Asian Research Journal of Gynaecology and Obstetrics

5(2): 34-39, 2021; Article no.ARJGO.67885

Peripartum Cardiomyopathy: An Enigma

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

Editor(s):
(1) Dr. Eghon Guzman B, Hospital Dr. Sotero del Rio, Santiago, Chile.
Reviewers:
(1) Erhan Huseyin Comert, Gole State Hospital, Turkey.
(2) Sanjana Narula Wadhwa , ESIC Post Graduate Institute of Medical Sciences and Research, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/67885

Review Article

Received 27 February 2021
Accepted 04 May 2021
Published 07 May 2021

ABSTRACT

Peripartum cardiomyopathy is a rare, potentially life-threatening disorder affecting women in late pregnancy & the postpartum period. In spite of identification of at-risk demographics, theories on etiology, and new targets of therapy for the entity , it still remains an enigma for obstetricians worldwide. The management of PPCM has been guideline-based treatment for cardiac failure with reduced ejection fraction. Though many newer studies have reported the efficacy of novel therapies, much more research needs to be done. Here an attempt is being made to review the pathogenesis and diagnosis of PPCM and discuss some of the newest therapies for this enigmatic entity.

Keywords: Cardiomyopathy; heart failure; peripartum cardiomyopathy; pregnancy; peurperium; reduced ejection fraction.

ABBREVIATIONS

CMP : Cardiomyopathy;
CHF : Congestive Heart Failure;
ECG : electrocardiography;
ECHO : echocardiography;
LVEF : Left Ventricular Ejection Fraction;
PPCM : Peripartum cardiomyopathy;
PCR : Polymerase Chain Reaction

1. INTRODUCTION

Peripartum Cardiomyopathy– the term officially coined by Demakis and Rahimtoola (1971) [1,2] as congestive heart failure (CHF), occurring during the peripartum period , was first described

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as early in 1849 in medical literature [1,3]. Since then, greater understanding of the condition through bigger data collection and improved diagnostic methods have led to PPCM becoming a well defined form of congestive heart failure. Even today, it remains a rare but significant cause of maternal morbidity and mortality [1]. This review is being undertaken with the purpose of summarizing the current data concerning epidemiology, etiology, proposed pathogenesis, diagnosis and new strategies for therapy and prognosis of peripartum cardiomyopathy.

The first diagnostics criteria proposed by Demakis and Rahimtoola were:

- Development of congestive cardiac failure in the last month of pregnancy or with in 5 months of delivery.
- Absence of any other etiology of congestive heart failure (CHF)
- Absence of cardiac disease before pregnancy [1,2]

In 1997, The National Heart, Lung and Blood Institute of Health adopted these 3 criteria and added echocardiographic (ECHO) criteria [1,4] –

- Left Ventricular Systolic Dysfunction with a left ventricular ejection fraction (LVEF) < 45 %
- A fractional shortening < 30 % or
- Both with/without Left Ventricular end-diastolic dimension > 2.7 cm/m^2 [1,5]

In 2010, The European Society of Cardiology Working group on PPCM released a modified definition with time specifications and LV dimensions of PPCM. The new modified definition stated peripartum cardiomyopathy as an idiopathic cardiomyopathy presenting with congestive heart failure towards the end of pregnancy or in the early months following delivery, where no other etiology of CHF is found in which Left Ventricle may or may not be dilated but the left ventricular ejection fraction (LVEF) is almost always < 45 % (1,6).

1.1 Epidemeology

Peripartum cardiomyopathy shows a wide geographic variation with higher incidences in developing world as compared to European or developed nations. In the US incidence ranges from 1/4075 – 1/3180, [1,6,7], Haiti - 1/300 live births [1,8], South Africa (1/1000) [9], 1/102 in Nigeria [10], 1/830 in Pakistan and 1/1374 in South India [1,11].

Several risk factors have been identified for development of Peripartum cardiomyopathy eg.

- African American ethnicity- highest risk (1/1421 births).
  Asians (1/2675) Caucasians (1/4075) and Hispanics (1/8861) [1,6,7]
- Age (age > 29.5 years)
- Pre eclampsia / Eclampsia
- Multiparity
- Multiple gestation
- Obesity
- Chronic hypertension
- Prolonged Tocolytic drugs usage

1.2 Etiopathogenesis of Peripartum Cardiomyopathy

Though the exact underlying mechanism remains unknown, numerous etiologic theories have been proposed for PPCM which include hormonal abnormalities, inflammatory response viral pathogens, autoimmunity and genetic predisposition [1,12,13,14,15,16,17].

- Numerous contributing factors have been identified eg. Traditional risk factors for cardiovascular diseases – namely hypertension, DM, cigarette smoking, atherosclerosis, dyslipidemia and obesity. Other pregnancy associated factors play significant role e.g. Number of pregnancies, multiple gestation, induction of labour, malnutrition, advanced maternal age. [1,18,19].

- **Prolactin, 16kDa prolactin and cathepsin D:**

Pregnancy is associated with an increase in oxidative stress which is accompanied by a delay in antioxidant capacity [1,18,19]. This increased oxidative stress leads to release of prolactin-cleaving protease and cathepsin D, which cleaves hormone prolactin from its 23 kDa form to its 16 kDa form (this isoform has proven deleterious effects on the cardiovascular system viz.

- Induction of endothelial cell apoptosis
- Capillary dissociation
- Capillary vasoconstriction

These disrupt the cardiomyocytic metabolism and function resulting in PPCM [1,19,20,21].

This cascade of events is further aided by bromocriptine (prolactin inhibitor) which has been shown to prevent development of PPCM in experimental studies on mice.

- **Inflammation:**

Though oxidative stress has been proved in the etiopathogenesis of PPCM, Inflammation also is an important contributing factor as evidenced by rise in serum markers, of nonspecific inflammation e.g., soluble death receptor aFas/Apr-1, C-reactive Protein, Interferon gamma, Interleukin IL- 6 and 8, in PPCM [1,17,19,21,22,23]. Furthermore, Pentoxifylline (an anti-inflammatory agent), has shown clinical benefit in a non-randomized trial of 59 PPCM patients [1,24].

- **Viral pathogen:**

Pregnancy represents a state of compromised immunity which leads to increased susceptibility not only to newly acquired viruses but also to the reactivation of otherwise latent viruses [1,25]. A study reported presence of viral genomes in cardiac tissue of 26 PPCM patients on endomyocardial biopsy and PCR testing [1,26]. 8 of these had detectable viral genomes associated with histologic evidence of inflammation. Ebsten Barr Virus (EBV), Human CytoMegaloVirus (CMV), Human Herpes virus 6 and Parvovirus [1,26,27]. Selle et al reported prevalence of viral myocarditis in PPCM ranging between 8.8%- 78% [1,27].

- **Genetics:**

PCM has been traditionally defined as a non-genetic / non- familial form of dilated cardiomyopathy (DCM) (1,31), However, numerous studies have suggested possibility of genetic predisposition [1] Mortals et al studied 520 families with non-ischemic DCM out of which 19 cases met the criteria set for PPCM [1]. And had the following genetic mutations – 3 with mutations in MYH7, SCN5A and PSEN2 and 2 were sporadic with mutations in MYHA6 and TNNT2. Van Spaendonak-Zwarts et al revived 90 families from a familial DCM registry and reported 5 (6%) families with patients who met the criteria for PPCM; 1 of which had mutation associated with TNCC1 gene which codes for cardiac troponin C [1] These findings could have implications concerning family counseling and prognosis in future.

1.3 Clinical Presentation

Patients can have variable presentations clinically ranging from mild symptoms to New York Heart Association (NYHA) Class IV symptoms. A high index of suspicion is necessary while diagnosing PPCM given the significant overlap of symptoms of early disease and physiological changes associated with pregnancy. Signs and symptoms e.g. Pedal edema, dyspnea on exertion, tiredness, easy fatiguability, orthopnoea, persistent cough is common in pregnancy and pregnancy related conditions e.g. anemia- which might delay in diagnosis. However, the commonest presentation initially is NYHA functional Class III or IV – therefore diagnosis is hard to miss. Some might present with ventricular arrythmias, cardiac arrest or frank congestive cardiac failure (CCF) [1].

Pregnancy, being a hypercoagulable state, in combination with a left ventricular ejection fraction (LVEF) < 35 %, increases the risk of Left Ventricular thrombus formation [1]. Many patients have reported initially with systemic embolism including cardiovascular diseases, mesenteric ischemia and myocardial infarction [1].

Almost 70-80% of patients present in the postpartum period (typically within the first four months after delivery). Only about 9-10% present in the last month of pregnancy while the remaining 10-12 % present either before the last month of pregnancy or more than 4 months post-delivery.

PPCM patients have the same physical findings on clinical examination as congestive heart failure with systolic dysfunction e.g. tachycardia, tachypnea, jugular venous distension, displaced apical impulse, Mitral Regurgitation and Tricuspid Regurgitation murmurs, loud S3,S3 gallop rhythm, pulmonary basal rales, hepato-splenomegaly, ascites and peripheral edema.

2. DIAGNOSIS

PPCM should be kept in the list of differential diagnosis while encountering any new onset heart failure especially in a pregnant or puerperal woman. It is a diagnosis of exclusion and one must rule out both cardiac and non-cardiac causes especially those related to the complex physiological changes associated with pregnancy [1,28,6]. A detailed and thorough history taking

and meticulous physical examination, initial workup including routine investigations ([CBC, basic metabolic panel, Liver Function Test, Thyroid Function Test, urine analysis], a 12-lead ECG and 2D-echocardiogram, chest x-ray

- **ECG**: electrocardiogram:

In the initial assessment of a patient with suspected peripartum cardiomyopathy- a 12 lead ECG is the first investigation required. Almost 95% of these patients have an ECG abnormality (pathologic Q-waves, ST- depression, T- wave inversion, 2nd degree or 3rd degree AV block, complete left or right Bundle Branch Block, Atrial Fibrillation or Atrial flutter and atrial or ventricular ectopy).Though ECG abnormalities are common in PPCM, a normal ECG tracing does not rule out the diagnosis.

- **ECHO**: Echocardiogram:

Transthoracic echocardiogram (TTE) is central to the diagnosis of peripartum cardiomyopathy- to establish a reduced LVEF (< 45%) which is mandatory for diagnosis of the same [1,28,6]. This also helps in ruling out other causes of heart disease and rule out Left Ventricular thrombus [1]. Apart from its diagnostic value, Left Ventricular End Diastolic diameter (> 60mm) and left ventricular ejection fraction (LVEF) <30% have been proven to be poor predictors of recovery of the left ventricular function [1].

- **Cardiac MRI:**

Cardiac MRI is more accurate in measuring the size of the heart chambers and Left Ventricular Function as compared to 2D Echo with a significantly higher sensitivity in detecting Left Ventricular thrombus. Though PPCM doesn't have any specific pattern of gadolinium enhancement, cardiac MRI is useful in excluding myocarditis and other forms of infiltrative disease affecting the myocardium.

- **Imaging Follow Up:**

Follow up of such patients is very important – not only to assess the disease status, but also to assess the return to normal cardiac functional status. Echocardiography should be repeated before discharging the patient which is to be followed by a transthoracic echocardiography at 6 weeks, 6 months and then every year to assess the response to therapy [1,4,28]. If MRI is the main imaging modality being used, it should be repeated at 6 months and 1 year after discharge [1,4,28].

- **Serum markers:**

The most widely used serum marker in peripartum cardiomyopathy is N-terminal Pro-BNP (NT-proBNP)—which has a good sensitivity and can provide efficient screening for PPCM [1,27,28]. since almost all the patients with PPCM have increased levels of serum NT-proBNP [1,26,27].

Other serum bio-markers being tried are microRNA-146a, cathepsin D and Interferon gamma (IF-γ) but lack of free availability, high cost factor and need for further research have limited their use routinely in evaluation and follow up of patients of peripartum cardiomyopathy [1,28,6].

2.1 Treatment of Peripartum Cardiomyopathy

The initial management of peripartum cardiomyopathy is same as treatment of other forms of dilated cardiomyopathy with drugs which are safe in pregnancy. ACE inhibitors, should not be used in 2nd or 3rd trimester , and goal-directed medical therapy should be instituted with selective beta-antagonist e.g. metoprolol as mainstay, nitrates and hydralazine are both safe in pregnancy, loop diuretics e.g. furosemide is used for symptomatic treatment of volume overload.

Patients presenting with fulminant cardiac failure with signs and symptoms of cardiogenic shock and/or low-output state – require Inotropes (dobutamine) to be initiated immediately. Anticoagulation is required if left ventricular thrombus is detected – with Heparin (UnFractionated / Low Molecular Weight Heparin) [1,4,28,6].

2.2 Novel Therapies for Peripartum Cardiomyopathy

- Bromocriptine: This is the most promising novel therapies used for peripartum cardiomyopathy and has showed greater return of left ventricular function (LVF) at 6 months in patients when treated with Bromocriptine therapy (due to reduction of oxidative stress).

- Pentoxiphylline: It is an anti-inflammatory drug which inhibits production of tumor necrosis factor alpha (TNF-α). Many randomized controlled studies studies on peripartum cardiomyopathy treated with and without Pentoxyphylline 400mg thrice daily showed promising results in follow-up; though further research is required in this field to be taken as a serious treatment modality for the same.
- Intravenous Immunoglobulin (IVIG): Autoimmunity also has been implicated in the etio-pathogenesis of peripartum cardiomyopathy, therefore, IVIG is a therapeutic option of promise. In a small study, IVIG group showed an improved absolute increase in Left Ventricular Ejection Fraction as compared to conventional treatment group (26% against 13%) [1,5,6].

2.3 Prognosis of Peripartum Cardiomyopathy

Though there is a lack of large prospective trials assessing the prognosis in patients with peripartum cardiomyopathy, nevertheless, many factors have been identified which might be independent predictors of prognosis – especially echocardiographic findings.

The favorable prognostic factors are:

- Small diagnostic dimension (< 5.5-6 cm)
- Elevated systolic function (LVEF > 30%) and fractional shortening > 20% at the time of diagnosis (1,37,38,40)
- The presence of persistent troponin elevation (> 0.04 ng/ml) 2 weeks after the initial presentation with PPCM is associated with persistent Left Ventricular dysfunction (LVEF ≤ 50%)
- African -American ethnicity – poor prognosis.
- Presence of Left Ventricular thrombus – poor prognosis and poor return to normal Left Ventricular function in future

Overall, with the advent of better diagnostic facilities and management options especially advent of device therapy has significantly improved the overall 5-year survival rate to 90-95 % in recent years [1,12,28,13].

3. COUNSELING OF THE PATIENT AND CONCLUSION

Peripartum cardiomyopathy, though rare, is a life-threatening condition which can result in significant morbidity and mortality if diagnosis and treatment is delayed. It has a high rate of relapse of congestive heart failure and mortality associated with subsequent pregnancy.

High rate of recurrence is seen in subsequent pregnancies especially in those with persistent Left Ventricular dysfunction [1]. Counseling patients with past history of peripartum cardiomyopathy on future pregnancies can be a difficult task which requires a multi-disciplinary approach involving an Obstetrician, Cardiologist and Neonatologist. Any patient with persistent Left Ventricular dysfunction and/or Left Ventricular Ejection Fraction 25% should be counseled against going for any subsequent pregnancies.

To conclude, peripartum cardiomyopathy, though is a diagnosis of exclusion, requires a high index of suspicion for not missing the entity and still remains an enigma today. Though early diagnosis and preservation of Left Ventricular Function are very important for better prognosis. In recent years, we have had significant development in the understanding, diagnosis and management resulting in improvement in survival of the patients. Novel therapeutic interventions e.g. Bromocriptine and Pentoxyphylline have shown promising results though more research and studies are required.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/67885