

Clinical characteristics and long-term outcomes of peripartum takotsubo cardiomyopathy and peripartum cardiomyopathy

Dong-Yeon Kim¹ , So Ree Kim² , Sung-Ji Park^{2*} , Jeong-Hun Seo² , Eun Kyoung Kim² , Jeong Hoon Yang² , Sung-A Chang² , Jin-Oh Choi² , Sang-Chol Lee²  and Seung Woo Park² 

¹Division of Cardiology, Department of Internal Medicine, Seoul Paik Hospital, Inje University, Seoul, Korea; ²Division of Cardiology, Department of Medicine, Cardiovascular Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Korea

Abstract

Aims Although some peripartum-associated cardiomyopathy patients present with features that are clinically and echocardiographically similar to those of takotsubo cardiomyopathy (TCM), little is known about the diagnosis and clinical course of peripartum TCM.

Methods and results In a tertiary hospital in Seoul, Korea, we searched the hospital database to find cardiomyopathy cases that were associated with pregnancy from January 1995 to May 2019. Applying the published diagnostic criteria, we sought peripartum cardiomyopathy (PPCM) and peripartum TCM patients for comparison. Of 31 pregnancy-associated cardiomyopathy patients, 10 cases of peripartum TCM and 21 cases of PPCM were found. Maternal near-miss death was significantly more common in the peripartum TCM group than in the PPCM group (100.0% vs. 57.1%, $P = 0.030$). Complete recovery was observed with all peripartum TCM cases, while 23.8% of the PPCM cases had residual left ventricular dysfunction. One death and one heart transplantation occurred in the PPCM group, while neither occurred in the peripartum TCM group. There was no difference between the two groups in terms of the rate of major adverse clinical events at 3 years of follow-up [PPCM group: 26.3% (5/19) vs. TCM group: 33.3% (3/9), $P = 0.750$].

Conclusions One-third of pregnancy-associated cardiomyopathy patients had peripartum TCM. With contemporary supportive care, both PPCM and peripartum TCM patients had a low mortality rate and excellent long-term outcomes.

Keywords Peripartum cardiomyopathy; Takotsubo cardiomyopathy; Apical ballooning

Received: 10 March 2020; Revised: 10 June 2020; Accepted: 24 June 2020

*Correspondence to: Sung-Ji Park, Division of Cardiology, Department of Medicine, Cardiovascular Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. Tel: 82-2-3410-3419; Fax: 82-2-3410-3849.

Email: tyche.park@gmail.com

Introduction

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening cardiac disease of the peripartum period, which is still poorly understood in terms of pathogenesis. Haemodynamic stresses during the peripartum period, myocardial inflammation, and prolactin-mediated vascular injury have been suggested as possible causes of PPCM.¹ PPCM is a diagnosis of exclusion. The current definition of PPCM by the European Society of Cardiology's working group on PPCM is an idiopathic cardiomyopathy presenting with heart failure

secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found.² Other cardiomyopathies that occur peripartum should be excluded to establish the diagnosis of PPCM.

Takotsubo cardiomyopathy (TCM) is a syndrome with severe LV dysfunction and the characteristic echocardiographic finding of apical ballooning, often triggered by emotional or physical stress, which should be considered as a differential diagnosis of heart failure during peripartum.^{3,4} Some morphological variants of mid-ventricular and basal ballooning

were reported.⁵ Alpha-adrenergic and beta-adrenergic stimulation and myocardial stunning and coronary vasospasm have been proposed to contribute to the pathogenesis of TCM. Labour pains and surgical stress, which accompany delivery, may contribute to the development of TCM during the peripartum period. Recently, there have been several case reports of peripartum TCM.^{3,6,7} Distinguishing PPCM from TCM or stress-induced cardiomyopathy during the peripartum period has been a diagnostic challenge as the two disease entities share similar clinical features. Even though Citro *et al.*³ suggested in their review of case reports that TCM patients have sudden onset of symptoms immediately after delivery and earlier LV function recovery compared with PPCM patients, it still remains unclear whether peripartum TCM has different clinical characteristics and outcomes when compared with PPCM. We conducted a retrograde chart audit in a single centre to compare the clinical characteristics and outcomes of peripartum TCM and PPCM patients.

Methods

Study setting and study subjects

We searched for the diagnostic codes of PPCM, or idiopathic dilated cardiomyopathy, limiting the search to women between the ages of 18 and 50 years, from January 1995 to May 2019. PPCM was defined as idiopathic cardiomyopathy during the last month of pregnancy or within 5 months after delivery, with an LV ejection fraction (EF) <45%.⁸ Those who had significant valvular heart disease other than tethering mitral regurgitation, previous prosthetic valve surgery, rheumatic heart disease, other known cardiomyopathy syndromes, pheochromocytoma, and acute coronary syndrome were excluded.

Peripartum TCM was defined as when a patient had transient regional wall motion abnormalities (RWMAs) that extended beyond a single epicardial vascular distribution during the last month of pregnancy or within 5 months after delivery, with either electrocardiographic abnormalities or modest cardiac troponin elevation, according to Mayo clinic criteria.⁹ Exclusion criteria for peripartum TCM were proven acute coronary syndrome, significant valvular heart disease, previous valve surgery, rheumatic heart disease, other known cardiomyopathy syndromes, pheochromocytoma, and myocarditis.

Echocardiographic data were obtained according to the guidelines of the American Society of Echocardiography.¹⁰ LV end-diastolic diameters and LV end-systolic diameters were measured by two-dimensional (2D) at parasternal long-axis view. LV EF (LVEF) was determined by modified Simpson's method or linear measurement from 2D images. The presence of right ventricular (RV) dysfunction was

determined by visual assessment on 2D echocardiography. Echocardiography results for all included patients were blindly reviewed by two cardiologists (D-Y. K. and S. R. K).

Clinical outcome measurement

Clinical outcomes measured were mortality before 3 year follow-up, early echocardiographic recovery, near-miss death (NMD), and major adverse cardiac event (MACE). Early echocardiographic recovery was defined as when the follow-up LVEF returns to normal range ($\geq 55\%$) within 1 month.¹¹ LVEF 55% or above was counted as complete recovery at any time of period during follow-up. NMD was defined as described by the World Health Organization Working Group on Maternal Mortality and Morbidity Classifications.^{12,13} The causes of severe maternal morbidity are divided into seven categories as follows: (i) cardiac dysfunction: shock, cardiac arrest (absence of pulse/heart beat and loss of consciousness), use of continuous vasoactive drugs, cardiopulmonary resuscitation, severe hypoperfusion (lactate >5 mmol/L or >45 mg/dL), or severe acidosis (pH < 7.1); (ii) respiratory dysfunction: acute cyanosis, gasping, severe tachypnoea (respiratory rate >40 breaths per minute), severe bradypnoea (respiratory rate <6 breaths per minute), intubation and ventilation not related to anaesthesia, or severe hypoxaemia (O_2 saturation $<90\%$ for ≥ 60 min or $PAO_2/FiO_2 < 200$); (iii) renal dysfunction: oliguria non-responsive to fluids or diuretics, dialysis for acute renal failure, or severe acute azotaemia (creatinine ≥ 300 $\mu\text{mol/L}$ or ≥ 3.5 mg/dL); (iv) coagulation/haematological dysfunction: failure to form clots, massive transfusion of blood or red cells (≥ 5 units), or severe acute thrombocytopenia (<50 000 platelets/mL); (v) hepatic dysfunction: jaundice in the presence of pre-eclampsia or severe acute hyperbilirubinaemia (bilirubin >100 $\mu\text{mol/L}$ or >6.0 mg/dL); (vi) neurological dysfunction: prolonged unconsciousness (lasting ≥ 12 h)/coma (including metabolic coma), stroke, uncontrollable fits/status epilepticus, or total paralysis; and (vii) uterine dysfunction: uterine haemorrhage or infection leading to hysterectomy.¹² MACE was defined as death, heart transplantation, pulmonary thromboembolism, the need for circulatory support, or stroke. The Samsung Medical Center Institutional Review Board approved this study.

Statistical analysis

Demographic and clinical data, echocardiographic findings, and clinical outcomes were presented using standard descriptive statistics. Clinical data were compared between PPCM and peripartum TCM. Data were shown as number, mean \pm standard deviation, percentage, or frequency. Nominal variables were compared using Fisher's exact test. Continuous variables with normal distribution were analysed using

Student's *t*-test for comparison. Continuous variables with non-normal distribution were presented with medians and inter-quartile and compared by Wilcoxon rank-sum test. Kaplan–Meier survival curves were drawn to compare the survival rates of the PPCM group and the peripartum TCM up to 3 years after the diagnosis. Binary logistic regression was performed to determine the independent predictors for early echocardiographic recovery within 1 month of diagnosis of PPCM or peripartum TCM. A *P* value <0.05 was considered statistically significant. All statistical analysis was performed with IBM SPSS statistical software (version 25.0 for windows, SPSS, Inc., Chicago, IL).

Results

Patient population

Forty-nine cases with cardiomyopathy associated with pregnancy were collected according to the diagnostic codes. Of these, 12 cases appeared to have other apparent causes of heart failure, such as significant valvular heart disease, congenital heart disease, chronic renal failure, pheochromocytoma, or other cardiomyopathy syndromes. Six additional patients did not meet the echocardiographic diagnostic criteria of either PPCM or peripartum TCM. Finally, 31 patients with pregnancy-associated cardiomyopathy were included (*Figure 1*). Ten patients had ballooning of LV. Diagnosis could not be agreed upon by the two cardiologists with regard to the ballooning morphology of three patients with RWMA. Eighteen patients had global hypokinesia. Of the 31 patients, 10 patients with ballooning (10/31, 32.30%) fulfilled the diagnostic criteria of peripartum TCM, while 21 patients (21/31, 67.74%) were diagnosed with PPCM.

Clinical characteristics and clinical outcomes

The mean age was 31.7 (± 4.6) years with no significant difference in age between the two groups. The median onset after delivery for PPCM and peripartum TCM occurred was 0.0 (inter-quartile 5.0) days and 1.0 (inter-quartile 5.0) days, respectively (*Table 1*). While 14.3% of the PPCM patients started to have symptoms before delivery, none of the peripartum TCM patients were symptomatic before delivery. Of the 10 patients with peripartum TCM, those who underwent caesarean section had a shorter mean number of days to onset than did those who had vaginal delivery, although this difference was not statistically significant (7/10, 1.3 ± 2.1 days vs. 3/10, 20.0 ± 3.2 days, *P* = 0.41).

There was no significant difference in serum creatinine, haemoglobin, N-terminal pro-B-type natriuretic peptide, creatine kinase muscle/brain isoenzyme, or cardiac troponin I level at the time of admission, between the PPCM group and the peripartum TCM group (*Table 1*). Twin pregnancy was common in both groups (38.1% in PPCM and 50.0% in peripartum TCM, *P* = 0.701). History of infertility treatment, such as *in vitro* fertilization, intrauterine insemination, or ovulation induction, was more common among PPCM patients than among peripartum TCM patients, without statistical significance (42.9% vs. 20.0%, *P* = 0.262). Caesarean section was common in both groups (71.4% in PPCM vs. 70.0% in peripartum TCM, *P* = 1.000). While all of the patients in the peripartum TCM group completely recovered, 23.8% of the PPCM group had residual myocardial dysfunction. Overall, 41.9% of the patients in this study needed mechanical ventilation apart from general anaesthesia. Four patients (19.0%) in the PPCM group and one patient (10.0%) in the peripartum TCM group underwent extracorporeal membrane oxygenation (ECMO). One patient in the PPCM group had heart

Figure 1 Inclusion of patients. LV, left ventricle; PPCM, peripartum cardiomyopathy; RWMA, regional wall motion abnormality; TCM, takotsubo cardiomyopathy.

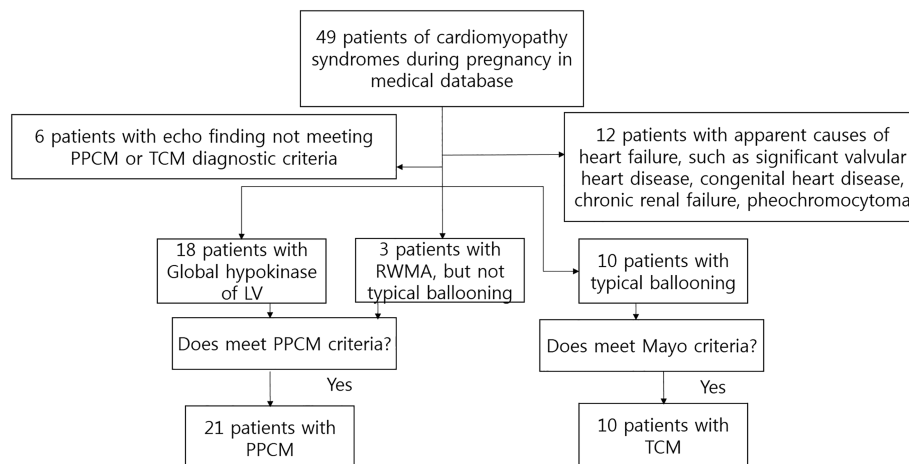


Table 1 Demographic and clinical characteristics

	All subjects (N = 31)	PPCM (N = 21)	Peripartum TCM (N = 10)	P value
Age (years)	31.7(4.6)	32.0 (4.9)	31.3 (3.8)	0.716
Median onset (days after delivery) ^a	0.5 (5.0)	0.0 (5.0)	1.0 (5.0)	0.840
SBP	126.3 (27.6)	122.6 (27.6)	134.2 (27.4)	0.280
DBP	83.0 (21.7)	80.8 (23.3)	87.7 (18.0)	0.417
Heart rate	106.5 (23.7)	105.7 (20.9)	108.3 (29.9)	0.782
NYHA class				
I-II	4 (12.9)	4 (19.0)	0 (0.0)	0.277
III-IV	27 (87.1)	17 (81.0)	10 (100.0)	
Medications				
ACEI/ARB	19 (61.3)	11 (52.4)	8 (80.0)	0.240
Beta blocker	14 (45.2)	7 (33.3)	7 (70.0)	0.121
Loop diuretics	22 (71.0)	14 (66.7)	8 (80.0)	0.677
Aldosterone antagonist	8 (25.8)	5 (23.8)	3 (30.0)	1.000
Inotropics	9 (29.0)	7 (33.3)	2 (20.0)	0.677
Onset before delivery	3 (9.7)	3 (14.3)	0 (0.0)	0.172
Onset within 1 month after delivery	26 (83.9)	17 (81.0)	9 (90.0)	
Onset beyond 1 month after delivery	1 (3.2)	0 (0.0)	1 (10.0)	
Not recorded	1 (3.2)	1 (4.8)	0 (0.0)	
Serum creatinine ^a (mg/dL)	0.84 (0.83)	0.98 (0.90)	0.69 (1.23)	0.583
Haemoglobin (g/dL)	10.94 (2.25)	10.83 (2.11)	11.15 (2.63)	0.744
NT-proBNP (pg/mL)	8801.70 (7903.21)	8819.29 (8763.93)	8762.13 (6044.94)	0.985
CK-MB (ng/mL) ^a	4.20 (4.28)	3.12 (12.83)	5.16 (12.73)	0.192
Tnl (ng/mL) ^a	0.38 (1.36)	0.18 (2.39)	1.21 (1.13)	0.270
Twin	13 (41.9)	8 (38.1)	5 (50.0)	0.701
Multipara	10 (32.3)	7 (35.0)	3 (30.0)	1.000
Pre-eclampsia	10 (32.3)	5 (23.8)	5 (50.0)	0.222
HELLP syndrome	2 (6.5)	0 (0.0)	2 (20.0)	0.097
GDM	1 (3.2)	1 (4.8)	0 (0)	1.000
IVF	8 (25.8)	7 (33.3)	1 (10.0)	0.222
IUI	2 (6.5)	1 (4.8)	1 (10.0)	1.000
Ovulation induction	1 (3.2)	1 (4.8)	0 (0.0)	1.000
All infertility treatment	11 (35.5)	9 (42.9)	2(20.0)	0.262
Caesarean section	22 (71.0)	15 (71.4)	7 (70.0)	1.000
DIC	4 (12.9)	2 (9.5)	2 (20.0)	0.577
Bleeding complications	8 (25.8)	4 (19.0)	4 (40.0)	0.381
Uterine embolization	5 (16.2)	2 (9.5)	3 (30.0)	0.296
TAH	5 (16.2)	3 (14.2)	2 (20.0)	1.000
Ventilator	13 (41.9)	8 (38.1)	5 (50.0)	0.701
ECMO	5 (16.2)	4 (19.0)	1 (10.0)	1.000
Early recovery within 1 month	16 (51.6)	9 (42.8)	7 (70.0)	0.252
Full recovery	26 (83.9)	16 (76.2)	10 (100.0)	0.147
Near-miss death (NMD)				
All causes	22 (71.0)	12 (57.1)	10 (100.0)	0.030
Cardiac	11 (35.4)	8 (38.1)	3 (30.0)	1.000
Respiratory	10 (32.3)	5 (23.8)	5 (40.0)	0.222
Renal	0 (0.0)	0 (0.0)	0 (0.0)	NC
Haematological	6 (19.4)	2 (9.5)	4 (40.0)	0.067
Hepatic	0 (0.0)	0 (0.0)	0 (0.0)	NC
Neurological	2 (6.4)	1 (4.8)	1 (10.0)	1.000
Uterine dysfunction	7 (22.6)	3 (14.2)	4 (40.0)	0.172
Mortality	1/28 (3.6)	1/19 (5.3)	0/9 (0.0)	1.000
Heart transplantation	1/28 (3.6)	1/19 (5.3)	0/9 (0.0)	1.000
Adverse event (HT, death, PTE, ECMO, LVAD, and stroke)	8/28 (28.6)	5/19 (26.3)	3/9(33.3)	0.750
3 year survival (HT-free and death-free)	26/28 (92.8)	17/19 (89.5)	9/9 (100.0)	0.324

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatinine kinase muscle/brain; DBP, diastolic blood pressure; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; GDM, gestational diabetes mellitus; HELLP, haemolysis, elevated liver enzymes, and low platelet; HT, heart transplantation; IUI, intrauterine insemination; IVF, *in vitro* fertilization; LVAD, left ventricular assist device; NC, not calculated; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PPCM, peripartum cardiomyopathy; PTE, pulmonary thromboembolism; SBP, systolic blood pressure; TAH, transabdominal hysterectomy; TCM, takotsubo cardiomyopathy; Tnl, troponin I.

Normally distributed continuous variables are expressed as means with standard deviation in brackets; non-normally distributed continuous variables as medians with inter-quartile in brackets; and all others represent numbers of patients with values in brackets representing percentages.

^anon-normally distributed continuous variables.

transplantation after bridging mechanical circulatory support (MCS) with ECMO and subsequent LV assist device. There was no immediate in-hospital mortality. One death occurred in the PPCM group on long-term follow-up at 21 months after delivery, while no deaths were reported in the peripartum TCM group (*Table 1*). The heart transplantation/death-free survival rates for the PPCM and peripartum TCM groups at 3 years were 89.5% and 100.0%, respectively. There was no significant difference in MACE at 3 years of follow-up between the two groups [26.3% (5/19) in the PPCM group and 33.3% (3/9) in the TCM group, $P = 0.750$] (*Figure 2*).

Overall prevalence of NMD in the study subjects was 71.0%. Maternal NMD was significantly more common in the peripartum TCM group than in the PPCM group (100.0% vs. 57.1%, respectively, $P = 0.030$). Haematological dysfunction and uterine dysfunction were numerically more common in the peripartum TCM group. Cardiac dysfunction was the most common cause of severe maternal morbidity, followed by respiratory, uterine, haematological, and neurological dysfunctions (*Table 1*).

Echocardiographic findings

The mean LVEF of the study subjects was $30.7 \pm 8.0\%$. The PPCM group and the peripartum TCM group had similar values for LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), and LVEF. Of the 10 peripartum TCM patients, five cases with apical-type, two cases with mid-type, and three cases with basal-type ballooning were noted (*Table 2*).

Binary logistic regression showed that an EF $> 30\%$ independently predicted early echocardiographic recovery within 1 month after the diagnosis of PPCM or peripartum TCM (odds ratio 331.33, 95% confidence interval 3.865–28 402.597, $P = 0.011$), when EF $> 30\%$, RV dysfunction, ballooning morphology in echocardiography, age < 30 years, pre-eclampsia, caesarean section, twin pregnancy, multipara,

and ventilator use were taken as independent variables (*Table 3*).

Discussion

Our study is a hospital-based retrospective study of pregnancy-associated cardiomyopathy cases that compared the clinical characteristics and long-term outcomes of PPCM and peripartum TCM. Distinguishing peripartum TCM from PPCM is a diagnostic challenge as the two disease entities share similar clinical features. Differential diagnosis usually relies on echocardiography, as there is no other useful diagnostic test in clinical practice. Echocardiographic findings of TCM may vary in terms of the involved areas and extent and might be less appreciable.⁵ Differentiating RWMA and global hypokinesia is often difficult and associated with inter-observer variation. In our study, two cardiologists could not reach the same conclusion on the diagnosis of either ballooning or global hypokinesia for three patients with wall motion abnormalities. We accepted only typical ballooning cases as peripartum TCM with the agreement of two cardiologists. In our study, one-third (32.3%, 10/31) of the pregnancy-associated cardiomyopathy patients were peripartum TCM cases. Yang *et al.*¹⁴ recently published retrospective series of 37 patients with peripartum-associated cardiomyopathy, which showed that 43.0% (16/37) of them had peripartum TCM that is comparable with our data. On unadjusted analysis, the study showed that 100% (16/16) of the peripartum TCM group and 59% (10/21) of PPCM had early complete recovery with LVEF 50% or above in a month. The peripartum TCM group had significantly higher LVEF than the PPCM group at follow-up echocardiography 1 month after diagnosis. In our study, 70.0% (7/10) of peripartum TCM and 42.8% (9/21) of the PPCM group had early complete recovery in a month. Notably, LVEF 55% or above was considered as complete LV function recovery in our study, which may lead to lower complete recovery rate, compared with the report

Figure 2 Kaplan–Meier survival curves for death/heart transplantation (HT)-free survival and cumulative adverse events (death, HT, pulmonary thromboembolism, requirement of circulatory supports, and stroke). PPCM, peripartum cardiomyopathy; TCM, takotsubo cardiomyopathy.

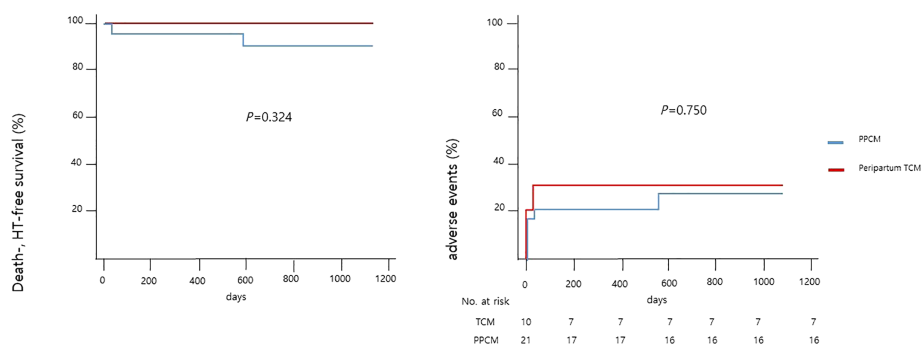


Table 2 Echocardiographic data of PPCM and peripartum TCM patients

	All subjects (N = 31)	PPCM (N = 21)	Peripartum TCM (N = 10)	P value
LVEDD (mm)	56.2 ± 5.57	57.3 ± 6.0	53.6 ± 3.6	0.083
LVESD (mm)	47.6 ± 6.1	48.7 ± 6.5	45.0 ± 4.2	0.215
EF (%)	30.7 ± 8.0	30.3 ± 8.6	31.8 ± 6.9	0.540
EF ≥ 30%	9 (29.0)	7 (33.3)	2 (20.0)	0.677
RV dysfunction	4 (12.9)	2 (9.5)	2 (20.0)	0.577
Ballooning type				N/A
Apical	N/A	N/A	5 (50.0)	
Mid			2 (20.0)	
Basal			3 (30.0)	

EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; N/A, not applicable; PPCM, peripartum cardiomyopathy; RV, right ventricular; TCM, takotsubo cardiomyopathy. Continuous variables are expressed as means with standard deviation in brackets; all others represent numbers of patients with values in brackets representing percentages.

Table 3 Binary logistic regression (predictors for early echocardiographic recovery within 1 month)

Independent variables	Odds ratio	95% confidence interval		P value
EF > 30%	331.33	3.865	28 402.597	0.011
RV dysfunction	43.525	0.337	5623.905	0.128
Ballooning	7.107	0.284	177.561	0.232
Younger age (<30 years)	0.007	0.000	0.632	0.031
Pre-eclampsia	0.084	0.003	2.103	0.131
Caesarean section	5.443	0.229	129.194	0.294
Twin	0.214	0.006	8.095	0.405
Multipara	10.783	0.278	418.963	0.203
Ventilator use	0.934	0.08	10.878	0.956

EF, ejection fraction; RV, right ventricular.

of Yang *et al.* In the Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, complete recovery was defined by LVEF 50% or above, which may include partial recovery, while Haghika *et al.* used a stricter definition of EF 55% or above as complete recovery like our study.^{11,15}

The time frame of PPCM is under debate. National Heart Lung and Blood Institutes and the Office of Rare Diseases defined PPCM as idiopathic cardiomyopathy during the last month of pregnancy or within 5 months after delivery.⁸ Sliwa *et al.*² argued that this definition may lead to under-diagnosis and the time frame of diagnosis should be extended up to 'the months following delivery', in spite of its ambiguity. We used the classical definition by National Heart Lung and Blood Institutes and the Office of Rare Diseases. In our study, 93.6% (29/31) of peripartum-associated cardiomyopathy occurred during 1 month prepartum and within 1 month post-partum. Only one patient with peripartum TCM (3.2%, 1/31) presented 1 month after delivery.

There are several potential mechanisms that may precipitate TCM during the peripartum period. First, pain during labour or caesarean section, anxiety, emotional stress, bleeding, and hypovolaemia are frequently encountered during the peripartum period and may induce a catecholamine surge, which is believed to cause myocardial dysfunction in TCM.^{4,16,17} Second, oestrogen may play a role in protecting myocardium in stress, and suddenly lowered oestrogen levels

after delivery may make the myocardium more susceptible to the catecholamine surge.¹⁸ TCM is strikingly more common among women, particularly after menopause.¹⁶ In several animal studies, chronic oestrogen replacement attenuated cardiac dysfunction induced by stress.^{19,20} Peripartum TCM presented exclusively after delivery in our study, which may support the role of oestrogen withdrawal in the development of peripartum TCM.

The median number of days from delivery to onset of symptoms was 0.0 (inter-quartile 5.0) days in the PPCM group and 1.0 (inter-quartile 5.0) days in the peripartum TCM group in our study (*Table 1*). Citro *et al.*³ reviewed 15 case reports of peripartum TCM and showed that the majority of patients (87%, 13/15) underwent an elective caesarean section at term and developed symptoms immediately after surgery, while the two cases with vaginal delivery had comparably delayed onset (17 and 40 days post-partum). Our study also showed that patients with peripartum TCM who underwent caesarean section tended to have a shorter mean time to onset than those who had vaginal delivery (7/10, 1.29 ± 2.14 days vs. 3/10, 20.00 ± 31.19 days, *P* = 0.41). This finding suggests that surgical stress during caesarean section may play an important role in developing peripartum TCM. The three peripartum TCM patients with vaginal delivery had onset of symptoms on 1, 3, and 56 days post-partum, with a wide range of deviation in our study. Therefore,

delayed onset should not be a reason to exclude the diagnosis of peripartum TCM when a patient has vaginal delivery. The reason for delayed onset of peripartum TCM after vaginal delivery is not clearly understood. In our study, the patient with delayed onset peripartum TCM had massive uterine bleeding due to uterine arteriovenous malformation one and a half months after vaginal delivery, which may explain the late presentation.

Citro *et al.*³ indicated that PPCM was associated with a worse outcome compared with peripartum TCM. Contrarily, complete recovery is a rule in TCM.⁹ In our study, the PPCM group had one case of mortality and one case of heart transplantation at long-term follow-up, and 23.8% had residual myocardial dysfunction, while the entire peripartum TCM group experienced complete recovery with no mortality (*Table 1*). Differences in mortality and MACE at long-term follow-up failed to reach statistical significance, most likely due to the small sample size and relatively low event rate in our study.

Maternal mortality rate is one of the poorest performing health indicators.¹³ Maternal death is an important adverse clinical event, but it is less useful in terms of measuring quality of care in health facilities where maternal death is not common. There is growing interest and evidence that the near-miss concept may improve the quality of obstetrical care.²¹

The mortality rate of PPCM varies greatly across reports. In one study in South Korea, the in-hospital mortality rate of PPCM was as low as 1.0%.²² Fett *et al.*²³ reported a mortality rate of 15.3% at 5 years of follow-up in Haiti. A statewide population-based study in North Carolina showed that the overall 7 year mortality rate was 16.5%, with a four-fold higher mortality rate among Black non-Hispanic women than White women.²⁴ One prospective multicentre registry in North America¹⁵ reported a mortality rate of 4.3% (4/91) at 12 months. LVEF < 30% was associated with an increase in adverse events.

In North America, the prevalence of maternal NMD in the general population is 1.38%.²¹ In our study, 71.0% of the patients with pregnancy-associated cardiomyopathy fulfilled the World Health Organization criteria of NMD. However, even with a relatively high prevalence of NMD, the mortality rate of PPCM and peripartum TCM at 3 years was as low as 4.8% and 0.0%, respectively (*Table 1*).

In our study, the peripartum TCM group was associated with a higher prevalence of NMD, compared with the PPCM group (100.0% vs. 57.1%, $P = 0.030$) (*Table 1*). This finding supports the theory that co-morbidities might have led to the catecholamine surge and peripartum TCM. In spite of the higher prevalence of NMD, there were no mortalities and no permanent LV dysfunction in the peripartum TCM group.

There were several case reports of cardiogenic shock due to PPCM treated with MCS.^{25,26} Sieweke *et al.*²⁶ reported five

cases of PPCM patients with cardiogenic shock. Bromocriptine was given alongside MCS. There were no deaths at 30 days of admission. Bouabdallaoui *et al.* performed veno-arterial ECMO for 10 PPCM patients with cardiogenic shock. Prompt central cannulation was performed for five patients afterwards. Five patients died, three patients recovered, and two patients survived after heart transplantation.²⁷ In our study, 19.0% of the PPCM group and 10.0% of the peripartum TCM group went through MCS due to cardiogenic shock. None of them had bromocriptine therapy. Of the five patients who underwent ECMO, no deaths were reported. One patient had heart transplantation. Notably, in one meta-analysis, MCS did not reduce mortality for patients with cardiogenic shock complicating acute myocardial infarction, in spite of the early beneficial effect on mean arterial pressure and arterial lactate level.²⁷ The wide gap in outcomes after MCS in different reports suggests that patient selection, timing of MCS, and quality of care may affect the management of cardiogenic shock due to PPCM. A study reported that high-sensitivity troponin T predicted cardiogenic shock requiring MCS after cardiac valve surgery.²⁸ However, until now, there are no data in regard to biomarkers predicting the need of MCS in PPCM patients. Further study is needed to determine the role of ECMO and prognostic predictors for the management of cardiogenic shock with pregnancy-associated cardiomyopathy.

In the PPCM and peripartum TCM groups, 38.1% and 50.0%, respectively, received mechanical ventilation not related to anaesthesia (*Table 1*). Our study subjects represented critically ill patients in a tertiary centre. Meticulous medical care including timely utilization of MCS may have prevented maternal death in the critically ill patients in our study.

Binary logistic regression showed that EF 30% or above predicted early complete recovery with EF 55% or above, while 95% confidence interval was wide in our study (*Table 3*). Other variables such as RV dysfunction, ballooning morphology in echocardiography, age <30 years, pre-eclampsia, caesarean section, twin pregnancy, multipara, and ventilator use did not reach statistical significance to predict early complete recovery in our study either. In the IPAC cohort, EF < 30% and LVEDD > 6.0 cm were independent predictors of poor LV function recovery, the need of mechanical support, and death.¹⁵ RV dysfunction measured by fractional area change predicted poor LV function recovery, too.²⁹ Pre-eclampsia and eclampsia were associated with the higher rate of LV function recovery in a Japanese study, while this finding was not consistent in the IPAC study.^{15,30} Even though EF 30% or above predicted early complete recovery in our study, 95% confidence interval was too wide to confirm this observation. A larger study should be performed to find independent predictors of early LV function recovery.

Limitations

First, our study was inadequately powered because of small number of patients and low event rate. Power analysis using general linear model showed that the power of our study to detect the difference of composite clinical outcome was 60.8%, when EF, LVEDD, age, pre-eclampsia, multipara, twin, ventilator use, caesarean section, and RV dysfunction were taken as co-variables. Second, the clinical features depicted in this study cannot be generalized because our subjects may represent severe cases in a tertiary centre. A larger multicentre study is warranted to better understand the clinical characteristics of both PPCM and peripartum TCM. Third, the diagnosis of PPCM and peripartum TCM relied on echocardiography in our study. Interobserver variation of echocardiography should be considered when interpreting our data.

Conclusions

One-third of pregnancy-associated cardiomyopathy patients had peripartum TCM. Peripartum TCM was more commonly

associated with NMD, compared with PPCM. Complete recovery was observed with all of the cases of peripartum TCM, while 23.8% of the PPCM cases had residual LV dysfunction. Peripartum TCM patients had onset of symptoms exclusively after delivery. With supportive care including ECMO, both PPCM and peripartum TCM patients had excellent long-term outcomes. LVEF > 30% was associated with early LV function recovery. A larger study is needed to identify and evaluate the shared and distinct clinical characteristics of the two disease entities.

Conflict of interest

None declared.

Funding

None to disclose.

References

- Arany Z, Elkayam U. Peripartum cardiomyopathy. *Circulation* 2016; **133**: 1397–1409.
- Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen D, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Papp Z, Mouquet F, McMurray J, Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2010; **12**: 767–778.
- Citro R, Giudice R, Mirra M, Petta R, Baldi C, Bossone E, Piscione F. Is Tako-tsubo syndrome in the postpartum period a clinical entity different from peripartum cardiomyopathy? *J Cardiovasc Med (Hagerstown)* 2013; **14**: 568–575.
- Ono R, Falcao LM. Takotsubo cardiomyopathy systematic review: pathophysiologic process, clinical presentation and diagnostic approach to Takotsubo cardiomyopathy. *Int J Cardiol* 2016; **209**: 196–205.
- Hurst RT, Askew JW, Reuss CS, Lee RW, Sweeney JP, Fortuin FD, Oh JK, Tajik AJ. Transient midventricular ballooning syndrome: a new variant. *J Am Coll Cardiol* 2006; **48**: 579–583.
- Kim SY, Yoon JH, Lee SH. Takotsubo-like severe left ventricular dysfunction after cesarean delivery in a 28-year old woman. *Korean Circ J* 2011; **41**: 101–104.
- Lee JY, Kwon HJ, Park SW, Lee YM. Acute pulmonary edema caused by takotsubo cardiomyopathy in a pregnant woman undergoing transvaginal cervical cerclage: a case report. *Medicine (Baltimore)* 2017; **96**: e5536.
- Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, Ansari A, Baughman KL. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. *JAMA* 2000; **283**: 1183–1188.
- Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008; **155**: 408–417.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer
- KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440–1463.
- Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, Tsikas D, Jordan J, Lichtinghagen R, Kaisenberg CS, Struman I, Bovy N, Sliwa K, Bauersachs J, Hilfiker-Kleiner D. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. *Basic Res Cardiol* 2013; **108**: 366.
- Souza JP, Say L, Pattinson R, Gülmezoglu AM, Bartlett L, Barret J. *Evaluating the quality of care for severe pregnancy complications: the WHO near-miss approach for maternal health*: World Health Organization; 2011 <https://www.who.int/reproductivehealth/publications/>

- monitoring/9789241502221/en/ Accessed date 2020/03/02.
13. Say L, Souza JP, Pattinson RC, WHO working group on Maternal Mortality and Morbidity classifications. Maternal near miss—towards a standard tool for monitoring quality of maternal health care. *Best Pract Res Clin Obstet Gynaecol* 2009; **23**: 287–296.
 14. Yang WI, Moon JY, Shim M, Yang PS, Kang SH, Kim SH, Kim WJ, Sung JH, Kim IJ, Lim SW, Cha DH, Ha JW. Clinical features differentiating Takotsubo cardiomyopathy in the peripartum period from peripartum cardiomyopathy. *Heart Vessels* 2020; **35**: 665–671.
 15. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, Modi K, Alexis JD, Ramani GV, Semigran MJ, Haythe J, Markham DW, Marek J, Gorcsan J 3rd, Wu WC, Lin Y, Halder I, Pisarcik J, Cooper LT, Fett JD, IPAC Investigators. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). *J Am Coll Cardiol* 2015; **66**: 905–914.
 16. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KEJ, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairaz O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015; **373**: 929–938.
 17. Pilati CF, Bosso FJ, Maron MB. Factors involved in left ventricular dysfunction after massive sympathetic activation. *Am J Physiol* 1992; **263**: H784–H791.
 18. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; **340**: 1801–1811.
 19. Ueyama T, Ishikura F, Matsuda A, Asanuma T, Ueda K, Ichinose M, Kasamatsu K, Hano T, Akasaka T, Tsuruo Y, Morimoto K, Beppu S. Chronic estrogen supplementation following ovariectomy improves the emotional stress-induced cardiovascular responses by indirect action on the nervous system and by direct action on the heart. *Circ J* 2007; **71**: 565–573.
 20. Morimoto K, Kurahashi Y, Shintani-Ishida K, Kawamura N, Miyashita M, Uji M, Tan N, Yoshida KI. Estrogen replacement suppresses stress-induced cardiovascular responses in ovariectomized rats. *Am J Physiol Heart Circ Physiol* 2004; **287**: H1950–H1956.
 21. Tuncalp O, Hindin MJ, Souza JP, Chou D, Say L. The prevalence of maternal near miss: a systematic review. *Bjog-Int J Obstet Gy* 2012; **119**: 653–661.
 22. Lee S, Cho GJ, Park GU, Kim LY, Lee T-S, Kim DY, Choi S-W, Youn J-C, Han SW, Ryu K-H, Na JO, Choi CU, Seo HS, Kim EJ. Incidence, risk factors, and clinical characteristics of peripartum cardiomyopathy in South Korea. *Circ Heart Fail* 2018; **11**: e004134.
 23. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. *Mayo Clin Proc* 2005; **80**: 1602–1606.
 24. Harper MA, Meyer RE, Berg CJ. Peripartum cardiomyopathy: population-based birth prevalence and 7-year mortality. *Obstet Gynecol* 2012; **120**: 1013–1019.
 25. Horn P, Saeed D, Akhyari P, Hilfiker-Kleiner D, Kelm M, Westenfeld R. Complete recovery of fulminant peripartum cardiomyopathy on mechanical circulatory support combined with high-dose bromocriptine therapy. *ESC Heart Fail* 2017; **4**: 641–644.
 26. Sieweke JT, Pfeffer TJ, Berliner D, König T, Hallbaum M, Napp LC, Tongers J, Kühn C, Schmitto JD, Hilfiker-Kleiner D, Schäfer A, Bauersachs J. Cardiogenic shock complicating peripartum cardiomyopathy: importance of early left ventricular unloading and bromocriptine therapy. *Eur Heart J Acute Cardiovasc Care* 2018 2048872618777876.
 27. Bouabdallaoui N, Demondion P, Leprince P, Lebreton G. Short-term mechanical circulatory support for cardiogenic shock in severe peripartum cardiomyopathy: La Pitié-Salpêtrière experience. *Interact Cardiovasc Thorac Surg* 2017; **25**: 52–56.
 28. Duchnowski P, Hryniewiecki T, Kusmierczyk M, Szymanski P. High-sensitivity troponin T predicts postoperative cardiogenic shock requiring mechanical circulatory support in patients with valve disease. *Shock* 2020; **53**: 175–178.
 29. Blauwet LA, Delgado-Montero A, Ryo K, Marek JJ, Alharethi R, Mather PJ, Modi K, Sheppard R, Thohan V, Pisarcik J, McNamara D, Gorcsan J 3rd, IPAC Investigators*. Right ventricular function in peripartum cardiomyopathy at presentation is associated with subsequent left ventricular recovery and clinical outcomes. *Circ Heart Fail* 2016; **9**: e002756.
 30. Kamiya CA, Kitakaze M, Ishibashi-Ueda H, Nakatani S, Murohara T, Tomoike H, Ikeda T. Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. Results from the Japanese nationwide survey of peripartum cardiomyopathy. *Circ J* 2011; **75**: 1975–1981.