Challenges in the diagnosis of peripartum cardiomyopathy: a case series

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Background
Peripartum cardiomyopathy (PPCM) is usually characterized by overt heart failure, but other clinical scenarios are possible, sometimes making the diagnosis challenging.

Case summary
We report a case series of four patients with PPCM. The first patient presented with acute heart failure due to left ventricular (LV) systolic dysfunction. Following medical treatment, LV function recovered completely at 1 month. The second patient had systemic and pulmonary thromboembolism, secondary to severe biventricular dysfunction with biventricular thrombi. The third patient presented with myocardial infarction with non-obstructed coronary arteries and evidence of an aneurysm of the mid-anterolateral LV wall. The fourth patient, diagnosed with PPCM 11 years earlier, presented with sustained ventricular tachycardia. A repeat cardiac magnetic resonance, compared to the previous one performed 11 years earlier, showed an enlarged LV aneurysm in the mid-LV anterolateral wall with worsened global LV function.

Discussion
Peripartum cardiomyopathy may have different clinical presentations. Attentive clinical evaluation and multimodality imaging can provide precise diagnostic and prognostic information.

Keywords
Cardiac magnetic resonance imaging • Case series • Echocardiography • Peripartum cardiomyopathy

Learning points
• Peripartum cardiomyopathy may have different clinical presentations: heart failure, chest pain, arrhythmias, pulmonary, and systemic thromboembolism.
• Accurate clinical evaluation and multimodality imaging are useful to achieve the differential diagnosis between peripartum cardiomyopathy and other pregnancy-related cardiac and non-cardiac disorders.

Introduction
Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy presenting towards the end of pregnancy or in the months following delivery, usually characterized by heart failure (HF) secondary to left ventricular (LV) systolic dysfunction.1 However, patients may present with chest pain, severe arrhythmias, and thrombo-embolic complications.2 In this case series, we present four patients with PPCM with different clinical presentations highlighting the role of multimodality imaging in the diagnosis of PPCM in different clinical scenarios.

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Case presentation

Patient 1
A 27-year-old woman with no past medical history was admitted at 35th gestational week for preeclampsia (blood pressure 160/115 mmHg) and underwent an uneventful Caesarian section. On the third post-operative day, she complained of dyspnoea with oxygen desaturation (88%). Physical examination revealed pulmonary and peripheral congestion, third heart sound and a pansystolic murmur. Electrocardiogram showed sinus tachycardia with diffuse ST alterations. Brain natriuretic peptide was increased (1500 ng/L).

Chest ultrasonography identified right pleural effusion (Figure 1A), and left pulmonary comet tails (Figure 1B), consistent with venous congestion. Transthoracic echocardiography (TTE) showed reduced left ventricular (LV) ejection fraction (EF 35%) (Figure 1C, Inline Video 1), and secondary severe mitral regurgitation (MR) (Figure 1D, Inline Video 1).

Following treatment with angiotensin-converting enzyme (ACE)-inhibitors, beta-blockers (BB), low molecular weight heparin (LMWH), and bromocriptine LV function recovered completely. At 1-month follow-up, LVEF was 60% (Figure 1E) (global longitudinal strain = -20%) with mild MR (Figure 1F, Supplementary material online, Video S1).

Patient 2
A 30-year-old woman with no past medical history presented with transient left amaurosis and dyspnoea one month after C-section. Transthoracic echocardiography showed severe biventricular dysfunction (LVEF 22%), severe mitral regurgitation, and biventricular thrombi. Cardiac magnetic resonance (CMR): LVEF 25%, right ventricular ejection fraction 21%. Medical treatment.

26/02/2008 Recurrent systemic embolism (spleen)
28/02/2008 Cardiac surgery: mitral restrictive annuloplasty, and thrombectomy. Post-operative low output syndrome. Extra corporeal membrane oxygenation (ECMO)
03/03/2008 Weaned off from ECMO
19/03/2008 Control CMR- LVEF 48%
22/03/2008 Discharged home

Patient 3
03/09/2018 Admission for chest pain at 33rd gestational week. Increased troponin I
04/09/2018 Corticosteroids for foetal lung maturation
05/09/2018 Abruptly increased chest pain and troponin I with transient ST-segment elevation. CMR without gadolinium: transmural oedema of the basal-mid-cavity left ventricular (LV) anterior and antero-septal segments. Emergent C-section followed by coronary angiography and intravascular ultrasound (IVUS): normal coronary arteries. Sharp postpartum normalization of electrocardiogram and TnI. Therapy: bromocriptine, angiotensin-converting enzyme-inhibitors, beta-blockers and low molecular weight heparin
12/09/2019 Discrete aneurysm formation on echo and CMR
14/09/2019 Repeat coronary angiography: normal coronary arteries
28/09/2019 Discharged home

Patient 4
March 2008 Peripartum cardiomyopathy during third delivery
June 2008 Transient ischaemic attack. First CMR study: LV aneurysm of the mid-cavity anterior wall with transmural late gadolinium enhancement (LGE), and an area of subepicardial LGE of the basal inferior wall, LVEF 48%. Coronary angiography: normal coronary arteries. Medical treatment.
04/01/2020 Ventricular tachycardia. Second CMR study: LV with a large aneurysm of the mid-cavity anterior and antero-septal walls with extensive transmural LGE, and epicardial LGE of the basal inferior wall with worsened function (LVEF 35%)
Figure 1 Transthoracic echocardiography at admission showing signs of congestion such as right pleural effusion (A, solid arrow) and left pulmonary comet tails (B, dashed arrow), reduced left ventricular function (C, left ventricular parasternal short-axis view in diastole and systole), and severe mitral regurgitation (D, left ventricular apical long-axis view); following adequate therapy transthoracic echocardiography demonstrated normalized left ventricular systolic function (E), and mild residual mitral regurgitation (F).

Video 1 Transthoracic echocardiography demonstrating reduced left ventricular function and severe secondary mitral regurgitation in peripartum cardiomyopathy presenting with heart failure.

Video 2 Transthoracic echocardiography identifying biventricular thrombi, biventricular dysfunction and severe secondary mitral regurgitation.
Figure 2. Transthoracic echocardiography apical views showing (A) biventricular apical thrombi (right ventricle, red arrow, A; left ventricle, green arrow, A and B) and a vacuolated mid-septal left ventricular thrombus (blue arrow, A and B). Colour-Doppler (C) showing secondary severe mitral regurgitation.

Figure 3. Transthoracic echocardiography in the same patient as in Figure 2 following an embolic systemic episode while on heparin therapy. (A) The left apical ventricular thrombus is no more evident and the mid-septal thrombus (arrow) looks bilobulated but not vacuolated. Computed tomography short-axis views shows bilateral pulmonary (B, solid arrows) and splenic (C, dashed arrow) embolism.

Colour-Doppler interrogation identified secondary severe MR (Figure 2C). She was started on unfractioned heparin, diuretics, BB, and ACE-inhibitors. On Day 3, she complained of an abrupt left flank pain. On TTE (Figure 3A) the LV apical thrombus was no longer evident, and the larger LV mass looked bilobulated, but no longer vacuolated. Total body computed tomography (CT) revealed bilateral lobar pulmonary artery defects (Figure 3B), and a splenic wedge-shaped hypoenhanced region (Figure 3C), consistent with embolization. Cardiac magnetic resonance (CMR) demonstrated a sessile mass obliterating the right ventricular apex and a bilobulated mobile mass attached to the anterior LV wall (Figure 4AB, Supplementary material online, Video S2). After gadolinium injection, both ventricular masses were not perfused (Figure 4C) and post-contrast images (Figure 4D) excluded the presence of biventricular late gadolinium enhancement (LGE). She underwent emergency cardiac surgery because of persisting thrombi with distal embolization despite anticoagulation. Through a heart miniport access, mitral...
annuloplasty was performed and ventricular masses were removed; histological analysis confirmed they were thrombi. Attempts at weaning cardiopulmonary bypass were unsuccessful, and she was therefore placed on extracorporeal membrane oxygenation mechanical circulatory support, which was weaned on the fourth post-operative day. The patient was discharged on Day 25 with LVEF 48% and trivial residual MR in the control CMR.

Figure 4 Cardiac magnetic resonance steady state free precession cine sequences showing right apical ventricular mass (A, red arrow), and bilobulated left ventricular mass (B, blue arrow). After gadolinium injection both ventricular masses look not perfused (C, red and blue arrows, right and left ventricle, respectively). Short-axis T1 weighted phase sensitive inversion recovery sequence acquired 10 min after gadolinium administration excluded late gadolinium enhancement (D).

Figure 5 Electrocardiogram at presentation (A) displaying rightward axis deviation and diffuse ST-segment abnormalities. Transthoracic echocardiography (B) parasternal short-axis view showing a thickened left ventricular wall, especially in the anterior segment (23 mm, arrow) with a moderately reduced left ventricular function. Electrocardiogram showing diffuse ST-segment depression with ST-segment elevation in aVL (C). Urgent cardiac magnetic resonance (T2-weighted short inversion time inversion recovery black-blood sequence) showing an extensive area of transmural oedema of the basal-mid anterior (D) and antero-septal (E) wall (arrows).
Patient 3
A 36-year-old woman with no past medical history presented at the 33rd gestational week with chest pain at rest, diffuse ST segment depression on electrocardiogram (ECG) (Figure 5A) and raised hs-I-troponin (3200 ng/L, upper normal value 20 ng/L). Transthoracic echocardiography showed a thickened (23 mm in diastole) LV wall, especially in the antero-septal segment (Figure 5B), with moderately reduced LVEF (40%), and mild pericardial effusion. Acute perimyocarditis was suspected. On Day 3, she experienced severe chest pain with marked ST depression in the infero-lateral leads, ST elevation in aVL (Figure 5C), and a remarkable increase in troponin (7000 ng/L). She underwent emergency CMR without gadolinium, due to concerns of foetal toxicity, which showed a large area of transmural oedema of the basal- mid-cavity LV anterior (Figure 5D) and antero-septal segments (Figure 5E). Coronary angiography and intravascular ultrasound, performed after emergency C-section, were unremarkable. ST-T wave abnormalities resolved after delivery (Figure 6A) with sharp TnI normalization. She was given bromocriptine, ACE-inhibitors, BB, and LMWH. On Day 6, a follow-up TTE (Figure 6B, Inline Video 3) showed a focal thinning of the LV mid-cavity anterior wall. Cardiac magnetic resonance was repeated with gadolinium, showing a discrete (10 mm × 11 mm) LV aneurysm (Figure 6C) with discrete, almost transmural, oedema (Figure 6D) and LGE (Figure 6E) of the mid-cavity anterior wall. Coronary angiography was repeated and confirmed normal coronaries. On control echo the dimension of the aneurysm remained stable; the patient was discharged home 2 weeks later in good general condition.

Video 3 Transthoracic echocardiography demonstrating increased left ventricular wall thickness and its evolution into a focal left ventricular aneurysm of the anterior wall.

Figure 6 (A) Electrocardiogram in the same patient as in Figure 5 following delivery showing sinus bradycardia and normal ST-T segment. Transthoracic echocardiography showing focal thinning of the anterior wall (B, arrow). Repeat cardiac magnetic resonance short-axis views showing a focal left ventricular aneurysm (arrows) (C, T1 weighted black blood sequence), with discrete oedema (D, T2-weighted short inversion time inversion recovery black-blood sequence), and late gadolinium enhancement (E, T1 weighted phase sensitive inversion recovery sequence acquired 10 min after gadolinium injection) of the basal anterior wall.
A 56-year-old woman presented with transient loss of consciousness and palpitations. Her ECG (Figure 7A) showed wide-complex ventricular tachycardia (VT) with right bundle branch block (RBBB) inferior axis morphology and QS complex in leads I, aVL. After direct current shock ECG showed incomplete RBBB, q waves in leads I-aVL and negative T waves in the inferior leads (Figure 7B). She had been diagnosed with PPCM during her third pregnancy at the age of 45. Her clinical presentation was shortness of breath at the 36th week of gestation with reduced LVEF at echocardiography. She received medical treatment with ACE-inhibitors and beta-blockers. Three months later she presented with a transient ischaemic attack. She underwent CMR, which showed an LV aneurysm of the mid-cavity anterior wall (Figure 7C) with transmural LGE (Figure 7D,E), and an area of subepicardial LGE of the basal inferior wall (LVEF 48%), in keeping with non-ischaemic cardiomyopathy. Coronary angiography was unremarkable. She was started on aspirin, ACE-inhibitors, and BB, with no further follow-up. CMR was repeated following VT, 11 years after the first CMR scan, and showed (Figure 8A) a remodelled LV with a large aneurysm of the mid-cavity anterior and antero-septal walls with extensive transmural LGE (Figure 8B), and discrete transmural LGE of the basal inferior wall (Figure 8C) with worsened function (LVEF 35%). An implantable cardioverter-defibrillator was implanted for secondary prevention.

Discussion

Peripartum cardiomyopathy is a potentially life-threatening disease presenting towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. Peripartum cardiomyopathy is under-recognized because of a low index of suspicion and because it is often difficult to distinguish from symptoms related to uneventful pregnancy (shortness of breath, fatigue, and oedema). Risk factors proposed for the development of PPCM are multiple gestation, multiparity, older age, gestational hypertension, preeclampsia, or eclampsia. In these latter conditions, pregnancy-related blood volume overload may precipitate heart failure and preeclampsia may be confused with PPCM. Echocardiography helps to differentiate these two diseases, as in patient no. 1: LVEF is reduced in PPCM, but it is generally preserved in preeclampsia. Significant diastolic dysfunction and Doppler findings suggestive of increased left atrial filling pressure indicate preeclampsia instead of PPCM. The precise pathophysiological mechanism of PPCM remains unknown with multiple possible aetiologies including myocarditis, autoimmunity,
vascular dysfunction, and genetic predisposition shared with dilated cardiomyopathy. More recently it has been postulated that oxidative stress-mediated cleavage of the nursing hormone prolactin into a smaller biologically active subfragment may be a major factor triggering endothelial damage initiating and driving PPCM. The use of bromocriptine, a drug inhibiting selectively prolactin production has demonstrated a beneficial effect on the outcome of PPCM. In an observational German registry on 115 women, 72% of women who had experienced an improvement in LV function had received bromocriptine, compared with 35% of women who did not improve. A recent randomized trial of 63 women with PPCM that compared 1 vs. 8 weeks regimens of bromocriptine found similar improvements in LVEF; there was, however, no control group. Considering the absent benefits of breastfeeding abolished by bromocriptine, the increased incidence of thrombo-embolic complications associated with bromocriptine and the lack of solid evidence, bromocriptine deserves prospective, randomized placebo-controlled trials before it is routinely recommended for the treatment of PPCM.

Peripartum cardiomyopathy, which is a diagnosis of exclusion, may have different clinical presentations. Echocardiography is the first-line imaging technique, providing complete morpho-functional cardiac evaluation, assessment of pulmonary congestion by ultrasound chest interrogation, and exclusion of differential diagnoses, namely pre-existing cardiac abnormalities such as cardiomyopathy, valvular (mainly stenosis) or congenital heart disease, acute pulmonary embolism, and acute coronary syndromes. Delays in diagnosis are associated with higher rates of complications and worse outcome. Thromboembolism is the most serious complication, affecting around 6% of patients with PPCM. Thrombosis may involve all cardiac chambers. Factors predisposing to cardiac thrombosis include cardiac dysfunction, endothelial damage, hypercoagulable state of pregnancy, and the post-operative status after C-section. In a study of 182 women with PPCM, major adverse cardiovascular events preceeded diagnosis in about 50% of patients, and cerebrovascular events were associated with residual brain damage. Clinicians must be aware of such dreadful complications and carefully search for thromboembolism using multimodality imaging, such as TTE and CT. Treatment is mainly based on LMWH in the antepartum period and warfarin in the postpartum period, while data on novel oral anticoagulants are lacking.

The incidence of acute coronary syndromes from atherosclerotic plaque rupture or spontaneous coronary artery dissection is 3–4 times higher in the early post-partum period compared with non-pregnant women. Myocardial infarction with non-obstructive coronary arteries includes plaque (causing ≤50% stenosis) rupture or erosion, coronary embolism and dissection, and coronary artery spasm. Diagnosis may require multiple diagnostic tools, including cardiac imaging or provocative tests, in addition to standard coronary angiography, according to clinical suspicion. Cardiac magnetic resonance plays a key role in confirming the diagnosis and excluding other diseases with similar clinical presentation. In patient no. 3, both spontaneous coronary dissection or embolism were repeatedly excluded with invasive tests, despite an acute presentation with a subacute evolution, in keeping with the acute coronary event. Coronary spasm could not be excluded although ST-segment elevation was observed just before delivery. However, the abrupt normalization of ECG and troponin immediately after delivery can be explained by a functional coronary occlusion or by a vasoactive ‘toxic’ effect of substances circulating during the last phase of pregnancy. Initial myocardial oedema mainly involved the anteroseptal mid-ventricular segment where a discrete LV aneurysm subsequently developed. Haghikia et al. in their study on 34 patients with PPCM undergoing CMR, found a distinct LV aneurysm subsequently developed. Duncker et al. found that there is a relevant risk for ventricular fibrillation in the first months after PPCM diagnosis.
with severely reduced LV function. In the majority of cases LV function recovers, but ventricular remodelling can provide substrate for ventricular arrhythmias. In patient no. 4, two CMR studies performed at 11-year interval could demonstrate extensive LV remodelling and fibrosis following PPCM as potential substrate for malignant arrhythmias. In this patient, the differential diagnosis should contemplate embolic myocardial infarcts (although atrial arrhythmias have never been recorded), pre-existing and evolving cardiomyopathy such as dilated cardiomyopathy or left-dominant arrhythmogenic cardiomyopathy.

Conclusions

With this case series, we aim at raising attention on the potentially different clinical presentations of PPCM. Adequate index of suspicion and multimodality imaging can lead to early diagnosis of PPCM, reducing the risk of serious and potentially life-threatening complications.

Lead author biography

Dr Fabio Chirillo is the head of the Department of Cardiology at the San Bassiano Hospital in Bassano del Grappa (Italy). He graduated and completed cardiology fellowship at the University of Padua, Italy, followed by training in transoesophageal echocardiography at Medizinische Hochschule Hannover, IVUS at Uniklinikum Essen, Cardiac CT at Uniklinikum Erlangen-Nuremberg, and CMR at Centro nazionale Ricerche Pisa. Fields of interest: Multimodality imaging, Infective endocarditis, Aortic Disease.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

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Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patients in line with COPE guidance.

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