

# Management of Peripartum Cardiomyopathy

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Peripartum cardiomyopathy (PPCM) is a form of heart failure that occurs in women within 1 month of pre-delivery and 5 months postdelivery. Echocardiography demonstrates features of cardiomyopathy with impaired ejection fraction; global dilatation and thinned-out walls are sometimes present. The symptoms and signs of PPCM are similar to those in patients with idiopathic dilated cardiomyopathy. The acute form of PPCM is a clinical syndrome, with reduced cardiac output, tissue hypoperfusion, and increase in the pulmonary capillary wedge pressure. Monitoring of the patient with the acute form of PPCM should be initiated as soon as possible. The types and levels of monitoring required for an individual patient vary widely depending on the severity of the cardiac decompensation and response to initial therapy. The syndrome carries a high morbidity and mortality, and diagnosis is often delayed. This review summarizes recent data charting the incidence, recent advances in the understanding of the pathophysiology of PPCM, and outlines the current treatment options available.

## Introduction

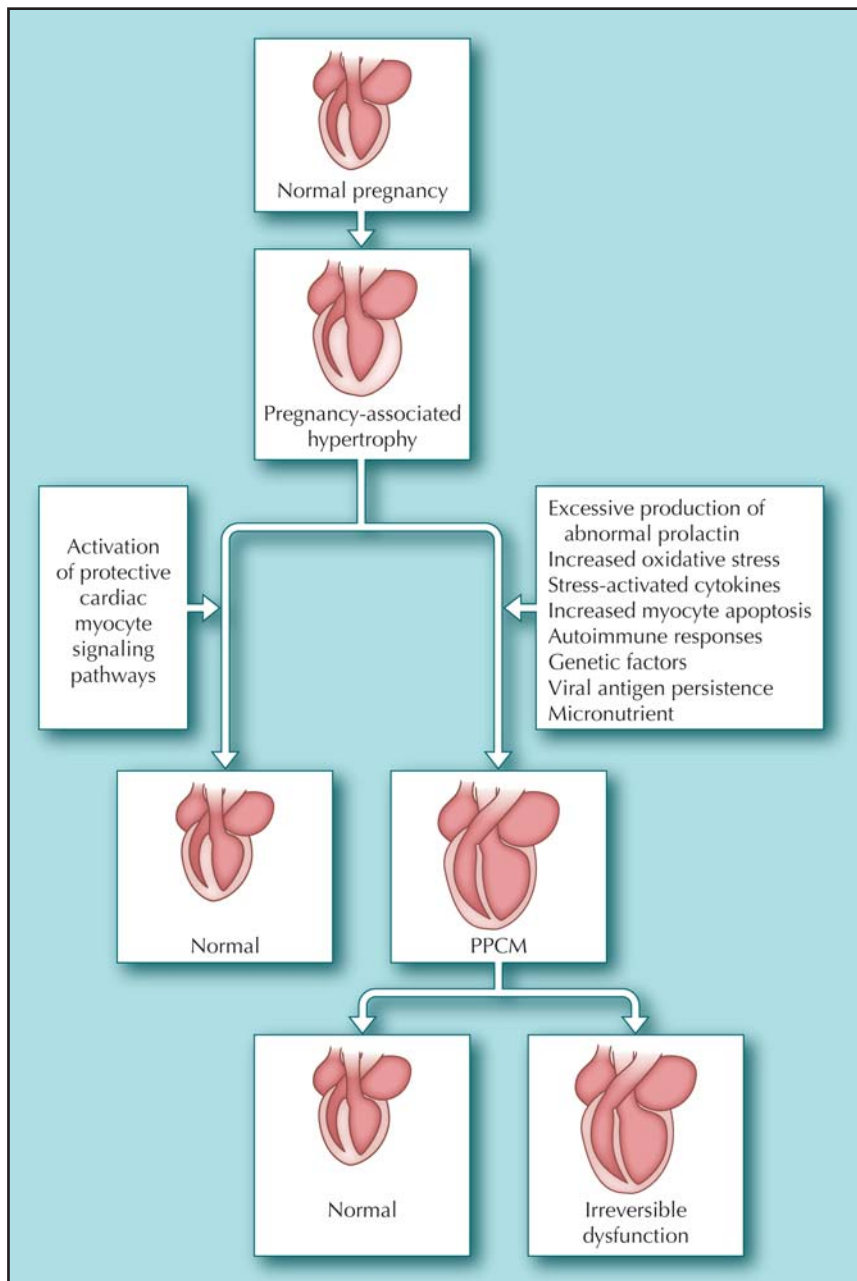
Peripartum cardiomyopathy (PPCM) is defined as a disorder of unknown pathogenesis, in which left ventricular dysfunction and symptoms of heart failure are present and occur between the last month of pregnancy and the first 5 months postpartum. By definition, PPCM occurs in the absence of an identifiable cause of heart failure and in the absence of recognizable heart disease prior to the last month of pregnancy [1,2•]. Some authors go beyond this defined time frame to include patients diagnosed with heart failure as early as 3 months of

pregnancy [3•]. Diagnosis requires echocardiographic evidence of left ventricular systolic dysfunction (ejection fraction < 45%) [4]. Heart failure that occurs in earlier pregnancy may be caused by previously unsuspected familial or other forms of cardiomyopathy that (unmasked by the hemodynamic and hormonal stress of pregnancy) forms a different entity. Diagnosis of PPCM should be established by ruling out other causes of perinatal heart failure, such as infectious diseases, metabolic disorders, and ischemic or valvular heart disease. Complications of late pregnancy that may have similar symptoms and signs to PPCM include pre-eclampsia, amniotic or pulmonary embolism, hemolysis, elevated liver enzymes, and low platelets [5].

The American College of Cardiology (ACC) guidelines classify PPCM as an entity of its own [6]. However, in the recently published European Society of Cardiology classification [7], PPCM is not listed as a specific disease and is placed under the category of “unclassified cardiomyopathies.” The more recently described cardiomyopathies, such as left ventricular noncompaction and Takotsubo cardiomyopathy, for which little of their pathogenesis is known, have been listed as “unclassified cardiomyopathies” [7], which promote ongoing interest and research into these conditions. Because gynecologists, physicians, and cardiologists have little awareness of PPCM, the condition is not diagnosed quickly and often leads to unnecessary morbidity and mortality. A recent publication by Deneux-Tharaux et al. [8] highlights the underreporting of pregnancy-related mortality in the United States and Europe. The study clearly shows the limitations of maternal mortality statistics based on the International Classification of Diseases cause of death codes.

## Epidemiology of PPCM

PPCM is most common in women of African descent [2•,9], but it has been reported in all major ethnic populations. The incidence varies from 1:100 to 1:10,000 between geographic regions. Due to diagnostic limitations, including limited access to echocardiography, the incidence in some areas may be overestimated.



**Figure 1.** Proposed mechanism that possibly contributes to pathogenesis of peripartum cardiomyopathy (PPCM).

### Etiology and Pathogenesis

There is considerable controversy regarding the etiology of human PPCM, but a number of recent publications have contributed to better understanding of its pathogenesis [10,11,12,13]. A number of mechanisms have been proposed in the development of PPCM, including nutritional deficiencies, genetic disorders, viral or autoimmune etiologies, hormonal imbalances, volume overload, alcohol, physiologic stress of pregnancy (Fig. 1), and unmasking of latent idiopathic dilated cardiomyopathy (DCMO) [2]. However, none of these mechanisms have been confirmed in detailed investigations or prospective studies [14]. The rare incidence of PPCM and the paucity of relevant animal models have limited guided research and understanding of the pathogenic mechanisms involved. Several authors

have suggested that multiparity may be a risk factor for PPCM. However, a study by Elkayam et al. [3] does not support this theory within their cohort in the United States because almost 40% of the cases occurred in association with a first pregnancy and more than 50% within the first two pregnancies.

### Clinical Presentation and Diagnosis

Features of a normal pregnancy include an expansion of blood volume, an increase in metabolic demands, relative anemia, and changes in vascular resistance that are associated with mild ventricular dilatation and an increase in cardiac output. These physiologic changes are due to an increase in preload and heart rate accompanied by a

decrease in afterload. Decompensation of patients with subclinical valvular, ischemic, or myopathic heart disease usually occurs during the second or third trimester of pregnancy. The onset of PPCM can be easily missed because many symptoms and signs of pregnancy and post-pregnancy stages are similar to those of early congestive heart failure (CHF) (eg, dyspnea, abdominal discomfort, and fatigue) [15]. Elkayam et al. [3•] reported that 7% of their patients in the United States were diagnosed within 1 month before delivery, whereas 75% were diagnosed during the first month postpartum, the remainder having fulfilled criteria for PPCM *before* the last 1 month of pregnancy. In contrast, patients in South Africa and Haiti developed symptoms almost exclusively within the postpartum period [16,17]. The symptoms and signs are similar to those in patients with idiopathic DCMO. Echocardiography usually demonstrates features of DCMO with impaired ejection fraction, often global dilatation, and sometimes thinned-out walls.

PPCM often presents with acute onset of heart failure (AHF). The presentation, with reduced cardiac output, tissue hypoperfusion, increase in the pulmonary capillary wedge pressure, and tissue congestion, is often life threatening and requires urgent treatment. The diagnosis of AHF is based on symptoms and clinical findings in combination with appropriate investigations, such as electrocardiography, chest radiograph, biomarkers, and echocardiography. Systematic clinical assessment of the peripheral circulation, venous filling, and peripheral temperature are important. Right ventricular filling in decompensated heart failure may be evaluated from the central jugular venous pressure. Caution is necessary in the interpretation of raised measures of central jugular venous pressure in AHF, as it may be a reflection of decreased venous compliance together with decreased right ventricular compliance [18]. Left-sided cardiac filling pressure is assessed by chest auscultation, with the presence of wet rales in the lung fields usually indicative of raised pressure. The confirmation, classification of severity, and clinical follow-up of pulmonary congestion and pleural effusions should be done using chest radiograph. Cardiac palpation and auscultation for ventricular and atrial gallop rhythms ( $S_3$ ,  $S_4$ ) and an electrocardiogram should be performed.

Chest radiograph and other imaging modalities should be conducted early for all patients with AHF to evaluate pre-existing chest or cardiac conditions and to assess pulmonary congestion. They are used for confirmation of the diagnosis and monitoring response to therapy. Chest radiograph allows the differential diagnosis of left-sided heart failure from inflammatory or infectious lung disease. A chest CT scan with or without contrast angiography and scintigraphy may be used to clarify pulmonary pathology and diagnose major pulmonary embolism [18].

A number of laboratory tests should be used in all patients with PPCM presenting with AHF: full blood count, urea and electrolytes, C-reactive protein (CRP), blood glu-

cose, D-dimer, creatine kinase-MB (CKMB), and cardiac troponin T (cTnT). In severe heart failure, international normalized ratio (INR) and arterial blood gas should also be performed. Transaminases, urinalysis, and plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NTproBNP) can be considered. Arterial blood gas analysis allows assessment of oxygenation ( $pO_2$ ), respiratory adequacy ( $pCO_2$ ), acid base balance (pH), and base deficit, and should be performed in all patients with severe heart failure. Noninvasive measurement with pulse oximetry and end-tidal carbon dioxide ( $E_tCO_2$ ) can often replace arterial blood gas analysis, but not in very low output vasoconstricted shock states [19]. BNP is released from the cardiac ventricles in response to increased wall stretch and volume overload and has been used to exclude or identify CHF in patients. NTproBNP has been found to be elevated in patients with PPCM presenting with AHF [12].

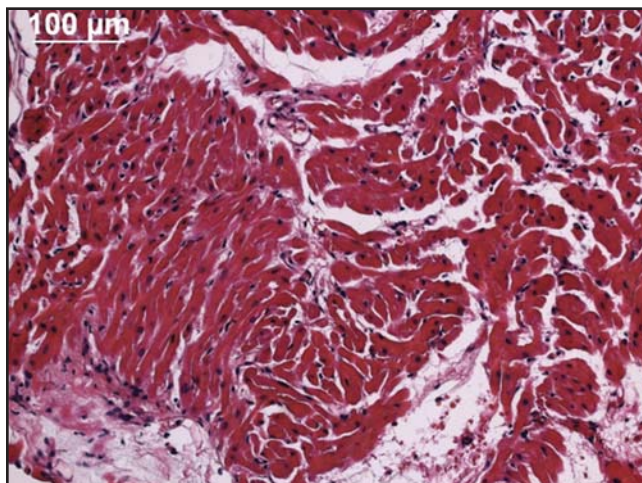
Echocardiography is an essential tool for evaluating the functional and structural changes underlying or associated with AHF. The most important measurement of ventricular function is the left ventricular ejection fraction for distinguishing patients with cardiac systolic dysfunction from those with preserved systolic function. Echocardiography with Doppler imaging should be used to evaluate and monitor regional and global left and right ventricular function, valvular structure and function, possible pericardial pathology, and mechanical complications. We have observed that patients with severe functional mitral regurgitation at presentation have a lower chance of full recovery of LV function (Sliwa, unpublished data). Appropriate echocardiographic Doppler study can also estimate pulmonary artery pressures and may help to detect the presence of pulmonary embolus.

### Monitoring of Patients With Newly Diagnosed PPCM

Monitoring of the patient presenting with AHF should be initiated as soon as possible. The extent and means in which to monitor for an individual patient vary widely depending on the severity of the cardiac decompensation and the response to initial therapy. However, we observed that because of their young age our patients often appear relatively well at first glance despite low cardiac output and marked tachycardia. Many women request inappropriate early discharge due to social pressures, including caring for their newborn, which may lead to rapid readmission or possible death (Sliwa, unpublished data).

### Current Theories on the Pathogenetic Mechanisms in PPCM

Over the past decade, accumulating evidence has suggested distinct pathogenetic mechanisms for PPCM, which may differ from those of other forms of DCMO. Apoptotic events—systemically and in the myocardium—appear to



**Figure 2.** Left ventricular biopsy from a patient with acute peripartum cardiomyopathy. Formalin and paraffin-embedded tissue was stained with hematoxylin and eosin (H&E). No significant infiltrations are visible.

be causally associated with PPCM. In this regard, transgenic mice with cardiac-restricted over-expression of  $G\alpha_q$  exhibit a lethal PPCM accompanied by strongly enhanced apoptosis [10]. Reduction in cardiac apoptosis by caspase inhibition through administration of the polycaspase inhibitor IDN-1965 improved left ventricular function and survival in pregnant  $G\alpha_q$  mice, suggesting that cardiac apoptosis plays a causal role in the pathogenesis of cardiomyopathy [10].

The apoptosis signaling surface receptor Fas/Apo-1 is known to trigger cell death in a variety of cell types. Patients with PPCM had significantly higher plasma levels of Fas/Apo-1 compared with healthy volunteers [16]. Elevated plasma levels of tumor necrosis factor (TNF)- $\alpha$  have also been found in a cohort of 100 patients with PPCM. Elevated TNF- $\alpha$  has also been implicated in the pathogenesis of idiopathic DCMO [20•].

There is evidence suggesting the role of viral illness or an autoimmune etiology in the development of PPCM [21–24], with histologic samples of myocardial tissue having shown inflammatory infiltrates similar to that of myocarditis. Biopsies from PPCM patients often do not show inflammatory infiltrates (Fig. 2). Furthermore, a high prevalence of viral genomes were detected in endomyocardial biopsy (EMB) specimens of PPCM patients in 8 of 26 PPCM patients, and in 10 of 33 control subjects (30.3%) [21]. Viruses identified (parvovirus B19 [PVB19], human herpesvirus 6 [HHV-6], human herpesvirus 5 [HCMV], and EMBs) have been related to inflammatory cardiomyopathy, but also exist at high prevalence in healthy populations [21]. Similar results were presented by Rizeq et al. [24], whose retrospective review of EMB specimens from 34 PPCM patients showed a comparable incidence of myocarditis (8.8%) to that found in age- and sex-matched patients undergoing transplantation for idiopathic DCMO (idiopathic cardiomyopathy: 9.1%). Thus, the role of EMB

remains controversial and is likely to be clinically useful only if performed early in the course of the disease.

Recently, we discovered increased serum levels of oxidized low-density lipoprotein (oxLDL), indicative of enhanced systemic oxidative stress together with significantly higher prolactin levels and increased activation of the prolactin-cleaving protease cathepsin D [11•,12] among PPCM patients compared with healthy nursing- and pregnancy-matched control women. Moreover, we detected substantial amounts of cleaved 16-kDa prolactin in some PPCM patients, but not in healthy nursing mothers [11•].

In a mouse model for PPCM that lacked the signal transducer and activator of transcription 3 (STAT3) in cardiac myocytes, we were able to demonstrate that increased oxidative stress is responsible for the activation of cathepsin D and the subsequent cleaving of prolactin in a 16-kDa fragment. Furthermore, we showed that the 16-kDa prolactin has detrimental effects on the maternal heart by impairing the cardiac microvasculature and the cardiac myocyte metabolism, all of which appear to be largely responsible for the development of PPCM in mice [11•]. Bromocriptine is a dopamine  $D_2$  receptor antagonist that is known to efficiently block prolactin release from pituitary glands in humans [25] and mice [26] and is widely used in stopping lactation in women who cannot or do not want to nurse. Bromocriptine prevented PPCM in mice [11•]. This observation supports a crucial role of prolactin, namely its 16-kDa form in prolactin for PPCM, and supports previous studies viewing prolactin as a potential factor in the pathogenesis of PPCM [27].

In a recent study, the kinetics of a set of biomarkers associated with cardiac function, oxidative stress, apoptosis, inflammation, remodeling, and pregnancy were monitored at 6-month follow-up of PPCM patients, comparing biomarkers between patients who improved clinically versus those who did not [12]. This study revealed that among all markers analyzed, only the kinetics of NTproBNP, oxLDL, and interferon- $\gamma$  (IFN- $\gamma$ ) correlated significantly with nonimprovement in there being a positive correlation. Moreover, NTproBNP correlated positively with oxLDL, IFN- $\gamma$ , and prolactin. Thus, the kinetics of NTproBNP in correlation with the kinetics of more disease-specific markers (oxLDL, IFN- $\gamma$ , and prolactin) may serve to distinguish patients with poor prognosis from those who may recover [12]. However, the role of each of these factors in disease progression is still unclear and needs further clinical and experimental analysis.

### Current Therapeutic Approaches Towards Heart Failure in PPCM

Treatment is directed toward symptomatic relief and improvement of cardiac function, similar to other forms of heart failure treatment. The maintenance of blood oxygen saturation within the normal range (95%–98%) is important to maximize oxygen delivery to the tissues and tissue

oxygenation, thus helping to prevent end-organ dysfunction and multiple organ failure. This is best achieved by first ensuring that there is a patent airway and then administering an increase in fraction of inspired oxygen ( $\text{FiO}_2$ ). Endotracheal intubation is indicated if these measures fail to improve tissue oxygenation. The use of continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV) in acute cardiogenic pulmonary edema is associated with a significant reduction in the need for tracheal intubation and mechanical ventilation [28]. Respiratory muscle fatigue is the most frequent reason for endotracheal intubation and mechanical ventilation in AHF. It may be diagnosed by decreasing respiratory rate associated with hypercapnia and a confused state of mind. Invasive mechanical ventilation should only be used if acute respiratory failure does not respond to vasodilators, oxygen therapy, and/or CPAP or NIPPV [18,29].

Administration of diuretics is indicated in the presence of symptoms secondary to fluid retention. Inotropic agents are indicated in the presence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary edema refractory to diuretics and vasodilators.

Temporary mechanical circulatory assistance may be indicated in patients with AHF who are not responding to conventional therapy and where there is reasonable potential for myocardial recovery, for use as a bridge to heart transplantation, or interventions that may result in significant recovery of heart function. These include an intra-aortic balloon pump and a left ventricular assist device [19].

Cardiac transplantation has been successfully performed in PPCM patients. Favorable outcomes have been attributed to the young age of the recipients and to the relatively short duration of heart failure, resulting in minimal end-organ damage. However, there are reports of increased transplant rejection [30]. In view of the success of transplantation in these young and otherwise healthy mothers, aggressive temporary life support measures, such as cardiopulmonary bypass or a left ventricular assist device, have been encouraged until a transplant becomes available [31].

Coexistence of systemic oxidative stress and significantly higher prolactin levels in patients with acute PPCM supports the notion of our previously published concept that oxidative stress-mediated prolactin cleavage into its detrimental 16-kDa form is crucial for the initiation of PPCM. A recent pilot study suggests that this process can be ameliorated or even abolished by bromocriptine, an inhibitor of the detrimental prolactin [11•,32]. In this light, trials assessing the therapeutic effects of prolactin blockade with bromocriptine have begun in PPCM patients. A few case reports suggest that the addition of bromocriptine to standard therapy of heart failure may be beneficial in patients with acute onset of PPCM [11•,32].

In patients with stable heart failure,  $\beta$ -blockers and angiotensin-converting enzyme (ACE) inhibitors should be initiated when the patient has stabilized after the acute

episode (usually after 4 days). ACE inhibitors should be titrated up to dosages shown to be effective in the large controlled trials of heart failure and not towards symptomatic improvement alone. ACE inhibitors are contraindicated during pregnancy because of teratogenicity, but should be considered a mainstay of treatment for PPCM after delivery.

$\beta$ -blockers, preferably carvedilol, should be considered for treatment of all patients with heart failure, unless there is a contraindication.  $\beta$ -blocker therapy reduces hospitalization, improves the New York Heart Association (NYHA) functional class, and leads to smaller proportions of patients whose heart failure worsens [29]. The initial dose should be small and increased slowly and progressively to the target dose used in the large clinical trials. Aldosterone receptor antagonists are recommended in addition to ACE inhibitors,  $\beta$ -blockers, and diuretics in advanced heart failure (NYHA III–IV) with systolic dysfunction to improve survival and morbidity. Angiotensin II receptor blockers (ARBs) can be used as an alternative to ACE inhibition in symptomatic patients who are intolerant to ACE inhibitors to improve morbidity and mortality. Digoxin therapy is associated with an increased risk of death from any cause among women, but not men, with heart failure and depressed left ventricular systolic function [33]. Retrospective analysis of data from the Digitalis Investigation Group (DIG) trial indicates a beneficial effect of digoxin on morbidity and no excess mortality in women at serum concentrations from 0.5 to 0.9 ng/mL, whereas serum concentrations of 1.2 ng/mL or greater appear harmful [34].

Thromboembolic phenomena have been reported frequently in PPCM patients. Pregnant patients are at increased risk of thromboembolic complications due to the hypercoagulable state of late pregnancy that may persist for up to 6 weeks postpartum. Left ventricular systolic dysfunction resulting in blood stasis additionally predisposes to formation of left ventricular, pulmonary, and cerebral thromboemboli. During the last weeks of pregnancy, low-molecular weight heparin is the agent of choice, whereas warfarin is preferred postpartum in patients with low ejection fraction (< 30 %) [18].

Appropriate birth control measures are recommended for patients with enlarged hearts. Oral contraceptives should be avoided because of the risk of increasing the incidence of thromboembolism.

### Prognosis and Subsequent Pregnancy

Echocardiography is an important diagnostic tool in PPCM and may provide significant prognostic information with regard to recovery of cardiac function [35•]. A fractional shortening value of less than 20% and a left ventricular end-diastolic dimension of more than 6 cm at the time of diagnosis are associated with a threefold or higher risk for persistent left ventricular dysfunction [4].

In a cohort of 100 patients from South Africa, a mortality of 15% within a 6-month period was reported. Baseline plasma levels of Fas/Apo-1 and NYHA functional class were identified as independent predictors of death [2•]. Compared with other forms of cardiomyopathy ( $n = 1230$ ), patients with PPCM ( $n = 51$ ) demonstrate better survival [36]. In a study from Haiti, the ratio of PPCM deaths for the 5-year period was 47.1 per 100,000 births, and the mortality rate was 15.3% during a mean follow-up period of 2.2 years. Only 28% of patients who were observed for at least 6 months regained normal left ventricular function [37].

One of the most common issues for women surviving an episode of PPCM is whether it is safe to become pregnant again. If a subsequent pregnancy occurs, it should be managed in close collaboration between the obstetrician and attending physician or cardiologist. Most authors agree that PPCM patients with persistent left ventricular dilatation and dysfunction are at high risk for complications and death should they become pregnant again [38].

In contrast, the issue of whether patients with PPCM and recovered left ventricular function can safely undergo a subsequent pregnancy remains controversial. Elkayam et al. [39] conducted a record review among members of the ACC in the United States and one hospital in South Africa and described the outcome of 60 subsequent pregnancies in 44 women with a history of PPCM. Among the first subsequent pregnancies in the 44 women, 28 occurred among women in whom left ventricular function had returned to normal (group 1) and 16 occurred in women with persistent left ventricular dysfunction (group 2). The pregnancies were associated with a reduction in mean left ventricular ejection fraction in each group; 19% of PPCM patients with sustained impaired systolic function, who then conceived their first subsequent pregnancy, eventually died [39]. Although the likelihood of maternal death seems to be very low in women who recovered their left ventricular function before a subsequent pregnancy, a reduction in left ventricular ejection fraction and symptomatic heart failure will occur in the majority of PPCM patients in subsequent pregnancies.

However, pilot data of bromocriptine trials are promising. Twelve patients who suffered from PPCM in a previous pregnancy presented with a subsequent pregnancy and therefore had a high risk for developing the disease again [11•]. Six patients obtained bromocriptine immediately after delivery, in addition to standard therapy for heart failure, and all of them had an uneventful postpregnancy follow-up. In contrast, all patients ( $n = 6$ ) in the group who obtained only standard therapy suffered from recurrence of PPCM, three of whom subsequently died. Since this pilot, another four patients have had similar positive outcome on bromocriptine, and further efforts to clarify its efficacy in preventing recurrence of PPCM continue to be encouraging (Sliwa, unpublished data).

## Conclusions

PPCM is a common disorder in some geographic regions and possibly goes unrecognized in others. Defining this disorder as an entity of its own may be justifiable given the recent discovery of an oxidative stress cathepsin D 16-kDa prolactin cascade in experimental and human PPCM serving as a specific pathophysiologic mechanism that may provide the rationale for a specific therapeutic intervention. Bromocriptine, a drug blocking the release of prolactin systemically and locally, has been used for many years in women to stop lactation, and now needs to be tested in randomized trials to treat women with PPCM. Systematic prospective data collection is required as well as international cardiac registries to study the etiology and different pathogenic mechanisms of PPCM, including potential genetic and lifestyle aspects. Furthermore, attempts to establish specific biomarker profiles and diagnostic tests are warranted for risk stratification and prevention of PPCM.

## Disclosures

No potential conflicts of interest relevant to this article were reported.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
  - Of major importance
1. Pearson GD, Veille JC, Rahimtoola S, et al.: **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.
  2. Sliwa K, Fett J, Elkayam U: **Peripartum cardiomyopathy.** *Lancet* 2006, 368:687–693.
- This article serves as a recent comprehensive review on PPCM.
3. Elkayam U, Akhter MW, Singh H, et al.: **Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation.** *Circulation* 2005, 111:2050–2055.
- This article reports on a large number of PPCM patients from a United States perspective and introduces comparative data on women otherwise diagnosed to be PPCM. The difference is that those presenting with failure as early as 3 months into pregnancy are also included.
4. Chapa JB, Heiberger HB, Weinert L, et al.: **Prognostic value of echocardiography in peripartum cardiomyopathy.** *Obstet Gynecol* 2005, 105:1303–1308.
  5. Kist WJ, Janssen NG, Kalk JJ, et al.: **Thrombophilias and adverse pregnancy outcome—a confounded problem!** *Thromb Haemost* 2008, 99:77–85.
  6. Maron BJ, Towbin JA, Thiene G, et al.: **Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups, and Council on Epidemiology and Prevention.** *Circulation* 2006, 113:1807–1816.

7. Elliott P, Andersson B, Arbustini E, et al.: Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008, 29:270–276.
  8. Deneux-Tharaux C, Berg C, Bouvier-Colle MH, et al.: Under-reporting of pregnancy-related mortality in the United States or Europe. *Obstet Gynecol* 2005, 106:684–692. [Published erratum appears in *Obstet Gynecol* 2006, 107:209.]
  9. Brar SS, Khan SS, Sandhu GK, et al.: Incidence, mortality, and racial differences in peripartum cardiomyopathy. *Am J Cardiol* 2007, 100:302–304.
  10. Hayakawa Y, Chandra M, Miao W, et al.: Inhibition of cardiac myocyte apoptosis improves cardiac function and abolishes mortality in the peripartum cardiomyopathy of Galpha(q) transgenic mice. *Circulation* 2003, 108:3036–3041.
  11. Hilfiker-Kleiner D, Kaminski K, Podewski E, et al.: A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* 2007, 128:589–600.
- This article reports on a novel pathomechanism involved in PPCM.
12. Forster O, Hilfiker-Kleiner D, Ansari A, et al.: Reversal of IFN-gamma, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. *Eur J Heart Fail* 2008, 10:861–868.
  13. Diwan A, Wansapura J, Syed FM, et al.: Nix-mediated apoptosis links myocardial fibrosis, cardiac remodeling, and hypertrophy decompensation. *Circulation* 2008, 117:396–404.
  14. Fett JD, Ansari AA, Sundstrom JB, Combs GF: Peripartum cardiomyopathy: a selenium disconnection and an auto-immune connection. *Int J Cardiol* 2002, 86:311–316.
  15. Lampert MB, Lang RM: Peripartum cardiomyopathy. *Am Heart J* 1995, 130:860–870.
  16. Sliwa K, Skudicky D, Bergemann A, et al.: Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma levels of cytokines and Fas/APO-1. *J Am Coll Cardiol* 2000, 35:701–705.
  17. Sliwa K, Skudicky D, Candy G, et al.: The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. *Eur J Heart Fail* 2002, 4:305–309.
  18. Forster O, Ansari AA, Sliwa K: Current issues in diagnosis and management of peripartum cardiomyopathy. *Womens Health* 2006, 2:587–596.
  19. Nieminen MS, Bohm M, Cowie MR, et al.: Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005, 26:384–416.
  20. Sliwa K, Forster O, Libhaber E, et al.: Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J* 2006, 27:441–446.
- This article reports on a prospective study with one of the largest number of PPCM patients to date and presents fundamental information on a sub-Saharan African cohort where prevalence appears to be among the highest.
21. Bultmann BD, Klingel K, Nabauer M, et al.: High prevalence of viral genomes and inflammation in peripartum cardiomyopathy. *Am J Obstet Gynecol* 2005, 193:363–365.
  22. Cenac A, Djibo A, Djangnikpo L: Peripartum dilated cardiomyopathy. A model of multifactor disease? [in French]. *Rev Med Interne* 1993, 14:1033.
  23. Fett JD: Viral infection as a possible trigger for the development of peripartum cardiomyopathy. *Int J Gynaecol Obstet* 2007, 97:149–150.
  24. Rizeq MN, Rickenbacher PR, Fowler MB, Billingham ME: Incidence of myocarditis in peripartum cardiomyopathy. *Am J Cardiol* 1994, 74:474–477.
  25. Harrison RG: Suppression of lactation. *Semin Perinatol* 1979, 3:287–297.
  26. Nagafuchi H, Suzuki N, Kaneko A, et al.: Prolactin locally produced by synovium infiltrating T lymphocytes induces excessive synovial cell functions in patients with rheumatoid arthritis. *J Rheumatol* 1999, 26:1890–1900.
  27. Kothari SS: Aetiopathogenesis of peripartum cardiomyopathy: prolactin-selenium interaction? *Int J Cardiol* 1997, 60:111–114.
  28. Peter JV, Moran JL, Phillips-Hughes J, et al.: Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis. *Lancet* 2006, 367:1155–1163.
  29. Nieminen MS, Böhm M, Cowie MR, et al.: Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005, 26:384–416.
  30. Johnson MR, Naftel DC, Hobbs RE, et al.: The incremental risk of female sex in heart transplantation: a multiinstitutional study of peripartum cardiomyopathy and pregnancy. Cardiac Transplant Research Database Group. *J Heart Lung Transplant* 1997, 16:801–812.
  31. Hovsepian PG, Ganzel B, Sohi GS, et al.: Peripartum cardiomyopathy treated with a left ventricular assist device as a bridge to cardiac transplantation. *South Med J* 1989, 82:527–528.
  32. Hilfiker-Kleiner D, Meyer GP, Schieffer E, et al.: Recovery from postpartum cardiomyopathy in 2 patients by blocking prolactin release with bromocriptine. *J Am Coll Cardiol* 2007, 50:2354–2355.
  33. Rathore SS, Wang Y, Krumholz HM: Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002, 347:1403–1411.
  34. Adams KF Jr, Patterson JH, Gattis WA, et al.: Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol* 2005, 46:497–504.
  35. 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.
- This article reports on one of the few prospective long-term studies of one of the largest number of PPCM patients to date and presents fundamental information on a cohort from Haiti.
36. Felker GM, Thompson RE, Hare JM, et al.: Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000, 342:1077–1084.
  37. Ellis JE, Ansari AA, Fett JD, et al.: Inhibition of progenitor dendritic cell maturation by plasma from patients with peripartum cardiomyopathy: role in pregnancy-associated heart disease. *Clin Dev Immunol* 2005, 12:265–273.
  38. Sliwa K, Forster O, Zhanje F, et al.: Outcome of subsequent pregnancy in patients with documented peripartum cardiomyopathy. *Am J Cardiol* 2004, 93:1441–1443.
  39. Elkayam U, Tummala PP, Rao K, et al.: Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med* 2001, 344:1567–1571. [Published erratum appears in *N Engl J Med* 2001, 345:552.]