

Peripartum Cardiomyopathy: a Review for the Clinician

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Abstract

Purpose of review This review summarizes the pathophysiology, diagnosis, and treatment of peripartum cardiomyopathy (PPCM), with a focus on recent discoveries of clinical relevance.

Recent findings An increase in oxidative stress and anti-angiogenic activity play key roles in the pathophysiology of peripartum cardiomyopathy. Therapies that target this dysregulation may have a future role in treatment. Suppression of prolactin release using bromocriptine, a dopamine-receptor antagonist, has been associated with more favorable outcomes in small studies but more research is needed. Similarly, VEGF agonists may prove to be a novel therapy by upregulating angiogenesis.

Summary Peripartum cardiomyopathy typically presents in the third trimester or in first few months postpartum. Both genetic and clinical risk factors for PPCM have been identified. Women with PPCM should be managed by a multidisciplinary team with experience in high risk pregnancy and the treatment of heart failure. These women benefit from the use of standard treatments for heart failure therapy with the exception of avoiding ACE inhibitors and ARBs while pregnant. While the rate of recovery of ventricular function in PPCM is higher than in other forms of dilated cardiomyopathy, mechanical circulatory support and/or cardiac transplantation are required in some cases.

Introduction

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy which develops either during the later stages of pregnancy or in the first months thereafter. Risk factors for PPCM include Black race, multifetal gestation, multiparity, increasing age, and preeclampsia or hypertension [1]. The prevalence of PPCM varies geographically and ethnically. It is as high as 1 in 300 live births in Haiti, compared to 1 in 1000–4000 live births in the USA [2–5].

The diagnosis of PPCM should be considered in women presenting with heart failure symptoms such as shortness of breath, lower extremity edema, orthopnea, or paroxysmal nocturnal dyspnea during the peripartum period [6]. This however can be challenging as these are often symptoms of a healthy pregnancy. Alternative causes of acute heart failure and non-cardiac causes of a similar presentation should also be excluded.

The etiology of PPCM is unknown and more research is needed to better understand the genetic underpinnings and pathophysiology. Individuals with PPCM have a high frequency of truncating variants in the gene for the sarcomere protein titan (TTN), similar to patients with idiopathic dilated cardiomyopathy [7•, 8].

The risk of PPCM increases when there is a relative increase in oxidative stress without antioxidant capacity late in pregnancy. Furthermore, an increase in anti-angiogenic activity has been associated with PPCM. Prolactin levels increase early post-partum and abnormal proteolytic cleavage of this hormone can result in an inhibition of angiogenic activity. Suppression of prolactin release using bromocriptine, a dopamine-receptor antagonist, has been associated with more favorable outcome in small studies. Soluble fms-like tyrosine kinase 1 (s Flt1) is a tyrosine kinase protein that is upregulated in preeclampsia and may also be involved in the pathogenesis of PPCM [6, 9, 10].

While PPCM is associated with significant morbidity and mortality, outcomes in women with PPCM are generally better than those in other types of cardiomyopathy. In the multicenter IPAC (Investigations of Pregnancy-Associated Cardiomyopathy) study, 72% of women achieved a LV ejection fraction (LVEF) \geq 50% at 1 year. Thirteen percent of women in this study had major events (left ventricular assist device (LVAD) placement, cardiac transplantation, or death) or had persistent severe cardiomyopathy by 1 year [11•]. These outcomes are similar to a recent study by Erbsoll et al., in which only 14.8% of women had a major adverse event, and almost 2/3 of women had a complete recovery [5]. Other studies have shown poorer outcomes, especially among women of African descent [12, 13]. LV thrombi and embolic events frequently complicate PPCM, occurring in 7–20% of women [12, 14].

Clinical factors associated with a lack of recovery of left ventricular (LV) function include LVEF \leq 30% at the time of diagnosis, significant LV chamber dilation (LV end-diastolic dimension \geq 6 cm), reduced RV function on echocardiography calculated by fractional area change, persistent troponin elevation, Black race, and presentation later in the postpartum period [5, 11•, 15, 16]. Women who possess TTN variants associated with dilated cardiomyopathy also appear to be less likely to recover LV function [7•]. Women with hypertensive disorders of pregnancy may have a milder course [5, 17].

The rate of recurrence of PPCM in subsequent pregnancies is approximately 20% in those who recover normal LV function, with a much higher risk in those who do not have LV functional recovery [18]. Women with a history of PPCM who are considering subsequent pregnancy should receive in-depth counseling regarding the risks of and alternatives to pregnancy at a center experienced in the management of high risk pregnancy.

Treatment

Diet and lifestyle

Diet

- A low salt diet is recommended for women with PPCM, as in other forms of heart failure [19].

Breastfeeding

- The recognition that the nursing hormone prolactin may play a pathogenic role in PPCM has led to concerns that breastfeeding may contribute to or worsen the course of PPCM [20].
- Data regarding the impact of breast feeding on the incidence and outcome of PPCM is very limited.
- While some have advocated for avoidance of breastfeeding in this population, there is currently no evidence to suggest that this strategy is beneficial.
- One study has shown that breastfeeding is positively correlated with LV recovery, but these results are difficult to interpret given that the potential for confounding is high [17]. For instance, successful breastfeeding in PPCM may be a marker for less severe disease. At the current moment, there is little data to guide recommendations regarding breastfeeding in PPCM.
- As breastfeeding is beneficial to the baby and mother, especially in less developed countries, our approach is to recommend continuing breast feeding.

Pharmacological treatment

Conventional heart failure therapies

- Women with PPCM benefit from the prompt initiation of standard therapies for heart failure with reduced ejection fraction. These include diuretics, beta-blockers, ACE inhibitors or ARBs, and mineralocorticoid receptor blockers (Table 1) [19].

Table 1. Dosing and safety profile of common medications

Drug class	Drug	Dose	Safety in pregnancy	Safety in lactation	Contraindications
Beta-blockers	Metoprolol succinate	12.5–200 mg daily	May be associated with IUGR	Yes	Hypotension or bradycardia
ACE inhibitors	Captopril Enalapril	3.25–50 mg TID 2.5–20 mg BID	No	Generally considered safe in lactation	Hypotension, renal failure, hyperkalemia
Mineralocorticoid receptor blockers	Sprinolactone	12.5–50 mg daily	No	Limited data	Hyperkalemia, acute renal failure
Loop diuretics	Furosemide	Oral: 20–40 mg once or twice daily (max 600 mg/day) IV: 20 to 40 mg/dose (max 200 mg/dose)	Yes	Yes but may reduce breast milk production	Renal failure, hypokalemia, sulfa allergy

- Treatment is more limited when PPCM develops during pregnancy. Beta-1 selective drugs like metoprolol are preferred in pregnancy [21]. Ultrasound monitoring for fetal growth restriction is often recommended due to both reported association between some beta-blockers and fetal growth restriction [22], as well as PPCM itself. Hydralazine and nitrates can be considered in place of ACE inhibitor or ARB therapy during pregnancy. The use of ACE inhibitors, ARBs, mineralocorticoid receptor blockers, and renin inhibitors is contraindicated in pregnancy.
- Most heart failure therapies can be used in breastfeeding women. Benazepril, enalapril, and captopril are generally felt to be safe and are the preferred agents in this population [23].
- European Society of Cardiology guidelines suggest that agents should be continued for at least 12 months before consideration of withdrawal, and that withdrawal, when it occurs, should be done in a stepwise manner [24]. Monitoring of ventricular function by echocardiography is recommended.

Beta-blockers

Drug: Metoprolol succinate (extended release)

Standard dose: 12.5–200 mg once daily

Contraindications: Bradycardia or hypotension

Main drug interactions

Main side effects: Bradycardia, hypotension, and fatigue

Inexpensive

Special points

May be associated with fetal growth restriction, avoid atenolol [21, 22].

Considered safe in lactation

Angiotensin converting enzyme inhibitors (ACE inhibitors)

Drug: Captopril or enalapril

Standard dosage:

Captopril 3.25–50 mg TID

Enalapril 2.5 mg–20 mg BID

Contraindications: Pregnancy, hypotension, acute renal failure, hyperkalemia

Main drug interactions

Main side effects: hypotension, rise in creatinine, hyperkalemia

Inexpensive

Special points

Contraindicated in pregnancy

Generally considered safe in lactation

Mineralocorticoid receptor blockers

Drug: Spironolactone

Standard dosage: 12.5 to 50 mg once daily

Contraindications: Hyperkalemia, acute renal insufficiency

Main drug interactions: may enhance the hyperkalemic effect of ACE inhibitors.

Main side effects: hypotension

Inexpensive

Special points

Contraindicated in pregnancy

Limited data in lactation, can reduce breastmilk production

Loop diuretics

Drugs: Furosemide or other loop diuretics

Standard dosage:

- Oral 20 to 40 mg once or twice daily (max 600 mg/day), dosing frequency to be adjusted based on patient specific needs
- IV: 20 to 40 mg/dose (max 200 mg/dose)
- IV continuous infusion: Initial 40 mg to 100 mg IV bolus over 1 to 20 min followed by IV infusion rate of 10 to 40 mg/h

Contraindications: Hypersensitivity to sulfonamide-derived products, acute renal failure, uncorrected hypokalemia

Main drug interactions

Main side effects: Hypotension

Special points

Frequently used in pregnancy

PPCM-specific therapy

Bromocriptine:

In the first, randomized controlled trial of 63 patients with PPCM and an LVEF $\leq 35\%$ 2.5 mg of bromocriptine daily for 7 days in addition to standard heart failure therapy was associated with more favorable outcomes compared to those not treated with bromocriptine. Given the small size of this study, more research is needed [25].

Anticoagulation

- Thrombotic events are common in PPCM [14•].
- Anticoagulation is indicated in the setting of LV thrombus or thrombotic complications.
- There are no data regarding the specific efficacy of different anticoagulants in PPCM; therefore, the choice of anticoagulant is at the discretion of the provider.

Interventional procedures

Obstetrical management

- When PPCM develops in pregnancy, preterm delivery is often required.
- Decision-making regarding the mode and timing of delivery is complex and should be made in consultation with a multidisciplinary team

including cardiology, high-risk pregnancy specialists, anesthesia, and neonatology.

- If possible, delivery should occur at a tertiary medical center with specific experience in the management of cardiac disease in pregnancy.
- Vaginal delivery is tolerated in many cases. Minimization of the hemodynamic stress of delivery is recommended, typically by the use of early epidural anesthesia and an assisted second stage of labor if appropriate [23].
- In woman with hemodynamic instability or significant hemodynamic compromise, cesarean section may be required.
- Close attention to the potential hemodynamic effects of pain, hemorrhage, and autotransfusion from the uteroplacental bed to the maternal circulation is advised [23]. In addition, the rise in systemic vascular resistance post delivery causes an abrupt increase in afterload.
- Hemodynamic monitoring may be required during delivery, and many women with PPCM benefit from admission to an intensive care unit or cardiology unit in the early postpartum period to monitor hemodynamics as often the highest risk time for CHF decompensation
- Arrhythmia monitoring is indicated, given that arrhythmias are common in this population and are associated with adverse outcomes [26].
- If timing and patient stability allow, optimization of the woman's volume status with diuretics is recommended before delivery.

Implantable cardioverter defibrillator and cardiac resynchronization

- There is an association between PPCM and malignant ventricular arrhythmias [26].
- There are no PPCM-specific guidelines regarding the use of ICDs and cardiac resynchronization therapy.
- In other forms of non-ischemic cardiomyopathy, ICD implantation is not recommended unless the left ventricular ejection fraction fails to improve after a period of goal directed medical therapy, usually at least 3 months [19].
- The high rate of recovery of LV function in PPCM means that many women will not go on to need ICD implantation.
- Some studies have documented continued improvement in LV function late after the development of PPCM [27]. The benefit of waiting longer to potentially avoid an ICD needs to be weighed against the risk of death from ventricular arrhythmia. The European Society of Cardiology PPCM guidelines state that waiting more than 6–12 months for myocardial recovery is unlikely to provide additional benefit, and exposes patients to excess harm [24•].
- A wearable defibrillator may be a good option for high-risk women during the waiting period.

Mechanical circulatory support

- A variety of mechanical support options exist for women with decompensated PPCM. Patients who are not responding to medical therapy

should be cared for at a tertiary care institution with mechanical circulatory support capability.

- A full discussion of the mechanical circulatory support options is beyond the scope of this review.

Cardiac transplantation

- Cardiac transplantation may also be an option for select women with decompensated PPCM. Consultation with a transplant center is recommended.

Emerging therapies

As discussed above, bromocriptine has been associated with more favorable outcomes in smaller studies but larger studies are needed [25]. Novel therapeutics for PPCM include targeting molecular pathways such as with VEGF agonists to promote angiogenesis, or with neutralizers of the micro-RNA, miR-146a, which is upregulated in PPCM and implicated in the pathogenesis [9].

Counseling on future pregnancy

Women with a history of PPCM should receive in depth counseling regarding the risks of and alternatives to subsequent pregnancy. Patients with a history of PPCM who do not recover LV function are at highest risk for complications and a new pregnancy is discouraged. In these women, contraception with a non-estrogen-based therapy (IUD) or partner sterilization should be considered.

The risk of recurrence in women who have recovered LV function can be as high as 20% but this is based on small retrospective studies. Women taking ACEi or ARB should discontinue these medications at least 3 months prior to conception. Hydralazine and isosorbide dinitrate together may be used instead. Data on safety of aldosterone antagonists (spironolactone) in pregnancy is limited and the general recommendation is to discontinue it. Beta 1 selective blockers can be continued during pregnancy and while the data is limited, metoprolol is felt to be generally safe. There are no guidelines to direct frequency of echocardiographic monitoring in pregnancy. Based on available literature and expert opinion, a baseline study and repeat echocardiogram after the first and second trimesters, 2–4 weeks prior to delivery, before discharge from the hospital, and 3 months after delivery are recommended. The clinician should have a low threshold for repeating an echocardiogram sooner when any concerning symptoms are reported by the patient.

Conclusion

Peripartum cardiomyopathy affects one in a thousand births worldwide. Both genetic and clinical risk factors for PPCM have been identified. The rate of recovery of ventricular function in PPCM is higher than in other

forms of dilated cardiomyopathy. Women with PPCM should be managed by a multidisciplinary team with experience in high-risk pregnancy and the treatment of heart failure.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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