Peripartum Cardiomyopathy: A Review

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Abstract
Peripartum cardiomyopathy (PPCM) is a rare, idiopathic, and often dilated cardiomyopathy that is marked by systolic dysfunction that presents in late pregnancy or the early postpartum period. A workshop convened by the US National Heart, Lung, and Blood Institute (NHLBI) in the 1990s defined PPCM as heart failure that develops in the last month of pregnancy or up to five months postpartum with left ventricular systolic dysfunction. Prior to the availability of echocardiography, diagnosis was based only on clinical findings. Recently, the inclusion of echocardiography has made diagnosis of PPCM easier and more accurate. Etiopathogenesis is still poorly understood, but recent evidence supports inflammation, viral infection, and autoimmunity as the leading causative hypotheses.

Keywords: Cardiomyopathy, Etiology, Features, Management, Peripartum, Pregnancy.

Introduction
Peripartum cardiomyopathy (PPCM) is a rare cause of cardiomyopathy that occurs during late pregnancy or the early postpartum period. This condition can be life-threatening and is characterized by significant left ventricular dysfunction and heart failure1. In 1971, Demakis, et al2 first defined PPCM with three distinctive criteria (Table-I). The strict time limit used in their diagnostic criteria was intended to exclude congenital and acquired causes of heart failure that usually manifest by the second trimester. Even so, the occurrence of PPCM has been overestimated. As a result, the PPCM workshop committee recommended the inclusion of echocardiographic features of left ventricular dysfunction to redefine PPCM3. Specific echocardiographic diagnostic criteria have been proposed (Table-II)4 and their addition has resulted in easier differentiation between PPCM and other causes of cardiac failure.

Incidence
The incidence of PPCM varies worldwide5. In South Africa, the reported incidence is higher 1:1000 live births6. A much higher incidence of 1:300 live births has been reported from Haiti,7 and an extremely high rate of 1% has been described in Nigeria8. Proposed reasons for this increase include rising rates of advanced maternal age, pre-eclampsia and multiple gestations, black race, obesity, malnutrition, gestational hypertension, pre-eclampsia, poor antenatal care, breast feeding, cesarean section, alcohol, cocaine and tobacco abuse, low socioeconomic condition, and positive family history11,12. Twin pregnancy appears to cause a higher risk of developing PPCM13. Typical etiological nature points towards hypertensive heart failure caused by fluid overload rather than a true variety of PPCM. Preeclampsia and hypertension have been associated with a significant number of PPCM cases14.

Risk Factors
Commonly reported risk factors for PPCM are advanced maternal age, multiparity, multiple gestations, black race, obesity, malnutrition, gestational hypertension, pre-eclampsia, poor antenatal care, breast feeding, cesarean section, alcohol, cocaine and tobacco abuse, low socioeconomic condition, and positive family history11,12. Twin pregnancy appears to cause a higher risk of developing PPCM13. Typical etiological nature points towards hypertensive heart failure caused by fluid overload rather than a true variety of PPCM. Preeclampsia and hypertension have been associated with a significant number of PPCM cases14.

Malnutrition, low socioeconomic status, poor antenatal care, and breast feeding are also mentioned as risk factors in earlier reports, but substantial correlations of these factors have not been found in further studies15. There are also reports of other rare risk factors such as maternal cocaine, alcohol, and tobacco abuse16. PPCM does not have a strong hereditary association17.
Table-I: Diagnostic criteria for PPCM.

- Development of heart failure within the last month of pregnancy or six months postpartum.
- Absence of any identifiable cause for heart failure.
- Absence of any recognizable heart disease before last month of pregnancy.

PPCM workshop committee recommended the inclusion of echocardiographic features of left ventricular dysfunction to redefine PPCM.

Table-II: Additional echocardiographic diagnostic criteria

Demonstrable echocardiographic criteria of left ventricular dysfunction:

- Left ventricular ejection fraction <45%
- Left ventricular fractional shortening <30%
- Left ventricular end-diastolic dimension >2.7 cm/m²

This review summarizes current literature on the pathogenesis, presentation, and management of PPCM.

Etiology

The actual etiology of PPCM is unknown. Several hypotheses like myocarditis, inflammatory cytokines, viral infection, autoimmune factors, and abnormal hemodynamic response to physiological changes in pregnancy, prolonged tocolytics and selenium deficiency have been postulated.

i. Myocarditis

Myocarditis is defined as dense interstitial as well as perivascular inflammatory infiltration of lymphocytes and macrophages in the presence of myocyte necrosis with or without fibrosis. Recently, idiopathic dilated cardiomyopathy (IDCM) has also been reported in PPCM which is near 9.1%.

ii. Inflammatory cytokines

In a study by Silwa et al, found higher concentrations of inflammatory cytokines like tumor necrosis factor α (TNFα), C-reactive protein (CRP), Interleukin-6 (IL-6) and Fas/Apo-1 (a marker of apoptosis) in PPCM patients.

iii. Viral infection

Viral infection has also been implicated as a cause of myocarditis. Depressed immunity during pregnancy may lead to viral infection. Polymerase chain reaction (PCR) and extraction of genomic material from contrast MRI-guided EMB (endomyocardial biopsies) may help in successful detection of viral genomes.

iv. Autoimmune factors

In the 1970s, several reports in support of the autoimmune nature of PPCM joined reports of fetal chimerism (presence of fetal cells in maternal circulation during and after pregnancy). It was also proposed that autoantibodies may be formed against the uterus, placenta, or fetus in pregnant patients.

v. Abnormal hemodynamic response to physiological changes in pregnancy

Blood volume and cardiac output (CO) increase, while systemic vascular resistance (SVR) decreases in pregnancy. Reduction of left ventricular function in advanced pregnancy and early puerperium is typically seen.

vi. Selenium deficiency

Keshan disease, a form of dilated cardiomyopathy, has been reported to be associated with selenium deficiency. Selenium supplementation has been shown to improve cardiac dysfunction in chronic tube-fed patients, stressing its importance in malnourished PPCM patients.

vii. Other factors

Some factors which may contribute to the development of PPCM are a) Prolonged tocolytic therapy: this treatment may unmask existing heart disease rather than play an etiologic role. b) Hormones: Relaxin, primarily an ovarian hormone, may cause excessive cardiac dilatation leading to cardiomyopathy. c) Persistent Chlamydia pneumonia infection: among so many propositions, no study has clearly delineated any definitive factor(s) responsible for PPCM though the etiology is multifactorial.

Pathological Features

Heart specimens appear pale, soft, dilated, and heavier in PPCM. Mural thrombi are invariably seen in one or more cardiac chambers in patients with persistent ventricular dysfunction. Gray-white patches of endocardial thickening are often seen at the sites of mural thrombi. Cardiac valves and coronary vessels appear normally with the occasional presence of pericardial effusion.

Clinical Presentation

i. Symptoms

Dyspnea on exertion, cough, orthopnea, and paroxysmal nocturnal dyspnea are commonly seen in patients with PPCM and often mimic left ventricular failure. Cardiac thrombus formations are not uncommon, and they may present with embolic features like chest pain, hemoptysis, and hemiplegia. Though extremely rare, single, or multiple coronary embolisms (and myocardial infarctions) have taken place in patients with PPCM. Nonspecific symptoms like palpitations, fatigue, malaise, and abdominal pain may be present in 50% of cases.

ii. Signs

Blood pressure may be normal, elevated, or low. Tachycardia, gallop rhythm, engorged neck veins and pedal edema are commonly found. Clinically, the heart may be normal or there may be mitral and/or tricuspid regurgitation with pulmonary...
crepitations and hepatomegaly. Patients may even present with seizures associated with cerebral edema and cerebellar herniation.

**Diagnosis**

Diagnosis of PPCM is based on excluding common causes of cardiac failure such as infection, toxins and metabolic, ischemic, or valvular heart disease.

**Investigations**

Every patient should have an electrocardiogram (ECG), chest radiograph (CXR) and Doppler echocardiography for diagnosis.

**i. Electrocardiogram (ECG)**

ECG usually shows sinus tachycardia, though there may be features of atrial flutter/fibrillation, left atrial and ventricular hypertrophy (LVH), left axis deviation, nonspecific ST-T abnormalities, low voltage complex, arrhythmia, Q wave in anteroseptal leads and conduction abnormalities like prolonged PR, QRS intervals and bundle branch block.

**ii. Chest radiograph (CXR)**

There may be evidence of cardiomegaly, LVH, pulmonary edema, pulmonary venous congestion, and bilateral pleural effusion on CXR or it may be normal.

**iii. Doppler echocardiography**

Doppler echocardiography is the most essential diagnostic tool for assessing the severity and gauging the prognosis of PPCM patients. The role of routine EMB in PPCM patients is controversial. In the early part of the disease process gives a better positive result. EMB always carries some procedural risk and so it is best considered if the patient does not improve even after two weeks of conventional management.

**iv. Endomyocardial biopsy (EMB)**

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**v. Cardiac catheterization**

Cardiac catheterization is used for evaluation of left ventricular function, obtaining EMB and performing coronary angiography. It reveals elevated cardiac filling pressures and decreased CO and PAH. Coronary angiography should always be considered in patients with positive clinical and ECG features of IHD, acute coronary syndrome, hyperlipidemia, history of smoking and diabetes mellitus.

**vi. Other less frequently used investigations:**

polymerase chain reaction (PCR), compliment fixation test, blood culture, radionuclide ventriculography, immunofluorescence and immunohistochemical staining, estimation of cardiac enzyme, routine hematological, biochemical, and serological tests.

**Complications and Management**

Complications of PPCM include thromboembolism, arrhythmias, and organ failure. Medical management of PPCM is like that of heart failure. Fluid and salt restriction, digoxin, diuretics, vasodilators, and anticoagulants are the mainstays of treatment. Safety in pregnancy and lactation should always be considered before selecting a drug.

**i. Non-pharmacological measures**

Strict bed rest of 6-12 months, as had been advocated previously, is associated with a lower incidence of cardiomegaly, but the same results can be achieved without prolonged bed rest. Bed rest may in fact predispose the patient to deep venous thrombosis, increasing the risk of subsequent pulmonary embolism. Salt and fluid intake should be restricted to 2-4 gm/day and 2 L/day, respectively and are also important in symptomatic improvement.

**ii. Pharmacological management**

**a) Digoxin**

It is beneficial for its ionotropic and rate reducing effect and provides symptomatic relief without reducing the mortality rate. Continuing digoxin for 6-12 months may reduce the risk of recurrence of PPCM.

**b) Diuretics**

These are safe in pregnancy and lactation and are indicated for preload reduction and symptomatic relief when salt restriction fails. Metabolic alkalosis may develop due to diuretic-induced dehydration. Addition of acetazolamide will cause reduction of alkalosis by removing bicarbonate. However, spironolactone may not be safe in pregnancy and is better avoided in the antepartum period.

**c) Vasodilator**

Because of preload and afterload lowering effects, vasodilators are vital in heart failure management. They improve both CO and the outcome of the failing heart. Angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) are now considered a mainstay of management and have been shown to reduce mortality significantly in heart failure patients. They are contraindicated in pregnancy due to teratogenicity; ACEI are excreted in breast milk and thus breastfeeding should be discontinued in patients requiring ACEI.

**d) Calcium channel blockers**

Initially, the use of calcium channel blockers (CCB) was not acceptable in heart failure because of their negative contractile effect and the potential risk of uterine hypoperfusion. Amlodipine Survival Evaluation (PRAISE) trial, suggesting a potential role in PPCM management. Because of the lack of safety reports, breast feeding should be avoided in patients taking levosimendan.

**e) Beta blockers**

Like CCB, earlier beta blockers were also contraindicated in heart failure. Recent studies have documented their safety and efficacy in heart failure patients, though the survival rate is somewhat
confusing. The reduction of mortality and hospitalization in chronic heart failure patients has been documented by the US Carvedilol Heart Failure Program. Carvedilol has been safely used in pregnancy and PPCM.  

f) Antiarrhythmic agents
Antiarrhythmic agents may sometimes be required to treat symptomatic patients. No antiarrhythmic agent is completely safe in pregnancy. Non-pharmacological means like assurance, carotid massage or the Valsalva maneuver may be tried initially. Quinidine and Procainamide should be tried first because of their higher safety profile. Digoxin can be considered for atrial arrhythmias and adenosine can also be used in an emergency.  

g) Anticoagulant therapy
Patients with LVEF <35% and bedridden patients with atrial fibrillation, mural thrombi, obesity and a history of thromboembolism benefit the most from anticoagulant therapy. This situation may persist for as long as six weeks in the puerperium, necessitating the use of heparin in the antepartum and heparin or warfarin in the postpartum period. Warfarin is contraindicated in pregnancy for its teratogenic effect, but the use of both heparin and warfarin is safe in lactation.  

h) Immunosuppressive therapy
Immunosuppressive therapy with azathioprine and prednisolone has been tried in myocarditis positive PPCM patients.  

i) Immunoglobulin therapy
Human intravenous immunoglobulin (Ig) has been shown to improve ventricular dysfunction in six PPCM patients.  

j) Interferon
It has been used in biopsy-proven cases of viral myocarditis, resulting in improvement in echocardiographic parameters, however, it did not produce much symptomatic benefit in PPCM patients.  

k) Immunomodulation
Pentoxifylline, an immune-modulating agent known to reduce production of TNFα, CRP and Fas/Apo-1, was recently shown to improve NYHA class, LVEF and outcome in PPCM patients when combined with conventional treatment. More evidence is required before pentoxifylline can be recommended. However, the Myocarditis Treatment Trial failed to demonstrate any advantage of immunosuppressive therapy in PPCM patients.  

iii. Surgical management
Cardiac transplants are reserved for those who are resistant to all medical management. Aggressive measures like intra-aortic balloon pumps, ventricular assist devices or cardiopulmonary or veno-atrial bypass may sometimes be needed as bridging measures until recovery of cardiac function or definitive cardiac transplant.  

iv. Obstetric management
PPCM during the antepartum period demands intensive fetal and maternal monitoring. Though routinely not required, induction of delivery should be considered if a patient’s condition deteriorates despite maximal medical management. A multidisciplinary approach involving an obstetrician, cardiologist, anesthesiologist, and perinatologist may be required to provide optimal care to such patients.  

Regional analgesia reduces the cardiac stress of labor pain, while application of outlet forceps or a vacuum device can minimize the cardiac stress of the second stage of labor. Cesarean section has increased risk of blood loss, endometriosis and pulmonary embolism and is best done for obstetric indications as well as in severe decompensated situations. Following delivery, these patients need monitoring in an Intensive Care Unit (ICU) for early detection and management of uterine auto transfusion-induced pulmonary edema. Because of the high risk of thromboembolism with oral contraceptive pills (OCP), barrier contraceptive devices are better options for family planning surgical sterilization techniques like tubal ligation and vasectomy have also been used.  
v. Postoperative management
All PPCM patients should be managed in an ICU as they are prone to develop LVF and pulmonary edema in this period, requiring strict intake/output management. They may require vasoactive drugs, mechanical ventilation, and circulatory support at any time. There is also a high risk of thromboembolism, demanding proper anticoagulation. Postoperative pain can be managed by RA or parenteral opioid-based techniques.  

Recovery from PPCM
Clinical recovery consists of improvements of symptoms and discontinuation of anti-failure medications. Recovery of ventricular dysfunction has been defined as LVEF 50% or >20% improvement and LVFS 30% in PPCM patients.  

Mortality Rate of PPCM
Mortality rates of up to roughly 50% have been reported in the literature. Approximately half die within the first month of presentation and the majority within the first three months of postpartum period.  

Risk of Recurrence in Subsequent Pregnancy
Most reports describe recurrence of PPCM in subsequent pregnancies. It is not clear whether this is due to exacerbation of previous subclinical failures or reactivation of the same disease process.
Conclusion
PPCM is a rare but devastating cardiac failure of indeterminate etiology occurring in late pregnancy or early puerperium. Diagnosis of PPCM should include echocardiographic evidence of left ventricular dysfunction. Older risk and etiological factors need current reevaluation in view of modified diagnostic criteria. The present diagnostic role of EMB in PPCM is dubious but may be considered in resistant cases. Routine medical management should be started with digoxin, diuretics, vasodilators, β blockers and anticoagulants. In resistant cases, treatment with immunosuppressive drugs, immunoglobulin and pentoxifylline can be considered. Severe cases may need intensive management, including mechanical circulatory support and heart transplant.

Induction of labor should be done in an intensive care setting. The cesarean section should be reserved for obstetric indications. Regional techniques are safer for labor analgesia as well as anesthesia. Invasive monitoring is recommended in severe cases. Prognosis is related to recovery of ventricular dysfunction. Future pregnancy is better avoided in patients with persistent cardiac failure. If unavoidable, subsequent pregnancy in patients with improved cardiac function should be managed in a multidisciplinary unit.

Conflict of Interest: The authors declared to have no conflicts of interest.

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