

# Current issues in the diagnosis and management of peripartum cardiomyopathy

Olaf Forster<sup>1†</sup>,  
Aftab A Ansari<sup>2</sup> &  
Karen Sliwa<sup>1,3</sup>

<sup>†</sup>Author for correspondence

<sup>1</sup>University of the  
Witwatersrand, Johannesburg  
Division of Cardiology, Chris  
Hani Baragwanath Hospital  
Soweto Cardiovascular  
Research Unit,  
2013 Soweto,  
South Africa

Tel.: +27 11 933 9848;

Fax: +27 11 938 8945;

E-mail: forstero@

medicine.wits.ac.za

<sup>2</sup>Emory University School of  
Medicine, Department of  
Pathology and Laboratory  
Medicine,

Atlanta, GA 30322, USA

Tel.: +1 404 712 2834;

Fax: +1 404 712 1771;

E-mail: pathaaa@emory.edu

<sup>3</sup>E-mail: sliwa-hahnlek@  
mdh-africa.org

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Peripartum cardiomyopathy is a form of heart failure that occurs in women within 1 month pre- and 5 months postdelivery. The syndrome carries a high mortality and predisposing factors are not known. The incidence and prevalence of peripartum cardiomyopathy appear to be increasing and this article aims to alert clinicians to consider a possible diagnosis of peripartum cardiomyopathy, outlines the current treatment options, and describes recent advances in the understanding of the pathophysiology of this condition.

Peripartum cardiomyopathy (PPCM) was first described by Virchow in 1870 and is defined as a disorder of unknown pathogenesis in which left ventricular (LV) dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first 5 months postpartum. PPCM is an exclusion diagnosis based on the absence of an identifiable cause of heart failure or recognizable heart disease prior to the last month of pregnancy [1]. Pregnancy-related cardiomyopathy may present during the second or third trimester. The clinical presentation and outcome of patients with pregnancy-associated cardiomyopathy diagnosed early in pregnancy are similar to those of patients with traditional PPCM, leading Elkayam and colleagues to the conclusion that these two conditions may represent a continuum of a spectrum of the same disease [2].

Diagnosis requires echocardiographic evidence of LV systolic dysfunction (ejection fraction < 45%, fractional shortening < 30%) [3]. Nuclear-medical investigations such as multi-gated acquisition scan may compliment echocardiography in nonpregnant women. Heart failure occurring earlier in pregnancy may be caused by previously unsuspected dilated cardiomyopathy unmasked by the hemodynamic and hormonal stress of pregnancy and possibly forms a different entity. Other possible causes of heart failure during the peripartum period, such as infectious, toxic or metabolic disorders, and ischemic or valvular heart disease need to be considered. Complications of late pregnancy, including toxemia and amniotic or pulmonary embolism, which may mimic heart failure, should be ruled out before the diagnosis of PPCM is made.

## Epidemiology of PPCM

The incidence of PPCM varies from 1/100 to 1/10000 between geographical regions (Table 1) and tends to be associated with low socioeconomic standards [4]. The highest incidence of pregnancy-associated heart failure in the world has been reported from the Zaria province of Nigeria. The incidence of PPCM might have been overestimated in some areas due to the absence of echocardiography, possibly resulting in other causes of systolic heart failure being diagnosed as PPCM. However, while the incidence in the USA has previously been described as 1/10000 [5], recent studies reported an incidence of 1/2392 to 1/4000 live births [6,7].

In order to further define the incidence, prevalence, determinants and outcome of PPCM, there is a need for large-scale studies on cardiomyopathy on the African continent, to form strategies for the optimal treatment and prevention of heart-muscle disease [12].

## Etiology & pathogenesis

There is considerable uncertainty with regards to the etiology of human PPCM. Although it is termed idiopathic, a number of mechanisms have been proposed as potential etiological agents, including nutritional deficiencies, genetic disorders, viral or autoimmune etiologies, hormonal problems, volume overload, alcohol, physiological stress of pregnancy, or unmasking of latent idiopathic dilated cardiomyopathy [13]. The rare incidence of PPCM and the absence of relevant animal models have limited research into the pathogenic mechanisms involved [3]. While early reports suggested that PPCM was more prevalent in women aged over 30 years, caused by heat, hard physical exertion

**Table 1. Incidence of PPCM in geographical regions.**

Location	Incidence
Nigeria (Zaria)	1/100
Haiti	1/300
South Africa (Durban)	1/1000
South Africa (Johannesburg)	1/3000
China (Taiwan)	1/6147
USA	1/2392–1/4000

PPCM: Peripartum cardiomyopathy.

Adapted from [1,5–11].

during pregnancy, hypertension, maternal cocaine abuse, sodium diet or selenium deficiency, these were based primarily on case reports and have not been proven in studies that have included a large number of patients. Fett and colleagues investigated selenium deficiency and malnutrition in PPCM patients from Haiti and reported that neither a macronutrient deficiency (e.g., protein and iron) nor a micronutrient deficiency (e.g., vitamin A, vitamin B12, vitamin C, vitamin E,  $\beta$ -carotene and selenium) played a significant role in the high incidence and prevalence of PPCM in this population [14]. Several authors have suggested that multiparity may be a risk factor for PPCM, but a recent study by Elkayam and colleagues does not support a strong association with multiparity in the USA, as almost 40% of the cases occurred in association with a first pregnancy and more than 50% with the first two pregnancies. Common associated conditions in this cohort were gestational hypertension (43%), tocolytic therapy (19%) and twin pregnancy (13%) [2].

Loss of myocytes due to apoptosis occurs in patients with end-stage cardiomyopathy, but its importance in the pathogenesis of PPCM is unknown. Support for the role of apoptosis in PPCM has been provided by a study that utilized transgenic mice with cardiac-restricted overexpression of Galpha(q). These mice exhibit a lethal form of PPCM accompanied by apoptosis. Hayakawa and colleagues confirmed the role for apoptotic mechanisms by demonstrating a reduction in cardiac myocyte apoptosis by caspase inhibition through administration of the polycaspase inhibitor IDN-1965, and improved LV function and survival in pregnant Galpha(q) mice. These findings suggest that cardiac myocyte apoptosis plays a causal role in the pathogenesis of cardiomyopathy [15]. The apoptosis signaling surface receptor Fas/APO-1 is known to trigger cell death in a variety of cell types. Sliwa and colleagues observed significantly

higher plasma levels of Fas/APO-1 in PPCM patients compared with healthy volunteers. The same group also reported significantly elevated plasma levels of tumor necrosis factor (TNF)- $\alpha$  in PPCM patients, which has been implicated in the pathogenesis of idiopathic dilated cardiomyopathy [16]. Several lines of evidence suggest that PPCM may be the result of myocarditis due to a viral illness or an autoimmune etiology. Bultmann and colleagues detected viral genomes in endomyocardial biopsy specimens in 8 of 26 PPCM patients (30.7%) but also in 10 of 33 control subjects (30.3%). The detected viruses (parvovirus B [PVB]-19, human herpesvirus [HHV]-6, Epstein-Barr Virus [EBV], human cytomegalovirus [HCMV]) have been suspected as etiological agents, but such viruses also have a high prevalence in healthy populations [17], making it difficult to interpret these findings. Kuhl and colleagues amplified viral genomes in endomyocardial biopsies of 165 (67.4%) of 245 patients with idiopathic dilated cardiomyopathy and found a similar spectrum of viruses (ectromelia virus [EV] = 9.4%; adeno-associated virus [ADV] = 1.6%; PVB-19 = 51.4%, HHV-6 = 21.6%; EBV = 52.0%; HCMV = 0.8%), including 45 cases (27.3%) with multiple infections [18]. The role of endomyocardial biopsy remains controversial. PPCM has also been linked to other infectious disease agents such as *Chlamydia pneumoniae* or enterovirus [3] through a process known as 'molecular mimicry', in which the infectious agents bear proteins that share sequence homology with normal cardiac tissue proteins. Thus, the immune response against these mimics immune responses against normal cardiac tissues, leading to myocyte loss. Stress-activated proinflammatory cytokines such as TNF- $\alpha$  or interleukin (IL)-1 have been implicated in the pathophysiology of idiopathic dilated cardiomyopathy, and Sliwa and colleagues reported significantly higher plasma levels of TNF- $\alpha$  and IL-6 in PPCM patients compared with healthy, age-matched controls [16].

#### Clinical presentation

Normal pregnancy is associated with an expansion of blood volume, an increase in metabolic demands, relative anemia and changes in vascular resistance that are associated with ventricular dilatation and an increase in cardiac output. These physiological changes are due to an increase in preload and heart rate accompanied by a decrease in afterload, peaking during the second trimester

of pregnancy. Decompensation of patients with subclinical valvular, ischemic or myopathic heart disease usually occurs during this time. The early stage of PPCM can easily be missed, since many symptoms and signs of pregnancy are similar to those of early congestive heart failure (CHF) (e.g., dyspnea, abdominal discomfort and fatigue) [19,20]. Elkayam and colleagues report that 7% of their US patients were diagnosed within 1 month of delivery and 75% of patients were diagnosed during the first month postpartum [2], while Sliwa and colleagues observed the onset of symptoms in South African patients primarily during the postpartum period [16,21], which is in accordance with findings by Fett and colleagues in Haitian patients [6,22]. The symptoms and signs are similar to those in patients with idiopathic dilated cardiomyopathy [23] and can be complicated by thromboembolic events and arrhythmia. Echocardiography usually demonstrates features of dilated cardiomyopathy with impaired ejection fraction, global dilatation and, sometimes, thinned-out walls.

#### Diagnosis of acute heart failure due to peripartum cardiomyopathy

PPCM is one cause of acute heart failure (AHF). The diagnosis of PPCM is often delayed and it is important for the clinician to consider this diagnosis in susceptible patients before preventable major complications develop. AHF is often life threatening and requires urgent treatment. AHF due to PPCM can occur due to decompensation of pre-existing stable PPCM or as a first manifestation of PPCM. AHF is a clinical syndrome with reduced cardiac output, tissue hypoperfusion, increase in the pulmonary capillary wedge pressure and tissue congestion [24]. The diagnosis of AHF is based on the symptoms and clinical findings in combination with appropriate investigations such as electrocardiogram (ECG), chest X-ray, 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 (CVP). Caution is necessary in the interpretation of a high measured CVP in AHF, as it may be a reflection of decreased venous compliance together with decreased right ventricular compliance. Left-sided filling pressure is assessed by chest auscultation, with the presence of wet rales in the lung fields usually indicating raised pressure. The confirmation, classification of severity

and clinical follow-up of pulmonary congestion and pleural effusions should be performed using the chest X-ray. Cardiac palpitation and auscultation for ventricular and atrial gallop rhythms (S3, S4) should be performed. The ECG often reveals nonspecific findings such as tachycardia and nonspecific ST-T wave changes.

Chest X-ray and other imaging should be performed early for all patients with AHF to evaluate pre-existing chest or cardiac conditions and to assess pulmonary congestion. It is used both for confirmation of the diagnosis and to monitor response to therapy, but the threshold for radiological examinations should be high in pregnant patients. Chest X-ray may show venous congestion or pulmonary edema, but the distinction from inflammatory or infectious lung disease is not always easy. A chest computed tomography scan with or without contrast angiography and scintigraphy may be used to clarify pulmonary pathology and diagnose major pulmonary embolism [24]. In pregnant women, careful decision making regarding procedures that expose the patient to radiation is mandatory.

A number of laboratory tests should be used in all AHF patients: full blood count, urea and electrolytes, C-reactive protein (CRP), blood glucose, D-dimer, creatine kinase-MB and cardiac troponin T. In severe heart failure, international normalized ratio and arterial blood gas should also be performed. Transaminases, urinalysis and plasma B-type natriuretic peptide (BNP) or N-terminal (NT)proBNP can be considered. Arterial blood gas analysis allows assessment of partial pressure of oxygen ( $pO_2$ ), partial pressure of carbon dioxide ( $pCO_2$ ), 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  $CO_2$  can often replace arterial blood gas analysis, but not in very low output, vasoconstricted shock states [24]. In a study with 100 PPCM patients, Sliwa and colleagues documented a positive correlation between plasma CRP levels at baseline with LV end-diastolic ( $r^2 = 0.33$ ;  $p = 0.0026$ ) and end-systolic ( $r^2 = 0.35$ ;  $p = 0.0012$ ) diameters, and an inverse relationship with LV ejection fraction (LVEF) ( $r_s = -0.27$ ;  $p = 0.015$ ) [25].

Plasma 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 [26]. In normal pregnancies, median BNP values are lower than 20 pg/ml and stable throughout gestation. In comparison,

plasma BNP levels are elevated in severe pre-eclampsia. This may reflect ventricular stress and/or subclinical cardiac dysfunction associated with pre-eclampsia [27]. Decision making cut-off points of 300 pg/ml for NTproBNP and 100 pg/ml for BNP have been proposed. Various clinical conditions may affect the BNP concentration, for example, renal failure and septicemia. If elevated levels are detected, further diagnostic tests are required, but otherwise BNP has a good negative predictive value to exclude heart failure [28]. It is important to note that the diagnosis of PPCM requires echocardiography and that increased levels of plasma BNP or NTproBNP carry important prognostic information, but the exact role of BNP remains to be fully clarified [29]. Echocardiography is an essential tool for the evaluation of the functional and structural changes underlying or associated with AHF. The most important measurement of ventricular function is the LVEF, 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. Cardiac output can be estimated by appropriate Doppler aortic or pulmonary time-velocity contour measurements [24]. An appropriate echo-Doppler study can also estimate pulmonary artery pressures and may indicate the presence of pulmonary embolus.

#### Monitoring of patients with acute heart failure

Monitoring of the patient with AHF should be initiated as soon as possible. The types and level of monitoring required for any individual patient vary widely depending on the severity of cardiac decompensation and the response to initial therapy [24].

#### *Noninvasive monitoring*

In all critically ill patients, measurements of blood pressure (BP), temperature, respiratory rate, heart rate and ECG are mandatory. Some laboratory tests such as electrolytes, creatinine, glucose, and markers for infection or other metabolic disorders should be carried out repeatedly. Hypo- or hyperkalemia must be controlled. Maintenance of normal BP is critical and should be measured regularly until the dosage of vasodilators, diuretics or inotropes has been stabilized. A pulse oximeter should be used on any patient

receiving oxygen. Cardiac output and preload can be monitored noninvasively by Doppler echocardiography, as described previously [24].

#### *Invasive monitoring*

Indications for the insertion of an indwelling arterial catheter are dictated by the need for either continuous beat-to-beat analysis of arterial BP due to hemodynamic instability or the requirement for multiple arterial blood analyses. A central venous line is useful for delivery of fluids and drugs and can be used to monitor CVP and venous oxygen saturation [24].

#### Current therapeutic approaches for heart failure in PPCM

##### *Treatment of acute heart failure in PPCM*

Treatment is directed toward symptomatic relief and improvement of cardiac function and is similar to other forms of CHF. The maintenance of an oxygen saturation (SaO<sub>2</sub>) 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 by administration of an increased fraction of inspired oxygen. 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. Respiratory muscle fatigue is the most frequent reason for endotracheal intubation and mechanical ventilation in AHF. It may be diagnosed by the presence of a decreased 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 [24].

Morphine is indicated in the early stage of treatment of patients with severe AHF, especially if associated with restlessness and dyspnea. Morphine induces venodilation and mild arterial dilatation and reduces heart rate. Anticoagulation should be initiated unless contraindicated to avoid both venous and arterial thromboembolic events. Careful monitoring of international normalized ratio and partial thromboplastin time is advised since autoanticoagulation due to hepatic congestion may be present.

Vasodilators are indicated as first-line therapy if hypoperfusion is associated with an adequate BP and signs of congestion with low diuresis, to open the peripheral circulation and to lower preload.

Angiotensin-converting enzyme (ACE) inhibitors are not indicated in the early stabilization of patients with heart failure. Administration of diuretics is indicated in the presence of symptoms secondary to fluid retention. There has been no study with  $\beta$ -blocker therapy in AHF targeted to acutely improve the condition. On the contrary, AHF has been considered a contraindication for this treatment.

It is important to note that management will differ in women who are still pregnant, since the threshold to perform X-rays or a computed tomography scan will be much higher. Before the administration of drugs, contraindications during pregnancy need to be observed.

In patients with chronic heart failure,  $\beta$ -blockers should be initiated when the patient has stabilized after the acute episode (usually after 4 days). 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 a potential for myocardial recovery, or as a bridge to heart transplantation or interventions that may result in significant recovery of the heart function (e.g., intra-aortic balloon pump, LV assist device) [24]. In clinical experience, PPCM often shows remarkable spontaneous improvement. The decision for heart transplantation should therefore only be made very carefully after all other options have been exhausted and sufficient time for recovery has been allowed.

Cardiac transplantation has been performed successfully in PPCM patients. Favorable outcomes have been attributed to the young age of the recipients and to the recent onset of heart failure, resulting in minimal end-organ damage. In view of the success that has been achieved with transplantation in these young and otherwise healthy mothers, aggressive measures such as temporary life support in form of cardiopulmonary bypass or a LV assist device until the availability of a transplant have been advocated [30].

### *Treatment of chronic heart failure in PPCM*

ACEIs are recommended as first-line therapy in patients with a reduced LV systolic function of less than 40–45% with or without symptoms [31], but are contraindicated during pregnancy due to teratogenicity [2]. Vasodilator therapy reduces afterload and improves cardiac output, resulting in a reduction in LV end-diastolic pressure and a decrease in pulmonary and systemic vascular resistances. Godsel and colleagues view an ACE inhibitor (ACEI) as the most valuable medication, not only due to its direct beneficial effects on the heart, but also due to its potential benefit to interrupt the chain of events in the pathobiology of PPCM [32]. ACEIs should be up titrated to dosages shown to be effective in large, controlled trials of heart failure and not on symptomatic improvement alone.

Diuretics are essential for symptomatic treatment when fluid overload is present and manifest as pulmonary congestion or peripheral edema, but their use should be carefully considered during pregnancy. In patients with chronic heart failure, diuretics should be administered in combination with ACEIs and  $\beta$ -blockers, if tolerated.

$\beta$ -blockers should be considered for treatment of all patients with stable, mild, moderate and severe heart failure, unless there is a contraindication.  $\beta$ -blocker therapy reduces hospitalizations, improves the New York Heart Association (NYHA) functional class and prevents worsening of heart failure. The initial dose should be low and increased slowly and progressively to the target dose used in the large clinical trials [31]. Carvedilol reduces the risk of death as well as the risk of hospitalization for cardiovascular causes in patients with heart failure. Vasodilating  $\beta$ -blockers such as carvedilol also reduce afterload through  $\alpha$ -1 adrenergic blockade. Lowes and colleagues reported functional improvement in idiopathic dilated cardiomyopathy patients related to treatment with  $\beta$ -blockers and an association with changes in myocardial gene expression.  $\beta$ -blocker-treated patients who showed an improvement in LVEF had an increase in sarcoplasmic reticulum calcium ATPase mRNA and  $\alpha$ -myosin heavy-chain mRNA, and a decrease in  $\beta$ -myosin heavy-chain mRNA [33]. Up titration should be adapted to individual responses. Aldosterone receptor antagonists are recommended in addition to ACEIs,  $\beta$ -blockers and diuretics in advanced heart failure (NYHA class III–VI) with systolic

dysfunction to improve survival and morbidity. In the Randomized ALdacton Evaluation Study (RALES), low doses of aldactone, added to standard of care for severe heart failure, improved survival by 30% and lowered hospitalization by 35% [34]. Angiotensin II receptor blockers (ARBs) can be used as an alternative to ACE inhibition in symptomatic patients intolerant to ACEIs to improve morbidity and mortality, but are also contraindicated during pregnancy. The Valsartan Heart Failure Trial (Val Heft) demonstrated a reduced incidence of atrial fibrillation after the addition of valsartan to heart-failure therapy [35] and the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) study showed reduction of atrial fibrillation and improved outcome for candesartan [36]. Digoxin therapy is associated with an increased risk of death from any cause among women, but not men, with heart failure and depressed LV systolic function [37]. A 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 of 0.5–0.9 ng/ml, whereas serum concentrations of 1.2 ng/ml or greater seem harmful [38]. Digoxin is a class C drug and should be avoided during pregnancy.

While ACEIs and ARBs are contraindicated during pregnancy, hydralazine might be the vasodilator of choice, although controversy exists [39]. Among the vasodilators, nitrates are another alternative during pregnancy. It is important to note that venous therapeutic modalities mentioned in this article have never been studied specifically in PPCM patients, but in dilated cardiomyopathy patients.

Thromboembolic phenomena have been reported in PPCM patients. Pregnant patients are at an increased risk of thromboembolic complications due to the hypercoagulable state of late pregnancy that may persist up to 6 weeks postpartum. LV systolic dysfunction resulting in blood stasis, additionally predisposes patients to develop LV, pulmonary and cerebral thrombemboli. The decision to treat the patient with anticoagulants should be made after careful consideration that should include dilated LV dimensions and low ejection fraction. It is important to stress that not all PPCM patients need anticoagulant treatment. During the last weeks of pregnancy, low-molecular-weight heparin is the agent of choice, while warfarin is preferred postpartum.

Maisch and colleagues recommend heart catheterization with endomyocardial biopsy to allow for the exact diagnosis of the underlying cardiac process (inflammatory and/or viral vs autoreactive myocarditis, or noninflammatory or nonviral forms) [40], but this is not an established routine procedure. Until a link between immunosuppressive therapy and resolution of myocarditis can be established in PPCM patients, the use of these agents is not recommended [19]. In fact, the benefit of immunosuppressive and antiviral therapy is a controversial topic [41].

Appropriate birth-control measures are recommended for patients with enlarged hearts. Oral contraceptives should be avoided due to the increased incidence of thromboembolism. However, the use of quarterly injections of depot hormone or other methods of preventive family planning need to be encouraged.

#### *Recommendations for delivery*

A possible indication for early delivery and the mode of delivery should be assessed through collaboration between obstetricians, cardiologists and anesthesiologists. Ideally, pregnancy should be permitted to continue to term in PPCM patients diagnosed during the last month of gestation. Urgent delivery of the fetus may be considered for patients who present with advanced heart failure with hemodynamic instability. Patients with adequate cardiac output may tolerate induction and vaginal delivery. Critically ill patients who require inotropic therapy or mechanical support should undergo cesarean delivery [42].

#### *Prognosis*

##### *Maternal outcome*

Echocardiography is an important diagnostic tool in PPCM and may provide significant prognostic information with regard to the recovery of cardiac function. LV end diastolic dimension of 6 cm or greater at the time of diagnosis has been shown to be associated with a more than three-fold higher risk for persistent LV dysfunction [43]. Dorbala and colleagues studied the LV contractile reserve in seven PPCM patients during dobutamine stress echocardiography and documented a correlation ( $r = 0.79$ ) with subsequent recovery of LV function [44].

In a cohort of 100 patients from South Africa, Sliwa and colleagues reported a mortality of 15% within a 6-month period. Baseline plasma levels of Fas/APO-1 (odds ratio [OR]: 1.30; 95% confidence interval [CI]: 1.11–1.54) and NYHA

functional class (OR: 2.88; 95% CI: 1.10–7.53) were identified as independent predictors of death [25].

In a study from the USA, Elkayam and colleagues reported heart transplantation in 4% of PPCM patients. Maternal mortality was 9% within a period of 2.2 years and was described as sudden in four patients and as a result of complications from heart transplantation in two patients. A total of 3% of the patients required implantation of an automatic implantable cardioverter–defibrillator, and 2% required implantation of a permanent pacemaker during the follow-up period. LVEF at the time of diagnosis was  $29 \pm 11\%$  and improved to  $46 \pm 14\%$  ( $p \leq 0.0001$ ) at follow-up. Normalization of LVEF occurred in 54% of patients and was more likely in patients with a LVEF of more than 30% at diagnosis [2].

Felker and colleagues found better survival rates in 51 PPCM patients than in patients with other causes of cardiomyopathy ( $n = 1230$ ) (adjusted hazard ratio for death: 0.31; 95% CI: 0.09–0.98) [45]. In a study from Haiti, the ratio of PPCM deaths for the 5-year period was 47.1/100,000 births compared with the US ratio of 0.62/100,000 births. The mortality rate was 15.3% during a mean follow-up period of 2.2 years. A total of 28% of patients who were observed for at least 6 months regained normal LV function. The difference in LV echocardiographic features at diagnosis between deceased patients and survivors was not statistically significant, but a statistically significant difference occurred at diagnosis between the recovered and the nonrecovered group for mean ejection fraction (28 vs 23%;  $p < 0.001$ ) and fractional shortening (17 vs 14%;  $p = 0.004$ ) [6].

#### *Neonatal outcome*

A recent study from the USA on neonatal outcome in mothers suffering from PPCM requires careful interpretation, since pregnancy-related hypertension was reported in 43% of patients and thus excludes these patients from a strict diagnosis of PPCM. Mode of delivery was cesarean section in 40 patients, which was performed for obstetrical reasons in 70% of the patients, cardiac reasons in 10% and unknown reasons in 20%. Duration of pregnancy (56 patients) ranged from 24 to 42 weeks, with an average of  $37.7 \pm 3.5$  weeks. Premature delivery (<37 weeks) was reported in 25% of these patients. Birth weight (51 patients) ranged between 1350 and 5000 g, with a mean of  $3092 \pm 745$  g, and the incidence of small-for-gestational-age infants was 5.9%. There were two

stillbirths and one neonatal death. Congenital anomalies in the newborn were reported in four cases and included hypospadias, coarctation of the aorta, dysmorphogenesis and macrosomia. Neonatal complications were reported in six cases and included one case each of hypothermia, poor suckling, apnea with seizure requiring intubation, hypoglycemia and death, and two cases of pulmonary edema [2].

#### Ongoing challenges

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 an obstetrician and a cardiologist. Most investigators agree that patients with PPCM and persistent LV dilatation and dysfunction are at high risk for complications and death should they become pregnant again. Sliwa and colleagues reported on six patients with previous PPCM with a subsequent pregnancy in a single-center study, resulting in reduction of ejection fraction by more than 10% in five patients at 1 month postpartum. Two patients with impaired ejection fraction and persistent cardiomegaly at onset of subsequent pregnancy died 3 months postpartum due to heart failure, despite optimal medical therapy [46].

In contrast, the issue of whether patients with PPCM and recovered LV function can safely undergo a subsequent pregnancy remains controversial. Elkayam and colleagues conducted a record review among members of the American College of Cardiology (MD, USA) 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 LV function had returned to normal (group 1) and 16 occurred in women with persistent LV dysfunction (group 2). The pregnancies were associated with a reduction in mean LVEF in each group (from  $56 \pm 7\%$  to  $49 \pm 10\%$  in group 1;  $p = 0.002$ , and from  $36 \pm 9\%$  to  $32 \pm 11\%$  in group 2;  $p = 0.08$ ). During these pregnancies, a decrease of more than 20% in LVEF occurred in 21% of women in group 1 and 25% of those in group 2, and symptoms of heart failure occurred in 21% of women in group 1 and 44% of those in group 2. The mortality rate was 0% in group 1 and 19% in group 2 ( $p = 0.06$ ) [47]. Although the likelihood of maternal death seems to be very low in women who recover their LV function

before a subsequent pregnancy, the fact that a reduction in LVEF and symptomatic heart failure may occur during subsequent pregnancy needs to be considered [5].

Future perspective

Multiple factors appear to be involved in the pathogenesis of PPCM and future research would need to identify their common pathways.

Advances in the field of proteomics and genomics may help identify genes and their products that are involved in the pathogenesis of PPCM, which may lead to more specific treatment for this form of heart failure, resulting in improved survival rates. The identification of risk factors or gene defects may create the option of screening tests before or during pregnancy and facilitate disease prevention.

Executive summary
<p><b>Introduction</b></p> <ul style="list-style-type: none"> <li>• Peripartum cardiomyopathy (PPCM) is defined as a disorder of unknown pathogenesis in which left ventricular dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first 5 months postpartum 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.</li> <li>• The diagnosis of PPCM is often delayed and it is important for the clinician to consider this diagnosis in respective patients before preventable major complications develop.</li> <li>• It is important to note that pregnancy-related cardiomyopathy may present during the second or third trimester.</li> </ul>
<p><b>Diagnosis</b></p> <ul style="list-style-type: none"> <li>• Echocardiography demonstrates features of dilated cardiomyopathy with impaired ejection fraction and global dilatation. The symptoms and signs are similar to those in patients with idiopathic dilated cardiomyopathy</li> <li>• The acute form of PPCM is a clinical syndrome with reduced cardiac output, tissue hypoperfusion, increase in the pulmonary capillary wedge pressure and tissue congestion.</li> </ul>
<p><b>Monitoring of PPCM patients</b></p> <ul style="list-style-type: none"> <li>• Monitoring of the patient with the acute form of PPCM should be initiated as soon as possible. The types and level of monitoring required for any individual patient vary widely depending on the severity of the cardiac decompensation and the response to initial therapy.</li> </ul>
<p><b>Treatment</b></p> <ul style="list-style-type: none"> <li>• Treatment is directed toward symptomatic relief and improvement of cardiac function and is similar to the treatment of other forms of congestive heart failure. Current recommendations for treatment of the acute and the chronic form of PPCM are outlined.</li> </ul>
<p><b>Prognosis</b></p> <ul style="list-style-type: none"> <li>• Maternal mortality differs between geographical regions and ranges between 9 and 15%.</li> <li>• Prognosis of a subsequent pregnancy in known PPCM appears to be related to left ventricular dimensions at conception.</li> </ul>

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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