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PERIPARTUM CARDIOMYOPATHY: A CONTEMPORARY REVIEW

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Abstract

Peripartum cardiomyopathy is a rare and potentially fatal disease. Though approximately half of the patients recover, the clinical course is highly variable and some patients develop refractory heart failure and persistent left ventricular systolic dysfunction. It is diagnosed when women present with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. Etiology remains unclear, and treatment is similar to other cardiomyopathies and includes evidence-based standard heart failure management strategies. Experimental strategies such as intravenous immunoglobulin and bromocriptine await further clinical validation.

Introduction

Peripartum cardiomyopathy (PPCM) is a rare and potentially fatal disease.¹ Although phenotypically it resembles nonischemic dilated cardiomyopathy (DCM), the clinical course is highly variable and differs significantly from other forms of cardiomyopathies.¹ Its clinical course is highly unpredictable — it may vary from rapid progression to end-stage heart failure within a few days² to spontaneous resolution and complete recovery in a few weeks to months.^{3–5}

Definition and Incidence

The initial definition of PPCM was established according to the four criteria adapted from the study by Demakis et al.¹ and recommended by a workshop convened in 1997 by the National Heart, Lung and Blood Institute and the Office of Rare Diseases of the National Institutes of Health.² The four criteria are as follows: (1) development of cardiac failure in the last month of pregnancy or within 5 months of delivery; (2) absence of an identifiable cause for the cardiac failure other than pregnancy; (3) absence of recognizable heart disease before the last month of pregnancy; and (4) left ventricular systolic dysfunction (LVSD) with left ventricular ejection fraction (LVEF) <45% by echocardiography, fractional shortening <30%, or both.² PPCM remains a diagnosis of exclusion; all other causes of DCM with heart failure must be systematically excluded before establishing the diagnosis of PPCM.⁶ Since 1997, the definition of PPCM has varied slightly. The European Society of Cardiology on the classification of cardiomyopathies has defined it as “a non-familial, non-genetic form of dilated cardiomyopathy associated with pregnancy.”⁷ The AHA Scientific Statement on contemporary definitions and classifications of the cardiomyopathies has defined it as “a rare and dilated acquired primary cardiomyopathy-associated LV dysfunction and heart failure.”⁸ The restriction of the time frame to last month of pregnancy or first 5 months postpartum for diagnosis has been challenged. In a study by Elkayam et al., almost 20% of the patients developed symptoms of heart failure and were diagnosed with PPCM earlier than the last gestational month.⁹ A comparison between patients with early presentation and those with traditional criteria of PPCM revealed no significant differences in age,

ethnic background, obstetrical history, and rate of gestational hypertension. Furthermore, maternal outcome, LVEF at the time of diagnosis, and its recovery over time were strikingly similar between the two groups.⁹ Hence, a slightly different definition was proposed in the position statement from the Heart Failure Association of the European Society of Cardiology Working Group on PPCM.² The authors believed that the time frame and echocardiographic cut-offs were arbitrary and could lead to underdiagnosis of PPCM. They eliminated the strict time limit to the diagnosis and proposed the following definition: “Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with HF secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found.” Again, it is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%.

The incidence varies geographically. Based on available literature, the incidence of PPCM appears to be 1 in 1,000 in South Africa and 1 in 300 in Haiti.^{2–4} Whereas, a detailed retrospective review of the National Hospital Discharge Survey database (1990–2002) reported an estimated lower incidence of 1 case per 3,189 live births in the United States.³ The study also reported that patients with PPCM were older (mean age 29.7 vs. 26.9 years), were more likely to be black (32.2% vs. 15.7%), and had a higher incidence of pregnancy-associated hypertensive disorders (22.5% vs. 5.87%) compared with national data. A similar study examined ICD-9 codes within the database of the Kaiser Permanent health system in southern California from 1996–2005 and estimated a PPCM incidence of 1 case per 4,025 live births, again reporting the highest incidence in African-American women.⁴ This study, however, had a high percentage of Hispanic women, the ethnicity with the lowest incidence of PPCM.

Risk Factors

The strongest risk factor for PPCM appears to be African-American ethnicity (OR 15.7; CI 3.5–70.6).⁵ Other reported risk factors include age, pregnancy-induced hypertension or preeclampsia,³ multiparity, multiple gestations, obesity, chronic hypertension, and the prolonged use of tocolytics (Table 1).¹⁰

PPCM Risk Factors
Ethnicity
<ul style="list-style-type: none"> • Highest incidence in certain ethnic groups in Africa • African-American ethnicity is the strongest risk factor in the United States
Age
Pregnancy induced hypertension or preeclampsia
Multiparity
Multiple gestations
Obesity
Chronic hypertension
Prolonged use of tocolytics

Table 1. Risk factors for peripartum cardiomyopathy.

Pathophysiology

The cause of PPCM remains unclear, but several mechanisms have been proposed, which indicates a potentially multi-factorial etiology (Table 2).

PPCM Pathophysiology
<i>Prolactin, 16-kDa Prolactin, and Cathepsin D Cascade</i>
Defective antioxidant mechanism <ul style="list-style-type: none"> • Increased cleavage of prolactin into an antiangiogenic and proapoptotic isoform
<i>Autoimmune Mechanism</i>
Class G and all subclass immunoglobulins against cardiac myosin heavy chain shown to be raised in PPCM <ul style="list-style-type: none"> • Fetal microchimerism (fetal cells in maternal blood) in patients with PPCM
<i>Inflammation</i>
Elevated serum markers of inflammation such as C-reactive protein, soluble death marker SFAS/Apo 1, interferon-gamma, interleukin (IL)-6, and TNF
<i>Viral Infection</i>
Role of viral infection less established
<i>Genetic Susceptibility</i>
Family clustering seen

Table 2. Pathophysiology of peripartum cardiomyopathy.

Prolactin, 16-kDa Prolactin, and Cathepsin D Cascade

There appears to be a cascade involving oxidative stress, the prolactin-cleaving protease cathepsin D, and prolactin in the pathophysiology of PPCM.⁹ Markers of cellular oxidation rise during pregnancy and hence an efficient antioxidant defense mechanism in the maternal heart is crucial, especially late in pregnancy and in the postpartum period. Experimental data in a mouse model of PPCM (mice with cardiomyocyte-restricted deletion of STAT3, signal transducer and activator of transcription-3) suggest that defective antioxidant mechanism may be responsible for the development of PPCM. Reduction in

STAT3 appears to be a trigger that leads to activation of cathepsin D in the cardiomyocytes, which subsequently causes increased cleavage of prolactin into an antiangiogenic and proapoptotic 16-kDa isoform.⁹ The 16-kDa prolactin fragment has potentially detrimental cardiovascular actions that could play a role in the pathophysiology of PPCM. It has been shown to inhibit endothelial cell proliferation and migration, induce endothelial apoptosis and disrupt already formed capillary structures, promote vasoconstriction, and impair cardiomyocyte function. The functional role of an activated oxidative stress-cathepsin D-16-kDa prolactin cascade is supported by the observation that in mice, treatment with bromocriptine, an inhibitor of prolactin secretion, prevented the development of PPCM. Also, patients with PPCM have increased serum levels of activated cathepsin D, total prolactin, and cleaved 16-kDa prolactin fragment.¹¹

Autoimmune Mechanism

High titers of auto-antibodies against selected cardiac tissue proteins have been found in the majority of women with PPCM.¹² Warraich et al. investigated the role of humoral immunity and showed that unlike the selective upregulation of immunoglobulins of the G3 subclass (IgG3s) in DCM, class G and all subclass immunoglobulins against cardiac myosin heavy chain were raised in PPCM.¹³ Of the serological variables, IgG3s (immunoglobulins with proinflammatory characteristics) discriminated NYHA functional status at diagnosis. IgG3-positive patients were in a higher NYHA class at initial presentation. Similarly, Ansari et al. investigated the role of fetal microchimerism (fetal cells in maternal blood) in patients with PPCM. In a small sample of patients, the amount of male chromosomal DNA in maternal plasma was significantly greater in patients with PPCM than in control mothers without PPCM during the third trimester of pregnancy, which could theoretically lead to the initiation of an autoimmune myocarditis.¹⁴

Inflammation

Serum markers of inflammation like C-reactive protein, soluble death marker SFAS/Apo 1, interferon-gamma, interleukin (IL)-6, and TNF all have shown to be elevated in PPCM.¹¹ In a study of 29 black women, IL-6 levels in patients with left ventricular thrombus were significantly higher compared with the rest of the study population.¹⁵ Pentoxifylline, an anti-inflammatory agent, was shown to improve clinical outcomes when added to conventional therapy in a small nonrandomized study of 59 patients.¹⁶

Viral Infection

The definitive role of viral infection in PPCM has not been well established. A study by Bultmann et al. identified viral genomes in cardiac tissue of PPCM patients by polymerase chain reaction (PCR) testing.¹⁷ PPCM patients who were viral-positive had histological evidence of a cardiac interstitial inflammatory process, while control patients who were viral positive did not. Viruses identified in 8 out of 26 PPCM patients (30.8%) included Epstein-Barr virus, human cytomegalovirus, human herpes virus 6, and parvovirus.^{17, 18} However, a study by Lamparter et al. reported no evidence of viral infection in snap-frozen tissue from 7 PPCM patients undergoing left ventricular endomyocardial biopsy within 48 hours of diagnosis, questioning the role of viral infections in PPCM.^{18, 19}

Genetic Susceptibility

Familial clustering of PPCM has been systematically evaluated in the two studies.^{20, 21} A study by van Spaendonck-Zwarts et al. suggested that a subset of PPCM may be a part of the spectrum of

familial DCM, presenting in the peripartum period.²⁰ In this study, the authors identified a substantial number of DCM families with PPCM (5 of 90, 6%). Also, undiagnosed DCM was identified in all three families of PPCM patients who did not show full recovery. Finally, the authors identified a mutation in a DCM family with one PPCM patient and another family member who had died suddenly soon after delivery. Hence the authors believe that it is justifiable to offer cardiological screening to first-degree relatives of recovered and unrecovered PPCM patients. A study of 520 pedigrees in the Familial Dilated Cardiomyopathy Research Project database found 45 cases of PPCM or pregnancy-associated cardiomyopathy (PACM) among 4,110 women.²¹ Evidence of familial clustering of dilated cardiomyopathy was noted in 23 of 42 unrelated cases. However, based on current levels of evidence, genetic testing is not recommended as routine but is currently being done as part of research projects.²²

Clinical Presentation and Diagnosis

Clinical presentation of patients with PPCM may be highly variable, but patients usually present with symptoms similar to those in patients presenting with systolic heart failure due to other causes. The signs and symptoms may be similar to normal physiological findings of pregnancy like edema of the legs, dyspnea on exertion, cough, paroxysmal nocturnal dyspnea, and orthopnea. Other symptoms may include abdominal discomfort, palpitations, dizziness, and chest pain.²² Most frequent initial presentation is NYHA class III or IV symptoms.²³ The majority of patients present with symptoms in the first 4 months after delivery (78%), and only 9% present in the last month of pregnancy.²² The remaining 13% present either before the last month of delivery or more than 4 months postpartum.²⁴ LV thrombus is common in PPCM patients, and some patients presenting with peripheral embolic episodes including cerebral and coronary embolism have been described in the literature.^{25,26} The diagnosis of PPCM involves a high index of suspicion as symptoms may be similar to those of physiological changes that occur during pregnancy. It also is a diagnosis of exclusion, and a thorough investigation must be done to rule out an alternative etiology of heart failure.²²

Initial investigation usually involves routine blood tests to rule out anemia, electrolyte disturbances, and liver, renal, and thyroid dysfunction. Serum B-natriuretic peptide (BNP) or NT-BNP are also commonly elevated in PPCM patients. Electrocardiogram (EKG) findings may be nonspecific. Sinus tachycardia, atrial fibrillation, atrial flutter, and ventricular tachycardia have been reported in patients with PPCM. An EKG QRS time of ≥ 120 ms has been identified as a predictor for mortality, indicating a potential impact of QRS time on the mortality of patients with PPCM.²⁷ Echocardiogram is used to rule out other causes of heart failure such as valve disease and to establish reduced ejection fraction. Among patients with LVEF $>30\%$ at diagnosis, restoration of normal LVEF is more likely. The left ventricle may not always be dilated; however, an initial left ventricular end-systolic diameter of ≤ 5.5 cm has been shown to predict recovery of left ventricle function.²⁷ LV thrombus has been found on initial echocardiography in 10–17% of patients.^{28,29} PPCM also is associated with an increased incidence of thromboembolism compared with DCM from other etiologies. Other imaging modalities such as cardiac MRI do not show any specific pattern in PPCM to help differentiate from other causes of cardiomyopathy, although it can give a more accurate measurement of chamber volumes and ventricular function than echocardiography.³⁰ The role of cardiac MRI in PPCM is being further investigated in the Investigation in Pregnancy Associated

Cardiomyopathy (IPAC) study. One of the study's objectives is to investigate the frequency of myocardial injury or inflammation on cardiac MRI and the ability of tissue characteristics to predict subsequent recovery of LVEF.³¹ Endomyocardial biopsy is not routinely recommended or a part of the typical diagnostic work up of PPCM. If a biopsy seems warranted based on suspicion of other infiltrative cardiomyopathies or treatable causes, it should be undertaken with caution. A variable proportion of patients with PPCM may have evidence of myocarditis, and since there are no pathognomonic findings in PPCM, there is an inherent risk in performing a biopsy of a dilated right ventricle.

Management

A multidisciplinary approach involving a cardiologist, obstetrician, intensivist, anesthesiologist, and pediatrician is essential and should be engaged as early as possible. Initial management is similar to that of other forms of nonischemic cardiomyopathy and includes oxygen, fluid restriction, loop-diuretics and/or other diuretics, nitrates, and hydralazine (safe to use during pregnancy), especially for hypertension. Angiotensin converting enzyme inhibitors should be avoided in the second and third trimester but are safe to use postpartum. Beta-blockers can be used when not contraindicated during pregnancy, and they can be used postpartum. During pregnancy, β -1 selective agents are preferred because β -2 receptor blockade may have an antitocolytic effect. Inotropic agents should be used in patients with signs of low cardiac output or with persistent congestion despite diuretics/afterload-reducing agents. Anticoagulation is recommended in patients with PPCM as these patients have a high incidence of LV thrombus, especially patients with an LVEF $<35\%$. Heparin (unfractionated and low-molecular-weight) is favored in pregnancy since, unlike warfarin, it doesn't cross the placenta. Warfarin should be avoided as it is teratogenic in early pregnancy and has a risk of causing fetal cerebral hemorrhage in the second and third trimester. After delivery, PPCM should be treated according to current guidelines for heart failure.²²

Specific Experimental Treatment Strategies Awaiting Further Validation

Immunosuppressive agents: The prevalence of myocarditis in PPCM varies from 9–78%.^{32,33} A single nonrandomized study suggested that immunosuppression may benefit women with biopsy-proven myocarditis.³⁴ However, the Myocarditis Treatment Trial did not show any benefit of immunosuppressive medications and, given the risks of immunosuppressive therapy, they are currently not widely utilized.^{33,35}

Intravenous immune globulin (IVIG): The role of IVIG in PPCM was evaluated in a retrospective study of six women treated with IVIG and 11 controls treated conventionally.³⁶ After a 6-month follow-up, the absolute increase in LVEF was greater in those treated with IVIG compared to controls (26% vs. 13%). However, the IMAC trial (Controlled Trial of Intravenous Immune Globulin in Recent-Onset Dilated Cardiomyopathy) showed that despite the potential therapeutic efficacy suggested by previous uncontrolled studies, immune globulin treatment of adult patients with recent-onset cardiomyopathy in this placebo-controlled trial did not affect improvements in LVEF or functional capacity during follow-up.³⁶

Bromocriptine: This treatment strategy is based on an experimental observation of preventing PPCM in mice via prolactin blockade with bromocriptine.¹¹ In a randomized open-label study performed in South Africa, 20 women with newly diagnosed PPCM were randomly assigned to receive either

standard care plus bromocriptine or standard care alone.³⁷ The 10 women receiving bromocriptine demonstrated significantly greater improvement in LVEF compared to the 10 women receiving standard care only (27% to 58% vs. 27% to 36%). One patient in the bromocriptine group died compared to four in the standard care group. Fewer patients in the bromocriptine group reached the composite endpoint of death, NYHA functional class III or IV heart failure, or LVEF <35% at 6 months as compared to patients in the standard care group (1 vs. 8). The generalizability of these results is unclear given the small sample size, the higher than expected mortality rate in the standard care group, and differences in PPCM characteristics in patients in Africa as compared to those elsewhere. Further studies aimed at clearly establishing the efficacy and safety of bromocriptine are needed before it can be recommended for the treatment of PPCM.

Pentoxifylline: In a single center study involving 59 patients with PPCM, Sliwa et al. sought to evaluate the effects of pentoxifylline, a drug known to inhibit the production of TNF- α , on clinical status, LV function, and circulating plasma levels of TNF- α .¹⁶ One group was treated with diuretics, digoxin, enalapril, and carvedilol, and the other group received pentoxifylline 400 mg three times daily in addition to the previous therapy. Treatment with pentoxifylline was an independent predictor of favorable outcome with better LVEF, NYHA class, and survival. The promising role of pentoxifylline remains experimental until it is validated by a larger scale, placebo-controlled, randomized clinical trial.¹⁶

Advanced Care and Device Therapy

Decisions about both the necessity and timing of CRT or ICD implantation in PPCM patients are extremely difficult and require careful consideration of the risks and benefits and the natural history of PPCM. However, if a patient has persistently depressed LV dysfunction 6 months following presentation despite optimal medical therapy, implantation of an ICD is advised. CRT should be considered if the patient has NYHA class III or IV symptoms and a QRS >120 msec. For patients who are dependent on inotropes or intra-aortic balloon pump despite optimal medical therapy, implantation of a mechanical assist device or cardiac transplantation may be considered.^{22,38}

Prognosis

Factors associated with favorable prognosis include small LV diastolic dimension (<5.5–6.0 cm) and elevated systolic function (LVEF >30–35% and fractional shortening >20%) at the time of diagnosis,^{39,40} absence of troponin elevation,⁴¹ absence of LV thrombus,²⁹ and non-African American ethnicity.⁴² Recent multivariate analysis by Goland et al. in 187 patients with PPCM found LVEF <30% and LV end-diastolic dimension <55 mm to be significantly related to LV recovery, suggesting a relationship between the degree of initial myocardial insult and recovery.⁴² These parameters, however, have limited sensitivity in predicting recovery in individual patients. Despite the strong association between LVEF at time of diagnosis and rate of recovery, 70% of patients in group I (LVEF 10–19%) and 87% of patients in group II (LVEF 20–29%) recovered almost beyond the “device threshold” at ≥ 6 months. Hence the authors suggest that baseline parameters of LV function should not be used alone as an indication for the premature use of devices or heart transplantation.

Subsequent Pregnancies

PPCM is associated with a high risk of recurrence in subsequent pregnancies both in patients who have recovery of LV function and in those with persistent LV dysfunction.^{43–46} Patients with PPCM who recover their LV function have a lesser chance of recurrence compared to those with persistent LV dysfunction.⁴⁶ The increased deterioration of LV function in subsequent pregnancy in patients with persistent LV dysfunction leads to a worse prognosis (20–30% mortality in subsequent pregnancy), whereas patients with a full recovery of LV function have negligible mortality in subsequent pregnancies.^{46,47} Appropriate counseling regarding subsequent pregnancies and contraception is important.⁴⁸ Every woman with PPCM should be informed about detrimental effects of a subsequent pregnancy on cardiac function, and women with LVEF of <25% at diagnosis of PPCM or persistent LV dysfunction should be advised against a subsequent pregnancy.⁴⁸ The safety of contraceptive use among women with PPCM has not been well studied.^{49,50} Counseling to women with recovered ventricular function is challenging. LV systolic function is considered a major prognostic factor for subsequent pregnancies in patients with PPCM.^{51,52} If a woman plans to become pregnant, echocardiography should be performed, and dobutamine stress echocardiography may be helpful.⁵¹ Dobutamine stress echocardiography can be used to determine the contractile reserve in patients with recovered LV function.^{53,54} Women with recovered LV function on both echocardiography and dobutamine stress test have approximately 35% risk of recurrence of PPCM during subsequent pregnancies.⁵¹ Still, every subsequent pregnancy in women with PPCM should be managed in high-risk perinatal centers, as subsequent pregnancies are associated with a high risk of recurrence despite recovered LV function.^{44,54,2}

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