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## Peripartum Cardiomyopathy

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**Peripartum cardiomyopathy (PPCM) is a condition that affects women during the reproductive years in the late pregnancy period and/or early postpartum period. Although it is associated with several risk factors and various hypotheses exist of its etiology the cause of this disorder is still unknown. Standard therapy for PPCM is the same as for heart failure. Studies examining new therapeutic approaches are adding to the armamentarium available to physicians treating**

**patients with PPCM. Despite all the current knowledge the mortality rates associated with PPCM remain relatively high. This article is a review of the current knowledge of etiology, diagnosis, treatment and prognosis of PPCM and attempts to present areas of need of further research.**

*Key words: Peripartum cardiomyopathy, Dilated cardiomyopathy, Heart failure in pregnancy, Heart failure, Pregnancy, Tocolytic therapy*

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**P**eripartum cardiomyopathy (PPCM) is a condition that occurs during the peripartum period first described in 1937 by Gouley et al. (1). It is a relatively rare cardiac disorder with high mortality rates, being the fifth leading cause of maternal death. It is recognized as a distinct entity. The etiology of this disorder is still not known, although several theories are currently under investigation. In April 1997, the National Heart, Lung and Blood Institute (NHLBI) and the Office of Rare Diseases of the National Institutes of Health (NIH) held a multidisciplinary review of the existing knowledge on PPCM, and developed recommendations for future research and education (2). This article will review the definition, etiology, diagnosis, treatment options and prognosis of PPCM.

### Definition

The definition of PPCM includes 4 criteria adapted from work by Demakis et al: (1) cardiac failure that develops during the period that includes the last month of pregnancy and the first 5 months after delivery; (2) absence of an identifiable cause for the heart failure; (3) absence of recognizable heart disease prior to the last month of pregnancy; (4) left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria:

decreased ejection fraction (<45%), fractional shortening (<30%), and end-diastolic dimension >2.7cm/m<sup>2</sup>. (3).

### Incidence

The exact incidence of PPCM is not known because population-based estimates are not available but is estimated to be approximately one in 3000 to one in 15,000 pregnancies (4-6). Risk factors for developing PPCM include increased maternal age, twin gestation, multiparity, preeclampsia and gestational hypertension, use of tocolytic therapy, and black race. It is unclear if black race is an independent risk factor or if the higher incidence of PPCM seen in black women is related to the higher incidence of arterial hypertension among blacks (3). Mortality rates range between 9% to 56% with most of the deaths reported to occur during the first three months postpartum (7).

### Etiology

The etiology of peripartum cardiomyopathy is unknown. Several hypotheses have been suggested to include infectious, immunologic, and drug-induced.

### Infectious

Myocarditis has been reported in cases of PPCM with variable incidence. One study found myocarditis in 29% of patients with PPCM, (8) while others have reported prevalence of 62%, (9) and as high as 76% (10). This could be explained by the decreased immunologic

response in women during pregnancy that makes them susceptible to viral mediated myocarditis. This is supported by studies in pregnant mice that demonstrated their increased susceptibility to viral myocarditis due to coxsackie viruses and echoviruses (11,12).

### **Immunologic**

Theories postulating an immune etiology of PPCM come from reports that have documented the occurrence of chimerism of the hematopoietic lineage cells from the fetus to the mother during pregnancy (13-15). There are some beliefs that fetal cells cross the placenta to the maternal circulation and into cardiac tissue. These cells are not destroyed due to the natural immunosuppressed state of the mother during pregnancy. During the postpartum period, as the mother recovers immune competence, these fetal cells are recognized as nonself by the maternal immune system triggering a pathologic immune response releasing cytokines and similar signaling molecules leading to an autoimmune response and myocarditis.

Support for the theory of abnormal immunologic activity comes from studies in which high titers of autoantibodies against select cardiac muscle proteins have been identified. These include autoantibodies to adenine nucleotide translocator (ANT), branched chain alpha-keto acid dehydrogenase (BCKD), and myosin (2,16).

### **Drug-Induced**

Peripartum cardiomyopathy has been suggested to be associated with prolonged exposure of mothers to tocolytic therapy. Lampert et al. reported 15 cases of women with PPCM and 4 of them had received prolonged terbutaline therapy (17). However, there is no convincing evidence at present to demonstrate that these agents are a cause of PPCM.

## **Diagnosis**

Due to the similarities between the symptoms of early congestive heart failure and the symptoms of normal late pregnancy diagnosing PPCM is a challenge. During the last month of pregnancy many mothers present dyspnea, fatigue, and pedal edema which are identical symptoms of early congestive heart failure. There are no specific criteria for differentiating the symptoms of late normal pregnancy from heart failure. Signs and symptoms that might increase suspicion of heart failure include paroxysmal nocturnal dyspnea (PND), neck vein distention, pulmonary crackles, new murmurs of regurgitation of atrioventricular valves, chest pain and cough.

Diagnosis of PPCM therefore requires a high grade of suspicion and exclusion of other causes of cardiomyopathy. The diagnosis is confirmed by

echocardiographic identification of left ventricular systolic dysfunction, with an ejection fraction  $<45\%$ , fractional shortening  $<30\%$ , and left ventricular end-diastolic dimension  $>2.7\text{cm/m}^2$  (3). Other presentations of PPCM reported include ventricular tachycardia, (18,19) ventricular thrombi, (20) thromboembolism, (21) pulmonary embolism, (22) and even embolic myocardial infarction (23). It has been highly recommended to screen family members of patients with PPCM because this could be a manifestation of a genetic predisposition to cardiomyopathy.

## **Treatment**

Treatment of PPCM is the same as for heart failure since there are no systematic studies comparing therapeutic approaches in PPCM. Care must be taken during the prepartum period not to use therapies that could have teratogenic effects and also to keep in mind the different excretion of drugs or its metabolites during breast feeding after delivery (2).

Standard heart failure therapy includes the use of angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blockers, diuretics and digoxin for symptomatic patients. ACE inhibitors are contraindicated during pregnancy due to their teratogenic effects. Therefore, for afterload reduction and vasodilation, hydralazine and nitrites can be used instead until delivery. ACE inhibitors can be started once the mother has given birth. The experience with the use of ACE inhibitors during breast feeding is limited, but captopril and enalapril appear to be safe (7).

Some beta-adrenergic blockers (bisoprolol, carvedilol, and sustained release metoprolol succinate) have been shown to have beneficial effects and reduce mortality in patients with heart failure. These drugs are not contraindicated during pregnancy but, there is no data evaluating them in PPCM, and this class of drugs has been associated with some long-term adverse effects such as low-birth-weight babies (24,25).

Calcium channel blockers can be used during pregnancy to control arterial hypertension and also have the benefit of decreasing uterine contractility, but many of these agents have negative inotropic effects that could worsen the clinical status of heart failure patients. However, amlodipine, a dihydropyridine calcium channel blocker, has been shown to improve survival in patients with nonischemic cardiomyopathy and could have an important role in the management of patients with PPCM. The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial showed a lower levels of IL-6 among patients treated with amlodipine, suggesting a potential use for amlodipine in the management of patients with PPCM (26).

Diuretics should be used with caution during the prepartum period to avoid uterine hypoperfusion and fetal distress secondary to dehydration of the mother. Digoxin should be used as needed. Breast feeding while on standard medical therapy for heart failure is safe.

Acutely ill patients with decompensated heart failure should be treated with intravenous inotropic agents including dopamine, dobutamine and milrinone, and with agents to reduce preload and afterload such as nitroprusside and nitroglycerin. These agents should be titrated slowly and with caution to maintain maternal intravascular euvolemia. It must be kept in mind that nitroprusside can cause fetal thiocyanate and cyanide intoxication.

For patients with significantly reduced left ventricular systolic function, ejection fraction of 35% or less, anticoagulation therapy should be considered. The Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy states that therapy with anticoagulants is indicated during pregnancy for the prevention and treatment of venous thromboembolism (VTE).<sup>27</sup> Unfractionated heparin (UHF) and low-molecular-weight heparin (LMWH) are the drugs of choice during pregnancy based on safety reports and case studies. Benefits of LMWH over UFH include a lower risk of heparin-induced osteoporosis and heparin-induced thrombocytopenia (HIT), a longer plasma half-life, therefore a more predictable dose response than UFH. These medications do not cross the placenta and are not secreted into breast milk so they do not have the potential to cause teratogenicity and can be continued in the postpartum period while breast feeding. Warfarin is not recommended as an anticoagulant therapy during pregnancy since it crosses the placenta and has teratogenic effects, but it is safe to use postpartum as it does not show an anticoagulant effect in the breast-fed infant.

Arrhythmias should be treated according to standard protocols avoiding the use of class 3 (amiodarone) and class 4 (verapamil) antiarrhythmic agents due to adverse effects on the fetus like fetal bradycardia, heart block, hypotension, hypothyroidism and premature delivery (28).

Since there are theories to suggest an immunologic etiology of PPCM several studies have looked into the role of immunosuppressive therapy in the treatment of this disorder. The drug pentoxifylline has been demonstrated to inhibit proinflammatory cytokines and has beneficial effects on New York Heart Association (NYHA) functional class, left ventricular ejection fraction and markers of apoptosis in patients with idiopathic dilated cardiomyopathy (28,29). Sliwa et al. reported a clinical trial studying the effects of this medication on patients

with PPCM. Results suggest that addition of pentoxifylline to conventional therapy, improves outcome in patients with PPCM. In this study a combined end-point of poor outcome defined as either death, failure to improve the left ventricular ejection fraction >10 absolute points or functional class III or IV at latest follow-up, occurred in 52% of patients on usual therapy and 27% of patients treated with pentoxifylline (30). In another study, an improvement in ejection fraction was seen in patients with PPCM treated with intravenous immune globulin compared to those treated with conventional therapy alone (31).

Nonpharmacologic treatment is an important aspect of the management of patients with PPCM. Salt intake should be restricted to less than 4 g per day, and fluid intake should be restricted to less than 2 L per day. Once symptoms of heart failure have been controlled patients should be encouraged to follow a modest exercise program. This may improve symptoms as well as peripheral muscular and arterial tone. Those patients who deteriorate despite optimal medical therapy should be considered for heart transplant.

Early delivery is not indicated in patients with PPCM unless clinically indicated. If heart failure in these patients is successfully managed medically, then spontaneous vaginal delivery can be carried out without contraindications. In patients not responding to medical therapy induction of labor for vaginal delivery is acceptable. Although vaginal delivery is preferable over delivery by cesarean section due to lower rates of complications, the cardiovascular benefit from prompt delivery is more important than the method of delivery. For this reason the mode of delivery should be assessed in collaboration with anesthesiologists, obstetricians and cardiologists.

## Prognosis

For patients suffering from PPCM prognosis is dependent on recovery of systolic function. If symptoms persist for more than 6 months, damage to the myocardium is most likely irreversible and the prognosis is grim. Studies comparing survivors with nonsurvivors, the survivors had higher left ventricular ejection fractions and smaller left ventricular end-diastolic diameters at the time of diagnosis (32).

Studies have shown a better prognosis for patients with PPCM when compared with patients with cardiomyopathies of other known causes like doxorubicin therapy, HIV infection, infiltrative myocardial disease, and ischemic heart disease. Women with PPCM also show substantially better long-term prognosis than patients with idiopathic cardiomyopathy (33).

There is no consensus at present time regarding

recommendations for future pregnancies in patients with PPCM. Women with persistent left ventricular dysfunction should be strongly counseled against subsequent pregnancies for fear of an inability to tolerate the increased cardiovascular workload associated with a normal pregnancy. In women with completely resolved cardiomyopathy counseling is more difficult. Some studies have reported cases of normal subsequent pregnancies and normal left ventricular systolic function during such pregnancies in patients with previous history of PPCM which had completely resolved. Other studies have reported cases of recurrent PPCM in patients with previous history of PPCM which had completely resolved. The risk of irreversible cardiac damage may increase with each subsequent pregnancy, therefore subsequent pregnancies should be avoided and if this is not possible they should be managed in a high-risk perinatal center (2).

### Summary

Peripartum cardiomyopathy is a rare cardiac disease associated with a high mortality rate since it was first described in 1937. Several hypotheses about its etiology have surfaced over the years but its cause is still unknown. Diagnosis of this disorder depends on high suspicion and on following very specific criteria. Management is the same standard therapy used to treat heart failure and collaboration of multiple specialists is essential for adequate treatment. Several studies have suggested new therapeutic approaches that should be studied further. Prognosis is dependent on recovery of systolic function. Subsequent pregnancies should be discouraged in patients with permanent left ventricular systolic dysfunction and maybe even in women who completely recover left ventricular function. As recommended in the multidisciplinary workshop and review of PPCM done in 1997, an international registry should be established to capture prospectively all women with PPCM to help to better document the incidence and prevalence estimates, to determine the risk factors and prognostic variables, ascertain cardiovascular risks for subsequent pregnancies, to establish a centralized serum and tissue bank to help identify the cause of PPCM, and evaluate therapeutic interventions (20).

Despite current knowledge of this disorder more research is needed to decrease mortality and improve therapeutic options.

### Resumen

La cardiomiopatía del puerperio es una condición que afecta a las mujeres en sus años reproductivos en el último mes de embarazo o en los primeros cinco meses después del parto. Aún cuando está asociada con algunos factores de riesgo y varias hipótesis existen sobre su etiología, la causa de esta condición todavía es desconocida. El tratamiento es el clásico de la insuficiencia cardíaca. Estudios que examinan nuevos tratamientos añaden al armamentario de médicos que atienden pacientes con cardiomiopatía del puerperio. Aún con el conocimiento que se tiene sobre esta condición la mortalidad de la misma se mantiene relativamente alta. Este artículo es un repaso del conocimiento que se tiene acerca de la etiología, diagnóstico, tratamiento y pronóstico de la cardiomiopatía del puerperio y un intento de presentar aquellas áreas que requieren de más investigación.

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