PERIPARTUM CARDIOMYOPATHY
AN OMINOUS DIAGNOSIS

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Discipline of Anaesthetics
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INTRODUCTION

The onset of cardiac failure in a previously well woman who has recently given birth or about to give birth, does not only complicate the peripartum period but also brings uncertainty to her prognosis and future. Peripartum cardiomyopathy (PPCM) is an uncommon type of dilated cardiomyopathy that is defined as development of heart failure (HF), towards the end of pregnancy or in the months following delivery, where no other cause of HF is found.¹

This disease is intriguing because of its heterogeneity and highly variable natural progression which may rapidly result in end-stage heart failure often within a few days. Contrary to other cardiomyopathies complete recovery may also occur and as well as varied incidence in different geographical regions.²,³ All this poses a great challenge to formulate uniform recommendations internationally. PPCM has the highest morbidity and mortality in parturients with cardiac disease.⁶

Heart failure in the peripartum period was noted as early as the 18th century, however the clinical and pathologic features were described by Gouley et al in 1937.⁴,⁵ Demakis and colleagues in 1971 called the condition PPCM and defined its diagnostic criteria after studying a series of 27 patients.⁷ This document will address the epidemiology, pathogenesis, risk factors, clinical presentation, diagnosis, management and prognosis of PPCM.

DEFINITION AND DIAGNOSTIC CRITERIA

The term PPCM describes the macroscopic pathology and the chronological spectrum of the disease, emphasising that the condition can present pre, intra, and postpartum. The definition and diagnostic criteria of PPCM as classically described by Demakis and later by the NHLBI in 2000, states it must develop during the last month of pregnancy or within 5 months of delivery, has recently been challenged.⁷,⁸

Elkayam et al have reported an identical condition that appeared earlier in pregnancy and other authors reported cases who presented at 6 months postpartum.⁹ This suggests that PPCM might have an expanded time interval for presentation than we previously thought. Hence the new proposed simplified and expanded definition by the Heart Failure Association of the ESC working group on PPCM 2010. However PPCM remains a diagnosis of exclusion.²
### Table 1 Difference between NHLBI and ESC definitions

<table>
<thead>
<tr>
<th><strong>NHLBI 2000 DEFINITION</strong></th>
<th><strong>ESC 2010 DEFINITION</strong></th>
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<tbody>
<tr>
<td>1. The development of HF in the last month of pregnancy or within 5 months post-partum.</td>
<td>1. Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery,</td>
</tr>
<tr>
<td>2. The absence of an identifiable cause of heart failure.</td>
<td>2. Where no other cause of HF is found.</td>
</tr>
<tr>
<td>3. The absence of recognizable heart disease prior to the last month of pregnancy.</td>
<td>3. It is a diagnosis of exclusion.</td>
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<tr>
<td>4. LV systolic dysfunction demonstrated by classical echocardiographic criteria. The latter may be characterized as an LV – EF of &lt; 45%, - fractional shortening of &lt;30%, or both, - a LV end-diastolic dimension ≥2.7 cm/m2 body surface area.</td>
<td>4. The LV may not be dilated but the LVEF is nearly always reduced below 45%</td>
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**NHLBI** - National Heart Lung and Blood Institute and the Office of Rare Diseases; **ESC** - Heart Failure Association of the European Society of Cardiology Working Group on PPCM 2010.

### EPIDEMIOLOGY

The true incidence of PPCM is unknown because there have been few population based studies and registries of the condition internationally. The Haitian PPCM registry is the only existing in the world. The incidence varies with geographical area as well as race. In USA the previous reported incidence is 1:4000 per livebirths, South Africa 1:1000, Haiti 1:300 and in Zaria Nigeria amongst Hausa tribe 1:100.

There is a perceived increase in the incidence across all geographic areas, most likely due to the improved awareness and diagnostic measures. In a Sowetan study PPCM formed 1.5% of all patients with heart failure attending the centre during the space of 1 year. PPCM incidence is significantly higher in women of African descent than in other races and also women of lower socioeconomic status.
AETIOLOGY

The definite cause of PPCM remains obscure and is likely to be multifactorial. There are several aetiological hypotheses that have been proposed. The possible causes include: viral myocarditis, abnormal immune response to pregnancy, hemodynamic stress of pregnancy, angiogenic imbalance, apoptosis and inflammation.

Viral Myocarditis
Physiologic changes with reduced cellular immunity that occurs in pregnancy makes women prone to viral myocarditis when infected with cardiotropic viruses such as coxsackie virus, adenovirus, echovirus, CMV, Parvovirus, herpesvirus. Work done by Sliwa et al found that HIV infection does not seem to be implicated in PPCM since HIV co-infection in this African cohort appeared to bear no additional risk for poor prognosis of PPCM.

The other pathomechanism suggested is that the virus triggers the development of a pathological immune response against native cardiac proteins leading to ventricular dysfunction. The reported prevalence of viral myocarditis confirmed by histologic diagnosis from endomyocardial biopsies vary from 8.8% - 76%. Confirming viral myocarditis has been practically challenging, however in future with newer technologies and PCR it will be easier to diagnose PPCM patients with actively replicating viruses and guide institution of antiviral treatment.

Prolactin and Cathepsin D
During pregnancy the myocardium undergoes hypertrophy and angiogenesis to adapt to the hemodynamic stress of pregnancy. Recent studies suggest that there is the role of prolactin, cathepsin D, and oxidative stress in the pathophysiology of PPCM.

The experimental work done in knockout mice for STAT-3 found exceptionally high incidence of PPCM compared to controls. STAT-3 is a signal transducer and activator of transcription 3 which is a cardiomyocyte specific DNA binding protein. STAT-3 mediates anti-oxidative processes, myocyte hypertrophy and angiogenesis.

Low STAT-3 levels in pregnant women blunt the induction of the antioxidant manganese superoxide dismutase, resulting in increased uncompensated oxidative stress. This then leads to increased expression of cardiac cathepsin D which has proteolytic activity. Cathepsin D cleaves prolactin to a 16kDa form which has antiangiogenic and pro-apoptotic effects. The 16kDa prolactin has negative effects on myocardial microvasculature resulting in myocardial hypoxemia, apoptosis and development of PPCM. The preliminary favourable outcome in a number of pilot studies where patients are treated with bromocriptine supports this hypothesis.
Cardiac Angiogenic Imbalance

Experimental work done on mice indicate that PPCM is an imbalance of systemic angiogenic factors accentuated by a pro-inflammatory state and raised reactive oxygen radicals (ROS) on the background of susceptibility. In addition to 16kDa prolactin, lack of PGC-1α a regulator of angiogenesis and anti-angiogenic factor sFLT1 expressed in late pregnancy play an interactive role in the pathogenesis of PPCM.

PGC-1α is a transcriptional factor that induces expression and production of pro-angiogenic factors like vascular endothelial growth factor (VEGF). Late pregnancy and post-partum period is characterised by presence of sFLT1 however it is excessively expressed in PPCM. The systemic inflammatory state and excessive ROS was found to cause repression of PGC-1α in cardiac samples from PPCM women.

Co-occurrence of preeclampsia and PPCM has been reported in literature and is usually associated with higher morbidity and mortality. Common to PPCM and pre-eclampsia is the anti-angiogenic state as evidenced by elevated sFLT1 and since not all pre-eclamptics develop PPCM it seems reasonable to suggest the need for a ‘second hit’ which could be abnormal PGC-1α’.

Abnormal Immune Response, Inflammation and Increased Myocyte Apoptosis

There is suggestion that abnormal maternal immunologic responses play a role in PPCM aetiopathogenesis. The triggers for this autoimmune response are:

- Foetal microchimerism – hematopoietic cells may gain entry into the maternal circulation and initiate an autoimmune response.
- Previous exposure to paternal major histocompatibility complex antigens expressed by spermatozoa or immunization from prior pregnancy.
- Antibodies against protein (actin, myosin) from the involuting uterus may cross-react with protein found in the myocardium.

Women with PPCM have been found to high titres of autoantibodies against cardiac tissue proteins and their titres are even higher compared to idiopathic dilated CMO. The titre levels are reported to correlate with the severity of the clinical presentation, NYHA functional class and ejection fraction. The autoantibodies so far elucidated are those against:

- human cardiac myosin heavy chains (200 kDa)
- human cardiac myosin light chains(27 kDa)
- human cardiac actin chains
- β1-adrenergic receptor
- human cardiac transaldolase (37 kDa),
- adenine nucleotide translocator
- branched chain alpha keto-acid dehydrogenase
However the most convincing evidence that exist is on myosin and β1-adrenergic receptors.

The antibodies attack the myocardial proteins causing damage and local tissue inflammation which leads to production of pro-inflammatory cytokines like TNF-α, IL-1, IL-6, IFN-γ. Pro-inflammatory cytokines expressed at high concentrations lead to worsening ventricular dysfunction, maladaptive ventricular remodelling and pulmonary oedema. An anti-inflammatory agent pentoxifylline was shown to improve clinical outcomes when added to conventional therapy in a small nonrandomized study of 59 patients.

Accelerated myocyte apoptosis is another postulated cause of PPCM based on elevated levels of serum Fas/APO-1 in PPCM women and murine models. The Fas/APO-1 is a cell surface receptor that triggers the caspase pathway which is involved in programmed cell death. Inhibition of caspase pathway results in myocyte apoptosis curtailment with consequently improved cardiac function in PPCM in Gαq overexpressing mice hence providing a potential therapeutic target for the condition.

**Abnormal Response to Hemodynamic Stress of Pregnancy**

The cardiovascular changes in pregnancy are characterized by an increased in blood volume of up to 30-50% by mid-trimester, stroke volume increase of 35%, heart rate increase by 25%, low resistance state, with the resultant cardiac output increase of up to 30% to 50% by the third trimester. These CVS changes further increase intra and postpartum and normally persist up to 2 or 3 weeks postpartum, and may not resolve to normal physiology until 12 weeks post-delivery.

Some authors have reported a reduction in both systolic and diastolic function near term. Systolic function as measured by the septal Doppler indices of the septal s’ velocity was significantly reduced to 6.7cm/s compared with early pregnancy values. It would appear that normal pregnancy at term is associated with a mild impairment of systolic and diastolic function.

The left ventricle normally undergoes hypertrophy and dilatation to facilitate the increase in cardiac output and LVEDV without any rise in end diastolic pressures. It is believed an exaggerated decrease in systolic function in the presence of the marked hemodynamic changes of pregnancy lead to development of PPCM.

**Genetic Susceptibility**

PPCM has been classified as a non-genetic form of dilated cardiomyopathy (DCM). However there is a strong signal in literature that there is a potential genetic mechanism of PPCM. The high prevalence of the condition amongst 1st degree relatives of women diagnosed with PPCM.
Work done by Morales et al and van Spaendonck-Zwarts et al support the hypothesis that PPCM may develop as a result of a complex interaction of pregnancy associated factors (e.g. hemodynamic, oxidative stress) against the susceptible genetic background, or may suggest that in a proportion of patients, PPCM represents cases of familial DCM that are unmasked or first recognized in pregnancy.  

Familial mutations in MYH7, SCN5A, and PSEN2 genes as well as sporadic mutations in MYH6 and TNNT1/2 DCM genes in peripartum cardiomyopathy patients have been identified.  

**RISK FACTORS**

Several factors are postulated to increase the risk of the development of PPCM. These include obesity, African ancestry, poor socioeconomic status, advanced maternal age, multiparity/gravidity, multiple pregnancy, chronic hypertension or gestational hypertension and prolonged tocolytic use.  

Earlier data from the US showed PPCM to be more prevalent in older women of high parity. However the largest prospectively identified case series reports, from Haiti and South Africa did not show this disproportionate role for older age, multiparity, and long-term use of tocolytic agents in the development of PPCM. The association between black race and PPCM might be confounded by the observed increased frequency of hypertension/PIH in this group of women and furthermore their low socioeconomic status.  

See table 2 for comparison of risk factors in the studies from 3 different geographical areas  

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Haiti (n=98)</th>
<th>SA (n=100)</th>
<th>USA (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.8 (8.1, 16–51)</td>
<td>31.6 (6.6, 18–45)</td>
<td>30.7 (6.4, 16–43)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>4.3 (1–10)</td>
<td>3 (1–7)</td>
<td>2.6 (1–10)</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>24 (24% 5%)</td>
<td>20 (20%)</td>
<td>37 (37%)</td>
</tr>
<tr>
<td>Hypertension/PIH</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
<td>43 (43%)</td>
</tr>
<tr>
<td>Use of tocolytics</td>
<td>0</td>
<td>9 (9%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>African descent</td>
<td>98 (100%)</td>
<td>100 (100%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>6 (6%)</td>
<td>6 (6%)</td>
<td>13 (13%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>15 (15.3%)</td>
<td>15 (15%)</td>
<td>9 (9%)</td>
</tr>
</tbody>
</table>

For Haiti, South Africa, and USA (2005), data are mean (SD, range) for age and mean (range) for gravidity.

*Table 2: Comparison of potential risk factors and mortality rates in PPCM*
CLINICAL PRESENTATION

A serious impediment in successfully managing peripartum cardiomyopathy is timely diagnosis. This results from low incidence of the condition, variable clinical presentation, overlap of signs and symptoms of pregnancy in the last trimester. \(^4\,^6\)

Hence most PPCM patients are diagnosed late when complications have occurred, or in extremis or presenting as cardiac arrest. Once they have arrested these patients are difficult to resuscitate. Delayed diagnosis can be associated with increased morbidity and mortality. Therefore diagnosis of PPCM requires a high index of suspicion. \(^3\,^5\,^6\,^11\)

Patients present with signs and symptoms of systolic heart failure frequently with NYHA III or IV functional status. Usually have a rapid onset and progression. Some women have arrhythmias, functional tricuspid/mitral regurgitation, and intracardiac mural thrombus with embolic phenomena namely cerebral, pulmonary, and mesenteric.

The differential diagnosis includes:

- severe pre-eclampsia,
- amniotic fluid embolism
- pulmonary embolism
- accelerated hypertension, diastolic dysfunction
- anaemia-induced puerperal heart failure
- myocardial infarction
- valvular heart disease
- viral myocarditis
- dilated cardiomyopathy \(^2\,^5\,^11\,^13\,^20\,^27\)

The diagnosis of PPCM is a diagnosis of exclusion, and a thorough systematic investigation must be done to rule out an alternative aetiology of heart failure should be considered whenever a woman presents with heart failure during the peripartum period.

DIAGNOSIS

The Electrocardiogram

A 12 lead ECG usually shows a sinus tachycardia with nonspecific ST-segment and T-wave abnormalities. Arrhythmias are also seen as with other cardiomyopathies and include atrial fibrillation, atrial flutter, frequent premature ventricular systoles, ventricular tachyarrhythmias, and bundle branch block, the later occurring amongst long-term cases. Other changes that may be seen are left atrial enlargement, LV hypertrophy, small QRS complexes, prolonged QRS time and QTc interval.
A QRS time of ≥120 ms has been identified as a predictor for mortality, indicating a potential impact of QRS time on the mortality of patients with PPCM. Although there are no pathognomonic ECG signs of PPCM, it is essential that it is done to exclude treatable complications like dysrhythmias. Literature quotes an incidence of 20-30% of ventricular arrhythmias in PPCM. There is a suggestion that arrhythmic deterioration probably precedes and precipitates decompensation of heart failure.6

**Blood Assays/Biochemical Tests**

Laboratory tests done are divided into those to exclude precipitants and other causes of heart failure as well as those specific for cardiac failure and prognostication.

- General blood assays
  - FBC, U+E’s, Ca, Mg, LFT’s, TFT’s
- Specific blood assays
  - CRP, BNP, pro-BNP, Troponins, Fas/APO1, TNF-α, IL-6

As mentioned PPCM is a diagnosis of exclusion, the general initial investigations are performed to rule out the other causes of HF like anaemia, thyroid disease, electrolyte derangements and complications such as renal and liver dysfunction.

The specific investigations are to confirm cardiac dysfunction and presence of systemic inflammatory response and oxidative stress. Serum BNP or pro-BNP levels are elevated secondary to ventricular strain in PPCM patients. CRP levels were found to be high in PPCM compared to control subjects indicating an inflammatory status. The levels also correlated with the severity of the NYHA class and poor LV function.

In a study done by Fett et al they showed that mean plasma BNP as well as hs-CRP in control patients at the same stage postpartum as PPCM patients at diagnosis differed significantly from PPCM patients (BNP: 1096.5 pg/ml in PPCM’s vs. 204.2 pg/ml in controls, p =0.00009; CRP: 144.3mg/l in PPCMs vs. 5.2 mg/l in controls, p =0.0003). They used a cut-off value of 250 pg/ml and 10 mg/l for BNP and CRP respectively in their study. The diagnostic levels for this population has not been clearly established as yet.18,20,22

C-reactive protein measurements could provide us with a readily available tool to identify patients with an ongoing inflammatory process and guide clinicians with management decisions.

Some centres involved in research have specialised tests to measure apoptotic myocardial marker Fas/Apo-1 available. Apoptosis in different human cell lines both in vitro and in vivo was demonstrated to be inhibited by the administration of pentoxifylline.31 Increased troponin levels in the acute phase of PPCM, without
myocardial infarction is common occurrence as the evidence of myocardial necrosis.\textsuperscript{27}

**Radiological Studies**

**X-Ray**

Chest radiography typically shows cardiomegaly, pulmonary congestion, and oedema, with or without pleural effusions.

**Echocardiography**

Echocardiography is used to rule out other causes of heart failure. ECHO is currently the gold standard for the definitive diagnosis and prognostication of PPCM. This modality is used to evaluate and monitor regional and global left and right ventricular function, valvular structure and function, possible pericardial pathological changes, and mechanical complications.

The ECHO findings seen in PPCM are:

- left ventricular systolic dysfunction (EF<45%).\textsuperscript{8}
- variable degrees of LV dilatation, with moderate to severe depression of systolic function. Right ventricular and biaatrial dilatation
- mitral and tricuspid regurgitation
- thinned-out cardiac walls
- increased pulmonary pressures
- elevated left ventricular end-diastolic volumes
- presence of intracardiac thrombus – very common amongst patients with LVEF <30% at diagnosis.\textsuperscript{2,3,20,25,27}

**Magnetic resonance imaging**

MRI has become increasingly used for diagnosis of PPCM and to assist in identifying the mechanism involved in pathogenesis and to predict outcome. This is due to the ability of cardiac MRI to assess myocardial kinesia and ejection fraction, tissue characteristics and view the shapes, sizes, and contents of the cardiac chambers more accurately than echo.

Further attributes of cardiac MRI is to elicit the presence of myocardial fibrosis using late enhancement imaging in cardiac MRI. Specific MRI techniques that utilise measurement of late enhancement following administration of gadolinium, give critical information in the differential diagnosis of myocarditis.

The European and American Society of Radiology both recommend that gadolinium should be avoided until after delivery, unless absolutely necessary because gadolinium crosses the placenta. However their recommendation on breast feeding mothers differs. After intravenous administration of gadolinium, the Europeans do not discontinuing breastfeeding whereas the Americans do interrupt breastfeeding for 24hrs, regardless of the fact that only 0.04% of the maternal dose of gadolinium passes into the breast milk.\textsuperscript{6,21,25}
The role of cardiac MRI in PPCM is being further investigated in the Investigation in Pregnancy Associated Cardiomyopathy (IPAC) study.²⁵

**Myocardial Biopsy and Immunohistochemistry**

Endomyocardial biopsy can exclude other causes of heart failure such as infiltrative cardiomyopathies, myocarditis and autoimmune mechanisms and further more facilitate decision making in terms of treatment strategies. Biopsy can be followed up with polymerase chain reaction analysis of biopsy DNA extracts for viral assays or immunohistochemical staining for autoantibody assays. Biopsies done under MRI guidance help improve accuracy.

However it is not routinely recommended nor is it part of the typical diagnostic work up of PPCM. It is done only if there are strong indications and even so, it should be undertaken with extreme caution since there are inherent risks in performing a biopsy of a dilated failing heart.⁶,²⁵

**PROGNOSIS**

Peripartum cardiomyopathy natural course is characterized by its rapid clinical progression and a probability for spontaneous recovery. The reported mortality rate of PPCM ranges from 6% to 50%, even when the mother survives; she may not recover to full myocardial function and may require chronic therapy for heart failure or cardiac transplantation. Most deaths occurring within 1ˢᵗ 3 months post-delivery, although some deaths occur even 2yrs later. The death result from progression of systolic dysfunction or sudden death associated with dysrrhythmias or pulmonary embolism.⁶,²⁶

The reported mortality rates of 15-30% in Haiti and South Africa are much higher than 0-9% reported in USA. This geographical disparity in morbidity and mortality rate could be related to the availability of resources and inherent risk factors of developing countries.²,³,²⁰,²⁸

Recovery from peripartum cardiomyopathy is defined as recovery of LVEF to ≥0.50 or improvement by >0.20 and achievement of NYHA class I. Historically recovery was said to occur between 3 and 6 months postpartum, but might occur as late as 48 months postpartum. Larger and more recent prospective studies of patients from lower and middle-income cohorts suggest only a quarter will fully recover by the end of the first 6 months, whereas 10% to 15% would die by 6 months. In addition they showed overall recovery in most of these PPCM patients were achieved only 18 to 24 months after diagnosis.(Fig 1) Therefore the natural history of PPCM goes far beyond what our 6-month prognoses had been suggesting in earlier years.⁶
Progression from shortest to longest time required for left ventricular systolic function recovery in peripartum cardiomyopathy.\textsuperscript{6}

Predictors of poor prognosis\textsuperscript{18,23,26,32}

- Black race
- Delayed diagnosis
- Higher NHYA functional class
- Poor LV function – EF <30%
- LVEDD > 5.5cm
- LV Thrombus
- QRS duration > 120msec
- Highly elevated Troponins and BNP
- Raised Fas/APO-1
- Raised inflammatory markers – TNF-α, IL-6, CRP\textsuperscript{20,23}

There remains a high risk of further cardiac damage, relapse and mortality with subsequent pregnancies even in women who have fully recovered left ventricular function. Currently there is no consensus regarding recommendations for future pregnancy after PPCM, but most clinicians advise against future pregnancies and cardiology assessment prior to falling pregnant to those women that insist in bearing more children.\textsuperscript{5,20,21}
MANAGEMENT

PPCM patients are best managed in a tertiary health centre. The management principles of peripartum cardiomyopathy are essentially the same as that of systolic of heart failure, except for the need to select medications carefully if treatment is required during pregnancy. And in addition the importance of a multidisciplinary approach early involving a cardiologist, obstetrician, intensivist, anaesthesiologist, and paediatrician can never be overemphasised to achieve optimal outcomes.

Compensated Cardiac Failure
Treatment focuses on reducing preload and afterload and increasing cardiac inotropy as well as attenuating the maladaptive neurohormonal responses.

- Non pharmacologic treatment
  - Fluid restriction
  - Low salt diet
  - Bed rest than graded CVS exercises as tolerated.
  - Cardiac resynchronisation therapy
  - Implantable cardioverter-defibrillators

- Pharmacologic
  - Preload reduction
    - Furosemide
    - Hydrochlorothiazide
  - Aldosterone inhibitors – post-delivery for prevention of myocardial fibrosis, ion channel remodelling, prolonged myocardial repolarisation and arrhythmias as per RALES/EPHESUS studies
  - Afterload reduction
    - Hydralazine for pregnant women
    - Calcium channel blockers
    - ACEI – post delivery, also for ventricular remodelling
  - Neurohormonal modification
    - B blockers – carvedilol
    - ACEI
  - Inotropy
    - Digoxin: for patients with EF< 40% and symptomatic, it also has sympatholytic effects.
  - Anticoagulation for EF < 30%
    - Heparin
    - LMWH
    - Warfarin \(^{(4,5,6,34)}\)
**Acute Decompensated Cardiac Failure**

Patient presenting in acute decompensated HF or impending respiratory failure from pulmonary oedema, management begins with the ABC’s (airway, breathing, circulation). Positive pressure ventilation with high PEEP may be required. Intravenous diuretics, intravenous preload and afterload reducing agents like nitroglycerine are recommended (e.g. starting at 10–20 up to 200 mg/min) in patients with a systolic blood pressure (SBP)>110 mmHg and have to be used with caution in patients with SBP below 110 mmHg.

Inotropic agents should be considered in patients with a low cardiac output state, indicated by signs of hypoperfusion and those with congestion which persists despite administration of vasodilators and/or diuretics. When needed, inotropic agents should be administered promptly and weaned as soon as adequate organ perfusion is restored and/or congestion reduced. Invasive monitoring would be required. Inodilators (dobutamine, milrinone) are preferable for managing biventricular failure however they must be used with caution in a hypotensive state.

Anticoagulation is highly recommended in patients with PPCM as these patients have a high incidence of LV thrombus, especially patients with a LVEF <35%.

Intra-aortic balloon pump, cardiac assist devices and cardiac transplant may be required for women with refractory cardiogenic shock despite maximum medical therapy. However for South Africa advanced cardiac assist device and transplant are unavailable due to resource constraints.

**Novel and Experimental Therapies**

- **Bromocriptine**

   Based on the purported PPCM pathomechanism of enhanced oxidative stress and cleavage of prolactin into an antiangiogenic and proapoptotic 16-kDa prolactin form that induces myocardial damage and heart failure. Bromocriptine a dopamine 2D agonist which blocks prolactin may be a novel disease-specific treatment for PPCM.

   Several case reports, series and small studies have suggested that the addition of bromocriptine to standard therapy for HF may be beneficial. Sliwa et al in her pilot study of 20 patients with acute onset of PPCM, showed improved LVEF and a composite clinical outcome in women who had in addition to heart failure therapy bromocriptine.

   Currently physicians add bromocriptine on an individual basis, mainly a more severe presentation and high risk of failure to LV recovery. There is a need for a larger randomised trial, however the biggest challenge of conducting such a study in a low socioeconomic population with serious paediatric problems of
malnutrition, infections and high infant mortality rate, would be to deprive babies emotional, nutritional and physical benefits of breastfeeding.\(^{(4,33,35,36,39)}\)

- Pentoxifylline and immunoglobulins.

Given the potentially inflammatory nature of PPCM which is characterised by up-regulated inflammatory cytokines TNF-\(\alpha\), IL-6, and Fas-Apo-1, there may be a role for immunomodulatory therapy. Pentoxifylline, a xanthine agent known to inhibit the production of tumour necrosis factor and prevent apoptosis has been looked at but not yet validated by larger RCT. A prospective study of 59 consecutive women with PPCM reported a significant reduction in TNF-\(\alpha\) and improved outcome in patients receiving pentoxifylline in addition to conventional therapy.\(^{31,39,40}\)

Bozkurt et al. added intravenous immune globulin to standard HF therapy in 6 women with PPCM and reported a significantly greater improvement in LVEFs compared with 11 control patients who received conventional therapy alone. Although the results seemed encouraging, a very small number of patients and the lack of a blindly randomized, well-matched control group limited the study.\(^{38}\)

**ANAESTHETIC MANAGEMENT OF LABOUR AND DELIVERY**

Anaesthetic management of the parturient with peripartum cardiomyopathy for labour analgesia and caesarean delivery can be very challenging. PPCM is one of the cardiac conditions that is associated with a high morbidity and mortality and therefore requires careful planning, preparation and monitoring.

An early predelivery anaesthetic consultation is desirable to plan a safe peripartum period. These patients present at different stages, others their mild clinical presentation may be unmasked by standard doses of induction agents or they may present with cardiac arrest.

The timing and mode of delivery in a patient diagnosed during pregnancy should be determined by the clinical status of the mother and the fetus. A collaborating multidisciplinary team, including an obstetrician, cardiologist and anaesthetist, should decide on the safest mode and timing of delivery in severe cases. Very importantly the mother’s condition should be stabilised as best as possible before delivery is attempted.

The caesarean section delivery is usually reserved for obstetric indications and severe HF and pulmonary oedema. The cardiovascular benefits from vaginal delivery most often outweigh that of surgical delivery. Vaginal delivery prevents potential risks associated with anaesthesia and surgical delivery that include hemodynamic fluctuations, larger blood loss, pain, infections, respiratory and thromboembolic complications.
On the other end, an elective caesarean section is more rapid, predictable and allows better planning of the time of delivery as well as the presence of the most experienced medical team during the delivery.

Early administration of a carefully titrated epidural will minimize sympathetic output, reduce afterload and preload, and decrease the fluctuations of cardiac output in labour. However anticoagulation should be sorted. Further more caution must be exercised in limiting fluid boluses and maintaining strict intake and output to avoid fluid overload. Shortening the second stage of labour with the use of low forceps or a vacuum device is recommended to reduce maternal efforts, shorten labour and minimize ventricular work. Careful administration of syntocinon. Close maternal monitoring intra and post-partum in a high care environment. Vasoactive drugs must be available to manage hemodynamic compromise.3,5,21,46

**Management of a Caesarean Section**

The peri-operative handling of PPCM patients must be meticulous as they have minimal or no cardiac reserve. Any insult to the cardiovascular system be it, myocardial contractility, heart rate, preload, afterload or cardiopulmonary interactions can cause profound hypotension and cardiac arrest refractory to resuscitative measures.

In addition to standard monitoring, an arterial line is established pre-induction routinely to detect hemodynamic changes early. Whereas use of cardiac output monitor using pulse contour analysis such as LiDCOplus, TOE, CV catheter for administration of vasoactive drugs is determined by the clinical status of the patient. Most physicians reserve the pulmonary artery catheter for severe cases to measure PAP’s and CO trends and guide for therapy.

The choices of anaesthetic techniques employed for these patients include

- general anaesthesia (GA) with volatile agent
- general anaesthesia with remifentanil
- epidural anaesthesia
- combined spinal-epidural (CSE)
- continuous spinal anaesthesia (CSA)41,42

In the past general anaesthesia was advocated as “most appropriate” for caesarean delivery for these patients with PPCM however current literature shows a growing trend towards careful use of regional techniques.45 There are no large randomised controlled studies examining which is the best type of anaesthetic technique in these patients and guidelines and standards are lacking. Current recommendations advocate individualizing the anaesthetic management according to the parturient’s cardiovascular status, general pathophysiological concepts and physician’s experience and expertise.
The advantages of general anaesthesia include controlled airway and positive pressure ventilation, use of TEE if needed. Most induction and inhalational agents have myocardial depressant and vasodilatory effects which could aggravate already depressed myocardial function. The hemodynamic swings observed on induction and extubation requires careful intelligent execution. Furthermore GA does not provide any degree of thromboprophylaxis as thromboembolic complications have been reported after general anaesthesia for Caesarean section in a patient with PPCM.

Regional anaesthesia established gradually on the other hand can be advantageous in PPCM because of sympatholysis induced reduction of preload and afterload. There have been reports of significant symptomatic improvement after effective onset of the block as seen by the decrease in severity of respiratory symptoms and some improvement in BP as well as SpO2 due to sympatholysis caused by regional anaesthesia suggesting its superiority in PPCM. Single-shot spinal anaesthesia is not recommended due to uncontrolled sympathetic blockade and acute hemodynamic instability which may precipitate an adverse cardiac event including arrest.

A 2008 publication by Dresner et al showed that a titrated continuous spinal anaesthesia using a spinal catheter in pregnant patients with mild to moderate signs of cardiac failure induced mild transient hypotension in 18% and was managed with phenylephrine.

In a prospective observational study done by E. Langesaeter et al, there is also a suggestion that pregnant women with high-risk cardiac disease may safely deliver via a caesarean section under regional anaesthesia. Haemodynamic stability can be obtained by titrated regional anaesthesia, intravenous volume, and phenylephrine infusion guided by invasive monitoring.

- **EPIDURAL**
  This approach has been one of the widely used regional techniques in PPCM. The advantages of epidural anaesthesia being the relative haemodynamic stability, slow titratability and familiarity with the technique by most anaesthesiologists. The disadvantage would be if an inadequate or a "patchy" block result, a need for conversion to GA following a sympatholysis could be potentially hazardous.

- **CSE**
  An increasing number of physicians are opting for a CSE which offers the reliability of an intrathecal blockade with the flexibility of an epidural catheter for titration to get the right sensory level and further more a haemodynamically stable anaesthesia. Various combinations of low dose spinal anaesthesia supplemented by incremental epidural anaesthesia for caesarean section have been described in the literature.
Continuous spinal anaesthesia (CSA) via an intrathecal catheter offers a number of advantages for cardiac obstetric patients. CSA allows careful titration with improved haemodynamic stability than a single shot spinal whilst producing a dense good quality block relatively fast. In experienced hands the hemodynamic stability has been found to be similar to that with epidural anaesthesia. However the potential disadvantage of this technique includes the risk of postdural puncture headache. Using a catheter-over-needle technique and smaller gauge catheters reduces the incidence of postdural puncture headache.41,42,43,44,45

The set usually used at our institution comprises of:

- An 18-gauge 88-mm Crawford type epidural needle with 1-cm markings.
- An over-the-needle spinal catheter system: 22- or 24-gauge 720-mm catheter with fusiform tip with an inner metallic guide mounted over a 27 or 29-gauge Quincke needle. This needle has distal and lateral holes so that flow of cerebrospinal fluid (CSF) can be observed.
- A loss-of-resistance (LOR) syringe.
- A catheter, Luer-lock screw connector and bacterial filter43

Meticulous administration of syntocinon and prophylactic use of furosemide on delivery to prevent fluid overload from autotransfusion must be observed. Postoperatively regardless of the anaesthetic technique, these patients should be routinely monitored in high care or ICU as they may require ventilation, inotropic agents, and mechanical circulatory support due to a higher risk of cardiovascular decompensation. Review and optimisation of anti-failure treatment accordingly including adding drugs that were contra-indicated in pregnancy.

**CONCLUSION**

PPCM is an ominous disease that is probably more prevalent than was previously thought. Its incidence being highest amongst Blacks and women of poor socioeconomic status renders it a highly morbid condition. Diagnosis of PPCM poses a great challenge since early it mimics the symptoms and signs of late pregnancy. In addition for objective diagnosis an ECHO is required, where in a resource poor country like South Africa its availability and skill is limited.

However with the anaesthetists performing more echocardiographic examinations for monitoring and diagnosis of hemodynamic instability the pick-up rate will increase. A favourable outcome depends on early diagnosis and management. A high index of suspicion and awareness can never be overemphasised to successfully manage these women, especially for an anaesthetist working in high volume state hospitals.
The causes and pathomechanisms are unclear but the current research and insight suggest a combination of oxidative state, inflammation, accelerated apoptosis, prolactin and angiogenic imbalance. The mortality associated with PPCM is very high warranting care of these patients by specialised multidisciplinary teams in a regional/tertiary centre. Correct diagnosis of a peripartum woman who survives the index pregnancy will facilitate reproductive counselling and prevention of maternal death in the future.
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