Peripartum Cardiomyopathy: An Update

MOHAMMAD WALIDUR RAHMAN, MANZOOR MAHMOOD, HARISUL HOQUE, FAKHRUL ISLAM KHALED, MD. ABU SALIM

Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka

Address of Correspondence: Dr. Mohammad Walidur Rahman, Resident, Department of Cardiology, BSMMU, Dhaka
E-mail: walid.dmck61@gmail.com

Abstract:
Peripartum cardiomyopathy is a life threatening entity of peripartum period characterized by left ventricular systolic dysfunction and heart failure in absence of any known cardiac disease. Though its incidence is rising but till now its incidence, pathogenesis, optimum management protocol are not known. Oxidative stress–prolactin hypothesis, anti-angiogenic-signalling excess hypothesis, viral myocarditis and genetic predisposition are some attractive etiologic explanation but nothing is proven comprehensively. Novel biomarkers and role of new imaging modalities are being investigated. As benefit by targeted therapy like bromocriptine or pentoxifylline are inconsistent, so controlling volume status, neutralizing maladaptive neurohormonal response and treatment of complications are required, prognosis is reasonably good. The aim of this review to highlight its pathophysiology, emerging investigations modalities, and updated management protocol.

Introduction:
Peripartum cardiomyopathy (PPCM) is an idiopathic form of cardiomyopathy where heart failure (HF) occurs due to impairment of left ventricular (LV) systolic function toward the end of the pregnancy or during the post-partum period in the absence of preexisting heart disease. The European Society of Cardiology (ESC) Working Group on PPCM has set the diagnostic criteria. In presence of heart failure, LV ejection fraction should be less than 45% but LV may not be overtly dilated. Though right ventricular dysfunction is not included in the diagnostic criteria but its presence denotes poor prognosis. It is a cause of significant mortality & morbidity among young woman throughout the world.

Epidemiology:
The exact incidence & prevalence of PPCM is unknown. It varies widely across different part of the world with highest incidence in north-south gradient, ranging from about one per 300 in Haiti, one per 1000 live births in South Africa and up to one per 3000 live births in US and Western Europe. Genetic and environmental factors, lack of uniformity in diagnostic criteria, cultural and puerperal practices may be responsible for these heterogeneity and its incidence is increasing over time reflecting growing awareness about this fatal entity. There is no data regarding the incidence of PPCM in Bangladesh.

Pathogenesis and contributing factors
The pathophysiology of PPCM is yet to be clarified. Though there are some attractive hypotheses but none is proven as single etiology. The identifiable contributing factors are black ethnicity, advanced maternal age, obesity, multifetal pregnancy, prolonged use of tocolytics and history of hypertensive disorders of pregnancy. Oxidative stress–prolactin axis hypotheses, angiogenic imbalance, viral myocarditis, abnormal response to hemodynamic stress of pregnancy, immune mediated injury, genetic predisposition, micronutrient deficiency are some probable pathophysiologic mechanism.

Oxidative stress–prolactin axis hypothesis suggests oxidative stress activates lysosomal enzyme, cathepsin D that in turn cleaves serum prolactin into its antiangiogenic and proapoptotic 16-kDa prolactin sub fragment. This subunit may cause microvascular dysfunction and cardiac injury.

Diagnosis

Clinical presentation
It’s a diagnosis of exclusion & high index of clinical suspicion is required. Symptoms of PPCM (dyspnea, orthopnea, oedema, palpitations) mimick symptoms of normal pregnancy so late presentation with complicatons like ventricular arrhythmias, venous or arterial emboli are not infrequent. Approximately 75%
of cases are diagnosed within the first month after delivery, and 45% occur in the first week. Physical examination may reveal signs of heart failure, including tachycardia, hypotension, elevated jugular venous pulsation, peripheral edema, and pulmonary crackles. Signs of LV dilatation like displaced apical impulse, third heart sound may be found but not invariably present.

**ECG**
Usually show sinus tachycardia with nonspecific changes. Bundle branch block, T-wave changes (59%), P-wave abnormality (29%), QRS-axis deviation (25%) were found in a case series.

**Echocardiography**
It is the single most important tool to diagnose PPCM, exclude the differentials, and find out the complications like embolism and pericardial effusion. It usually demonstrates global hypokinesia of LV with impairment of systolic function (LVEF<45%). LV dilatation is not obligatory. Diastolic dysfunction of LV may also predominate sometimes. Right ventricle is frequently affected though its not included in the diagnostic criteria. Functional regurgitation involving mitral and tricuspid valve may be found along with pulmonary hypertension. New echocardiographic modalities like speckle tracking is yet to be validated in PPCM.

**Chest X ray**
Features of vascular redistribution, cardiomegaly and pleural effusion are usually found.

**Biomarkers**
B type natriuretic peptide are increased in acute stage which reflects increased end diastolic pressure.

**Novel biomarkers**
Few potential novel biomarkers that need to be validated in near future are combination of cathepsin D, miR-146a, ratio VEGF/sFlt1 and serum asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction.

**Cardiac magnetic resonance imaging (MRI)**
CMRI can exclude other form of cardiomyopathy and detect LV volumes and function more precisely but can not predict LV function recovery. Whether PPCM is characterized by a specific late gadolinium enhancement (LGE) pattern predictive of recovery is still debated.

**Endomyocardial biopsy**
Endomyocardial biopsy is not currently recommended in diagnosis and prognosis assessment of PPCM.

**Differential Diagnoses**
As it is a diagnosis of exclusion so more common cause of heart failure like rheumatic heart disease, myocarditis, dilated cardiomyopathy from other cause, coronary artery disease must be excluded prior to making diagnosis.

**Management**

**Acute phase**
Treatment is focused on controlling volume status, counteracting maladaptive neurohormonal response and preventing complications like thromboembolism and arrhythmias. In case of congested patients salt and fluid should be restricted. Judicious use of diuretics should be ensured during pregnancy as there is risk of placental hypoperfusion. If systolic blood pressure allows then intravenous vasodilators like hydralazine and nitroglycerine can be considered. Angiotensin converting enzyme inhibitors and angiotensin receptors blockers should be avoided during pregnancy due to fetotoxicity. Enalapril, captopril and benazepril are preferred during breastfeeding. Beta blockers preferably metoprolol can be used throughout the entire period after stabilization of acute heart failure. In our center, digoxin is being used along with standard treatment with reasonably good outcome.

In case of low cardiac output syndrome, inotropes like dobutamine and levosimendan can be used. If the patient does not response to the medical management then mechanical circulatory support in the form of intra-aortic balloon counterpulsation (IABP) is instituted. In case of multiorgan dysfunction syndrome and non responder to IABP is managed with ECMO as a bridge to recovery, to LV assist device (LVAD) implantation or to heart transplantation.

Patient should be anticoagulated and continued for at least two months postpartum, if LVEF<35% or other indications for anticoagulations are present. Vitamin K antagonists (VKAs) are contraindicated in first trimester if the dose exceeds 5mg per day. Heparin and unfractionated heparin are safe in all trimester , and the former is preferred near term because of its shorter half-life.

**Targeted therapy**
Bromocriptine, an ergot alkaloid and dopamine D2-receptor antagonist has emerged as a potential useful treatment for PPCM. Due to lack of consistent results in the trials and risk of thromboembolic complications
like cerebral ischaemia and myocardial infarction its routine use is currently limited.\textsuperscript{23}

Immunomodulation by pentoxifylline and intravenous immunoglobulin have failed to offer any benefit.\textsuperscript{24,16}

**Long term management**

As clinical course is variable and LVEF recovery may take up to six months in the majority of patients invasive therapies (cardiac resynchronization therapy and/or intracardiac defibrillator (ICD) implantation) may be wisely postponed for up to six months.\textsuperscript{1} However, in case of increased risk of sudden cardiac death, subcutaneous ICD or wearable external defibrillator may be considered immediately.\textsuperscript{25}

In advanced and refractory HF or in whom LVAD weaning fails, heart transplantation is the only therapeutic option though the prognosis is variable.\textsuperscript{1}

**Treatment duration**

There is no general agreement, for how long the treatment should be continued. ESC working group on PPCM has advocated to continue ACE inhibitors and beta blockers for at least one year but decision should be individualized based on clinical and echocardiographic recovery.\textsuperscript{1}

**Obstetric management**

**Delivery**

There is no data available to support optimum timing and mode of delivery and decision should be taken by a team consisting of cardiologists and obstetricians. Strategy and timing depend upon hemodynamic status of mother, fetal maturity and obstetrical factors.\textsuperscript{26} In case of hemodynamic instability, urgent delivery should be targeted preferably by C section, irrespective of gestational age.\textsuperscript{26} Vaginal delivery is preferred in stable cases as it is associated with less blood loss, less thromboembolic and infectious complications.\textsuperscript{1}

Pain control

Epidural analgesia is preferred.\textsuperscript{1}

**Breast Feeding**

Though breast feeding avoidance may be theoretically beneficial according to oxidative stress-prolactin axis hypothesis but it is not evidence based. Rather recovery rate is higher in lactating mother challenging this hypothesis.\textsuperscript{27}

**Subsequent pregnancies**

Recurrence risk of PPCM depends upon extent of LV recovery. Patients with full recovery (LVEF>55%) have 17% chance of recurrent failure whereas who recover incompletely (LVEF<55%) have 46.2% risk of heart failure in subsequent pregnancies.\textsuperscript{28} So, family planning counselling is of paramount importance. Dobutamine stress echocardiography can be used to risk stratify women with subnormal LVEF.\textsuperscript{29}

**Predictors of recovery and prognosis**

Improvement of LVEF>50% at six months is defined as recovery from PPCM.\textsuperscript{1} In BSMMU, 72% patients improved clinically, 15% developed persistent cardiomyopathy, 14% had thromboembolic events and 13% died.\textsuperscript{30}

LVEF and LV dimensions are the best predictors of recovery.\textsuperscript{16} Lower level of plasma troponin and brain natriuretic peptide, diagnosis made after delivery, breast feeding, non-African ethnicity favorably affect the outcome.\textsuperscript{16,27}

**Conclusion:**

High index of clinical suspicion is required to diagnose this potentially dangerous syndrome. Significant progresses have been made regarding the pathogenesis over the last few years but this attractive hypotheses should be translated into treatment benefit. Further studies are required regarding safety and efficacy of bromocriptine prior to its routine use. Though the chance of recovery is high but chance of relapse is also not less in subsequent pregnancies.

**References:**

1. Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: A position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail 2010; 12: 767–778.

2. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy : National Heart Lung and Blood Institute and Office of Rare Diseases (National Institute of Health) workshop recommendations and review. JAMA 2000; 283: 1183-1188.

3. Nadia Bouabdallaoui1, Frederic Mouquet2, Guillaume Lebret1, Pierre Demondion1, Thierry H Le Jenet3 and Pierre V Ennezat. Current knowledge and recent development on management of peripartum cardiomyopathy. European Heart Journal: Acute Cardiovascular Care 2017, Vol. 6(4) 359–366.

4. Blauwet LA and Cooper L. Diagnosis and management of peripartum cardiomyopathy. Heart 2011; 97: 1970–1981.

5. Mieleniczuk LM, Williams K, Davis DR, et al. Frequency of peripartum cardiomyopathy. Am J Cardiol 2006; 97: 1765–1768.

6. Hilfiker-Kleiner D and Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. Nat Rev Cardiol 2014; 11: 364–370.
7. Melvin KR, Richardson PJ, Olsen EG, et al. Peripartum cardiomyopathy due to myocarditis. N Engl J Med 1982; 307:731–34.
8. Rizeq MN, Rickenbacher PR, Fowler MB, et al. Incidence of myocarditis in peripartum cardiomyopathy. Am J Cardiol 1994; 74: 474–477.
9. Ansari AA, Fett JD, Carraway RE, et al. Autoimmune mechanisms as the basis for human peripartum cardiomyopathy. Clin Rev Allergy Immunol 2002; 23: 301–24.
10. Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell 2007; 128: 589–600.
11. Van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, et al. Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. Circulation 2010; 121: 2169–75.
12. Patten IS, Rana S, Shahul S, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature 2012; 485: 333–38
13. Halkein J, Tabruyn SP, Riche-Hoch M, et al. MicroRNA-146a is a therapeutic target and biomarker for peripartum cardiomyopathy. J Clin Invest 2013; 123: 2143–54.
14. Goland S, Modi K, Bitar F, et al. Clinical profile and predictors of complications in peripartum cardiomyopathy. J Card Fail 2009; 15: 645–50.
15. Elkayum U. Clinical characteristics of peripartum cardiomyopathy in United States: diagnosis, prognosis, and management. J Am Coll Cardiol. 2011; 58: 659-70.
16. Arany Z, Elkayum U. Peripartum cardiomyopathy. Circulation. 2016; 133: 1397-1409.
17. Tibazarwa K, Lee G, Mayosi B, et al. The 12-lead ECG in peripartum cardiomyopathy. Cardiovasc J Afr 2012; 23: 322–29.
18. Grant AD, Negishi K, Negishi T, et al. Grading diastolic function by echocardiography: hemodynamic validation of existing guidelines. Cardiovasc Ultrasound 2015; 13: 28.
19. Walenta K, Schwarz V, Schirmer SH, et al. Circulating microparticles as indicators of peripartum cardiomyopathy. Eur Heart J 2012; 33: 1469–79.
20. Mouquet F, Lions C, de Groote P, et al. Characterisation of peripartum cardiomyopathy by cardiac magnetic resonance imaging. Eur Radiol 2008; 18: 2765–69.
21. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006; 354: 2443–51.
22. Gevaert S, Van Bellegem Y, Bouchez S, et al. Acute and critically ill peripartum cardiomyopathy and ‘bridge to’ therapeutic options: A single center experience with intra-aortic balloon pump, extra corporeal membrane oxygenation and continuous-flow left ventricular assist devices. Crit Care 2011; 15: R93.
23. Fett JD. Caution in the use of bromocriptine in peripartum cardiomyopathy. J Am Coll Cardiol 2008; 51: 2083–84.
24. Ansari AA, Fett JD, Carraway RE, et al. Autoimmune mechanisms as the basis for human peripartum cardiomyopathy. Clin Rev Allergy Immunol 2002; 23: 301–24.
25. de Bie MK, Thijsen J, van Rees JB, et al. Suitability for subcutaneous defibrillator implantation: Results based on data from routine clinical practice. Heart 2013; 99: 1018–23.
26. Phillips SD and Warnes CA. Peripartum cardiomyopathy: Current therapeutic perspectives. Curr Treat Options Cardiovasc Med 2004; 6: 481–88.
27. Safirstein JG, Ro AS, Grandhi S, et al. Predictors of left ventricular recovery in a cohort of peripartum cardiomyopathy patients recruited via the internet. Int J Cardiol 2012; 154: 27–31.
28. Fett JD, Sannon H, Thélisma E, et al. Recovery from severe heart failure following peripartum cardiomyopathy. Int J Gynaecol Obstet 2009; 104: 125–127.
29. Dorbala S, Brozena S, Zeb S, et al. Risk stratification of women with peripartum cardiomyopathy at initial presentation: A dobutamine stress echocardiography study. J Am Soc Echocardiogr 2005; 18: 45–48.
30. Fatema N, Banerjee SK, Ahmed CM, et al. Clinical profile and outcome of peripartum cardiomyopathy: a study in tertiary cardiac hospital of Bangladesh. Mymensingh Med J. 2018 Apr;27(2): 298-303