

Peripartum Cardiomyopathy

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Abstract

Peripartum cardiomyopathy (PPCM) is a rare form of unexplained cardiac failure of unknown origin, unique to the pregnant woman with highly variable outcome associated with high morbidity and mortality. PPCM is fraught with controversies in its definition, epidemiology, pathophysiology, diagnosis and management. PPCM is frequently under diagnosed, inadequately treated and without a laid down follow-up regimen, thus, the aim of this review. Publications on PPCM were accessed using Medline, Google scholar and Pubmed databases. Relevant materials on PPCM, selected references from internet services, journals, textbooks, and lecture notes on PPCM were also accessed and critically reviewed. PPCM is multifactorial in origin. It is a diagnosis of exclusion and should be based on classic echocardiographic criteria. The outcome of PPCM is also highly variable with high morbidity and mortality rates. Future pregnancies are not recommended in women with persistent ventricular dysfunction because the heart cannot tolerate increased cardiovascular workload associated with the pregnancy. Although, multiparity is associated with PPCM, there is an increased risk of fetal prematurity and fetal loss. PPCM is a rare form of dilated cardiomyopathy of unknown origin, unique to pregnant women. The pathophysiology is poorly understood. Echocardiography is central to diagnosis of PPCM and effective treatment monitoring in patients of PPCM. The outcome is highly variable and related to reversal of ventricular dysfunction.

Keywords: Cardiomyopathy, Echocardiography, Peripartum, Pregnancy

Introduction

Peripartum cardiomyopathy (PPCM) is defined as the development of cardiac failure between the last month of pregnancy and 5 months postpartum, the absence of an identifiable cause, the absence of recognizable heart disease prior to the last month of pregnancy, and left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria.^[1-6]

PPCM is a rare form of dilated cardiomyopathy of unknown origin, that is unique to the pregnant women of all reproductive ages.^[4,7,8] It affects previously healthy pregnant women with a low incidence of 0.1% of pregnancies but has a high morbidity and mortality rate ranging from 7% to 50%.^[8-10] The outcome of PPCM is highly variable.^[4]

In some patients, the clinical and echocardiographic status improve rapidly and may return to normal while for others it may progress and the clinical condition rapidly worsens, even with medical therapy to chronic cardiac failure and sudden cardiac death.^[3,11]

The pathophysiology is still controversial. The basis of human PPCM cannot be explained by a single etiology, thus, the disease has multifactorial origin.^[6] In acute cases, treatment may involve the use of intravenous vasodilatation, inotropic medications, an intra-aortic ballon pump, ventricular-assist devices, and extracorporeal membrane oxygenation. In severe cases, women experience a rapid deterioration in health without improvement even with medical therapy, and may require cardiac transplantation or die of heart failure, thrombo-embolic events and cardiac arrhythmias.^[11] However, the initial severity of left ventricular dysfunction or dilatation is not necessarily predictive of long-term functional outcome.^[11] Survivors of PPCM often recover from the left ventricular dysfunction, however, they may be at risk of recurrence for heart failure and death in subsequent pregnancies. Women with chronic left ventricular dysfunction should be managed according to guidelines of the American College of Cardiology Foundation and the American Heart Association.^[12] Careful assessment of

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the risk-factors in pregnant women could help in the prevention of PPCM. Monitoring equipment (tools) to stratify women by risk who have recovered from PPCM are needed to predict the risk of future pregnancies.

In this article, we reviewed the current status of PPCM.

Materials and Methods

A search of literature on PPCM published in English was conducted. Relevant materials on PPCM were selected, selected references, conference papers, technical reports, journal articles, abstracts, relevant books, lecture notes and internet articles using Medline, Google scholar, and Pubmed databases were critically reviewed.

Historical perspective/developments/refinements

PPCM was first defined in 1971 as myocardial disease that occurs for the first time towards the end or in the early stage of pregnancy.^[13] In 1978, PPCM was described in Zaria (Northern Nigeria).^[14] A high prevalence was reported in Nigeria-1 in 100 live births.^[15,16] This is the highest incidence of PPCM in the world. It is attributed to traditional practices of the people of Zaria province of Nigeria. It occurs in the hot season with its etiology linked with hypervolemia following prolonged lying on heated mud beds for about 18 h a day according to the local custom for Hausa woman. Room temperatures may reach as high as 40°C and the woman is made to increase her salt intake excessively by ingesting 'Kanwa' salt from Lake Chad for 40 days after delivery in attempt to stimulate breast milk production. The high salt intake leads to volume overload.^[14] This custom is now practiced only in the rural areas with little or no modern obstetric care.^[14]

A modification of the earlier definition in 1971 was done in 2000^[3] with addition of a strict echocardiographic criterion.^[5] The National Heart, Lung, and Blood Institute and the Office of Rare Diseases workshop adopted the modified definition in 2000.^[3] In 2010, the European Society of Cardiology Working Group on PPCM,^[17] proposed a modification to the existing definition of PPCM. PPCM is defined as an idiopathic cardiomyopathy manifested as heart failure due to left ventricular systolic dysfunction toward the end of pregnancy or in the months after delivery when no other cause of heart failure is found. Thus, PPCM is a diagnosis of exclusion, suggesting that a broader definition would eliminate PPCM as a missed diagnosis.^[17]

Epidemiology

The real incidence is unknown.^[15] The incidence varies among geographical regions.^[15] Reported incidences range from 1 in 299 live births in Haiti,^[16] to 1 in 100 in Northern parts of Nigeria^[15,16] to 1 case per 6000 live births in Japan,^[18] to 1 in 1000 in South Africa,^[19] to 1 in 2229 live births in Southern California,^[20] to 1 in 4000 live births in the

United State.^[3] There is wide variation in the incidence of PPCM because the diagnosis is not always consistent and a comparison with age-matched non-pregnant women does not exist.^[3,18,21] Furthermore, the wide variation may be as a result of geographic differences and reporting patterns.^[22] In low resource setting, limited access to echocardiography may lead to over estimation of PPCM.^[23]

Risk factors

Multiple risk-factors have been identified and include advanced maternal age, multiparity, multiple pregnancies, pregnancies complicated by pre-eclampsia, gestational hypertension, long term tocolysis, and African race.^[2,3,18,19,24] PPCM is more frequent in women at the extremes of childbearing ages and in older women of higher parity.^[3,25] PPCM has been reported in 24-37% of young primigravidae.^[10,18,26]

Etiology

The etiology of PPCM is unknown. The precise mechanism that leads to PPCM remain poorly understood. Multiple etiological processes have been suggested.^[3,22,27,28] Recently, a familial predisposition to PPCM has been reported.^[29-31] The underlying genetic variants common to dilated cardiomyopathies are being proposed,^[32] a genetic basis specific to PPCM has not been systematically studied.^[33] A position statement from the European Society of Cardiology Working Group of Myocardial and Pericardial disease currently classifies PPCM as a non-familial non-genetic form of dilated cardiomyopathy.^[34]

Pathophysiology

Numerous hypotheses have been proposed, yet PPCM is fraught with controversies, poorly understood and cannot be explained by a single etiology, thus from multifactorial origin. PPCM may be caused by viral myocarditis, abnormal immune response to pregnancy, maladaptive response to hemodynamic stresses of pregnancy, stress-activated cytokines, excessive prolactin excretion, selenium deficiencies and malnutrition, and prolonged tocolysis.^[3,22,27,28]

Viral myocarditis

This was first reported by Goulet, *et al.*^[35] as the main mechanism for PPCM. This proposal was later supported by Melvin, *et al.*^[36] from three endomyocardial biopsies he collected from three women. The biopsy specimens showed features of myocarditis with dense lymphocytic infiltration with a variable amount of myocytic edema, necrosis and fibrosis. Recently, Felker, *et al.*^[37] and Midei, *et al.*^[38] reported an association between PPCM and viral myocarditis.

Abnormal immune response

Ansari *et al.*,^[39] studied autoimmune mechanism as the basis for human PPCM. The works of other researchers^[3,7,18,28] support this theory that during pregnancy fetal cells released into the maternal bloodstream are not rejected by the mother because of the natural immunosuppression that occurs during

pregnancy. However, after delivery, women lose the increased immunity, and if fetal cells reside on cardiac tissue when the fetus is delivered, a pathological autoimmune response can occur, leading to PPCM in the mother after birth.

Abnormal hemodynamic response

Physiological changes in the cardiovascular system in pregnancy results in an increase in blood volume and cardiac output^[3] with a decrease in after load because of relaxation of vascular smooth muscle.^[25] These changes result in a reversible hypertrophy of the left ventricle to meet the needs of the mother and fetus.^[9] In a normal pregnancy, this transient left ventricular dysfunction during the third trimester and early postpartum period resolves shortly after birth.^[9,28] PPCM might be due to an exaggerated decrease in left ventricular function when these hemodynamic changes of pregnancy occur.^[3]

Apoptosis and inflammation

Women with PPCM have been identified with an increased concentration of plasma inflammatory cytokines such as tumor necrosis factor, c-reactive protein and Fas/Apo-1, a plasma marker for apoptosis (programmed cell death).^[10] Levels of Fas/Apo-1 were higher in women with PPCM than in healthy volunteers.^[10] Women with PPCM who died had higher levels of Fas/Apo-1 than other women with PPCM who survived. However, a correlation between increased plasma cytokine levels and left ventricular function or outcomes has not been demonstrated. Van Hoven *et al.*^[40] further concluded that ejection fraction at the time of clinical findings suggestive of PPCM was the strongest predictor of outcome.

Excessive prolactin excretion

Hilfiker *et al.*^[7] proposed a new pathogenic mechanism for PPCM in their recent insights in PPCM as a result of excessive prolactin production. Levels of prolactin are associated with increased blood volume, decreased blood pressure, decrease angiotensin responsiveness, and a reduction in the levels of circulating erythropoietin and hence hematocrit levels.^[28] Hilfiker – Kleiner *et al.*^[41] discovered that PPCM develops in mice bred to have a cardiomyocyte specific deletion of STAT 3 (a protein that plays a key role in cell growth and apoptosis). The detection of STAT 3 led to enhanced expression of cardiac cathepsin D, promoting the formation of a 16–KD form of prolactin. In women with PPCM, STAT 3 protein levels were low in the heart, and serum levels of activated cathepsin D and 16–KD prolactin were evaluated.^[7,41]

Selenium deficiencies and malnutrition

Deficiencies in selenium and other micronutrients were thought to play a role in the pathogenesis of PPCM.^[13,36] Deficiencies of selenium increase cardiovascular susceptibility to viral infections, hypertension and hypocalcaemia. However, Felt *et al.*^[42] concluded that neither low serum levels of selenium or deficiencies of other micronutrients (vitamins A, B₁₂, C, E), played a significant role in the development of PPCM

in Haitian women. In contrast, women with PPCM from the sahelian region of Africa had low levels of selenium.^[43]

Prolonged tocolysis

Lampert *et al.*^[44] found an association between use of tocolytic therapies and development of pulmonary edema in pregnant women and proposed a link between prolonged tocolysis and PPCM.

Pathology

The heart is pale and flabby with hypertrophy surrounded by interstitial edema and chronic inflammatory infiltrates with dilatation of all the chambers.^[2,13,14] There may be focal areas of endocardial fibrosis in the ventricles.

Clinical manifestations

Normal pregnancy is associated with physiological change in cardiovascular system such as increased blood volume, increased metabolic demands, mild anemia, changes in vascular resistance associated with ventricular dilatation and increased cardiac output.^[23] Thus, the onset of PPCM can easily be masked and missed because the manifestations can mimic those of mild heart failure. Women with PPCM present with dyspnea, dizziness, chest pain, cough, neck vein distention, fatigue, and peripheral edema.^[22,25,26] Women can also present with arrhythmias, embolic events due to the dilated, dysfunctional left ventricle and acute myocardial infarction due to decreased perfusion to the coronary arteries.^[3,22,45] They can also present with hypoxia, jugular venous distention, S₃ and S₄ gallop, crepitations and hepatomegaly.^[45] Blood pressure may be normal or decreased and tachycardia is common.^[30]

Diagnosis

The diagnosis of PPCM is one of exclusion^[1,4] thus, a good history and physical examination are necessary to make a diagnosis in this rare condition. Obvious signs of heart failure such as pulmonary crackles, paroxysmal nocturnal dyspnea, chest pain, cough, new murmurs and neck vein distention should necessitate further workup.^[8,46] Echocardiography is central to diagnosis of PPCM.^[14] It is used for diagnosis and effective treatment monitoring.^[3,26,47,48] PPCM is diagnosed by echocardiographic evidence of new left ventricular systolic dysfunction that occurs in the peripartum period. The diagnosis is often difficult because a large percentage of healthy pregnant women present with signs of fatigue, pedal edema, and shortness of breath in the final month of pregnancy. Suspicion of cardiomyopathy may be raised by the finding of increased heart size in the chest radiograph of an otherwise healthy pregnant or postpartum woman. Four criteria have been suggested for the diagnosis of PPCM.^[49] These criteria are important in making the correct diagnosis.

Diagnostic criteria for PPCM

1. Echocardiographic evidence of new left ventricular systolic dysfunction that occurs in the peripartum period.

2. Onset of heart failure in the last month of pregnancy or in the first 5 months postpartum.
3. Absence of determinable cause of cardiac failure.
4. Absence of demonstrable heart disease before the last month of pregnancy.

Echocardiography is noninvasive and allows serial evaluations in pregnant women.^[5] Echocardiographic findings in women with PPCM are consistent with the findings in heart failure such as decreased ejection fraction, global dilatation and thinned out cardiac walls.^[3,23,50] Cardiac magnetic resonance can be used as a complementary tool in the diagnosis of PPCM and evaluation of women with PPCM.^[25,31,40] Cardiac Magnetic Resonance Imaging can be used to measure global and segmental myocardial contraction, can help in characterizing the pathogenesis of the disease and can reveal inflammatory processes.^[25] Laboratory studies are unhelpful.^[4] Women with other types of cardiomyopathy will generally present in the second or early third trimester when the hemodynamic stresses are greatest. The majority of women with PPCM (75%) will present in the postpartum period.^[8] When PPCM is suspected it is important to establish the diagnosis rapidly.^[26]

Differential diagnosis

The differential diagnosis of PPCM are myocardial infarction, amniotic fluid embolism, severe pre-eclampsia, pericarditis, pulmonary thrombo-embolism, myocarditis, sepsis, drug toxicity, metabolic disorders and aortic dissection.^[4,27,51]

Management

Management of PPCM is similar to standard treatment for other forms of dilated cardiomyopathies.^[1-3,8,12,52] However, no clinical trials have been done to evaluate these therapies specifically in PPCM.^[6] The aims in treating heart failure are to improve hemodynamic status, minimize signs and symptoms, and optimize the long term outcomes.^[6] Multiple disciplinary approach is the rule in the management of PPCM.^[3,8] Collaboration among medical specialists in obstetrics, perinatology, cardiology, neonatology and anesthesia are essential in care of women with PPCM.

The main stay of treatment includes sodium restriction, diuretics, vasodilators and digoxin.^[3,9,45] Beta-blockers such as carvedilol have been shown to reduce mortality in dilated cardiomyopathy.^[53] Anticoagulation with heparin should be initiated, if thrombus is noted on echocardiography. Warfarin can be given postpartum. Special attention must be paid to fetal safety and to changes in drug and drug metabolite excretion during breast feeding.^[3,8] Angiotensin-converting enzyme inhibitors and spironolactone are contraindicated in pregnancy but should be initiated post-delivery.^[3,25,50] In addition, bromocriptine, a dopamine antagonist that inhibits prolactin secretion, prevented the expected deterioration in the size of the left ventricle and systolic function when given in addition to standard heart failure therapy in a woman with

PPCM.^[54] The results of assessment of the therapeutic effects of prolactin blockade with bromocriptine are promising, and trials are being done in women with PPCM.^[7,41] However, some authors are of the opinion that bromocriptine should be used with caution.^[55]

Pregnant women with acute decompensating heart failure are better managed with the airway, breathing, circulation.^[45] Women with impending respiratory failure from pulmonary edema require rapid initiation of supported ventilation.^[56] Endotracheal intubation may be required. Breathing is supported with supplemental oxygen to relieve signs and symptom related to hypoxemia, and is assessed in a continuous pulse oxymetry. There is need for cardiac monitoring.^[25,45] Blood pressure should be monitored with noninvasive blood pressure cuffs until arterial catheters are placed. Venous and arterial access should be obtained early for medications and monitoring.^[45] Medical therapy can be unsuccessful in women with PPCM, and mechanical cardiovascular support with an intra-aortic balloon pump or ventricular assist device may be required.^[57,58] Left ventricular assist devices can be a bridge to recovery or to transplantation.^[25,58-60] Women in whom maximal medical management is unsuccessful may be candidates for cardiac transplantation.^[26,42,57]

Follow-up

Aggressive treatment and follow-up are paramount for patients diagnosed with PPCM. The majority of maternal deaths occur within 3 months of the initial onset of symptoms.^[8] Collaboration among medical specialist including obstetricians, cardiologists, perinatologists, neonatologist and anesthesiologists, is essential in the care of women with PPCM.^[6,9]

Prognosis

Prognosis is positively related to the recovery of ventricular function.^[2,3,27,61] Failure of heart size to return to normal is associated with increased mortality, and morbidity.^[3] Approximately 50% of affected women will continue to have symptoms of failure and cardiomegaly beyond 6 months.^[61] These women should be advised against pregnancy as the incidence of recurrent disease is high with mortality rates approaching 100%.^[62] Generally, reports of mortality rates in women with PPCM vary widely (range from 7% to 50%).^[8-10,36-38] The usual causes of death in patients with PPCM are progressive heart failure, arrhythmia or thromboembolism. The mortality rate related to embolic events has been reported to be as much as 30%.

Women who have survived PPCM often become very depressed, after elation of a successful birth with the development of a life threatening illness that is traumatic.^[4] Factors associated with poor prognosis in PPCM include a lower left ventricular ejection fraction at 6 months after delivery, larger left ventricular end-diastolic dimension, advanced maternal age, multiparity and African American descent.^[47]

Patient counseling

Pregnancy and delivery are associated with pronounced happiness but when faced with severe complications, patients feel scared, angry, helpless and withdrawn. Therefore, it is important to discuss these issues that may arise with your patient so that she will understand what she is going through. Tell her the diagnosis and possible causes so that she will know that it was not due to what she did in the past. This is followed by evaluation and treatment with an opportunity for her to ask questions. These empower the patient by involving her in the decision-making process.

The drive to become pregnant and bear children is enormous in women. The women affected by PPCM may be willingly to accept the risk of an adverse outcome, but the obstetrician should make objective recommendations and document it for future records and should not be seen to compromise his or her best medical judgment because of a patient's emotional desires.

Issues in PPCM

The women that survive PPCM are being confronted with problems surrounding pregnancy. There are doubts whether they can become pregnant after PPCM.^[11,26] There is no fully established status on recommendations for future pregnancies among these women.^[30] This is because left ventricular recovery and functions are considered the most reliable prognostic factors and predictors of survival in subsequent pregnancies.^[30] Future pregnancies are not recommended in women with persistent ventricular dysfunction, because the heart cannot tolerate increased cardiovascular workload associated with the pregnancy.^[11,25] Those women who have recovered from PPCM are more difficult group to counsel^[3] because subsequent pregnancies can increase the risk for recurrent episodes of PPCM and multiparity has been associated with PPCM. Furthermore, irreversible cardiac damage and decreased left ventricular function, worsen a woman's clinical condition and may result in death.^[3,26] The women with persistent left ventricular systolic dysfunction should be counseled against subsequent pregnancies. The risks are 19% higher for maternal death than among women with PPCM whose heart failure has resolved.^[6,45] Furthermore, there is an increased risk of fetal pre-maturity and fetal loss.^[15]

Conclusion

PPCM a rare form of dilated cardiomyopathy is a diagnosis of exclusion and should be based on classic echocardiographic criteria.^[3,5,49] There is no single explanation of the pathogenesis of PPCM that is relevant for all women. The disease has a multifactorial origin. Careful assessment of risk factors in pregnant women could help in the prevention of PPCM. Tools and follow up measures are needed to classify women who have recovered from PPCM in order to predict the risk of future pregnancies. Furthermore, trials have to be intensified on the therapeutic effects of prolactin blockade with bromocriptine.

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