



An Update on Peripartum Cardiomyopathy in the 21st Century

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Abstract

Peripartum cardiomyopathy (PPCM) is a pregnancy-associated idiopathic cardiomyopathy secondary to marked left ventricular systolic dysfunction. The disease presents towards the end of pregnancy through the first 5 months post-delivery, with ethnic and geographic variation in incidence and outcomes. While it is relatively rare, PPCM is associated with significant morbidity and can be fatal. The purposes of this review are to summarize the diagnostic criteria, epidemiology, and proposed etiologies of PPCM; present the complications and treatments; and provide a systematic approach to assess risk of PPCM in subsequent pregnancy.

Keywords

Peripartum cardiomyopathy, Pregnancy, Congestive heart failure

Introduction

Heart failure (HF) in the setting of pregnancy has been recognized as far back as the 18th century. It was not until 1937, however, that a definitive form of postpartum cardiomyopathy was first described in a case series report by Gouley et al. [1]. The report described 7 women who developed severe, clinical HF in the late months of pregnancy with histologic examination showing widespread and severe focal inflammatory reaction, often with necrosis and followed by fibrosis. In 1971, Demakis et al. described a case series of 27 women with pregnancy-associated cardiomyopathy (PACM) including those who presented with HF in the peripartum period, following which the term “peripartum cardiomyopathy” (PPCM) was first used [2]. The disease remains relatively rare, of unclear etiology, and challenging to recognize and diagnose early. The purpose of this review is to provide an update on the definition and epidemiology of PPCM, proposed mechanisms of disease, clinical manifestations and diagnosis, treatment strategies, and prognosis – particularly with regards to subsequent pregnancies.

Definition

The classic diagnostic criteria for PPCM, defined by Demakis et al., included the following: (1) development of HF in the last month of pregnancy or within 5 months of delivery; (2) absence of an identifiable cause for HF; and (3) absence of recognizable heart disease prior to the last month of pregnancy [3]. In 1997, following a workshop of the National Heart, Lung, and Blood Institute (NHLBI) and Office of Rare Diseases of the National Institutes of Health (NIH), these criteria were expanded to include echocardiography (TTE) criteria of left ventricular systolic dysfunction (left ventricular ejection fraction, LVEF <45%), fractional shortening of <30%, or both [4,5]. The diagnostic criteria for PPCM are summarized in Table 1.

Although the majority of women with PPCM are diagnosed between the last month of pregnancy and the fifth postpartum month, it is not uncommon for women to present earlier. Elkayam et al. [6] reported that in a series of 123 women with a history of cardiomyopathy diagnosed during pregnancy or in the postpartum period, 100 met criteria for traditional PPCM, while 23 were diagnosed with PACM earlier than the last gestational month, with the earliest diagnosis at 17 weeks. Comparison between the two groups revealed no significant difference in age, ethnic background, obstetric history, or gestational hypertension history. Both groups had similar LVEF at the time of diagnosis, maternal outcome, and recovery rates over time. The early PACM patients did, however, have an increased rate of premature deliveries. This was felt to be related to the earlier development of HF, higher incidence of twin pregnancy, and physician reluctance to continue the pregnancy once the diagnosis was made. Given the otherwise lack of any distinguishing features between the two groups, the authors proposed that perhaps PACM and PPCM in fact represent a spectrum of the same disease [6]. Early presentation of disease has been confirmed in a number of studies and the European Society of Cardiology has expanded their definition of PPCM to include idiopathic cardiomyopathy presenting towards the end of pregnancy and in the months following delivery [7-10].

Table 1: Definition of peripartum cardiomyopathy [3-5]

Development of heart failure in the last month of pregnancy or within the 5 months following delivery
Absence of determinable etiology of heart failure
Absence of demonstrable heart disease prior to the diagnosis of heart failure
Left ventricular ejection fraction < 45%, or fractional shortening <30%, or both

Epidemiology

The incidence of PPCM in the U.S. is estimated at 1 in 3200 deliveries, with a range from 1 in 1149 to 1 in 4350 live births [11-15]. A study in 2006 reported an increasing incidence in PPCM from 1990 to 2002, likely a reflection of multiple factors including rise in maternal age, rise in multi-gestational pregnancies secondary to infertility treatments, and increased awareness and recognition of the disease itself [13]. In the U.S., the incidence of PPCM has been reported to be up to 16-fold higher in African American women than in non-African American women [14,16]. Higher incidences of PPCM have also been reported in South Africa (up to 1 in 1000) and in Haiti (1 in 3000) [17,18].

Risk factors that are associated with PPCM include advanced maternal age, multiparity, multi-fetal pregnancy, hypertension (chronic, pregnancy induced, or preeclampsia), and African American race [2,6,13,15,19,20]. A recent study of 535 patients with PPCM found that in addition to these established risk factors, substance abuse, asthma, anemia, and auto-immune disease were also associated with PPCM [21].

Etiology

The underlying cause of PPCM remains unknown. A number of proposed mechanisms include: viral myocarditis, abnormal immune response, hemodynamic response to pregnancy, hormonal abnormalities, and malnutrition [4,22-26]. In addition, a large cohort study of PPCM patients has demonstrated elevated plasma levels of tumor necrosis factor- α , Fas-Apo-1, interleukin-6, and C-reactive protein, suggesting an inflammatory component to development of the disease [27].

In 2007 Hilfiker-Kleiner et al. published findings of a novel mechanism for PPCM with a proposal for targeted drug therapy [28]. The investigators demonstrated that female mice with a cardiomyocyte-specific depletion of STAT3 protein developed attenuated expression of manganese sodium dismutase (MnSOD), a known reactive oxygen species (ROS) scavenging enzyme. This resulted in release of cathepsin D (CD), a ubiquitous lysosomal enzyme, which cleaves the hormone prolactin from its 23kDa form to a 16kDa form. This latter form of prolactin induces endothelial cell apoptosis, capillary dissociation, vasoconstriction, and eventually impairs cardiomyocyte metabolism and function, leading to PPCM [28,29]. The group then demonstrated that blockade of prolactin with the dopamine-2D receptor agonist bromocriptine prevented the development of PPCM in mice and subsequently in 6 women at high risk for PPCM due to prior history of PPCM [28]. In 2010 Sliwa et al. published results from a proof-of-concept pilot study in which women diagnosed with PPCM were treated with standard care versus standard care plus bromocriptine [30]. The women who received bromocriptine demonstrated greater recovery of left ventricular ejection fraction (LVEF) compared to the standard therapy group at 6 months. Women in the bromocriptine group experienced far less composite endpoint of poor outcome (death, NYHA function class III/IV, or LVEF <35%) at 6 months compared to the standard therapy group. The findings warrant further study in a large, randomized control trial.

Genetics

PPCM was previously classified as a non-genetic form of dilated cardiomyopathy (DCM). Recent studies, however, have shown familial clustering of PPCM [9,31]. In a study of 4110 women from 520 families of patients with DCM, 45 were identified as having either PACM or PPCM, and familial clustering was found in 23 (55%) of the 42 unrelated cases [32]. Resequencing data was available for 19 women from this group, of which 6 had mutations identified in genes that have been shown to be associated with DCM. Subsequent studies have further supported these findings and additionally shown that screening of first degree relatives of patients with PPCM has resulted in unmasking familial DCM [9,33]. These studies would suggest that there are likely genetic factors implicit in the development of PPCM in a proportion of these patients.

Clinical Presentation and Diagnosis

Most patients diagnosed with PPCM present with typical signs and symptoms of HF. These symptoms often overlap with those of pregnancy itself, which can result in a delay or missed diagnosis and ultimately the development of PPCM-associated complications [15]. Early presentation of PPCM during pregnancy is being increasingly recognized as demonstrated by Elkayam et al., with no significant differences in the clinical characteristics or outcomes between those who present within the traditional PPCM timeframe and those who present earlier [6].

As with any new presentation of HF, the standard evaluation for any woman suspected of PPCM includes a detailed history and physical examination, 12-lead electrocardiogram, 2-dimensional TTE with Doppler, chest radiograph, and the following laboratory tests at baseline: complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, blood glucose, liver function tests, lipid profile, and thyroid-stimulating hormone [34].

From a diagnostic testing standpoint, the electrocardiogram in PPCM patients typically shows sinus tachycardia with non-specific ST-segment and T-wave changes [11]. A TTE study must show depressed LVEF for diagnosis. Other TTE findings may include dilation of the LV and/or other chambers, valvular compromise including moderate to severe mitral and tricuspid valve regurgitation, mild to moderate pulmonic valve regurgitation, and pulmonary hypertension [5,10]. Chest radiograph will often show cardiomegaly, pulmonary venous congestion, and occasionally pulmonary edema or pleural effusion [11].

Further testing should be obtained based on the clinical presentation and risks of the individual patient. Both endomyocardial biopsy and coronary angiography should not be considered parts of the routine evaluation of patients with suspected PPCM [34]. The ACC/AHA guidelines currently recommend endomyocardial biopsy only in clinical scenarios where determining a specific etiology for HF may have treatment implications. This includes the setting of unexplained, new-onset heart failure of less than 2 weeks duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise, and new-onset heart failure of 2 weeks to 3 months duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks [35]. Reports of endomyocardial biopsy findings in women with PPCM have demonstrated variable rates of myocarditis. In a series of 57 endomyocardial biopsy samples evaluated for suspected PPCM, Rizeq et al. report 34 patients were confirmed to have PPCM with 3 (8.8%) biopsy samples demonstrating focal myocarditis [8]. There were no significant morphological differences in degrees of myocyte hypertrophy, fibrosis, coronary artery pathology, or small intramyocardial vessels between samples from women with PPCM and those with idiopathic dilated cardiomyopathy. Coronary angiography is only recommended as part of the evaluation for new onset HF if there is a strong clinical suspicion of coronary artery disease and therefore should not be considered part of the routine evaluation of patients with suspected PPCM [34]. There is limited data on the use of cardiac magnetic resonance imaging (cMRI) in the diagnosis of PPCM, although findings of myocardial delayed enhancement on cMRI have been reported and cMRI may be used to identify thrombus in the setting of left ventricular dysfunction in PPCM [36]. The use of gadolinium is not recommended as it can cross the placenta [37].

From the standpoint of serum biomarkers, B-type natriuretic peptide (BNP) levels remain unchanged for the most part during normal pregnancy, can be slightly elevated in the setting of preeclampsia, and become markedly elevated in PPCM, as is the case in other forms of HF [38]. Troponin levels may be elevated in PPCM, depending on the degree of myocardial injury incurred at the time of diagnosis [39]. Of most importance from a diagnostic standpoint

is that a high index of suspicion for heart failure be maintained at the first signs and symptoms of HF. Common symptoms such as dyspnea, fatigue, and mild edema should not be assumed to be related to pregnancy itself, lack of sleep, or other conditions such as bronchitis; PPCM must also be considered in this patient population.

Complications and Prognosis

PPCM is a significant cause of morbidity and mortality in pregnant patients. Complications associated with the disease include severe HF, cardiogenic shock, arrhythmias, thromboembolic complications, cardiopulmonary arrest, and death [20,40]. Kao et al. recently reported that compared to non-PPCM patients, those with PPCM have higher rates of stillbirth, Cesarean section, major adverse events, and longer length of hospital stay [21]. In a series of 182 patients with PPCM, the rate of major adverse events was reported to be 25%, with 80% of these events occurring in the first six months after the diagnosis [40]. Mortality rates reported to date are around 15%, which is less than that associated with other forms of cardiomyopathy [14,41]. In a series of 17 cases of death in PPCM patients, 18% of deaths occurred within one week of delivery and 87% within 6 months [42]. The cause of death in these cases was either sudden cardiac death or progressive HF. Geographical differences exist with higher mortality rates reported in Haiti, South Africa, and Turkey compared with the U.S. [21]. Mortality risk is increased with older age, multiparity, African American race, severe LV dysfunction (LVEF <25%), and delay in diagnosis [42].

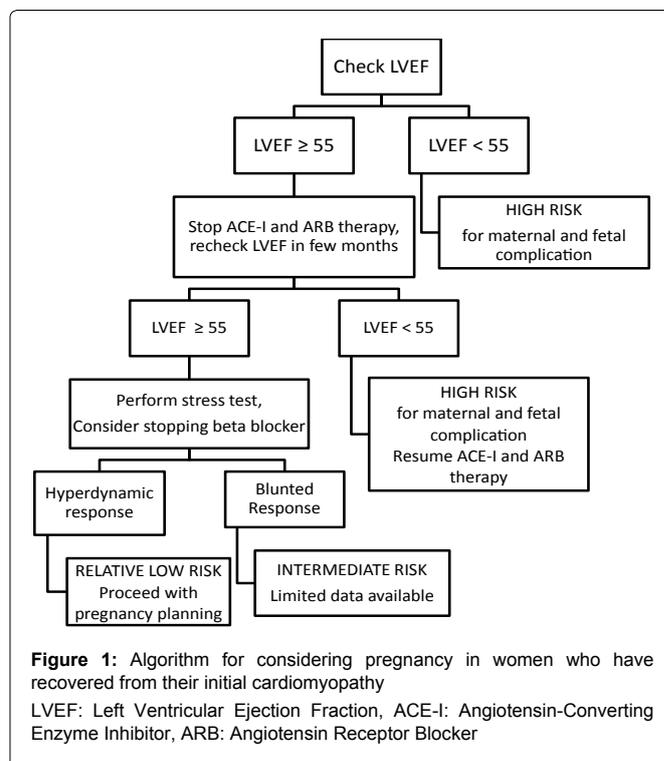
The rate of cardiac transplantation in PPCM patients is anywhere from 6-23% [20,43]. In a recent report from the United Network for Organ Sharing (UNOS) database, Rasmussen et al. report that patients with PPCM who underwent cardiac transplant were younger, had higher sensitization, required more intense cardiovascular support pre-transplant, and had higher listing status [44]. PPCM patients had more post-transplant rejection (during index hospitalization and in the year to follow), inferior graft survival, and worse age-adjusted overall survival.

With regards to recovery of LV function, recent publications indicate that at least 50% of PPCM patients have improvement in cardiac function within 2 to 6 months following the diagnosis [6,20]. Amos et al. reported outcomes a single-center experience on 55 PPCM patients and found that factors associated with lack of LV function recovery were LVEF at 2 months, LV end-diastolic dimension >5.6cm, the presence of LV thrombus, and African-American race. LVEF at the time of diagnosis was not predictive of recovery [20].

Subsequent Pregnancies

Given that PPCM is a relatively rare form of HF, information on the outcome of subsequent pregnancies is limited. In 2001, Elkayam et al. reported the outcomes of 44 women who had PPCM with a total of 60 subsequent pregnancies [45]. The women were divided into two groups: group 1 consisted of those in whom LV function had returned to normal; group 2 consisted of those with persistent LV dysfunction. Both groups were noted to have a reduction in mean LVEF measurement with the subsequent pregnancy, however, a substantial reduction in LVEF (>20%) was seen in 21% of group 1 and 44% of group 2. A higher proportion of patients in group 2 experienced symptoms of HF. Mortality rate for group 1 was 0%, while for group 2 was 19%. Subsequent studies have shown worsening of HF symptoms in nearly 30% of women with history of PPCM during subsequent pregnancies [43,46]. A recent study by Fett et al. of 61 subsequent pregnancies in women with prior PPCM reported a relapse rate of 29% with a significantly higher rate in women with LVEF <55% [47]. It has been suggested that demonstration of normal contractile reserve in those patients with recovered LV function may portend a better outcome; however this has not been validated in a study to date. The findings of the aforementioned studies suggest that subsequent pregnancies are associated with a risk for recurrent and/or persistent HF symptoms and LV dysfunction, and even death.

A systematic approach to patients who wish to become pregnant



again is depicted in Figure 1. In summary, a baseline echocardiogram should be obtained, along with a serum BNP level. Women with preserved LV function (>55%) should have a repeat echocardiogram a few months after discontinuing angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), as these medications are contraindicated in pregnancy. If at that time LVEF is still preserved, consideration should be given to stopping beta blocker therapy and performing a stress echocardiogram to assess contractile reserve. Should the findings of a stress test demonstrate hyperdynamic response, the patient would be considered relatively low risk for maternal and fetal adverse outcomes and may be counseled to proceed with pregnancy planning with close monitoring and follow up. They should be counseled that they still have a risk of recurrence but that they are relatively lower risk. Should the response to stress test be no augmentation of LVEF, or a blunted response, then the patient would be considered moderate risk, a group for which we have limited to no data to guide recommendations. If the baseline LVEF is <55% at the start of subsequent pregnancy planning, the patient would be considered high risk and should be strongly advised against second pregnancy, or should be counseled accordingly regarding options including termination of pregnancy. In all risk groups, any subsequent pregnancy warrants follow up echocardiography at a minimum during the early second and third trimesters, the last gestational month, and for any development or progression in HF symptoms [15]. Repeat BNP may be helpful in distinguishing HF symptoms from pregnancy symptoms.

Treatment

Treatment for PPCM is based on guidelines for standard HF treatment, including ACE-inhibitors, ARBs, beta-blockers, spironolactone, digoxin, diuretics, vasodilators and inotropes if needed [48]. Initiation and treatment with any HF therapies should be done under the supervision of a multi-disciplinary team including the patient's cardiologist and obstetrician. The mainstays of treatment for acute decompensated PPCM include diuretics and renin-angiotensin inhibiting agents for patients that are hemodynamically stable. For patients in cardiogenic shock inotropes with or without mechanical support may be required. Once stabilized, beta-blockers, aldosterone-antagonists and additional therapies should be initiated and up-titrated as tolerated in the outpatient setting, particularly in the setting of persistent LV dysfunction. HF drug therapies and their pregnancy and lactation safety profiles are summarized in Table 2.

Table 2: Heart failure drug safety profile in pregnancy and lactation

Medication	FDA Pregnancy category	Lactation Safety
Diuretics		
Bumetanide	C	Unknown
Furosemide	C	Enters breast milk; may suppress lactation
Torsemide	B	Unknown
Hydrochlorothiazide	B	Enters breast milk; not recommended
Metolazone	B	Enters breast milk; not recommended
ACE Inhibitors		
Captopril	D	Enters breast milk; not recommended
Enalapril	D	Enters breast milk; not recommended
Lisinopril	D	Unknown
Ramipril	D	Unknown
Angiotensin receptor blockers		
Candesartan	D	Unknown
Losartan	C (1 st trimester) D (2 nd /3 rd trimester)	Unknown
Valsartan	D	Unknown
Beta Blockers		
Bisoprolol	C	Unknown
Carvedilol	C	Unknown
Metoprolol succinate	C	Enters breast milk; use with caution
Metoprolol tartrate	C	Enters breast milk; use with caution
Aldosterone antagonists		
Eplerenone	B	Unknown
Spironolactone	C	Enters breast milk; not recommended
Vasodilators		
Hydralazine	C	Enters breast milk; use with caution
Isosorbidedinitrate	C	Unknown
Isosorbidemononitrate	B/C	Enters breast milk; use with caution
Digoxin	C	Enters breast milk; use with caution
Anticoagulants		
Enoxaparin	B	Unknown
Unfractionated heparin	C	Does not enter breast milk
Warfarin	D (women with mechanical heart valves); X (other indications)	Does not enter breast milk

Food and Drug Administration (FDA) Pregnancy categories: A: controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote. B: No evidence of risk in studies. Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters; C: Risk cannot be ruled out. Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus; D: Positive evidence of risk. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective); X: Contraindicated in pregnancy. Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant. ACE: Angiotensin-Converting Enzyme

A small study of 11 PPCM patients demonstrated that IV immune globulin resulted in improvement in LVEF in the treatment group compared to standard therapy [49]. Another small study has reported improved outcomes in the combined endpoint of persistent LV dysfunction, NYHA functional class, and death with pentoxifylline therapy for PPCM [50]. Sliwa et al. reported the findings of treatment with bromocriptine in a proof-of-concept study, discussed earlier in this review [30]. Larger clinical studies are warranted to clearly establish the role of these newer therapies for PPCM.

As PPCM is associated with a risk of arrhythmias and sudden cardiac death, current recommendations are to consider implantation of an implantable cardioverter-defibrillator (ICD) in patients with persistent LV dysfunction despite optimal HF therapy [40,42,51]. While LV recovery occurs in most patients between 2 to 6 months postpartum, an individual's likelihood of recovery is still relatively unpredictable [20]. Therefore, it is reasonable to consider a wearable external defibrillator or a subcutaneous ICD as a bridge to recovery or ICD implantation, should LV dysfunction persist.

There are reports of an increased incidence of thrombus formation in patients who develop PPCM and thus consideration of anticoagulation is warranted [1,2,48,49]. For patients who develop fulminant HF symptoms and hemodynamic instability during or after pregnancy, therapies such as intra-aortic balloon pump, LV assist devices, and extracorporeal membrane oxygenation may be considered for use as a bridge to recovery or heart transplant. Outcomes post heart transplant have been discussed earlier in this review.

Conclusions

PPCM is a rare but potentially lethal disease that remains a challenge to diagnose, prognosticate, and treat. The latest updates to the definition of the disease itself now broaden the timeframe of diagnosis to include earlier stages of pregnancy. It is increasingly recognized that the condition is often diagnosed late which may portend a poor prognosis. While the etiology of the disease remains unclear, a novel mechanism involving a mutation in a protein implicated in cleaving

prolactin resulting in myocardial damage warrants further study. In addition, a genetic component is likely present, with familial clustering of PPCM reported in families with DCM. Predictors of recovery of LV function include race, LV function, and LV dimensions at follow up. The mainstay of treatment today include standard HF therapies, however, newer therapies such as bromocriptine, IV immunoglobulin, and pentoxifylline are on the horizon and warrant further study. We suggest a large, international registry be created to follow PPCM patients longitudinally. At present, the NHLBI sponsors the Peripartum Cardiomyopathy Network (PCN), a network of physicians and nurses at clinical sites across the United States and Canada dedicated to both clinical care and investigation of PPCM. Such a database will be beneficial in providing baseline characteristics of these patients, family history that would allow for genetic testing in the future and postpartum assessments including echocardiography and/or stress test data to help better predict morbidity and mortality in this population. Lastly, a registry would eventually serve as a resource for the conduction of clinical treatment trials, an area where there is much need in this high risk population.

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