

Peripartum cardiomyopathy: a review

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Abstract: Peripartum cardiomyopathy (PPCM) is a form of dilated cardiomyopathy of unclear etiology affecting women without preexisting heart disease during the last month of pregnancy or during the first 5 months postpartum. Its incidence shows marked geographic and ethnic variation, being most common in Africa and among women of African descent. Most women present in the first month postpartum with typical heart failure symptoms such as dyspnea, lower extremity edema, and fatigue. These symptoms are often initially erroneously diagnosed as part of the normal puerperal process. Diagnosis can be aided by the finding of a significantly elevated serum brain natriuretic peptide. The etiology of PPCM is unclear; however, recent research suggests abnormal prolactin metabolism is seminal in its development, and prolactin antagonism with bromocriptine shows promise as a novel treatment for PPCM.

Keywords: pregnancy, pregnancy complications, cardiovascular, cardiomyopathy, dilated

Introduction

Peripartum cardiomyopathy (PPCM) is a form of dilated cardiomyopathy of unclear etiology affecting women without preexisting heart disease during the last month of pregnancy or during the first 5 months postpartum.¹ Historically, the association between heart failure and pregnancy has been recognized since at least the nineteenth century;² however, it was not until 1971 that Demakis labeled the disease PPCM, and set forth three criteria for its diagnosis.¹ A fourth criteria incorporating modern echocardiographic findings was added in 2000 (Table 1).²

In 2005, Elkayam et al³ reviewed 123 women with cardiomyopathy associated with pregnancy and found that 23 of these patients presented with symptoms before the last month of pregnancy; in all other respects, these patients were similar to patients who met all diagnostic criteria for PPCM. The investigators concluded that some women with PPCM may present earlier than the last month of pregnancy.³ Recognizing that strict diagnostic criteria for PPCM may lead to under-diagnosis, the following definition has been proposed by the European Society of Cardiology Working Group on Peripartum Cardiomyopathy:

Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with HF [heart failure] secondary to LV [left ventricular] dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found.⁴

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Table 1 PPCM diagnostic criteria

- Development of heart failure in the last month of pregnancy or the first 5 months postpartum.¹
- Absence of a determinable etiology for cardiac failure.¹
- Absence of known heart disease prior to the last month of pregnancy.¹
- Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria such as depressed shortening fraction or ejection fraction.²

Abbreviation: PPCM, peripartum cardiomyopathy.

Incidence

The true incidence of PPCM is unknown, with current estimates based primarily on case series from single institutions, and a limited number of recent population-based studies. The reported incidence varies widely and appears to fluctuate with ethnicity as well as geography. In the United States, the currently accepted incidence of between one in 3000 and one in 4000 live births is supported by several recent studies.² Mielniczuk et al⁵ used National Hospital Discharge Survey data from 1990 to 2002 to review 3.6 million patient discharges and found an incidence of PPCM of one in 3189 live births, while Brar et al⁶ found an incidence of one in 4025 live births in a population of women in Southern California studied between 1996 and 2005.

The incidence of PPCM may be increasing. Mielniczuk et al⁵ noted an insignificant increase in PPCM incidence from one in 4350 during 1990–1993 to one in 2229 during 2000–2002. This is consistent with recently published data by Gunderson et al⁷ showing an incidence of PPCM of one in 2066 in a Northern California hospital system during the years between 1995 and 2004. Postulated reasons for this observed increase include increasing maternal age, an increasing number of multifetal pregnancies due to assisted reproductive techniques, and increased recognition of PPCM.⁸

The incidence of PPCM shows striking geographic variability (see Table 2), being rare in Japan, more common in the United States, and quite common in Haiti and parts of Africa.^{5,7,9–11} In addition, there is a disproportionately high incidence in certain ethnic groups such as those of African descent, and a much lower incidence in Hispanics.⁷ The highest reported incidence, of one in 100 live births, is among the Hausa and Fulani ethnic groups of northern Nigeria. This may be related to the traditional practice of eating rock salt and heating the body on a hot clay bed for 40 days postpartum in an effort to enhance breast milk production. It is postulated that these women have a tendency towards hypertension, as they develop intravascular volume overload due to excess sodium intake.¹²

Presentation and diagnosis

Most patients will present postpartum, with the vast majority of these individuals presenting in the first postpartum month and the remainder presenting in the first 4 months postpartum. Elkayam et al³ reported that of 100 patients with PPCM, 75 were diagnosed during the first postpartum month, and only seven presented antepartum. Other authors have reported a roughly 25% to 75% split between ante- and postpartum presentation.^{9,13}

Classic heart failure symptoms include dyspnea, dyspnea on exertion, lower extremity edema, and fatigue, and these are often the presenting symptoms. Unfortunately, these symptoms can be indistinguishable from symptoms common in normal late pregnancy and the postpartum period, making the diagnosis challenging.^{4,14} Diagnosis is delayed by more than 1 week in 48% of cases,¹³ and by several weeks to months in 30% of cases,¹⁵ with symptoms frequently attributed to normal pregnancy or lack of sleep, or erroneously diagnosed as pneumonia.¹⁶ Indeed, most patients have advanced symptoms (New York Heart Association [NYHA] stage 3 or 4) by the time the diagnosis of PPCM is made.^{11,17} Further complicating the diagnosis are mild cases of PPCM, which may evade clinical attention,⁷ and atypical presentations including thromboembolic events (cerebral, peripheral, mesenteric emboli) can present as stroke, transient ischemic attack, limb ischemia, or abdominal pain.^{4,14}

Physical exam findings in PPCM may reveal signs of volume overload such as pulmonary rales, increased respiratory rate, tachycardia, pathologic S3 or S4 heart sounds, distended neck veins, and lower extremity edema.^{1,2} While there are no specific electrocardiography (ECG) findings that are particularly helpful in diagnosing PPCM, a recent study of 78 South African women who had ECGs performed at the time of diagnosis revealed only 4% had a completely normal ECG, with sinus tachycardia and T-wave abnormalities commonly present.¹⁸ This is supported by a different study of 97 women with PPCM which found ST-T wave changes in 96%, and left ventricular (LV) hypertrophy in 66%.¹¹ Chest radiograph findings of cardiomegaly, pulmonary venous congestion, and pleural effusion may be seen.^{1,14} Cardiac imaging, usually echocardiography, is essential in diagnosing PPCM and may provide useful information regarding prognosis and presence of LV thrombus.⁴ While the finding of LV dilation is inconsistent, LV ejection fraction (EF) is always reduced, sometimes severely.^{2,9} Golland et al¹³ found a mean baseline LVEF of 31% in 136 patients, and an LVEF of 24% in 46 patients who went on to have significant complications or who died of their disease.

Table 2 Geographic incidence of PPCM

Country/area	Years studied	Incidence	Ethnicity of study cohort	Incidence by ethnicity	Author
Japan	2007–2008	1:20,000	Japanese 100% ^a	Japanese (1:20,000)	Kamiya et al ⁹
United States	1995–2004	1:2066	White 41%, Hispanic 27%	AA ^b (1:664) Filipino (1:978) White (1:2450) Hispanic (1:6729)	Gunderson et al ⁷
United States	1990–2002	1:3189	White 79%, AA ^b 16%, Other 5%	Not stated	Mielniczuk et al ⁵
United States	1996–2005	1:4025	AA ^b 28%, White 27%, Hispanic 20%, Asian 17%, Other 8%	AA ^b (1:1421) Asians (1:2675) Whites (1:4075) Hispanic (1:9861)	Brar et al ⁶
United States Augusta, GA	2003–2008	1:540	AA ^b 93%, Other 7%	AA ^b (1:294) Other (1:4167)	Gentry et al ²²
South Africa	1986–1989	1:1000	“Black African” 99%, Asian 1%	Not stated	Desai et al ¹¹
Sudan	1975–1979	1:662	Not stated	Not stated	Suliman ⁴⁸
Haiti	2000–2005	1:300	^c	Not stated	Fett et al ¹⁰
Nigeria	2003–2005	1:100	Hausa and Fulani ethnic groups 85%	Not stated	Isezuo and Abubakar ⁴⁹

Notes: ^aKamiya CA, personal communication, April 22, 2012; ^bnon-Hispanic AA; ^cauthors report study population consisted of “an ethnic population overwhelmingly descended from West African slaves.”¹⁰

Abbreviations: PPCM, peripartum cardiomyopathy; AA, African American.

Elkayam et al³ reported a mean LVEF at baseline of 29% in 93 women presenting with PPCM. Cardiac magnetic resonance imaging can provide information regarding LV function and dilation. Gadolinium crosses the placenta and thus should not be given antepartum. Breast feeding after gadolinium administration is considered safe.¹⁹

Brain natriuretic peptide (BNP) levels have been studied in normal pregnancy and postpartum. BNP levels are approximately twice as high in pregnant versus nonpregnant women, but do not vary significantly during a given normal pregnancy or postpartum.²⁰ A study of 38 patients with PPCM were compared to healthy peripartum controls, and it was found that NT-proBNP levels were approximately five times higher in patients with PPCM.²¹ Another study of 102 patients with PPCM found only four patients had a BNP under 100 pg/mL, and a mean serum BNP of 1258 pg/mL.⁹ Thus although a mild elevation of BNP can be expected with normal pregnancy, higher elevations of BNP have been reported with PPCM.

Risk factors

Multiple risk factors for the development of PPCM have been evaluated and include increased maternal age, multiparity, hypertensive disorders (HD) complicating pregnancy, multiple gestation pregnancy, African descent, use of tocolytics, poverty, tobacco use, malnutrition, and anemia

during index pregnancy.^{5,7,8,10,14,22} The strongest associated factors seem to be being of African descent, advanced maternal age, HD, and multiple gestation pregnancy.⁸

African descent

Geographically, PPCM occurs with the greatest frequency in areas where a large portion of the population is African or of African descent, and African descent has been identified as a risk factor for PPCM in multiple studies. In a population-based study utilizing United States National Hospital Discharge Survey data, Mielniczuk et al⁵ found that 32.2% of PPCM cases occurred in women identified as African American, while the percentage of African American mothers in the population during the same time period was 15.7%. Gunderson et al⁷ reviewed 110 PPCM cases in California and found non-Hispanic African American race to be an independent predictor for the development of PPCM. Most recently, Gentry et al²² published data on PPCM in Augusta, Georgia concluding that African American race increased the univariate odds of PPCM 15.7-fold.

Multiparity

Although PPCM has been reported more frequently in multiparous women, cases in primigravidas are by no means rare. Studies have reported that 18%–37% of cases occurred in primigravid women with mean parity ranging

from 2.1 to 4.3.^{3,10,11} In addition, a study of 102 women with PPCM in Japan was the first large study to report a majority of cases (54%) occurring in primigravid women with a mean parity of 1.65.⁹

Age

Although advanced maternal age has been reported as a risk factor for PPCM, the relationship between PPCM and age is not clear. While United States-based studies by Demakis et al²³ and Elkayam et al³ have reported an increased incidence of PPCM in women ≥ 30 years old, a recent case control study by Gentry et al²² did not identify maternal age as a risk factor for PPCM. A prospective study from Haiti did not identify maternal age as a risk factor,¹⁰ while a retrospective case control study in South Africa found that the mean age of the controls (25) was lower than that of the patients with PPCM (29), and concluded that PPCM is more likely to occur in older mothers.¹¹ A large population-based study of California mothers also identified advanced maternal age as an independent predictor for the development of PPCM. In this study, the incidence of PPCM per 10,000 live births was increased in mothers 35–39 years old, and markedly increased in mothers ≥ 40 years old.⁷

Multiple gestations

Studies in the United States have consistently shown an increased incidence of multifetal pregnancies in women with PPCM when compared to the general population.^{3,7,13,24}

Hypertensive disorders complicating pregnancy

Included in this group are women with chronic hypertension, gestational hypertension, preeclampsia, and eclampsia. While the prevalence of HD in all pregnant women in the United States has been estimated as 6%–8%,²⁵ several recent studies of women with PPCM in the United States have reported HD in 29%–46% of patients.^{3,7,22,26} In Japan, HD in women with PPCM has been reported in 41% of patients.⁹

Etiology

Proposed etiologies for PPCM include inflammation, apoptosis, abnormal response to the physiologic stress of pregnancy, autoimmune factors, viral myocarditis, nutritional deficiencies, and prolonged tocolysis;^{4,7,9,21,25} however, none has emerged as a convincing single etiology. This may be because PPCM represents a heterogeneous group of disease process with a multifactorial etiology.^{21,25} Recently a growing body of evidence has pointed to abnormal

prolactin metabolism as crucial in the etiology of PPCM, and prolactin inhibition is being explored as a novel treatment for PPCM.^{15,27}

Prolactin and PPCM

Prolactin is produced by the anterior pituitary in response to physiologic stress, sleep, nipple stimulation, nursing, and pregnancy. Levels are increased in normal pregnancy and peak at the time of delivery.²⁸ Experimental evidence has implicated abnormal prolactin metabolism as fundamental in the pathogenesis of PPCM. The proposed mechanism is unbalanced oxidative stress leading to activation of the protease cathepsin D, which acts to cleave full length 23 kDa prolactin to an angiostatic and proapoptotic 16 kDa form.²⁹ It is this 16 kDa prolactin fragment which exerts negative systemic effects on the endothelium of systemic and cardiac vasculature and causes myocardial dysfunction leading to the clinical findings of PPCM.²⁹ Blockade of prolactin with bromocriptine has been shown to prevent PPCM in experimental models.¹⁵ Additionally, a recent prospective study randomized 20 patients into groups receiving standard heart failure treatment and standard heart failure treatment plus bromocriptine. Patients in the bromocriptine group showed greater recovery of LVEF at 6 months, fewer deaths, and better NYHA functional outcomes.²⁷

Management

Treatment of PPCM generally follows the management of heart failure due to other etiologies, except for when medications are contraindicated due to deleterious effects on the fetus or nursing infant. Beta blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and diuretics are the cornerstones of therapy;³⁰ however, it should be kept in mind that ACE inhibitors and ARBs are contraindicated in pregnancy.³¹ In these patients, the combination of hydralazine and nitrates may be used.⁴ Patients with persistent LV dysfunction, despite optimal medical treatment, are at risk of sudden death from ventricular arrhythmias.⁸ Recent professional society guidelines recommend implantable cardioverter defibrillators for patients with nonischemic cardiomyopathy and LVEF of $\leq 40\%$ for optimal medical therapy.³² Evidence for these recommendations come from a meta-analysis of large studies involving patients with both ischemic and nonischemic dilated cardiomyopathy, and are not based on any studies specifically involving patients with PPCM.³³

Patients presenting with or progressing to decompensated heart failure may exhibit hypoxemia, fulminant pulmonary

edema, low cardiac output, and evidence of insufficient organ perfusion, and these individuals often require specialized care in an intensive care unit. Inotropic support, mechanical ventilation, as well as circulatory support in the form of intraaortic balloon pump counterpulsation, LV assist device, and cardiac transplantation all have been used in patients with PPCM.^{34,35}

Thromboembolism warrants particular mention, as patients with PPCM have an increased risk of thromboembolic complications due to the hypercoagulable state associated with pregnancy, as well as the prothrombotic effects associated with heart failure.³⁶ In a review of 182 patients with PPCM, Goland et al¹³ reported four thromboembolic complications occurring between 5 days and 3 months postpartum. Demakis et al²³ reported a 33% thromboembolic complication rate in his review of 27 patients followed for up to 21 years, but the specific timing of events was not given. Thus, the risk of thromboembolism is present and may extend beyond the acute phase of the illness.

Complications and prognosis

Reported maternal mortality has varied widely, and in older published case series it has been found to be as high as 28%.³⁷ However, more recent population based studies by Mielniczuk et al⁵ and Brar et al⁶ have found mortality rates of 2.1% and 3.3%, respectively; conversely, a review of 55 patients diagnosed with PPCM at a single institution between 1990 and 2003 reported 0% mortality.²⁴ This decreasing mortality may be due to better heart failure treatment that includes beta blockers, ACE inhibitors, and the use of mechanical circulatory support. Mortality due to PPCM usually occurs in the first 6 months postpartum, and is often due to ventricular arrhythmias, progressive heart failure, or thromboembolic complications.³⁸

Significant nonfatal complications of PPCM include circulatory failure requiring temporary circulatory support, ventricular arrhythmias, thromboembolism including cerebrovascular accidents and peripheral arterial embolism, progressive heart failure, and the need for a heart transplant, implantable cardioverter defibrillator, or pacemaker placement. Goland et al¹³ found major adverse events in 25% of patients in a review of 182 patients with PPCM, with most (80%) of these complications occurring in the first 6 months postpartum. Baseline EF of $\leq 25\%$ and non-Caucasian race were significant predictors of a major adverse event.¹³ The correlation between a depressed EF at the time of diagnosis and worse outcomes has been supported by several other studies.^{3,9,10,14,38} However, other researchers

have found no correlation between initial LVEF and survival, or recovery of LV function.^{17,21,24} A sobering statistic from Goland et al's group of patients is that one-third of patients with a major adverse event who survived without transplant suffered anoxic brain injury from cardiopulmonary arrest or cerebrovascular accidents.¹³

Patients with PPCM may have recovery of normal LVEF, and this recovery may be greater than in other subsets of patients with nonischemic dilated cardiomyopathy. Cooper et al³⁹ prospectively studied a cohort of 373 patients with recent onset nonischemic dilated cardiomyopathy, including 39 patients with PPCM. Recovery of normal LVEF at 6 months was found in 48% of the PPCM group. This was greater than the recovery seen in men and in nonperipartum women.³⁹ Several retrospective studies also suggested that improvement of LVEF occurs, often within 6 months of diagnosis.^{40–42} Delayed recovery of LV function may occur. A prospective study of 42 patients found that of the 20 women with recovery of normal LV function, 70% took longer than 6 months to recover.⁴³

Whether improvement in LV function is related to modern medical treatment with beta blockers and ACE inhibitors is not clear. Amos et al²⁴ described the outcomes of 55 women with PPCM treated between 1990 and 2003. The authors reported improvement of LVEF in 62% and recovery of normal LV function in 45% of patients. These outcomes are improved when compared to several earlier reports.²⁴ Although ACE inhibitors and beta blockers were used in a high percentage of patients, there were similar outcomes in the patients taking and not taking beta blockers.¹³ Demakis and Rahimtoola¹ reported on 27 patients with PPCM in the pre-ACE inhibitor and prebeta blocker era, with 52% exhibiting clinical improvement to NYHA class 1 or 2 symptoms, and resolution of cardiomegaly on chest radiographs. Unfortunately, objective data on LV function are unavailable; however, these findings add to the speculation that recovery of LV function in approximately 50% of patients may represent the natural history of the disease uninfluenced by medical treatment.

Recovery of LV function does appear to vary directly with the initial degree of myocardial dysfunction, as evidenced by LV end diastolic dimension, fractional shortening, and EF.⁴⁴ Other factors associated with a lower likelihood of recovery of LV function include non-Caucasian race,² presence of LV thrombus, and lack of breastfeeding.⁴ Persistently depressed LV function beyond 6 months is associated with a poorer prognosis and increased 5-year mortality.⁸ Even with echocardiographic normalization of LV function, patients

will often demonstrate decreased contractile reserve on stress echocardiography.⁴⁵

Subsequent pregnancy

Women who undergo subsequent pregnancies after an episode of PPCM are at increased risk for recurrent heart failure.⁴⁶ However, this risk does not appear to be equal for all PPCM survivors, and risk stratification is possible based on recovery of normal LV function following the initial episode of PPCM. Fett et al⁴⁷ reviewed 61 PPCM survivors with recurrent pregnancies and found the risk of recurrent heart failure varied inversely with EF at the start of pregnancy. Women with an initial EF of greater than 55% had a 17% incidence of recurrent heart failure, while women with an initial EF of less than 55% had a 46.2% incidence. In addition, this risk seems to be graded with the risk of recurrent heart failure increasing to 66.7% in women with an initial EF of less than 45%.⁴⁷ Elkayam et al⁴² reported on the subsequent pregnancies of 44 women who had previous pregnancies complicated by PPCM, and similarly found the risk of recurrent heart failure varied inversely with initial EF. Twenty-one percent of women with an initial EF of greater than 50% developed recurrent heart failure compared with 44% among women with an initial EF of less than 50%. In this study, no women with an initial EF of greater than 50% died, while the death rate was 19% among the group of women whose initial EF was less than 50%.⁴² Thus it seems that for women with a diagnosis of PPCM, the risk of developing heart failure in a subsequent pregnancy is quite high even with initial normal resting LV function. Dobutamine stress echocardiography may allow for further risk stratification of these women, as some individuals demonstrate impaired LV function on stress testing that is not apparent on resting echocardiography.⁴⁵ This may allow for the identification of women who will go on to develop heart failure with the hemodynamic stress of a subsequent pregnancy.⁴⁵

In the near future, prolactin manipulation may be an effective treatment to decrease the risk of recurrent heart failure for PPCM patients who desire another pregnancy. A small study of 12 PPCM patients with subsequent pregnancies divided patients into groups receiving standard treatment with and without bromocriptine for prolactin inhibition. In the bromocriptine group, all patients had preserved or increased LV function for up to 3 months postpartum, and none died. Of the six patients not treated with bromocriptine, all had deterioration of LV function,

and there were three deaths.¹⁵ Clearly this is a small study and further research is needed; however, the results are promising.

Conclusion

Peripartum cardiomyopathy is a rare disease diagnosed by the onset of heart failure in women near the end of pregnancy or in the first few months postpartum, when no other cause for heart failure can be identified. The true incidence of PPCM is unknown, but it is thought to affect one in 3000 to one in 4000 live births in the United States, and it may affect far more women in other parts of the world such as in parts of Africa and Haiti. Women typically present in the early postpartum period with heart failure symptoms, which are often mistaken for being part of the normal puerperal experience. Risk factors for the development of PPCM include being of African descent and having multiple gestation pregnancies. While the etiology of PPCM remains unknown, recent work has implicated abnormal prolactin metabolism as critical in its development, and prolactin inhibition is being explored as a novel and promising treatment for PPCM. Management of the patient with PPCM generally follows guidelines for the management of patients with heart failure due to other etiologies, with the exception that there is an avoidance of using ACE inhibitors and ARBs in pregnant patients. Maternal mortality has been reported in various studies, and it may be higher in older studies. Serious nonfatal complications including cardiac dysrhythmias, progressive heart failure requiring heart transplantation, and thromboembolic events manifesting as cerebral vascular accidents and peripheral arterial embolism may also occur.

Disclosure

The author reports no conflicts of interest in this work.

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