventricular recovery persisted (adjusted OR 2.08, 95% CI 1.21–3.57) (*Table 3*). When blood pressure was analysed as a continuous variable, the likelihood of left ventricular recovery increased with each 10 mmHg increase in systolic blood pressure (adjusted OR 1.15, 95% CI 1.03–1.28) and the pattern was consistent when odds across the spectrum of systolic blood pressure were examined (*Table 3*, online supplementary *Figure S2*).

Neonatal outcomes

Birth weight and APGAR scores were highest in babies born to women with PPCM-noHTN and lowest in babies born to women with PPCM-PE (*Table 2*). Neonatal death occurred in 1.8%, 5.6% and 9.1% of babies born to women with PPCM-noHTN, PPCM-HTN and PPCM-PE, respectively ($P < 0.001$). An adverse neonatal outcome (termination, miscarriage, low birth weight, or neonatal death) was 3.5 times more likely in women with PPCM-PE (unadjusted OR 3.54, 95% CI 2.30–5.46) and 2.2 times more likely in women with PPCM-HTN (unadjusted OR 2.17, 95% CI 1.20–3.93) than women with PPCM-noHTN, (*Table 3*; *Figure 3*). The association between PPCM-PE (but not PPCM-HTN) and an adverse neonatal outcome persisted after adjusting for differences in maternal characteristics (adjusted OR 2.84, 95% CI 1.66–4.87) (*Table 3*). Systolic and diastolic blood pressure increases of 10 mmHg were associated with a greater likelihood of an adverse neonatal outcome (adjusted ORs 1.17, 95% CI 1.05–1.30 and 1.23, 95% CI 1.06–1.43, respectively).

Discussion

We have identified several notable differences in women with PPCM in this registry according to the presence or absence of hypertensive disorders. Firstly, women with PPCM-PE presented with more severe symptoms and more frequent signs of heart failure than those with PPCM-noHTN, despite having better baseline cardiac function. Secondly, women with PPCM-PE had a greater likelihood of left ventricular recovery compared to women with PPCM-noHTN. Thirdly, neonatal death occurred most often in women with PPCM-PE and least often in women PPCM-noHTN and PPCM-PE was associated with a greater likelihood of an adverse neonatal outcome.

Among women with PPCM in this international registry, the prevalence of any kind of hypertensive disorder was 39%, and of pre-eclampsia was 25%. This is comparable to reports elsewhere in the literature.[3,8–10,13,14] While there was a similar pattern of hypertensive subtypes in women from Africa and Europe, pre-eclampsia was more common in women from Asia-Pacific and less common

Table 3 Associations between hypertension group and outcomes

	Hazard or odds ratio (95% confidence interval)				
	Unadjusted	Adjusted for baseline LVEF	Adjusted for region	Adjusted for BMI, region, creatinine	Adjusted for baseline LVEF, BMI, region, creatinine
Death from any cause					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	0.18 (0.02–1.35)	0.23 (0.03–1.69)	0.18 (0.02–1.32)	0.11 (0.01–2.12)	0.14 (0.01–2.78)
PPCM-PE	1.05 (0.50–2.19)	1.23 (0.58–2.60)	1.00 (0.46–2.16)	1.11 (0.50–2.46)	1.23 (0.56–2.71)
Per 10 mmHg increase, SBP	0.76 (0.64–0.90)	0.81 (0.68–0.96)	0.75 (0.62–0.89)	0.83 (0.68–1.00)	0.86 (0.71–1.03)
Per 10 mmHg increase, DBP	0.83 (0.67–1.02)	0.87 (0.70–1.08)	0.81 (0.64–1.01)	0.87 (0.69–1.11)	0.90 (0.71–1.14)
Rehospitalization for any cause					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	0.42 (0.15–1.17)	0.51 (0.18–1.43)	0.41 (0.15–1.16)	0.42 (0.12–1.44)	0.51 (0.15–1.80)
PPCM-PE	0.80 (0.43–1.50)	0.91 (0.49–1.71)	0.84 (0.45–1.60)	0.91 (0.44–1.86)	0.99 (0.49–2.01)
Per 10 mmHg increase, SBP	0.83 (0.73–0.95)	0.87 (0.76–0.99)	0.83 (0.73–0.95)	0.84 (0.72–0.98)	0.88 (0.75–1.02)
Per 10 mmHg increase, DBP	0.86 (0.73–1.02)	0.89 (0.75–1.06)	0.87 (0.73–1.03)	0.91 (0.75–1.10)	0.93 (0.77–1.12)
Rehospitalization for heart failure					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	0.40 (0.09–1.72)	0.50 (0.12–2.16)	0.42 (0.10–1.79)	0.24 (0.03–2.05)	0.27 (0.03–2.34)
PPCM-PE	0.83 (0.35–1.96)	0.97 (0.41–2.30)	0.90 (0.37–2.17)	0.87 (0.33–2.30)	0.95 (0.36–2.47)
Per 10 mmHg increase, SBP	0.83 (0.69–1.00)	0.88 (0.73–1.05)	0.83 (0.69–1.01)	0.86 (0.69–1.07)	0.90 (0.72–1.11)
Per 10 mmHg increase, DBP	0.93 (0.74–1.17)	0.97 (0.77–1.22)	0.93 (0.73–1.19)	0.96 (0.73–1.26)	0.97 (0.75–1.27)
Thromboembolism or stroke					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	0.95 (0.38–2.38)	0.88 (0.33–2.39)	0.96 (0.38–2.42)	0.49 (0.13–1.81)	0.61 (0.16–2.30)
PPCM-PE	1.19 (0.60–2.36)	1.07 (0.52–2.24)	1.39 (0.69–2.83)	1.04 (0.45–2.36)	1.02 (0.43–2.43)
Per 10 mmHg increase, SBP	1.06 (0.94–1.20)	1.05 (0.92–1.20)	1.06 (0.94–1.20)	1.07 (0.92–1.25)	1.10 (0.95–1.29)
Per 10 mmHg increase, DBP	1.03 (0.86–1.24)	0.99 (0.82–1.21)	1.05 (0.88–1.27)	1.02 (0.82–1.26)	0.99 (0.79–1.24)
Left ventricular recovery					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	1.33 (0.78–2.27)	1.08 (0.61–1.90)	1.32 (0.75–2.30)	1.50 (0.78–2.91)	1.29 (0.65–2.56)
PPCM-PE	1.91 (1.24–2.94)	1.87 (1.19–2.94)	1.75 (1.11–2.77)	2.05 (1.22–3.45)	2.08 (1.21–3.57)
Per 10 mmHg increase, SBP	1.16 (1.06–1.26)	1.12 (1.02–1.22)	1.13 (1.03–1.23)	1.18 (1.06–1.31)	1.15 (1.03–1.28)
Per 10 mmHg increase, DBP	1.10 (0.99–1.23)	1.09 (0.97–1.22)	1.07 (0.96–1.20)	1.09 (0.96–1.25)	1.11 (0.97–1.27)
Severe left ventricular dysfunction					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	0.60 (0.31–1.19)	0.78 (0.38–1.61)	0.59 (0.29–1.20)	0.43 (0.18–1.03)	0.52 (0.20–1.35)
PPCM-PE	0.48 (0.27–0.84)	0.55 (0.30–1.01)	0.52 (0.29–0.95)	0.46 (0.24–0.90)	0.47 (0.23–0.97)
Per 10 mmHg increase, SBP	0.81 (0.72–0.90)	0.86 (0.77–0.97)	0.82 (0.73–0.92)	0.77 (0.67–0.89)	0.82 (0.71–0.95)
Per 10 mmHg increase, DBP	0.82 (0.71–0.95)	0.86 (0.74–1.00)	0.83 (0.72–0.97)	0.76 (0.64–0.92)	0.78 (0.65–0.94)
Severe left ventricular dysfunction or death					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	0.50 (0.26–0.95)	0.66 (0.33–1.32)	0.48 (0.25–0.95)	0.32 (0.13–0.75)	0.40 (0.16–0.99)
PPCM-PE	0.57 (0.35–0.92)	0.70 (0.41–1.17)	0.59 (0.36–0.98)	0.52 (0.30–0.92)	0.59 (0.32–1.07)
Per 10 mmHg increase, SBP	0.79 (0.72–0.87)	0.85 (0.77–0.95)	0.80 (0.72–0.89)	0.79 (0.70–0.89)	0.84 (0.75–0.96)
Per 10 mmHg increase, DBP	0.81 (0.71–0.92)	0.85 (0.74–0.98)	0.82 (0.72–0.94)	0.78 (0.67–0.91)	0.81 (0.69–0.95)
Adverse neonatal outcome					
PPCM-noHTN (reference)	1.00	1.00	1.00	1.00	1.00
PPCM-HTN	2.17 (1.20–3.93)	2.08 (1.15–3.78)	2.13 (1.15–3.96)	1.66 (0.78–3.52)	1.60 (0.75–3.40)
PPCM-PE	3.54 (2.30–5.46)	3.48 (2.23–5.41)	4.06 (2.55–6.47)	3.00 (1.77–5.09)	2.84 (1.66–4.87)
Per 10 mmHg increase, SBP	1.14 (1.05–1.23)	1.13 (1.04–1.23)	1.15 (1.06–1.25)	1.18 (1.06–1.31)	1.17 (1.05–1.30)
Per 10 mmHg increase, DBP	1.22 (1.09–1.37)	1.21 (1.07–1.36)	1.23 (1.09–1.39)	1.24 (1.07–1.43)	1.23 (1.06–1.43)

Adverse neonatal outcome is defined as a composite of termination, miscarriage, low birth weight or neonatal death.
BMI, body mass index; DBP, diastolic blood pressure; LVEF, ventricular ejection fraction; PPCM-HTN, women with peripartum cardiomyopathy and hypertension alone; PPCM-noHTN, women with peripartum cardiomyopathy without hypertension; PPCM-PE, women with peripartum cardiomyopathy and pre-eclampsia; SBP, systolic blood pressure.

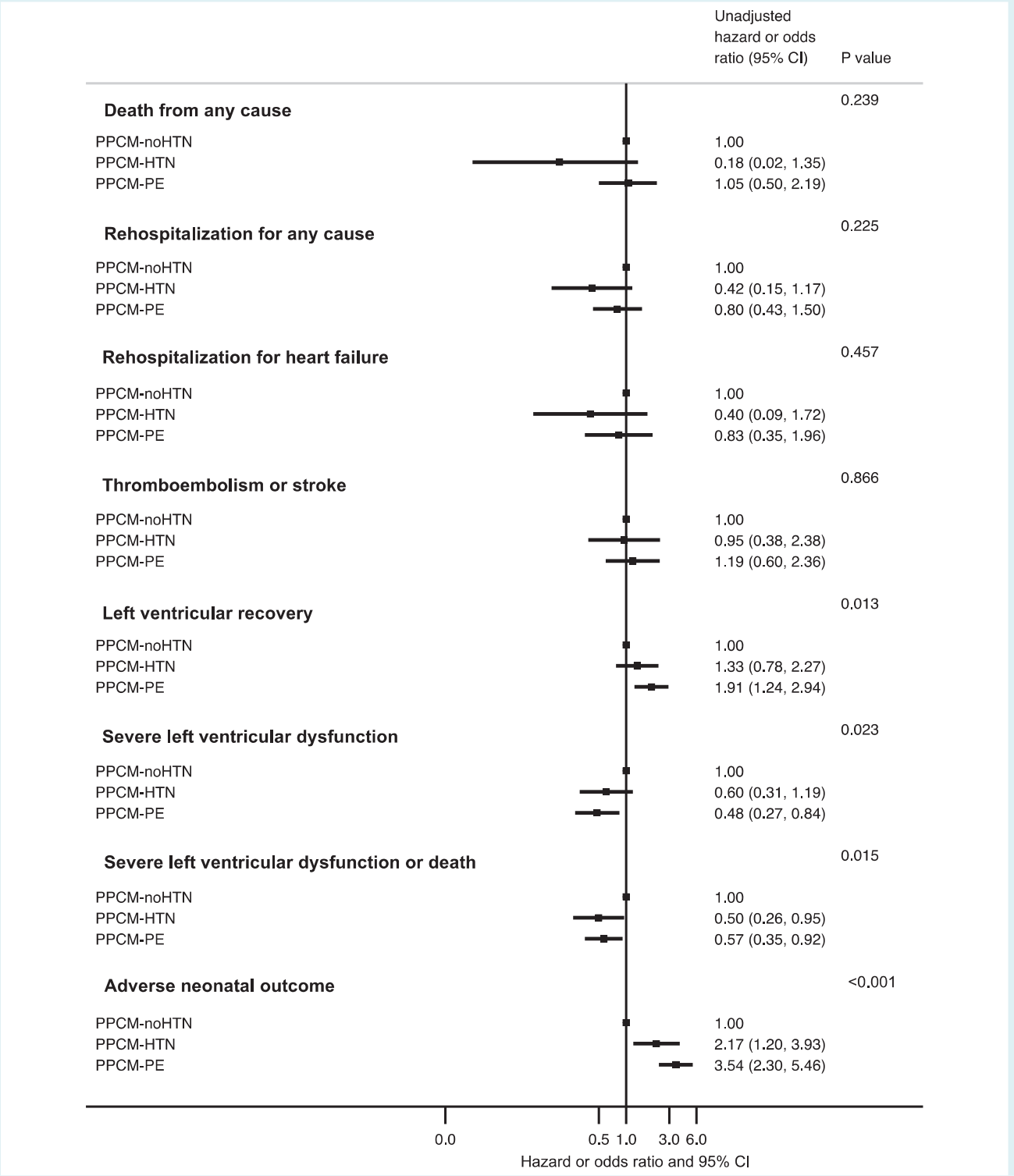


Figure 3 Forest plot of outcomes according to hypertension group. Plots show the point estimate for the unadjusted risk or likelihood of each outcome according to hypertension group, referent to the group of women without hypertension. Bars show the 95% confidence intervals (CI). The line of unity at 1.0 represents the point at which no difference is evident. PPCM-HTN, women with peripartum cardiomyopathy and hypertension alone; PPCM-noHTN, women with peripartum cardiomyopathy without hypertension; PPCM-PE, women with peripartum cardiomyopathy and pre-eclampsia.

in women from the Middle East. In some parts of the Asia-Pacific region, pre-eclampsia remains a major maternal health problem. Given that risk factors such as diabetes and multiparity were generally not more common in women from Asia-Pacific than other regions,[4] differences in access to health care, specialist management and early detection may be of importance.

Women with PPCM-PE reported greater symptom severity than women with PPCM-noHTN and symptom onset tended to occur later in pregnancy, concentrated around the time of delivery. Pre-eclampsia is a disorder of placental function, the development of which may be mediated by an ischaemic cascade, initiated by impaired remodelling of the spiral artery and resulting in an excess of circulating anti-angiogenic factors.[15] In healthy women, levels of soluble fms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor (VEGF) released from the placenta, peak at delivery and return to normal within 48–72 hours postpartum.[16] In pre-eclampsia, up-regulation of sFlt-1 has been shown to induce endothelial dysfunction, reduce capillary density and oppose VEGF-induced vasodilatation, resulting in hypertension, proteinuria and oedema.[5,16,17] Elevated levels of sFlt-1, and a lower ratio of sFlt-1 to placental growth factor (a type of VEGF) have also been identified in women with PPCM, with higher levels of sFlt-1 in women with more marked heart failure symptoms.[5,18,19] This pathological surge around the time of delivery, together with lower albumin levels and increased capillary permeability, may account for the differences in onset and severity of symptoms between women with PPCM with and without pre-eclampsia.

Paradoxically, although women with PPCM-PE had a more severe clinical presentation of heart failure, LVEF at the time of diagnosis was higher in these women than in women with PPCM-noHTN. Prior studies have identified similar differences in cardiac function at baseline according to the presence or absence of co-existing hypertensive disorders.[7,8,10] Pre-eclampsia is associated with afterload-driven left ventricular concentric remodelling and abnormal diastolic function, though reductions in radial, circumferential and longitudinal strain have been shown to precede a decline in ejection fraction.[20,21] Women who develop pre-eclampsia preterm are more likely to have left ventricular dysfunction than those who develop pre-eclampsia later in pregnancy.[22] This could reflect differences in levels of circulating sFlt-1, which has been shown to correlate with degree of cardiac dysfunction in animal models.[5] Furthermore, the increase in afterload which occurs with hypertension is more likely to impact the left, rather than the right, ventricle. In this registry, severe right ventricular dysfunction was less common in women with PPCM-PE than in those with PPCM-noHTN.

Another key finding of this study was the association between pre-eclampsia and left ventricular recovery, which persisted even after accounting for differences in baseline LVEF, and also for other factors likely to be important, such as region. Women with PPCM-PE were more than twice as likely to recover than those with PPCM-noHTN. The propensity for recovery in women with PPCM (which is greater than that for unselected patients with dilated cardiomyopathy) is especially important when providing counselling regarding subsequent pregnancies, and when considering device therapies. The prognostic significance of hypertensive disorders in women with PPCM is not entirely novel, but not all reports from prior studies are consistent.[7,9,10,14] One possible explanation for this finding is that women with PPCM and concomitant hypertensive disorders are treated differently, as higher blood pressure may allow more aggressive optimization of heart failure therapies. In this registry, more women with PPCM-PE were on an ACE inhibitor or ARB at 6 months, although fewer were on a MRA. The renin–angiotensin–aldosterone system (RAAS) is upregulated in normal pregnancy, but has been shown to function differently in pre-eclampsia, with an increase in angiotensin II sensitivity and overactivation of the AT1 receptor.[23] Whether this increases the efficacy of RAAS inhibition is unknown.

In addition, recovery of left ventricular function in pre-eclampsia may follow more rapidly upon resolution of hypertension (with removal of increased afterload), than a slower, reverse remodelling process in patients with dilated cardiomyopathy due to other causes. Reverse remodelling has been reported up to 2–5 years following diagnosis in several series of women with PPCM.[24,25] It is also possible that there are pathophysiological processes in women with PPCM without co-existing hypertensive disorders that account for their apparent disadvantage. We found that women with PPCM-noHTN were more likely to behave like patients with 'conventional' dilated cardiomyopathies than women with PPCM-PE, with more severe biventricular dysfunction, more frequent electrocardiographic changes, such as left bundle branch block, and more often with a family history of cardiomyopathy. An implicated gene abnormality has been reported in around 15% of women with PPCM, and, in these women, the prevalence of hypertension may be lower and recovery less common.[26] These findings support a hypothesis that there may be two pathophysiological processes involved in the development of PPCM – one vascular, associated with more frequent recovery, and one genetic, associated with persistent, dilated cardiomyopathy.

Our findings suggest that pre-eclampsia may confer a degree of early benefit for women with PPCM with respect to recovery of left ventricular function. In contrast, there is a growing body of evidence that hypertensive disorders of pregnancy increase the risk of cardiovascular disease later in life, including coronary artery disease, stroke and chronic kidney disease.[27,28] The long-term impact of hypertensive disorders in women with PPCM who have recovered, is, as yet, unknown. Nonetheless, the co-existence of hypertension or pre-eclampsia and PPCM, even in women with apparent normalization of cardiac function, warrants consideration of long-term cardiovascular risk factor modification.

In this registry, pre-eclampsia was associated with a greater likelihood of an adverse neonatal outcome, even after accounting for region. In women without PPCM, the detrimental foetal and neonatal effects of hypertension and pre-eclampsia are well-documented,[29] but little is known about neonatal outcomes in the context of hypertensive disorders and PPCM together. Substantial variation in neonatal morbidity and mortality associated both with pre-eclampsia (ranging from approximately 1% in high-income countries, to approximately 10% in low-middle income countries)[2,30] and with PPCM (ranging from 2% in Europe to 9% in the Middle East)[4] has previously been reported. The frequency of neonatal death in women with PPCM-PE in this registry was approximately five times that of women with PPCM-noHTN and

approximately two times that of all women in the registry. That women with PPCM-PE had less severe cardiac dysfunction than women with PPCM-noHTN suggest that pre-eclampsia (and, in particular, abnormal placental perfusion driving its development) may be more influential on neonatal morbidity and mortality than maternal cardiac function.

There are inherent limitations in conducting an unfunded global registry. These include possible non-consecutive recruitment and higher rates of patients lost to follow-up than in industry-funded randomized clinical trials. The diagnosis of hypertension and pre-eclampsia was clinician-reported and objective clinical parameters such as degree of proteinuria, severity of pre-eclampsia, and timing of the diagnosis were not recorded. We attempted to mitigate this by presenting outcomes according to blood pressure as a continuous variable. Pregnancy duration was not recorded for the majority of women and so was not adjusted for. The definition of left ventricular recovery was based on LVEF and did not include biomarkers or other measures of cardiac structure or function.

In conclusion, we found that women with PPCM and pre-eclampsia presented with more frequent signs and more severe symptoms of heart failure, despite a higher baseline LVEF, than women with PPCM without hypertension. Pre-eclampsia was associated with a greater likelihood of left ventricular recovery, but also of an adverse neonatal outcome and more frequent neonatal death.

Supplementary Information

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

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