Review Article

# Peripartum Cardiomyopathy

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## Abstract

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction following delivery, where no other cause is found. Thus, it is a diagnosis of exclusion. Ejection fraction may decrease to nearly 45%. The incidence of PPCM is 0.46 per 1000 deliveries (0.18 for apparent PPCM and 0.28 for other cardiomyopathies, and higher incidence has been reported in African-American women). The 16-kDa prolactin leads to increased microRNA 146a expression in endothelial cells, which exerts angiostatic effects and impairs the metabolic activity of cardiomyocytes. PPCM is more likely to occur in women aged > 30 years with history of pregnancy associated with hypertension and women with multifetal pregnancies. Bromocriptine has become standard therapy for PPCM. However, only approximately 50% patients with PPCM recover to baseline ventricular function within 6 months of delivery. Therefore, PPCM is a potentially life-threating cardiac disease that appears during the peripartum period. Although few patients recover cardiac function, long-lasting morbidity and mortality are common. Subsequent pregnancies in such patients are associated with a very high mortality rate and thus should be avoided. Women with PPCM continue to have significant mortality despite the use of conventional drugs for managing heart failure.

## Keywords

- Peripartum cardiomyopathy
- Ejection fraction
- Bromocriptine
- Ventricular function

## Definition and diagnostic criteria

Peripartum cardiomyopathy (PPCM) is defined as a non-familial form of peripartum heart failure characterised as an 'idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found'.[1] PPCM is diagnosed when the following four criteria are met:

1. Heart failure develops in the last month of pregnancy or within 5 months of delivery.

2. Heart pumping function is reduced, with an ejection fraction (EF) < 45% (LV fractional shortening < 30% or LV end-diastolic dimension > 2.7 cm/m$^2$ of body surface area).

3. No other cause of heart failure with reduced EF can be found.

4. Absence of recognizable heart disease prior to the last month of pregnancy.

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## Incidence

The incidence of PPCM was reported to be 1 case per 1374 live births by an Indian study.[2] The mean incidence of PPCM is 1 in 3186 live births in the United States, ranging from 1 in 1149 to 1 in 4350 live births, and is approximately 1 in 100 live births in Africa.[3,4] The rising incidence is attributable to socio-economic changes, rising maternal age and infertility-related treatments leading to multifoetal pregnancy.

## Etiology and risk factors

Several cardiovascular changes take place during pregnancy to increase blood flow to the placenta and developing foetus. The total volume of circulating blood increases by > 40%. The heart rate increases from an average of 75 beats/min before pregnancy to nearly 90 beats/min in the third trimester. A similar increase in the amount of blood ejected with each beat also occurs. There is a slight increase in the average blood pressure, while the blood vessels relax to accommodate increased blood flow. During the stress of labor, these physiological changes increase further and subsequently return to normal by approximately 6 weeks after delivery. Several hormones released from the uterus, kidney, heart and lungs circulate in the blood and stimulate these changes. In PPCM, the stress is presumed to be pregnancy, but the mechanisms are poorly understood.

Risk factors associated with PPCM include older maternal age, multiparity, multifoetal pregnancy, African descent, hypertension, toxin exposure (e.g., cocaine), etc. It is important to note that although PPCM is more likely to occur in a woman over the age of 30 years who is pregnant with twins and has had prior pregnancies, it can also occur in a younger woman who is pregnant with her first child. As pregnancy leads to a relatively immunocompromised state, the role of viral infection in inducing PPCM cannot be denied; however, the results for this are controversial. The highly variable prevalence of myocarditis in patients with PPCM (ranging from 8.8% to 78%) suggests that viral infections may be among the triggers for PPCM in some cases. Prolactin has also been implicated in the aetiology of PPCM.

A potentially beneficial hormone in PPCM is relaxin, which is produced in the ovaries, breast and placenta with receptors in the heart, smooth muscle and connective tissue. It has a variety of haemodynamic effects, including increased cardiac output and decreased systemic vascular resistance, as well as anti-inflammatory and anti-fibrotic properties. Higher levels of relaxin are associated with increased rates of myocardial recovery.

## Clinical evaluation and investigative modalities

The major symptoms of PPCM are those of heart failure and include fatigue, shortness of breath and fluid retention. Because there is a significant overlap between symptoms related to heart failure and those related to pregnancy, particularly towards the end of the third trimester or after delivery, the diagnosis may be initially missed or delayed.

The evaluation of PPCM should begin with a complete medical history and physical examination. The key aims of the medical history are ruling out heart disease that may have predated pregnancy, identifying other potential causes or precipitants of heart failure, including a family history of heart disease, and defining symptom severity. Similarly, the physical examination may help in uncovering other non-cardiac conditions associated with cardiomyopathy while assessing for signs of reduced heart function and fluid retention.

When PPCM is suspected, an electrocardiogram, natriuretic peptide measurement and echocardiogram should be urgently performed. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is a marker whose concentration is usually markedly elevated in most patients with PPCM. The levels of asymmetric dimethylarginine (ADMA), a marker for endothelial dysfunction and cardiovascular risk, may also be elevated. Levels of cathepsin D show an increased activity in the plasma of patients with PPCM. Soluble FMS-like tyrosine kinase 1 (sFlt-1), a biomarker of pre-eclampsia, which is supposed to clear rapidly after delivery, is increased in PPCM. Micro ribonucleic acid (miRNA) is specifically increased in patients with PPCM than in healthy postpartum women and patients with dilated cardiomyopathy. Diagnostic accuracy needs to be further evaluated for markers such as 16-kDa protein, interferon gamma (IFNγ), ADMA, cathepsin D, sFlt-1 and miRNA 146a. Failure to normalise a biomarker profile, including NT-proBNP, oxidised low-density lipoprotein, IFNγ and prolactin, is associated with adverse outcome in patients with PPCM.

The most common finding on an electrocardiogram is a sinus tachycardia with ST-T changes. Echocardiography in PPCM is characterised by left (and often right) ventricular dilatation and dysfunction. Secondary mitral valve regurgitation is common, and LV thrombus may also be observed.

## Labour

When PPCM is diagnosed prepartum, an urgent assessment by a multi-disciplinary team involving cardiologists, obstetricians, neonatologists and anaesthetists is necessary. Involvement of cardiac

surgeons (if it is felt likely that mechanical circulatory support may be required) should also be considered. Timing as well as the mode and location of delivery should be the focus of discussion between the clinical team and the patient as early as possible, and this should take into account the patient's wishes. Patients with PPCM should be delivered in a high-risk obstetric or cardiac unit by a specialist multi-disciplinary team with expertise in managing pregnancy in women with cardiac disease. There should be access to Level 3 intensive- and neonatal intensive-care units. Clinical status of the mother, severity of LV dysfunction and growth of the foetus are all markers that are used to guide when and how a woman with PPCM delivers. Spontaneous vaginal delivery is often possible, but Caesarean section is preferred if the mother is critically ill. Steroids should be administered prior to delivery for neonatal lung maturity.

## Management

Medications are used to stabilise heart function, improve blood flow to vital organs and reduce fluid overload. This includes vasodilators [e.g., hydralazine, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers], loop diuretics, β-blockers (e.g., carvedilol and metoprolol), digitalis, spironolactone, etc.

### *Anti-coagulants*

Anti-coagulation is indicated in the presence of LV thrombus or atrial fibrillation because the possibility of occurrence of thromboembolic events is as high as 6%. Initially, low molecular heparin and, subsequently, warfarin may be considered in such cases.

### *Anti-arrhythmics*

During pregnancy, β-blockers, sotalol and intravenous procainamide can be used. Amiodarone is a third-line agent that can be administered intravenously or orally during or after pregnancy; however, it may be toxic to the foetus and thus requires careful monitoring of liver, thyroid and lung function.

An implantable cardioverter-defibrillator is indicated after delivery in patients with life threatening arrhythmias and poor EF because the possibility of occurrence of sudden cardiac death is as high as 38%.

### *Prognosis*

Prognosis of PPCM is positively related to the recovery of ventricular failure. Only about 50% patients with PPCM recover from baseline ventricular function within 6 months of delivery.[5] Patients with the lowest EF are least likely to recover. Patients with low NT-proBNP and troponin levels are more likely to recover. Failure of the heart to return to normal size is associated with increased mortality and morbidity. Future pregnancies are not recommended in patients with PPCM because there is an increased risk for the recurrence of PPCM in subsequent pregnancies.

### *Breastfeeding*

The advantages and disadvantages of breastfeeding should be discussed with the mother. Although there are few hard data, ACE inhibitors, ßeta blockers and spironolactone are generally considered safe during breastfeeding. ACE inhibitors may be avoided in nursing mothers in the first few weeks after delivery, particularly in preterm infants due to the risk of neonatal hypotension. The amount of ßeta blocker and spironolactone present in breast milk is negligible. The use of warfarin is also considered safe. If bromocriptine is used, lactation is suppressed.

### *Long-term medications*

Women who have echocardiographically recovered myocardial function after PPCM are usually keen on stopping their medical therapy. There are limited data to guide this decision. One study of 15 patients found no deterioration in LV function after 2 years off therapy. Some patients with apparently normal LV function have abnormal contractile reserve on stress echocardiography. Anecdotally, some women do have deterioration in cardiac function after withdrawal of therapy. Withdrawal decisions should be discussed with the patient and family and sequential withdrawal of treatment seems reasonable with monitoring of cardiac function.

## Conclusion

PPCM is a pregnancy-associated rare but severe myocardial disease with a mean incidence of approximately 1 in 3186 live births in the United States. Likely causes include viral infections, toxins, environmental and geographic factors, familial predisposition, hormonal abnormalities, haemodynamic burden of pregnancy, malnutrition and inflammation. NT-proBNP, cathepsin D and sFlt-1 may be elevated and can be used as biomarkers for the diagnosis of PPCM. For symptomatic management, administration of ßeta-blockers and diuretics (thiazide and furosemide) in the lowest possible doses and restriction of dietary sodium are recommended. Prognosis of PPCM is positively related to the recovery of ventricular failure. Only approximately 50% patients with PPCM recover to baseline ventricular function within 6 months of delivery. Failure of the heart to return to normal size is associated with increased mortality and morbidity. Future pregnancies are not recommended in patient with PPCM as there is an increased risk for recurrence of PPCM in subsequent pregnancies.

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