

# 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

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Peripartum cardiomyopathy (PPCM) is a cause of pregnancy-associated heart failure. It typically develops during the last month of, and up to 6 months after, pregnancy in women without known cardiovascular disease. The present position statement offers a state-of-the-art summary of what is known about risk factors for potential pathophysiological mechanisms, clinical presentation of, and diagnosis and management of PPCM. A high index of suspicion is required for the diagnosis, as shortness of breath and ankle swelling are common in the peripartum period. Peripartum cardiomyopathy is a distinct form of cardiomyopathy, associated with a high morbidity and mortality, but also with the possibility of full recovery. Oxidative stress and the generation of a cardiotoxic subfragment of prolactin may play key roles in the pathophysiology of PPCM. In this regard, pharmacological blockade of prolactin offers the possibility of a disease-specific therapy.

**Keywords** Peripartum cardiomyopathy • Definition

## Introduction

Heart failure (HF) in the puerperium was recognized as early as the nineteenth century.<sup>1</sup> Peripartum cardiomyopathy (PPCM) is not

caused by aggravation of an underlying idiopathic dilated cardiomyopathy (IDCM) by pregnancy-mediated volume overload. Haemodynamic stresses reach their peak just before delivery and volume load is greatly reduced after delivery, which is when

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PPCM often presents. Instead, it is now widely accepted that PPCM is distinct from other types of HF,<sup>2</sup> although the cardiac phenotype of PPCM resembles that of a DCM. The clinical course, however, is highly variable and rapid progression to end-stage HF may occur, often within a few days.<sup>3</sup> On the other hand, spontaneous and complete recovery of ventricular function may also occur. Both features are unusual in other forms of cardiomyopathy.<sup>4,5</sup>

## Definition and epidemiology

Peripartum cardiomyopathy has been variably defined (Table 1).<sup>2,6,7</sup> The definition of the Workshop held by the National Heart Lung and Blood Institute and the Office of Rare Diseases (2000) states that it must develop during the last month of pregnancy or within 5 months of delivery. We believe that this time frame along with echocardiographic cut-offs are arbitrary and may lead to under-diagnosis of PPCM. We propose the following simplified definition:

'Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with HF secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. It is a diagnosis of exclusion. The LV may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%'.

## Incidence

Very little is known about the incidence of PPCM (Table 2).<sup>5,8–12</sup> Most studies have been conducted in the USA, South Africa, or Haiti with few from the rest of the world, including Europe. The studies that have been performed were mostly single-centre case series. From the available literature, the incidence of PPCM appears to be around 1 in 2500–4000 in the USA, 1 in 1000 in South Africa, and 1 in 300 in Haiti (Table 2). Prospective, population-based, well-conducted, epidemiological studies are required.

## Pathophysiology

The precise mechanisms that lead to PPCM remain ill-defined, but a number of contributing factors have received attention. These include general risk factors for cardiovascular disease (such as hypertension, diabetes, and smoking) and pregnancy-related factors (such as age, number of pregnancies, number of children born, use of medication facilitating birth, and malnutrition).<sup>13</sup>

## Prolactin, 16 kDa prolactin, and cathepsin D

Recent data suggest involvement of a cascade involving oxidative stress, the prolactin-cleaving protease cathepsin D, and the nursing-hormone prolactin, in the pathophysiology of PPCM. Oxidative stress appears to be a trigger that activates cathepsin D in cardiomyocytes and cathepsin D, subsequently, cleaves prolactin into an angiostatic and pro-apoptotic subfragment.<sup>3</sup> Patients with acute PPCM have increased serum levels of oxidized low-density lipoprotein, indicative of enhanced systemic oxidative stress, as well as increased serum levels of activated cathepsin D, total prolactin, and the cleaved, angiostatic, 16 kDa prolactin fragment.<sup>3</sup>

In a mouse model, the 16 kDa prolactin fragment has potentially detrimental cardiovascular actions that could play a pathophysiological role in PPCM. It inhibits endothelial cell proliferation and migration, induces endothelial cell apoptosis and disrupts already formed capillary structures.<sup>3</sup> This form of prolactin also promotes vasoconstriction<sup>3</sup> and impairs cardiomyocyte function.<sup>3</sup> Consistent with the idea that 16 kDa prolactin-mediated apoptosis may contribute to the pathogenesis of PPCM, pro-apoptotic serum markers (e.g. soluble death receptor sFas/Apo-1) are increased in PPCM patients and are predictive of impaired functional status and mortality.<sup>13,14</sup>

In this regard, an efficient antioxidant defence mechanism in the maternal heart, late in pregnancy and the post-partum period, seem crucial as markers of cellular oxidation rise during pregnancy, culminating in the last trimester (as part of normal pregnancy-related physiology).<sup>15</sup> Experimental data in a mouse model of PPCM (i.e. mice with a cardiomyocyte-restricted deletion of the signal transducer and activator of transcription-3, STAT3) suggest that defective antioxidant defence mechanisms may be responsible for the development of PPCM.<sup>3</sup>

Furthermore, a key functional role of an activated oxidative stress–cathepsin D–16 kDa prolactin cascade in PPCM is strongly supported by the observation that suppression of the production of prolactin by the dopamine D<sub>2</sub> receptor agonist, bromocriptine, prevented the onset of PPCM in the mouse model of PPCM.<sup>3</sup>

Preliminary reports of the possible clinical effects of bromocriptine in patients with acute PPCM are discussed below.<sup>16–18</sup>

## Other putative pathophysiological mechanisms

### Inflammation

In addition to oxidative stress, inflammation may play a role in the pathophysiology of PPCM. Serum markers of inflammation [including the soluble death receptor sFas/Apo-1, C-reactive protein, interferon gamma (IFN- $\gamma$ ), and IL-6] are elevated in patients with PPCM.<sup>3,13,14,19</sup> This mechanism is underscored by the apparent clinical benefit of the anti-inflammatory agent pentoxifylline in a non-randomized trial in 58 patients with PPCM.<sup>20</sup> Furthermore, that failure to improve is clinically associated with persistently elevated IFN- $\gamma$  suggests that inflammatory status is important in the prognosis of patients with PPCM.<sup>19</sup>

### Viruses

Viral infection of the heart is another possible cause of peripartum inflammation, although clinical data are far from conclusive. Although some reports have implicated cardiotropic enteroviruses in PPCM,<sup>21,22</sup> others have not found a higher frequency of viral infections in patients with PPCM than in those with IDCM.<sup>23</sup> Human immunodeficiency virus infection does not seem to be implicated in PPCM.<sup>24</sup>

### Autoimmune system

In addition, autoimmune responses may play a role in the pathophysiology of PPCM. For example, serum derived from PPCM patients affects *in vitro* maturation of dendritic cells differently than serum from healthy post-partum women.<sup>25</sup> High titres of auto-antibodies against selected cardiac tissue proteins have

**Table 1** Definition/classification of peripartum cardiomyopathy

	Definition of PPCM
European Society of Cardiology on the classification of cardiomyopathies <sup>49</sup>	A non-familial, non-genetic form of dilated cardiomyopathy associated with pregnancy
AHA Scientific Statement on contemporary definitions and classifications of the cardiomyopathies <sup>7</sup>	A rare and dilated acquired primary cardiomyopathy associated LV dysfunction and heart failure
Workshop held by the National Heart Lung and Blood Institute and the Office of Rare Diseases <sup>2</sup>	The development of heart failure in the last month of pregnancy or within 5 months post-partum The absence of an identifiable cause of heart failure The absence of recognizable heart disease prior to the last month of pregnancy LV systolic dysfunction demonstrated by classical echocardiographic criteria. The latter may be characterized as an LV ejection fraction <45%, fractional shortening <30%, or both, with or without an LV end-diastolic dimension >2.7 cm/m <sup>2</sup> body surface area
Heart Failure Association of the European Society of Cardiology Working Group on PPCM 2010	PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%.

HF, heart failure; LV, left ventricular.

been found in the majority of women with PPCM.<sup>26</sup> Circulating auto-antibodies to every type of cardiac tissue were identified in all 10 cases screened by Lamparter *et al.*<sup>27</sup> Warraich *et al.* reported higher titres of antibodies (IgG and IgG subclasses) against cardiac myosin heavy chain in patients with PPCM compared with those with IDCM. Furthermore, these titres correlated with clinical presentation and with New York Heart Association (NYHA) functional class.<sup>28</sup> In addition, the potential role of microchimerism, due to the introduction of foetal cells of haematopoietic origin into the maternal circulation, has been raised.<sup>29</sup>

Whether or not these findings are causal in PPCM, or secondary to cardiac damage due to another mechanism, is not clear.

## Genetic susceptibility to peripartum cardiomyopathy

Few data are available with which to formally evaluate any genetic contribution to susceptibility to PPCM and the studies that have been published are largely case reports rather than systematic studies. There are a number of reports in the literature of PPCM in women with mothers or sisters who had the same diagnosis. A widely cited study from the 1960s<sup>30</sup> identified 3 of 17 probands with PPCM who had a definite family history of the condition. Since that time, there have been several other carefully documented examples of two or three affected female first-degree relatives.<sup>31–34</sup> Frequently, uncertainty exists about whether such cases fulfil formal PPCM diagnostic criteria (i.e. absence of pre-existing heart disease) or whether, in contrast, the affected women have an inherited DCM that only became apparent during the haemodynamic stress of pregnancy. There have been reports of women with PPCM, who have male relatives affected by DCM, arguing that at least some familial cases are examples of DCM rather than a specific PPCM.<sup>35</sup> Recently, however, there have been two reports which more strongly support the suggestion that some cases of PPCM may in fact be part of familial DCM.<sup>36,37</sup> In one study from the Netherlands, van

Spaendonck-Zwarts *et al.*<sup>36</sup> studied 90 families with familial DCM and investigated the presence of PPCM; in addition, they also examined PPCM patients and performed cardiac screening of their first-degree relatives. Their data suggest that a subset of PPCM is an initial manifestation of familial DCM and this was corroborated by the identification of a causative mutation in one family. In another study from the USA, Morales *et al.*<sup>37</sup> did similar observations in a large cohort study. These findings together may have important implications for cardiology screening in such families.

Nevertheless, the very high incidence in certain communities is suggestive of environmental risk factors,<sup>38</sup> although a common genetic founder mutation cannot be excluded. Studies in immigrant populations in the USA suggest an intermediate level of risk in African-Americans and a low incidence in Hispanics (more in keeping with changing environment than genetic origins).<sup>9</sup>

Within populations, there clearly remains scope for variable genetic susceptibility, just as there is with other forms of HF. Future research could evaluate both the common variants: common disease contribution to PPCM susceptibility and, potentially, analysis of uncommon larger-effect alleles (e.g. by re-sequencing). A number of candidate gene pathways would be promising targets, e.g. genetic variants in the JAK/STAT signalling cascade;<sup>3</sup> however, no associations have been detected to date.

On the basis of these results, general genetic testing is not recommended as a routine but is currently being done as part of research projects.

## Clinical presentation and diagnosis

The clinical presentation of patients with PPCM is similar to those with other forms of systolic HF secondary to cardiomyopathy, but may be highly variable. Patients with only mild symptoms have been reported.<sup>37</sup> Early signs and symptoms of PPCM may often mimic normal physiological findings of pregnancy and include pedal oedema, dyspnoea on exertion, orthopnoea, paroxysmal

**Table 2** Incidence of peripartum cardiomyopathy

Author	Year	Country	Case series or population based	Retrospective (R) or prospective (P)	Number with PPCM	Incidence	Mean age	Race	Definition of PPCM
Mielniczuk <i>et al.</i> <sup>8</sup>	1990–2002	USA	Population based	R	171	1990–2002: 1:3189; 2000–02: 1:2289	30	42% White; 32% African-American with PPCM	ICD 9 code 674.8 (plus least one of 514, 428, 425.4, 648.64) and then 2 reviewers of each potential case—PPCM if consensus
Brar <i>et al.</i> <sup>9</sup>	1996–2005	USA	Population based	R	60	Total (all races): 1:4025; 1:4075, Whites; 1:1421, African-Americans; 1:9861, Hispanics; 1:2675, Asians	33	NA	ICD 9 codes 428.0, 428.1, 428.4, 428.9, 425.4, and 425.9 and then case note review: (i) LVEF < 0.50 (ii) Framingham criteria for HF (iii) new symptoms of HF or initial echocardiographic diagnosis of left ventricular dysfunction occurred in the month before or in the 5 months after delivery
Fett <i>et al.</i> <sup>5</sup>	2000–2005	Haiti	Case series (single institution)	P	98	1:300	32	Afro-Caribbean	(i) CHF 1-month before to 5 months after delivery (ii) no pre-existing heart disease (iii) no other cause identified for CHF (iv) LVEF < 45% or FS < 30%
Chapa <i>et al.</i> <sup>10</sup>	1988–2001	USA	Case series (single institution)	P	32	1:1149	27	80% African American; 20% White	(i) FS < 30% (ii) LVEDD > 4.8 cm (iii) no other cause identified for CHF (iv) LVEF < 45% or FS < 30%
Desai <i>et al.</i> <sup>11</sup>	1986–1989	South Africa	Case series (single institution)	P	97	1:1000	29	Black Africans; except 1 Asian	Not stated; echocardiography performed—no results presented
Witlin <i>et al.</i> <sup>12</sup>	1986–1994	USA	Case series (single institution)	R	28	1:2406	NA	21 Black; 6 White; 1 Asian	(i) CHF 1 month before to 5 months after delivery (ii) no other cause identified for CHF (iii) absence of heart disease before the last month of pregnancy

Only studies recruiting after 1985 using echocardiography are included (except Mielniczuk—no echocardiography). Only studies including >25 patients after 1985 patients are included. NA, not available; LV, left ventricular; LVEF, left ventricular ejection fraction; EDD, end-diastolic diameter; NYHA, New York Heart Association.

<sup>a</sup>Date of publication.

nocturnal dyspnoea, and persistent cough. Additional symptoms experienced in PPCM include abdominal discomfort secondary to hepatic congestion, dizziness, praecordial pain, and palpitations, and, in the later stages, postural hypotension can occur. In many cases, women with PPCM and their doctors or midwives may believe that these symptoms are either due to gravidity or general tiredness, due to having given birth recently, and the associated lack of sleep. In addition, patients may be anaemic.

In the majority of patients, symptoms develop in the first 4 months after delivery (78%). Only 9% of patients present in the last month of pregnancy. Thirteen per cent present either prior to 1 month before delivery, or more than 4 months post-partum.<sup>39</sup> In at least some countries, patients often present later than 5 months post-partum as their symptoms are not initially attributed to HF (K.S., South Africa, personal experience). Such patients have not been included in any studies to date as they do not meet current criteria for a diagnosis of PPCM. It is also possible that some women who present later in life with DCM have previously unrecognized PPCM.

The most frequent initial presentation is with NYHA functional class III or IV symptoms,<sup>11</sup> but this may vary from NYHA I to IV symptoms. Some patients may present with complex ventricular arrhythmias or cardiac arrest.<sup>40</sup>

Only one study has reported physical signs in PPCM. Of 97 South African patients, 72% had a displaced apical impulse, 92% a third heart sound, and 43% mitral regurgitation.<sup>11</sup>

Left ventricular thrombosis is not uncommon in PPCM patients with an LVEF < 35%.<sup>31,41</sup> Peripheral embolic episodes, including cerebral embolism, with serious neurological consequences, coronary and mesenteric embolism, have been reported.<sup>42,43</sup> Haemoptysis and pleuritic chest pain may be presenting symptoms of pulmonary embolism.

Prospective registries are needed to accurately quantify the risk of systemic and venous thrombo-embolism.

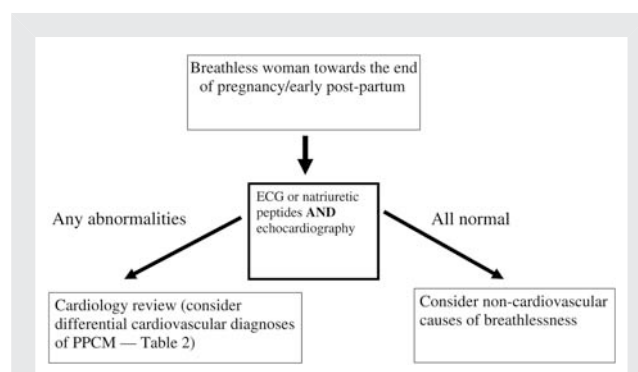
## Investigation of peripartum cardiomyopathy

As PPCM is a diagnosis of exclusion, all patients should have a thorough investigation to identify any alternative aetiology of HF (Figure 1). Both cardiac and non-cardiac causes of symptoms should be considered.

## Electrocardiogram

An electrocardiogram (ECG) should be performed in all patients with suspected PPCM as it can help distinguish PPCM from other causes of symptoms. Two studies investigated the prevalence of ECG abnormalities in PPCM.<sup>11,40</sup> In 97 South Africans with PPCM, 66% had voltage criteria consistent with LV hypertrophy and 96% ST-T wave abnormalities. On presentation, the ECG of PPCM patients in HF is seldom normal. However, studies with larger sample sizes are needed.

Patients with PPCM are as susceptible to arrhythmias as those with other cardiomyopathies, particularly if LV systolic dysfunction becomes chronic.<sup>44</sup>



**Figure 1** Exclusion of peripartum cardiomyopathy in the breathless woman towards the end of pregnancy/early post-partum.

## B-type natriuretic peptide

As a result of elevated LV end-diastolic pressure due to systolic dysfunction, patients with PPCM commonly have an increased plasma concentration of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP).<sup>19</sup> Of 38 patients with PPCM, all had abnormal NT-proBNP plasma levels (mean 1727.2 fmol/mL) when compared with 21 healthy mothers post-partum (mean 339.5 fmol/mL),  $P < 0.0001$ .

## Cardiac imaging

Cardiac imaging is indicated in any peripartum woman with symptoms and signs suggestive of cardiac failure in order to establish the diagnosis and, if PPCM is present, to obtain prognostic information.

Not all patients present with LV dilatation,<sup>2</sup> but a LV end-diastolic diameter > 60 mm predicts poor recovery of LV function (as does a LVEF < 30%).<sup>10,44,45</sup> Imaging is also important in ruling out LV thrombus, particularly where the LVEF is severely depressed.<sup>41</sup> Imaging should be carried out as quickly as possible. Although echocardiography is the most widely available imaging modality, magnetic resonance imaging (MRI) allows more accurate measurement of chamber volumes and ventricular function than echocardiography<sup>46</sup> and also has a higher sensitivity for the detection of LV thrombus.<sup>47</sup> In addition, specific MRI techniques, such as measurement of late enhancement following administration of gadolinium, provide critical information in the differential diagnosis of myocarditis. The European Society of Radiology recommends that gadolinium should be avoided until after delivery, unless absolutely necessary. Breast feeding does not need to be interrupted after administration of gadolinium.<sup>48</sup>

Echocardiography should be repeated before patient discharge and at 6 weeks, 6 months, and annually to evaluate the efficacy of medical treatment. If available, cardiac MRI can also be repeated at 6 months and 1 year to get a more accurate assessment of changes in cardiac function.

Peripartum cardiomyopathy is a diagnosis of exclusion with a large differential diagnosis (Table 3). Confusion may arise when cardiac changes accompany pregnancy-induced hypertension (pre-eclampsia). The inclusion of patients with this complication in both the index and prior pregnancies has probably contributed to the discrepancy between studies in the reported characteristics of

**Table 3 Differential cardiovascular diagnoses of peripartum cardiomyopathy**

	Distinguishing features	Diagnosis/investigation
Pre-existing idiopathic dilated cardiomyopathy (IDC) unmasked by pregnancy	PPCM most commonly presents post-partum, whereas IDC (unmasked by pregnancy) usually presents by the 2nd trimester IDC usually presents during pregnancy with larger cardiac dimensions than PPCM	History, ECG, BNP, echocardiography
Pre-existing familial dilated cardiomyopathy (FDC) unmasked by pregnancy	PPCM most commonly presents post-partum, whereas FDC usually presents by 2nd trimester Positive family history in FDC FDC usually presents during pregnancy with larger cardiac dimensions than PPCM	History, ECG, BNP, echocardiography, genetic testing, family screening
HIV/AIDS cardiomyopathy	HIV cardiomyopathy presents often with non-dilated ventricles	HIV test
Pre-existing valvular heart disease unmasked by pregnancy	Rheumatic mitral valve disease is often unmasked by pregnancy PPCM most commonly presents post-partum whereas valvular heart disease usually presents by 2nd trimester	History, examination, ECG, echocardiography
Hypertensive heart disease	Exclude pre-existing severe hypertension in those presenting before delivery	
Pre-existing unrecognized congenital heart disease	Previously unrecognized congenital heart disease often has associated pulmonary hypertension PPCM most commonly presents post-partum, whereas congenital heart disease usually presents by 2nd trimester	History, ECG, echocardiography
Pregnancy-associated myocardial infarction	History (but can present atypically)	History, ECG, cardiac enzymes, coronary angiography, echocardiography
Pulmonary embolus	History	Medical history, ECG, D-dimers; consider echocardiography, ventilation/perfusion scan, CT pulmonary angiogram

ECG, echocardiogram; HIV, human immunodeficiency virus; BNP, B-type natriuretic peptide.

patients with PPCM and in the timing of presentation. Studies with greater proportions of patients with pre-eclampsia (and of patients with more severe pre-eclampsia) report a far greater frequency of PPCM cases presenting in the last month of pregnancy.<sup>45</sup> In contrast, studies that have attempted to minimize the inclusion of patients with pre-eclampsia (or which only include patients with milder hypertension) show a clear post-partum peak in the presentation of PPCM, most commonly 2–62 days after delivery.<sup>5,14,44</sup>

## Management

### Management of acute heart failure in peripartum cardiomyopathy

#### Initial management

The principles of managing acute HF due to PPCM are no different than those applying to acute HF arising from any other cause and are summarized in the recent ESC/ESICM guidelines.<sup>49</sup> Briefly, rapid treatment is essential, especially when the patient has pulmonary oedema and/or hypoxaemia. Oxygen should be administered in order to achieve an arterial oxygen saturation of  $\geq 95\%$ , using, where necessary, non-invasive ventilation with a positive end-expiratory pressure of 5–7.5 cm H<sub>2</sub>O. Intravenous (i.v.) diuretics should be given when there is congestion and volume

overload, with an initial bolus of furosemide 20–40 mg i.v. recommended. Intravenous nitrate is recommended (e.g. nitroglycerine starting at 10–20 up to 200  $\mu\text{g}/\text{min}$ ) in patients with a systolic blood pressure (SBP)  $> 110$  mmHg and may be used with caution in patients with SBP between 90 and 110 mmHg.

Inotropic agents should be considered in patients with a low output state, indicated by signs of hypoperfusion (cold, clammy skin, vasoconstriction, acidosis, renal impairment, liver dysfunction, and impaired mentation) and those with congestion which persists despite administration of vasodilators and/or diuretics. When needed, inotropic agents (dobutamine and levosimendan) should be administered without unnecessary delay and withdrawn as soon as adequate organ perfusion is restored and/or congestion reduced.

#### Mechanical ventricular support and cardiac transplantation

If a patient is dependent on inotropes or intra-aortic balloon pump counterpulsation, despite optimal medical therapy, implantation of a mechanical assist device or cardiac transplantation should be considered. Since the prognosis in PPCM is different from DCM with a significant proportion of patients normalizing their LV function within the first 6 months post-partum,<sup>50</sup> an LV-assisted device (LVAD) may be considered before listing the patient for cardiac transplantation, although the optimum strategy is not known and discussion

between experts on a case-by-case basis may be helpful. However, implantation of LVAD should certainly be considered as a rescue measure in a life-threatening situation ('bridge to transplantation').

Left ventricular-assisted devices have improved mechanically and experience with their use has increased greatly in recent years, with a large number of LVADs implanted in Europe as either a 'bridge to transplantation' or as 'destination therapy'.<sup>51</sup> Nevertheless, complications related to their use remain high<sup>52</sup> and thrombotic complications may occur more often in patients with PPCM than in others because PPCM is a pro-thrombotic condition. Size of device also remains a limiting factor as not all fully implantable devices will fit into a small woman.

After clinical improvement of the patient and recovery of cardiac function, weaning from the device may be attempted. Since no data are available specifically for PPCM, the criteria developed for DCM should be used.<sup>53</sup> If weaning cannot be attempted, or is not successful, transplantation should be considered.

Published data show that between 0 and 11% of patients with PPCM undergo heart transplantation (Table 4). So far, the two largest published series each included just eight patients.<sup>54</sup> Both reported similar outcomes in women with PPCM compared with patients with HF due to other causes.

International registries could greatly increase knowledge of both the use of cardiac transplantation and LVADs in PPCM.

## Management of stable heart failure in peripartum cardiomyopathy

### Drug therapy

After delivery, PPCM should be treated in accordance with the current ESC guidelines for HF.<sup>49</sup>

*During pregnancy*, the following restrictions to these guidelines apply.

**Angiotensin-converting enzyme-inhibitors and angiotensin-II receptor blockers.** Angiotensin-converting enzyme (ACE)-inhibitors and angiotensin-II receptor blocker (ARB) are contraindicated because of serious renal and other foetal toxicity (I-C).<sup>55,56</sup>

**Hydralazine and long-acting nitrates.** It is believed that this combination can be used safely, instead of ACE-inhibitors/ARBs, in patients with PPCM.<sup>57</sup>

**$\beta$ -Blockers.** These have not been shown to have teratogenic effects.<sup>58</sup>  $\beta$ -1-selective drugs are preferred because  $\beta$ -2 receptor blockade can, theoretically, have an anti-tocolytic action.

**Diuretics.** Diuretics should be used sparingly as they can cause decreased placental blood flow.<sup>13,59</sup> Furosemide and hydrochlorothiazide are most frequently used.

**Aldosterone antagonists.** Spironolactone is thought to have anti-androgenic effects in the first trimester.<sup>60</sup> Because the effects of eplerenone on the human foetus are uncertain, it should also be avoided during pregnancy.

**Antithrombotic therapy.** Fetotoxicity of warfarin needs to be considered in all patients with PPCM and LVEF <35%. Unfractionated or low-molecular-weight heparin can be used. Fetotoxicity of warfarin needs to be considered.

### Cardiac resynchronization therapy and implantable cardioverters/defibrillators

Peripartum cardiomyopathy patients are not specifically discussed in the section on implanting implantable cardioverters/

defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in the 2008 ESC guidelines. Decisions about both the necessity and the timing of ICD and CRT implantation in these patients are extremely difficult and require careful consideration of the pros and cons in the context of the natural history of PPCM. The obvious issues are the cost and potential complications of implanting a device in a patient who may not need it for long because of subsequent recovery of ventricular function. However, if a patient with PPCM has persistently severe LV dysfunction 6 months following presentation, despite optimal medical therapy, many clinicians would advise implantation of an ICD (combined with CRT if the patients also has NYHA functional class III or IV symptoms and a QRS duration >120 ms).

International registries should be structured in a way to include PPCM as a specific diagnosis and thereby to provide information for the future.

### New therapeutic strategies

As indicated earlier, bromocriptine may be a novel disease-specific treatment for PPCM.<sup>16</sup> Several case reports have suggested that the addition of bromocriptine to standard therapy for HF may be beneficial in patients with acute onset of PPCM.<sup>16,17,31,61</sup> In addition, a proof-of-concept randomized pilot study of patients with newly diagnosed PPCM presenting within 4 weeks of delivery also showed promising results.<sup>18</sup> Patients receiving bromocriptine 2.5 mg twice daily for 2 weeks, followed by 2.5 mg daily for 4 weeks, displayed greater recovery of LVEF (27% at baseline to 58% at 6 months,  $P = 0.012$ ) compared with patients assigned to standard care (27% at baseline to 36% at 6 months, NS). One patient in the bromocriptine-treated group died compared with four patients in the placebo group.

Bromocriptine has been used for more than 20 years in postpartum women to stop lactation. The use in this period has been associated with several reports of myocardial infarction.<sup>62</sup> Because of these, anti-coagulation therapy is strongly encouraged in PPCM patients with a low LVEF in general and in those taking bromocriptine in particular. Furthermore, with adequate anti-coagulation therapy, thrombo-embolism in all PPCM patients treated with bromocriptine has not been observed.<sup>18,31</sup> However, the data available are limited.

The safety of bromocriptine was also examined in a survey of more than 1400 women who took the drug primarily during the first few weeks of pregnancy. No evidence of increased rates of abortion or congenital malformation was reported.<sup>63</sup>

Before this treatment can be recommended as a routine strategy, there is a need for a larger randomized trial, although some physicians currently add bromocriptine to conventional therapy on an individual basis.

### Timing and mode of delivery

Women who present with PPCM during pregnancy require joint cardiac and obstetric care. Possible adverse effects on the foetus must be considered when prescribing drugs. A baseline ultrasound scan is important for subsequent monitoring of foetal growth and well-being.

Timing and mode of delivery in PPCM are important issues currently not addressed by randomized trials or large cohort studies.

**Table 4** Prognosis of peripartum cardiomyopathy

Author	Year	Country	Study type	n	Age (mean)	Mortality (mean follow-up)	LV function	Transplantation and VAD	Predictors of mortality
Population-based studies									
Mielniczuk et al. <sup>8</sup>	1990–2002	USA	Retrospective, population based	171	30	1.36% in-hospital, 2.05% 'long term'	NA	NA	NA
Brar et al. <sup>9</sup>	1996–2005	USA	Retrospective, population based	60	34	3.3% (4.7 years)	NA	0%	NA
Case series									
Sliwa et al. <sup>24</sup>	2005–08 <sup>a</sup>	South Africa	Prospective, single centre	80, 100% African descent	30	10% (6 months), 28% (2 years)	Mean LVEF: baseline 30%, 24 months 51%	NA	NA
Sliwa et al. <sup>14</sup>	2003–05	South Africa	Prospective, single centre	100, 100% African descent	32	15% (6 months)	Mean LVEF: baseline 26%, 24 months 43%, 23% normal LV function after 6 months	NA	Fas/Apo-1 and NYHA functional class independent predictors of mortality
Fett et al. <sup>5</sup>	2000–05	Haiti	Prospective, single centre	98, 100% African descent	32	15% (2.2 years)	28% normal ventricular function after 2.2 years	NA	LVEDD and LVEF at presentation not predictive of mortality
Fett et al. <sup>72</sup>	1994–2001	Haiti	Prospective + retrospective, single centre	47	32	14% (time period not available)	NA	NA	NA
Duran et al. <sup>44</sup>	1995–2007	Turkey	Prospective + retrospective, single centre	33	33	30% (47 months)	24% of patients recovered completely, 39% were left with persistent LV dysfunction	6%	QRS > 120 ms – 1
Modi et al. <sup>73</sup>	1992–2003	USA	Single centre, retrospective	44 patients, 39 African-American	NA	15.9%	LV function returned to normal in 35%	NA	LVEF did not predict mortality
Sliwa et al. <sup>41</sup>	1996–97	South Africa	Single centre, prospective	29	29	27.6% (6 months)	Mean LVEF: baseline 27%, 6 months 43%	NA	NA
Desai et al. <sup>11</sup>	1986–89	South Africa	Single centre, retrospective	99	29	14% (time period not available)	NA	NA	NA
Felker et al. <sup>75</sup>	1983–98	USA	Single centre (those referred for cardiac biopsy)	51	29	6% (5 years)	NA	7%	NA
Chapa et al. <sup>10</sup>	1988–2001	USA	Single centre, retrospective	32	27	9.6% (time period not available)	59% persistent LV dysfunction (46 months)	6.5%	NA



Witlin et al. <sup>12</sup>	1986–94	USA	Single centre, prospective	28; 21 black, 6 white, 1 Asian	NA	18% (time period not available)	64% persistent LV dysfunction	11%	18%
Carvalho et al. <sup>76</sup>	1982–88	Brazil	Single centre, prospective	19	26	16% (21 months)	NA	NA	Increased LVEDD and late onset of symptoms
Survey	2005; 1997–98	USA	Survey (2% response rate)	100; 19% African descent; 67% White	31	9% (2 years)	LV function returned to normal in 54%	4%	NA

Only studies including >25 patients after 1985 are included. NA, not available; LV, left ventricular; LVEF, left ventricular ejection fraction; EDD, end-diastolic diameter; NYHA, New York Heart Association; ECG, echocardiogram.

<sup>a</sup>Date of publication.

Unless there is deterioration in the maternal or foetal condition, there is no need for early delivery.<sup>64</sup> Urgent delivery, irrespective of gestation, may need to be considered in women presenting or remaining in advanced HF with haemodynamic instability.<sup>65</sup> A team (comprising a cardiologist, obstetrician, anaesthesiologist, neonatologist, and intensive care physician) should discuss the planned mode and conduct of delivery in each case, taking into account the woman's or couples wishes. The primary consideration should be maternal cardiovascular benefit.<sup>64</sup> In general, spontaneous vaginal birth is preferable in women whose cardiac condition is well controlled with an apparently healthy foetus.<sup>64,66</sup> Planned Caesarean section is preferred for women who are critically ill and in need of inotropic therapy or mechanical support.<sup>65</sup> Cardiovascular challenges during labour and delivery include supine hypotension, increased cardiac output, blood loss, and administration of i.v. fluids.<sup>67</sup>

Labour is best conducted in a high care area where there is experience in managing pregnancies with cardiac disease. Principles of management are similar to those for women with other cardiac disease in pregnancy.<sup>68,69</sup> Continuous invasive haemodynamic monitoring is recommended,<sup>70</sup> with continuous urinary catheter drainage. Care must be taken to prevent fluid overload and pulmonary oedema from i.v. infusions. Antenatal oral medications are continued, but heparin should not be given after contractions have started.

The foetus is monitored with continuous cardiocography. The left lateral position has been suggested to ensure adequate venous return from the inferior vena cava,<sup>66,71</sup> but a sitting-up position may be needed for women in cardiac failure. For analgesia and anaesthesia, an experienced anaesthesiologist should be consulted. Epidural analgesia is preferred during labour as it stabilizes cardiac output.<sup>69</sup> For Caesarean section, continuous spinal anaesthesia and combined spinal and epidural anaesthesia have been recommended.<sup>64</sup> The second stage of labour is a time of increased exertion and strong contractions and prolonged bearing down efforts must be discouraged. Where spontaneous delivery cannot be achieved rapidly, low forceps or vacuum-assisted delivery will reduce exertion and shorten the second stage.<sup>64,67</sup> The third stage of labour can be managed actively, using a single dose of intramuscular oxytocin. Ergometrine is contraindicated.<sup>68</sup> After delivery, auto-transfusion of blood from the lower limbs and contracted uterus may significantly increase pre-load. A single i.v. dose of furosemide is commonly given at this stage. If used, anticoagulants should be restarted in consultation with the obstetrician and anaesthesiologist when post-partum bleeding has stopped and the epidural or spinal catheter has been removed.

### Breastfeeding

On the basis of the postulated negative effects of prolactin subfragments described above, breastfeeding is not advised in patients with suspected PPCM, even if this practice is not fully evidence-based. Several ACE-inhibitors (captopril, enalapril, and quinapril) have been adequately tested and can be used in breastfeeding women.<sup>58</sup>

### Prognosis

Disappointingly, there are no European studies of the prognosis of PPCM in any population. The worldwide data that are available

suggest that the prognosis of PPCM appears to vary geographically (Table 4).<sup>5,8–12,14,24,44,45,72–76</sup> It had been thought that mortality was lowest in the USA. However, a recent study by Modi et al.<sup>73</sup> reported recovery of LV function and survival rates of PPCM patients in the USA similar to those reported from Haiti and South Africa. No population-based studies have been performed in the USA. In South Africa, case series have demonstrated that mortality rates have slowly improved over time but 6-month and 2-year mortality rates remain at 10 and 28%, respectively. Single-centre studies in Brazil and Haiti report mortality rates of 14–16% within 6 months. In Turkey, a single tertiary centre reported a mortality rate of 30% over 4-year follow-up.

The proportion of patients in whom LV systolic function returns to normal is more consistent in case series in the USA, Haiti, and Turkey at 23–41%.

Factors that independently predict mortality are not clear.<sup>18</sup> Candidates for further study are NYHA class, LVEF, QRS duration, and late onset of symptoms.

### Subsequent pregnancies, counselling, and contraception

Family-planning counselling is very important as women with PPCM are usually in the middle of family building. Only a few studies have reported on subsequent pregnancies of women with a history of PPCM.

In a retrospective investigation, Elkayam et al.<sup>77</sup> studied 44 women with PPCM and a subsequent pregnancy and found that LVEF increased after the index pregnancy but decreased again during the subsequent pregnancy, irrespective of earlier values. Development of HF symptoms was more frequent in the group where LVEF had not normalized before the subsequent pregnancy (44 vs. 21%). In addition, three of the women with a persistently low LVEF entering the subsequent pregnancy died, whereas none with normalized LVEF died. There was no perinatal mortality. In a retrospective study, Habli et al. compared 70 patients with PPCM, where 21 had a successful subsequent pregnancy, 16 terminated the pregnancy, and the remaining 33 had no subsequent pregnancy. Ejection fraction at diagnosis was higher in those who had a successful subsequent pregnancy, but had no relation to worsening clinical symptoms, which developed in nearly one-third of these patients.<sup>78</sup>

Because of the sparse knowledge in this field, it is difficult to give individual counselling, but with a LVEF of <25% at diagnosis or where the LVEF has not normalized, the patient should be advised against a subsequent pregnancy. All patients should be informed that pregnancy can have a negative effect on cardiac function and development of HF and death may occur.

Women with PPCM need careful counselling about contraception because, as indicated above, they have a high risk of relapse in subsequent pregnancies and terminating pregnancy may not prevent the onset of PPCM.

Intrauterine devices (copper and progestogen-releasing IUDs) are very effective and long-lasting forms of contraception which do not increase the risk of thrombo-embolism. Combined hormonal contraceptives contain oestrogens and progestins (synthetic forms of progesterone) and should be avoided. Oestrogens

increase the risk of thrombo-embolism and should be avoided, but intramuscular, subcutaneous, and subdermal forms of progesterone-only contraception appear to be safe.<sup>79</sup> Barrier methods of contraception are not recommended because of their high failure rate. Sterilization options can be considered and include vasectomy, tubal ligation, and insertion of intratubal stents. Because of the psychological impact, women should be counselled carefully and educated about the effective alternatives. In addition, anaesthetic risk must be considered in women with persisting severe LV dysfunction.

## Conclusion and way forward

Peripartum cardiomyopathy remains a difficult condition to both diagnose and treat. Prior definitions, emphasizing strict time windows and echocardiographic cut-offs for diagnosis, have probably led to women with the condition being overlooked or misdiagnosed. The rarity of the condition and lack of awareness of it among physicians and nurses/midwives often leads to late diagnosis and treatment. National and international registries, with systematic, prospective collection of data, are needed to better document the incidence, modes of presentation, current treatment practices, complications, and prognosis (including recovery) of PPCM. Multi-centre studies are also required to improve the understanding of the pathogenic mechanisms of PPCM, including potential genetic and life-style aspects.

With the recent discovery of an oxidative stress–cathepsin D–16-kDa prolactin cascade in experimental and human PPCM, a specific pathophysiological hypothesis for PPCM has emerged, which may provide the rational basis for a specific therapeutic intervention. This intervention, bromocriptine, which is a drug that blocks the release of prolactin, and which has been used for many years in women in order to stop lactation (or a related compound), should now be tested in a number of prospective randomized controlled trials in women with PPCM.

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