Peripartum Cardiomyopathy

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ABSTRACT

Although described as early as 1849 by Richie[1], Seftel et al[2] recognized the occurrence of heart failure in late pregnancy and used the term "Peripartum Cardiomyopathy." The risk factors identified include older maternal age, multi-parity, multiple gestations and black race. The exact etiology is not known but various factors have been proposed which include, myocarditis, abnormal immune response to pregnancy, maladaptive response to haemodyanmic stress of pregnancy, stress activated cytokines. The X- Ray chest, ECG and 2 –D Echo are usually helpful for the diagnosis of the condition. The present article reviews further details of peripartem cardiomyopathy and its management.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a rare form of heart failure which affects healthy young women with devastating consequences. Although described as early as 1849 by Richie[1], Seftel et al[2] recognized the occurrence of heart failure in late pregnancy and used the term "Peripartum Cardiomyopathy" in their paper presented in British heart Journal. However, the condition was not well characterized until 1971 when Demakies et al[3,4] established the current diagnostic criteria. A workshop by NHLBI in 1997 standardized the definition of PPCM as "onset of cardiac failure with no identifiable cause in last month of pregnancy or within five months after delivery in absence of heart disease before the last month of pregnancy"[5]. Left ventricular systolic dysfunction demonstrated by echocardiography is essential for diagnosis of PPCM.

Epidemiology

Peripartum cardiomyopahty has an incidence of 1:1500 to 1:4000 live births. In United States the estimated prevalence is 1 case per 1300 to 1500 live births while in Japan it is 1 case per 6000 live births. The condition appears to be more prevalent in South Africa with reported prevalence of 1 case per 1000 live births. Reports from Haiti show a relatively high incidence of 1 case per 350 - 400 live births[6].

The risk factors identified include older maternal age, multi-parity, multiple gestations and black race. African American women seem to be at higher risk of developing PPCM. African Americans have higher incidence of hypertension and it is unclear whether race is an independent risk factor or it is the interaction of the race and hypertension.

Etiology and Pathogenesis

PPCM is considered as a distinct entity as the incidence is higher than the incidence of Idiopathic dilated cardiomyopahty unmasked by pregnancy. The exact etiology is not known but various factors have been proposed which include, myocarditis, abnormal immune response to pregnancy, maladaptive response to haemodyanmic stress of pregnancy, stress activated cytokines.

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Recently there have been reports of familial cardiomyopathy being unmasked by pregnancy. Some of the proposed mechanisms as discussed below

Myocarditis- Presence of myocarditis on endomyocardial biopsy was reported first by Melvin and colleagues[7] in 3 consecutive patients of PPCM. However, the incidence of myocarditis in the subsequent reports have varied probably due to difficulties in establishing the diagnosis by endomyocardial biopsy and variable interval between presentation and timing of the biopsy. During pregnancy the immune response is depressed which may allow unchecked viral replication leading to a greater likelihood of developing myocarditis. Studies in pregnant mice have shown enhanced susceptibility to viral myocarditis due to coxsackievirus and echoviruses[8].

Abnormal immune response – It is postulated that fetal cells may escape in maternal circulation and remain there without being rejected due to weak immunogenecity. These chimeric haematopoetic cells make take up residence in the cardiac tissue during the immuno-suppressed pregnant state. Following postpartum recovery of immune system, they are recognized as non self and this can trigger a pathologic autoimmune response mediated through release of cytokines and similar signaling molecules inducing a nonspecific bystander myocyto-toxicity and myocarditis. This hypothesis is supported by the observation that in patients with PPCM auto-antibodies against select cardiac proteins are elevated. [9,10]

Haemodynamic Stress - The haemodyanmic stresses of pregnancy are considered as a possible cause of PPCM. Homodynamic alterations during pregnancy include a reversible decrease in LV systolic function during second and third trimester which persists during early postpartum period, returning to baseline thereafter. It is possible that PPCM is an exaggerated response in decrease in systolic function [11].

Inflammation and Oxydative stress- A pro-inflammatory response in PPCM is described by Sliwa et al from South Africa. Studying a large cohort of PPCM they have described elevated plasma levels of TNF-alpha,Fas/Apo-1 and IL-6 and a positive correlation between C-reactive protein levels ,LV end-diastolic and end systolic diameters at the diagnosis [12].

Enhanced oxidative stress is reported in a mouse model of PPCM. It is postulated that in PPCM enhanced oxidative stress triggers activation of cathepsin D, a ubiquitous lysosomal enzyme which subsequently cleaves serum prolactin to its anti-angiogenic and pro-apoptotic 16 KDa form. This metabolite is also shown to promote endothelial inflammation and impair cardiomyocyte metabolism and contraction [13] Full length 23-KDa form of prolactin is up regulated post delivery and has been implicated in cardiac tissue injury and modulation of autoimmune response. Thus unbalanced oxidative stress and generation of 16 KDa form of prolactin may represent a crucial step in initiation of PPCM. In fact pharmacological inhibition of prolactin release has been shown to prevent PPCM in mice studies and to be beneficial in patients in preliminary studies.

Recent reports from the Netherlands strongly suggest that a subset of PPCM is actually an initial manifestation of familial DCM. The authors suggest that PPCM develops as a complex interaction between pregnancy associated and genetic factors. On the background of genetic susceptibility, factors associated with pregnancy could lead to PPCM [14] (11). Indeed another recent paper has identified mutation in 6 genes in patients with PPCM [15].

Clinical Presentation

The women suffering from PPCM have generally no significant history except that in

the last month of pregnancy they may complain of dyspnoea, fatigue and peripheral edema. More than eighty percent patients develop cardiac symptoms post partum while 7% of them develop symptoms during last month of pregnancy. About half of the patients are more than 30 years of age and 71% are in their third or subsequent pregnancy. Twins and toxemia occur in 7 and 22% of these patients [3,4].

Patients present with features of left heart failure including fatigue, dyspnoea and orthopnoea. Peripheral edema and abdominal discomfort occurs in about half of them. Coughing and haemoptysis are features of pulmonary embolism to which these patients are particularly predisposed. Clinical sings include moderate to severe respiratory distress, elevated jugular venous pressure, pedal edema and hepatomegaly. The heart is enlarged with an active left ventricular impulse. Enlarged right ventricle may give left parasternal impulse. Murmurs of mitral and tricuspid regurgitation are common and tend to disappear as the left ventricular function improves. Left ventricular third heart sound is noted in majority of the patients.

Chest x ray shows cardiomegaly with pulmonary venous congestion. ECG exhibits sinus tachycardia left ventricular hypertrophy and non specific ST –T changes. PR interval may be prolonged and some patients demonstrate widening of QRS complex indicating intraventricular conduction disturbances. Bundle branch blocks are present occasionally.

Echocardiography is the most important diagnostic tool which usually shows a dilated globally hypokinetic left ventricle. The diagnostic echo criteria include a) LVEF <45% b) Fraction LV shortening <30% and c) LV end diastolic dimensions >2.7 cm per square meter of body surface area. Echo also helps to define the severity of mitral and tricuspid valve regurgitation.

Management

The medical management of patients with PPCM is similar to those with left heart failure due LV systolic dysfunction except that the potential effects of the medications on the fetus or lactation become the primary concern in these patients.

For women presenting in the last month of pregnancy with symptoms of congestion, loop diuretics in appropriate doses can be started. Generally, a small daily dose of digoxin can be added with good benefits. Hydrallazine and nitrates can be safely used as vasodilators to reduce afterload in pregnancy. Although, use of beta blockers is generally appears safe during pregnancy for treatment of hypertension, less is known about their effect in patients with PPCM. ACE inhibitors are the most important drugs to treat LV systolic dysfunction otherwise, cannot be used during pregnancy due to the unwanted effects on the fetus.

For patients presenting following delivery, ACE inhibitors form the cornerstone of therapy. Loop diurectics and digoxin can be added to ACE inhibitors to decrease pulmonary congestion. Addition of beta blockers would be important in patients who remain symptomatic despite optimization of these drugs. Caution needs to be exercised in occasional patient presenting with severe systolic dysfunction without significant ventricular dilatation, who may tolerate beta-blockers poorly.

Thrombotic and embolic complication may occur in PPCM, like they occur in other forms of heart failure. Anticoagulation must be considered in patients presenting with systemic embolism or those with mural LV thrombi. During pregnancy heparin therapy must be considered as oral anti coagulation is contraindicated. Role of LWMH or newer drugs like Fondaparinaux is not established as yet. Anticoagulation needs to be continued for at least six months postpartum. Need for

continued therapy can reassessed according recovery of LV function at 6 months.

Ventricular arrhythmias can occur as in other forms of heart failure and need to be managed conventionally with use of beta-blockers and adequate doses of amiodarone. Occasionally, implantable defibrillator (AICD) may be needed in patients with malignant ventricular arrhythmia despite conventional therapy. The risk of arrhythmia decline with recovery of LV function and therapy may be withdrawn after 6 months when the LV function normalizes completely.

Physical activity is encouraged as much as the functional status of the patients allows, however aerobic activities and heavy lifting are discouraged for at least six months. Breast feeding is strongly discouraged due to heavy metabolic demands of lactation. Some of the drugs may also be secreted in the breast milk causing untoward effects to the baby.

Newer Therapeutic Agents- Immune modulation therapy is considered by some authors due to inflammatory nature of PPCM. Medei et al used prednisone and azathioprine in a small series of patients and were able to show marked improvement in 9 out of 10 patients treated [16]. Similarly, Bozkurt et al [17] in a retrospective analysis found that patients with PPCM when treated with IV Immune Globulin given in a dose of 2 g/kg over two days significantly improved LV function at 6 months. Results of both these studies need to be interpreted with caution as other studies of immune modulation therapy in active myocarditis have failed to show significant improvement so far. [18,19]

Treatment with pentoxyphylline, a xanthine derivative has been shown to inhibit production of TNF-alpha and improves functional class in LV function in patients with Idiopathic dilated cardiomyopathy. Sliwa et al[20] studied effects of addition of pentoxyphylline to 30 consecutive patients with PPCM in a dose of 400mg TID in addition to standard therapy. A lower mortality rate and better functional class was observed in patients treated with pentoxyphylline. Significant reduction in LV diameters was also observed in this group of patients.

The same group recently studied effects of prolactin blockade with Bromocriptine (a dopamine 2D agonist) in patients with PPCM [21]. In this small open label randomized study of 20 patients (10 standard therapy and 10 with bromocriptine 2.5 mg twice daily for 2 weeks followed by 2.5 mg OD for 6 weeks) , a significant improvement in functional class, LV systolic and diastolic function and degree of functional mitral regurgitation was observed. Use of bromocriptine was based on their recent observation that oxidative stress of pregnancy converts prolactin to its 16 KDa form which leads to myocardial toxicity. Although encouraging it should be remembered that bromocriptine is known to cause cerebral and cardiovascular complications including stroke, seizure and coronary artery thrombosis. Risk of thrombosis is already high in the postpartum phase due to altered coagulation system. However, in this small study no thrombotic complications were noted in the 9 surviving patients. Further, bromocriptine treated women cannot breast feed and there is a risk of malnutrition of the infant, especially in the developing countries. Hence these promising results need to be replicated in larger studies before bromocriptine is used as a standard therapy for PPCM. A single dose of Cabergoline, a strong and long acting prolactin antagonist has been shown to be beneficial in treating a patient of PPCM has been reported by de Jong et al [22]. Heart transplant is another option for end stage heart failure due to PPCM and occasional transplanted patient has been reported to have undergone successful subsequent pregnancy. [23]

Natural History and Prognosis

Historic data from the series of Demakis et al [3,4] shows that 50% of the patients with PPCM shows complete regression of cardiomegaly at 6 months have good prognosis. Long term mortality in patients showing complete regression of heart size was 14% in their series (significantly higher than those without PPCM). Patients having persistent cardiomegaly beyond 6 months, have a worse prognosis with a very high mortality rate exceeding 75% in next 2 to 3 years. Modern treatment with ACE inhibitors, beta-blockers has improved the survival of patients with PPCM. Recent data from Felker et al [24] shows very good long term survival of patients with PPCM (94% at 5 years, Fig-1), which is significantly higher than survival for any other form of dilated cardiomyopathy. Recent data from Forster et al [25] shows that levels of serum NT pro BNP, Interferon-gamma, oxidized LDL and prolactin correlate with outcome. Persistently high levels of these inflammatory markers spells worse prognosis as compared to those who show reduction in the levels of these markers.

Subsequent pregnancy in patients with PPCM is the real concern. Although pregnancy in patients who show normalization of LV function can be considered, almost 20% of them develop symptoms of heart failure during subsequent pregnancy[26]. It appears that even though the LV function at rest is normal, patients who have suffered PPCM in previous pregnancy have impaired contractile reserve. Lampert et al[27] have demonstrated this phenomenon using dobutamine stress echocardiography. For those who show only partial improvement, the risk is considerably higher with more than 50% developing heart failure in the subsequent pregnancy. Short term mortality for this group remains high at 19% and they tend to have unfavorable fetal outcome with 50% premature deliveries and 25% therapeutic abortions [28]. In view of the above observations, subsequent pregnancy in a patient who has suffered PPCM needs to be strongly discouraged. For those who get pregnant again, a systematic care in tertiary care institute with close cardiologic monitoring is mandatory to avoid catastrophic outcome.

Conclusions

Peripartum Cardiomyopathy remains a rare but devastating complication of pregnancy. Current recommended therapy remains the standard of care therapy for LV systolic dysfunction. Almost half of the patients tend to recover their LV function in 6 months following delivery, however almost 20% of them can develop heart failure during subsequent pregnancy. Patients showing incomplete recovery of LV function need to be discouraged strongly from getting pregnant again as maternal and fetal outcomes are worse in this group. Given the rarity of the condition, an international collaborative registry is essential to gain further knowledge in management of these patients.

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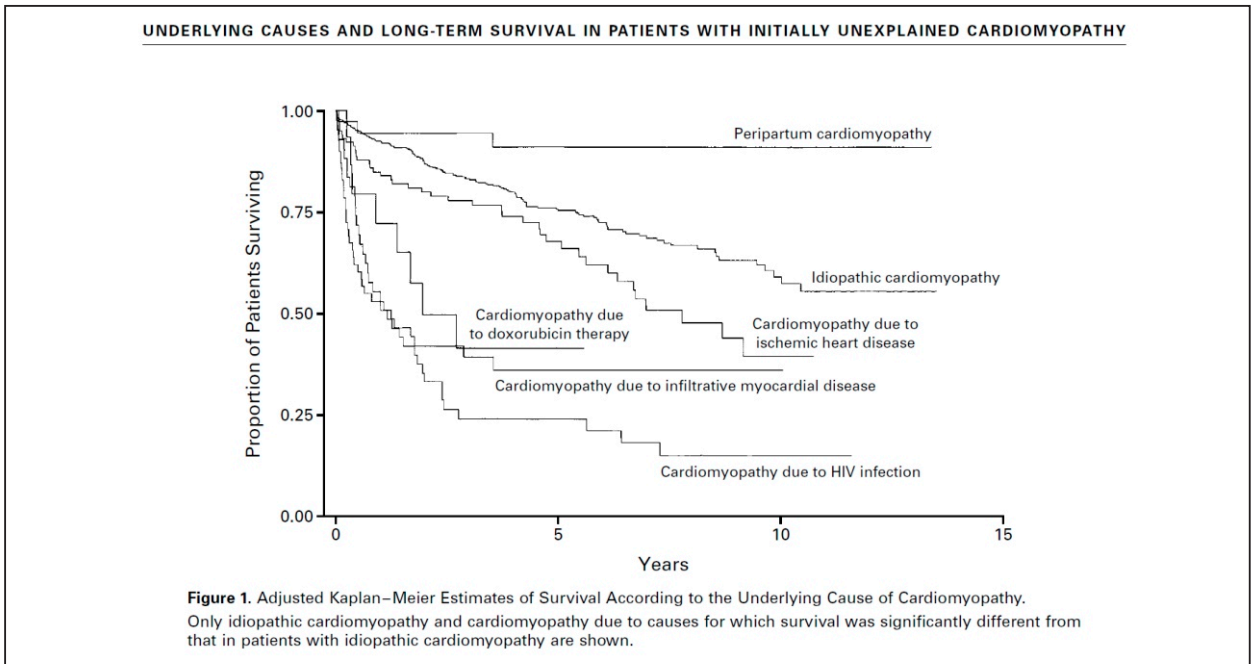

Fig 1: Adopted from Felker et al N Eng J Med 2000;342:1077-1084