CURRENT MANAGEMENT OF PERIPARTUM CARDIOMYOPATHY: A REVIEW

DODIYI-MANUEL S.T, EZENNAKA R.C
Department of Internal Medicine, University of Port Harcourt Teaching Hospital

ABSTRACT

BACKGROUND
Demakis et al in 1971 described 27 patients who presented during pueperium with cardiomegaly, abnormal electrocardiographic findings, congestive heart failure and named the syndrome “peripartum cardiomyopathy”. The aim of this review is to document the current concepts in the management of peripartum cardiomyopathy.

MATERIALS AND METHODS
A search of the literature was done using PubMed, Google scholar and books from authors’ collections.

RESULTS
The cause of the disease might be environmental and genetic factors. Diagnostic echocardiographic criteria include left ventricular ejection fraction of less than 45% or a combination of M-mode fractional shortening of less than 30% and end diastolic dimension of greater than 2.7cm/m². Electrocardiogram, magnetic resonance imaging, endomyocardial biopsy and cardiac catheterization aid in the diagnosis and management of peripartum cardiomyopathy. Treatment includes both conventional pharmacological heart failure and peripartum cardiomyopathy targeted therapies. Therapeutic decisions are influenced by drug safety profiles during pregnancy and lactation. Mechanical support and transplantation might be necessary in severe cases.

CONCLUSION
Peripartum cardiomyopathy is an uncommon but life threatening cardiac failure of unknown aetiology encountered in late pregnancy or postpartum period. Management aims at improving heart failure symptoms through conventional therapies and then at administering targeted therapies. The risk of recurrence in future pregnancies should always be considered.

KEYWORDS: Cardiomyopathy, Heart failure, Peripartum.

EPIDEMIOLOGY
Peripartum cardiomyopathy is a relatively rare condition. In Nigeria, a rate of 1% has been reported. In South Africa, reported incidence is higher than 1 in 1000 live births while 1 in 300 live births has been reported in Haiti. In the United States, the reported incidence range from 1 in 1149 to 1 in 4350 live births with a mean of 1 in 3186 live births. The higher prevalence in developing countries may be attributed to environmental, ecological, cultural, puerperal and post puerperal practices besides diagnostic criteria and reporting standards.

RISK FACTORS
The incidence of PC is higher in multiparity, advanced maternal age, multiple pregnancy, preeclampsia and gestational diabetes. African American race, obesity, maternal cocaine and alcohol abuse, smoking and long term tocolytic therapy have also been attributed as risk factors.

INTRODUCTION
Heart failure during pregnancy was described in 1849 but was first described as a distinctive form of cardiomyopathy in the 1930s. In 1971, Demakis et al described 27 patients who presented during pueperium with cardiomegaly, abnormal electrocardiographic findings, congestive heart failure and named the syndrome “peripartum cardiomyopathy”.

The European Society of Cardiology defined Peripartum Cardiomyopathy (PC) as a form of dilated cardiomyopathy that presents with signs of heart failure in the last month of pregnancy or within 5 months of delivery.

Corresponding Author: Dr S.T Dodiyi-Manuel
Department of Internal Medicine,
University of Port Harcourt Teaching Hospital
E-mail: tbtspcial@yahoo.com
Tel: 0803349562

Niger Med2015: 363-369
Copyright © 2015. Nigeria Journal of Medicine
AETIOPATHOGENESIS

Although the aetiology of PC is still unknown, some plausible causes have been identified but none of them is definite. They include:

A) **NUTRITIONAL FACTORS**: Higher incidence in some African countries has been attributed to the consumption of “Kanwa”, a tradition for 40 postpartum days. Kanwa is a dry salt and causes hypervolaemia and hypertension. Ninety percent of PC occurs within 2 months of delivery. 11, 12

B) **MYOCARDITIS**: Myocarditis has been found on endometrial biopsy of the right ventricle in patients with PC with a dense lymphocytic infiltrate and variable amounts of myocyte oedema, necrosis and fibrosis. The prevalence of myocarditis in patients with PC ranged from 8.8 to 78% in different studies. On the other hand, the presence or absence of myocarditis alone does not predict its outcome. 1, 13, 14

C) **CHEMERISM**: In this phenomenon, cells from the fetus take up residence in the mother (or vice versa), sometimes provoking an immune response. The serum of patients with PC has been found to contain auto antibodies in high titres, which are not present in serum from patients with idiopathic cardiomyopathy. Most of these antibodies are against normal human cardiac tissue proteins of 37, 33, and 25KD. Multiparty is a risk factor for the development of this disorder suggesting that previous exposure to fetal or paternal antigen may elicit an abnormal myocardial infiltrative response. The timing of presentation in the immediate postpartum period supports an autoimmune pathogenesis. 15, 16

D) **APOPTOSIS AND INFLAMMATION**: Apoptosis (programmed cell death) of cardiac myocytes occur in heart failure and may contribute to progressive myocardial dysfunction. Experiments in mice suggest that apoptosis of cardiac myocytes has a role in PC. Fas and Fas ligand are cell surface proteins that play a key role in apoptosis. Silwa et al. in a single center prospective, longitudinal study from South Africa, followed 100 patients with peripartum cardiomyopathy for 6 months. During this time, 15 patients died and those who died had significantly higher levels of Fas/Apo-1 (p < 0.05). In the same study, plasma levels of c-reactive protein and tumor necrosis factor alpha (markers of inflammation) were elevated and correlated with higher left ventricular dimensions and lower left ventricular ejection fractions at presentation.

In the studies of left ventricular dysfunction, circulating levels of tumor necrosis factor alpha and interleukin 6 increased in patients as their functional heart failure classification deteriorated.

E) **AN ABNORMAL HAEMODYNAMIC RESPONSE**: During pregnancy, blood volume and cardiac output increase. In addition, afterload decreases because of relaxation of vascular smooth muscle. The increases in volume and cardiac output during pregnancy cause transient and reversible hypertrophy of the left ventricle to meet the needs of the mother and foetus. Cardiac output reaches its maximum around 20 weeks of pregnancy. The transient left ventricular systolic dysfunction during the third trimester and early post partum period returns to baseline once the cardiac output decreases. 17

CLINICAL FEATURES AND DIAGNOSIS

Postpartum cardiomyopathy involves the left ventricular dysfunction in women with no history of heart disease. It can be diagnosed only if other causes of cardiomyopathy are absent. Diagnostic criteria for PC include:

1) Cardiac failure developing in the last month of pregnancy or within 5 months of delivery.
2) No identifiable cause of cardiac failure.
3) No recognizable heart disease before the last month of pregnancy.
4) An ejection fraction of less than 45% or the combination of an M-mode fractional shortening of less than 30% and an end-diastolic dimension greater than 2.7 cm²/m².

Symptoms of PC are similar in patients with systolic dysfunction who are not pregnant. New or rapid onset of symptoms like cough, orthopnoea, paroxysmal nocturnal dyspnea, fatigue, palpitations, weight gain, haemoptysis, chest pain and unexplained abdominal pain would require prompt evaluation. Physical examination frequently reveals enlarged heart, tachycardia and decreased pulse oximetry. There may be abnormal blood pressure, elevated jugular venous pressure, third heart sound, mitral and/or tricuspid regurgitation and pulmonary rales. Worsening of peripheral oedema, ascites, hepatomegaly and arrhythmias are frequently seen. There may also be small to moderate peripheral oedema. Generally, clinical presentation and haemodynamic changes are indistinguishable from those found in other forms of dilated cardiomyopathy. High output cardiac failure has also been recorded in a few patients.
Pre eclampsia should be excluded. It occurs after 20 weeks of gestation and is characterized by high blood pressure, proteinuria, pitting pedal oedema, sudden weight gain, headaches and changes in vision. A latent form of PC without clinical signs and symptoms has been reported.

The aims during diagnosis are to exclude other causes of cardiomyopathy and to confirm left ventricular systolic dysfunction by echocardiography. Whether endomyocardial biopsy should be done in this setting is still controversial and recent guidelines do not recommend it.

Magnetic Resonance Imaging (MRI) may be used as a complementary tool to diagnose PC and also identify the mechanisms involved. It can measure global and segmental myocardial contraction and it can characterize the myocardium. Leurent et al. advocate using cardiac MRI to guide biopsy of the abnormal area. This may be more useful than blind biopsy.

**TREATMENT**

1) **DURING PREGNANCY**: Early diagnosis and treatment are keys to a successful outcome. The welfare of the fetus is considered along with that of the mother. Multidisciplinary approach involving the physician and obstetrician is essential. Oxygen therapy should be promptly administered in acute heart failure to relieve symptoms, with a target arterial saturation of ≥95%. Digoxin, beta blockers, loop diuretics and drugs that reduce afterload such as hydralazine and nitrates are safe and are the mainstay of medical therapy of heart failure during pregnancy. Digoxin is effective due to its inotropic and rate reducing effects while diuretics are useful in reduction of preload and salt restriction. Even though, they are relatively safe in pregnancy, there should be caution regarding volume depletion leading to dehydration and consequent uterine hypoperfusion and fetal distress.

In patients with persistent congestion despite diuretic and or vasodilator therapy, dobutamine or levosimendan are strongly recommended. Beta blockers have strong evidence of efficacy in patients with heart failure but they have not been tested in PC. However, they have long been used in pregnant women with hypertension without any known adverse effect on the fetus, and patients taking these agents prior to diagnosis can continue to use them safely.

2) **DURING POST PARTUM PERIOD**: Treatment is identical to that of non-pregnant women with dilated cardiomyopathy. Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARBs) are useful. The usual target dose is one half the maximum antihypertensive dose. Diuretics are given for symptomatic relief. Spironolactone or digoxin is used in patients who have New York Heart Association class III or IV symptoms. The dose of spironolactone is 25mg daily after dosing of other drugs is maximized. The goal with digoxin is the lowest daily dose to obtain a detectable serum digoxin level which should be kept at less than 1.0ng/ml. Beta blockers are recommended for peripartum cardiomyopathy as they improve symptoms, ejection fraction and survival. Non-selective beta blockers like carvedilol with a goal dosage of 25mg twice a day and selective beta blockers like metoprolol with a goal dosage of 100mg once a day have shown benefit.

**ANTICOAGULANT TREATMENT**

There is an increase risk of thromboembolic complications during pregnancy due to higher concentrations of coagulation factors II, VII, VIII, X and fibrinogen and this may persist up to 6 weeks post partum. Cases of arterial, venous and cardiac thrombosis have been reported in women with peripartum cardiomyopathy and the risk may be related to the degree of chamber enlargement and systolic dysfunction and the presence of atrial fibrillation. Therefore, the use of heparin is advocated in the antepartum period and that of heparin and warfarin in the postpartum period as warfarin is contraindicated in pregnancy because of its teratogenic effect while use of both heparin and warfarin is safe in lactation. Patients with evidence of systemic embolism with systemic left ventricular dysfunction or documented cardiac thrombosis should receive anticoagulation. Anticoagulation should be continued until the return of normal left ventricular function is documented.

**ANTIARRHYTHMIC DRUGS**

In patients presenting with ventricular tachycardia with haemodynamic compromise, an implantable cardioverter defibrillator may be used. For patients with symptomatic ventricular tachyarrhythmia who are haemodynamically well tolerated, management can be tempered by the potential transient nature of the myopathy and amiodarone therapy at 200 to 400mg orally 6 hourly is an alternative. If left ventricular function recovers, the risk of serious arrhythmic event is markedly diminished and amiodarone therapy can be discontinued. For patients with asymptomatic non-sustained ventricular tachyarrhythmia, the focus is on correction of metabolic abnormalities and addition of a beta receptor antagonist (if not already being utilized).
CARCIC TRANSPLANTATION/VENTRICULAR ASSISTED DEVICES
Patients with severe heart failure despite maximal drug therapy need cardiac transplantation to survive and improve their quality of life. However, since fewer than 3000 hearts are available for transplantation worldwide per year, ventricular assisted devices are indicated as a bridge to transplantation.

CURRENT CONCEPTS
1) PENTOXIFYLLINE: This is a xanthine derived agent known to inhibit the production of tumor necrosis factor alpha (which is elevated in these patients). It improves outcomes, left ventricular function and symptoms when added to conventional therapy in small prospective study.
2) BROMOCRIPTINE: Recently, some studies have suggested the role of prolactin breakdown products in the aetiology of peripartum cardiomyopathy. Prolactin secretion can be reduced with bromocriptine which had beneficial effects in small study. In one study with the use of cabergoline which is a strong and long lasting antagonist of prolactin, significant improvement in left ventricular function was reported.
3) IMMUNOMODULATING THERAPY: Immunosuppressive and immunomodulatory therapy have been used due to the inflammatory nature of peripartum cardiomyopathy and the occasional appearance of myocarditis on endomyocardial biopsy. Intravenous immunoglobulin improved the ejection fraction in several studies and also markedly reduced the levels of inflammatory cytokines. Plasmapheresis has also been tried and may be used as an alternative to immunoglobulin therapy in peripartum cardiomyopathy. Other proposed therapies which might be useful are calcium channel antagonists, statins, monoclonal antibodies and interferon beta.

PROGNOSIS
1) Left ventricular function: Women with peripartum cardiomyopathy have a high rate of spontaneous recovery of left ventricular function. On echocardiography in postpartum period, nearly half of the women will normalize ejection fraction during follow up within 6 months. The prognosis is directly correlated to recovery of left ventricular function. For those women whose left ventricular function normalizes during follow up, the prognosis is excellent. In women whose left ventricular function does not recover, prognosis remains guarded and mortality rate as high as 10-50% has been reported. Factors predicting normalization of left ventricular function were an initial left ventricular end systolic dimension of 5.5cm or less or 30%.
2) Left ventricular size: It’s an important predictor as women presenting without significant left ventricular dilatation appeared to have greater chance of spontaneous recovery during follow up. In contrast, women with marked left ventricular dilatation at presentation appeared to have a greater likelihood of developing into chronic cardiomyopathy.
3) TROPONIN T: Hu et al reported that the serum cardiac troponin T concentration measured 2 weeks after the onset of peripartum cardiomyopathy correlated inversely with the left ventricular ejection fraction at 6 months. However, the sensitivity was low: a troponin T concentration of ≥ 0.04ng/ml predicted left ventricular dysfunction with a sensitivity of only 50% and specificity of 91%.
4) QRS Duration of ≥ 120ms has been identified as a predictor of death.

RECOMMENDATIONS
1) If left ventricular ejection fraction is < 25% at diagnosis or failure to recover following treatment, the advice should be against further pregnancies.
2) If left ventricular function is normal, the patients ought to have stress echocardiography: women with an abnormal left ventricular inotropic response to dobutamine have a moderate risk of relapse and pregnancy is not recommended.
3) Women with complete recovery on both echocardiography and dobutamine stress test can be informed about the low rate of complications. In this group, despite a 35% rate of risk of recurrence, pregnancy can be completed in almost all cases.
4) In the postpartum period, it is imperative to give contraceptive counseling and educate the patient about the existent alternatives and women who had PC should avoid pregnancy until left ventricular function has recovered. The combined oral contraceptives containing oestrogen and progestin are contraindicated as oestrogen increases the thromboembolic risk. Progesterone contraception alone is permitted. Vasectomy, tubal ligation and insertion of intratubal stent may be considered.
5) Protocols for decision making when counseling women with PC about risk of subsequent pregnancies are not strongly established. It is however advisable that previous PC patients should be considered at risk of recurrence and closely monitored by the cardiologist.

CONCLUSION
Peripartum cardiomyopathy is an uncommon but potential life threatening cardiac failure of unknown aetiology encountered late in pregnancy or in the postpartum period. Diagnosis should include echocardiographic substantiation of left ventricular dysfunction. Usefulness of diuretics, vasodilators, digoxin, beta blockers and anticoagulants is well established. ACE inhibitors and ARB blockers should be avoided during pregnancy but started in postpartum period. In resistant cases, pentoxifylline, immunoglobulin and immunosuppressive drugs may be used. Prognosis is linked to recovery of left ventricular function. Considering the risk of recurrence in subsequent pregnancies, a cardiologist should always be involved in the management of these patients.


