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REVIEW

Peripartum Cardiomyopathy: Risks Diagnosis and Management

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Abstract: Peripartum cardiomyopathy is a rare cause of heart failure that occurs during late pregnancy or in the early postpartum period. Delays in diagnosis may occur as symptoms of heart failure mimic those of normal pregnancy. The diagnosis should be considered in any pregnant or postpartum woman with symptoms concerning for heart failure. If there are clinical concerns, labs including N-terminal pro-BNP should be checked, and an echocardiogram should be ordered to assess for systolic dysfunction. Prompt medical treatment tailored for pregnancy and lactation is essential to prevent adverse events. Outcomes are variable, including complete recovery, persistent myocardial dysfunction with heart failure symptoms, arrhythmias, thromboembolic events, and/or rapid deterioration requiring mechanical circulatory support and cardiac transplantation. It is essential that care is provided as part of a multidisciplinary cardio-obstetrics team including obstetrics, cardiology, maternal fetal medicine, anesthesiology, and nursing. All women with peripartum cardiomyopathy should have close follow-up with a cardiologist, although optimal duration of medical therapy following complete recovery is unknown. Women considering a subsequent pregnancy require preconception counseling and close collaboration between obstetrics and cardiology throughout pregnancy.

Keywords: peripartum, cardiomyopathy, pregnancy, heart failure

Introduction

Peripartum cardiomyopathy (PPCM) is a rare and idiopathic form of systolic heart failure affecting childbearing women towards the end of pregnancy or in the early postpartum period.

The 2019 Heart Failure Association of the European Society of Cardiology Working Group defines PPCM as

> an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause is found.[1]

Echocardiography is essential for the diagnosis, and diagnostic criteria require that the left ventricular ejection fraction (LVEF) is <45%, with or without left ventricular dilatation (Figure 1).[1–3]

In the United States, reported incidence ranges from 1 in 900 to 1 in 4000 and this number is likely increasing given the increased recognition of the disease, rise in maternal age, and increase in multifetal pregnancies due to assisted reproductive techniques.[4–6] Incidence is four times higher in African American women than in white women, and lowest in Hispanic women.[5,7–9] Even though less than 15% of the US population is African American, in two recent US studies African American women accounted for nearly half of PPCM cases.[5,10] Global estimates of the incidence of PPCM vary widely throughout the world, as high as 1 in 96 deliveries in parts of Nigeria and as low as 1 in 20,000 deliveries in Japan.[11–13]

In this article, we aim to review the data regarding the pathogenesis, typical presentation, risk factors, recommendations for diagnosis, and the management of PPCM, including counseling considerations for breastfeeding and subsequent pregnancies.

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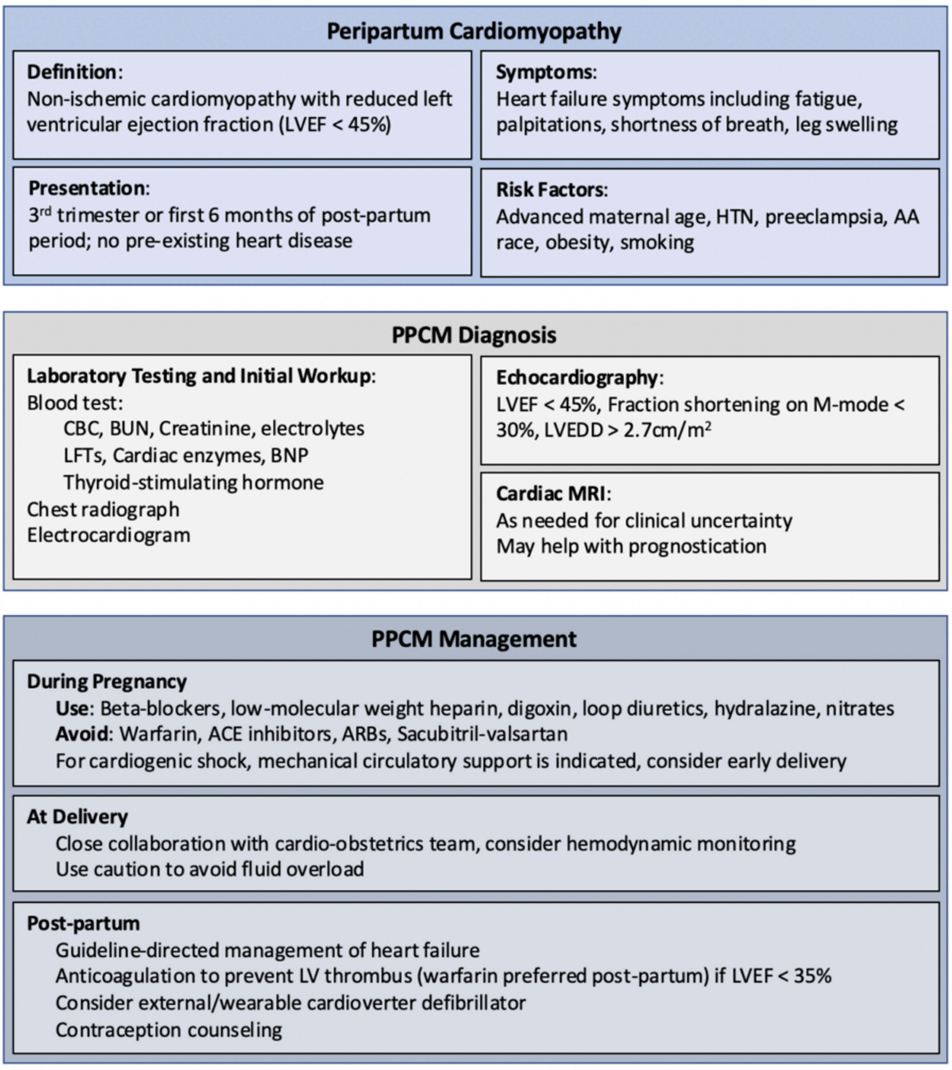

Figure 1 Presentation, risk factors, diagnosis, and management of peripartum cardiomyopathy (PPCM).
Abbreviations: LVEF, left ventricular ejection fraction; HTN, hypertension; AA, African American; CBC, complete blood cell count; BUN, blood urea nitrogen; LVEDD, left ventricular end diastolic dimension; LFTs, liver function tests; MRI, magnetic resonance imaging; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; NT-pro-BNP, N terminal pro-brain natriuretic peptide.

Pathogenesis and Presentation

The precise pathogenesis of PPCM remains unknown, with prior hypotheses related to autoimmune processes, nutritional deficiencies, and hemodynamic stress of pregnancy.[14–17] Currently, the development of PPCM is understood with a "two-hit" model, where a vascular insult caused by hormonal effects of late pregnancy and the early postpartum period induce cardiomyopathy in patients with an underlying genetic predisposition.[18–23] Some studies have suggested the vascular insult may be due to a prolactin-mediated oxidative stress on the myocardium.[24] Given the association of PPCM with pre-eclampsia, it is also thought that placental angiogenic factors could provide a shared pathophysiologic mechanism.[25,26] Furthermore, it has been shown that certain anti-adrenergic and anti-sarcomeric protein antibodies are more common in PPCM, which could suggest an additional autoimmune mechanism for PPCM.[27,28]

The typical clinical presentation involves typical signs and symptoms of heart failure including shortness of breath on exertion, orthopnea, paroxysmal nocturnal dyspnea, edema, and chest tightness. On physical examination, patients typically demonstrate tachypnea, tachycardia, elevated jugular venous pressure, pulmonary rales, and peripheral edema.[29] More severe, but uncommon presentations include serious arrhythmias, cardiac arrest, thromboembolic

complications, and cardiogenic shock.[30,31] Between 50% and 80% of the affected women recover systolic function to a normal LVEF of ≥50%, with the majority of the recovery occurring in the first 6 months.[32,33] Partial recovery is defined as improving LVEF by at least 10%. However, some women will have serious complications including arrhythmias, thromboembolism, and cardiogenic shock in some instances requiring mechanical support or cardiac transplantation.[5,13,32,34] Medical management centers around standard treatment for heart failure with reduced ejection fraction, with special attention to increased risk of thromboembolism in these women, adverse effects of some medications on the fetus for women who are still pregnant, and risk of lethal arrhythmias in the postpartum period. Timing and mode of delivery should be discussed with the patient and carefully planned by a multidisciplinary cardio-obstetrics team, including obstetrics, cardiology, maternal fetal medicine, anesthesiology, and nursing.[35] There is risk of relapse with subsequent pregnancies, and thus close collaboration and follow-up by cardiology and obstetrics is essential even in patients who have recovered systolic function.

Risk Factors

The incidence of PPCM is higher in women of African descent. Possible reasons for this include genetic predisposition, higher incidence of pre-eclampsia in these women, and regional nutritional deficiencies; however, racial and ethnic disparities in outcomes also exist and are likely related to systemic inequities and racism.[36,37] While PPCM occurs in approximately 1 in 100 live births in Nigeria, the rate is approximately 1 in 10,000 in Denmark and 1 in 20,000 in Japan.[11,12,38] In the United States, several statewide studies have reported PPCM occurring 3 to 4 times as often in African American women compared with white women, and the rates are lowest in Hispanic women.[5,7–9]

Hypertension and pre-eclampsia are strongly associated with PPCM. A meta-analysis of 22 studies of PPCM reported that pre-eclampsia was present in 22% of the women with PPCM as compared to 5% of the other pregnancies, and that other hypertensive disorders were present in 37% of the women with PPCM as compared to 13% of all pregnancies.[39,40] The majority of women with pre-eclampsia do not develop PPCM, which requires a decreased systolic function for diagnosis. Rather, hypertension and pre-eclampsia lead to predominant diastolic dysfunction.

PPCM also appears to be associated with increasing maternal age, with one-half of cases occurring in women over 30 years of age with an adjusted odds ratio of 1.8 compared to those younger than 30 years.[9,29] Furthermore, one study found that women over 40 years of age had an odds ratio of 10 of developing PPCM compared to women under 20 years of age.[5] This trend is reflected in an analysis of US data that showed an incidence of 1 in 1200 of PPCM in women 20–29 years of age and 1 in 270 in women greater than 40 years of age.[5] Multigestational pregnancies are also shown to increase the risk of PPCM with a threefold risk reported for twin gestations.[41] In the United States, 7–14.5% of the women with PPCM occur in the setting of a multigestational pregnancy.[41–43]

Multiple serum biomarkers have been associated with PPCM. Serum prolactin level has been shown to be significantly elevated at baseline in patients with PPCM compared to controls. While the baseline prolactin level has not been shown to be prognostic, the failure of this to decrease over time is associated with lack of PPCM recovery.[44] Similarly, the persistent elevation of markers of inflammation and oxidative stress such as oxidized low-density lipoprotein (ox-LDL) and interferon-gamma (INF-g) have also been associated with lack of recovery while elevations of C-reactive protein (CRP), white blood cell (WBC) count and monocyte to high-density lipoprotein ratio (MHR) may be predictive of persistent systolic dysfunction.[45,46] Additionally, early post-partum serum biomarkers of vascular endothelial dysfunction have also been prognostic. Relaxin-2 is associated with greater recovery and less ventricular remodeling, while soluble Fms-like tyrosine kinase (sFlt1) is associated with disease progression and poorer prognosis.[26]

Multiple studies have identified a genetic component to PPCM. In fact, approximately 16% of the patients report a family history of HF.[47] A study assessing 43 genes with a known association with dilated cardiomyopathy in patients with PPCM showed a positive association in 15%.[21] Specific associated genes include a gene for the sarcomeric protein titin (TTN), a mutation near the vascular homeostasis parathyroid hormone-like hormone (PTHLH) gene, as well as the dystrophic gene.[21] Additional genes include the beta-myosin heavy chain (MYH7), a sodium voltage-gated channel alpha subunit 5 (SCN5A), and myosin binding protein C (MYBPC3).[48] Truncating variants of the TTN gene have been shown to carry a worse prognosis in PPCM. Given our understanding, genetic testing may be a useful screening tool in patients with a family history of PPCM.[49] However, the genetic origin of PPCM is most likely

incompletely penetrant since most women do not have a family history of PPCM and do not always develop recurrent PPCM in subsequent pregnancies.[3]

Closer surveillance of women at high risk during pregnancy is essential as earlier detection of PPCM can lead to more appropriate treatment and safer delivery as well as postpartum care.

Diagnosis

Due to under-recognition of PPCM and the overall similarity in signs and symptoms of normal pregnancy with those of heart failure, there are frequent delays in diagnosis. PPCM is a diagnosis of exclusion, and it is essential that the patient is evaluated for possible pre-existing heart disease. Lab testing should include checking levels N-terminal pro-BNP (NT-pro BNP), which do not change significantly during pregnancy but will be markedly elevated in PPCM. The electrocardiogram is often normal but may show nonspecific abnormalities.[50,51] An echocardiogram is essential in any suspected case of PPCM. In addition to systolic dysfunction, the echocardiogram may demonstrate left ventricular dilatation, functional mitral and/or tricuspid regurgitation, right ventricular dysfunction, pulmonary hypertension, and atrial enlargement.[52,53] The left ventricular apex should be clearly visualized to evaluate for intracardiac thrombus. If echocardiogram is inadequate, cardiac magnetic resonance imaging should be considered for a more accurate measure of systolic function and chamber measurements.[54] Notably, gadolinium is avoided during pregnancy. If there is concern for an alternative diagnosis that would require different management, endomyocardial biopsy may be considered but is rarely needed. Further research is needed to address knowledge gaps regarding the optimal diagnostic strategy, which may include a combination of genetic testing, serum biomarkers, laboratory values, and imaging findings.

Management

Very few studies of management have been performed specifically in patients with peripartum cardiomyopathy. As a result, the treatment of PPCM is derived from a combination of expert opinion as well as recommendations for other forms of systolic heart failure. The guidelines advise that standard treatment for systolic heart failure is indicated for patients with PPCM, with special consideration for fetal safety in pregnant patients and for safety of newborns in breastfeeding mothers.[53,55,56] The first-line therapy of volume management is dietary sodium restriction, but loop diuretics can be used safely in patients with peripheral or pulmonary edema.[57] Beta-blockers, hydralazine/nitrates, and digoxin can also be used safely during pregnancy.[22,52,58,59] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEi/ARBs), sacubitril-valsartan, sodium glucose co-transporter 2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists should be avoided during pregnancy.[59–62] Heart failure medications that are compatible with breastfeeding include evidence based beta-blockers, certain ACEi such as captopril or enalapril and mineralocorticoid inhibitors. (Table 1)

In patients who develop acute decompensated heart failure, nitroglycerine may be necessary and is preferred to nitroprusside owing to the potential risk of cyanide toxicity in the latter. There is one study that suggested β-agonists (ie dobutamine) in patients with PPCM and severe left ventricular dysfunction (LVEF ≤25%) may be detrimental and precipitate the need for left ventricular assist device or transplantation.[63] However, more studies are needed. Bromocriptine is a dopamine (D2) agonist that inhibits prolactin production and is a promising drug under investigation in the REBIRTH study for treatment in women with PPCM.[64] At present, it may be reasonable in patients with cardiogenic shock or severe LV dysfunction (EF <25%).[65–68] As it suppresses lactation, implications for breastfeeding should be discussed prior to initiation.

After delivery, cardiac medications are continued indefinitely in the presence of persistent cardiac dysfunction.[22] Optimal duration of treatment is unknown after systolic recovery. However, expert opinion suggests that in low-risk patients with fully normalized myocardial function for at least a year, medications could be slowly weaned in a stepwise approach with frequent clinical assessment and echocardiographic monitoring, potentially every 3–6 months. All patients who have recovered function should continue with annual clinic assessment by a cardiologist. We discuss some special consideration in treatment and counseling of patients with PPCM below.

Table 1 Peripartum Cardiomyopathy Medications and Safety in Pregnancy and with Lactation

Medication	Indications	Adverse Effects	During Pregnancy	During Lactation
Beta blockers	Standard heart failure (HF) treatment	Intrauterine growth restriction (IUGR), fetal bradycardia, hypoglycemia	Yes	Yes
Loop diuretics	Volume management	Hypovolemia and hypotension	Yes	Yes
Vasodilators • Hydralazine • Nitrates	Afterload reduction during pregnancy	Hypotension	Yes	Yes
Digoxin	Symptomatic HF treatment	None	Yes	Yes
Angiotensin-Converting Enzyme inhibitors (ACEi)/Angiotensin Receptor Blockers (ARB)	Guideline-directed medical therapy for afterload reduction	IUGR, stillbirth, pulmonary atresia, oligohydramnios, neonatal hypotension, neonatal death	No	Yes for enalapril, captopril, and benazepril
Aldosterone receptor antagonists	Guideline-directed medical therapy for HF	Antiadrenergic effects with spironolactone	No	Yes
Sacubitril-valsartan	Guideline-directed medical therapy for HF	IUGR, stillbirth, pulmonary atresia, oligohydramnios, neonatal hypotension, neonatal death	No	No data in humans
Low-molecular weight heparin	Prevention and treatment of thromboembolic complications in pregnancy, bridge to warfarin post-partum	Caution at time of delivery	Yes	Yes
Warfarin	Postpartum treatment of thromboembolic complications	Warfarin embryopathy and fetopathy	No	Yes

Anticoagulation

Pregnant women and those in the early post-partum period are at increased risk of thrombosis due to the hypercoagulable state of pregnancy.[69] Furthermore, patients with PPCM have been found to have an increased incidence of left ventricular thrombi when compared to other forms of cardiomyopathy.[5,13,51,70] Thus, anticoagulation may be considered in the setting of severe left ventricular dysfunction in the peripartum period to 8 weeks postpartum[53,55] Anticoagulation is also recommended in patients who receive bromocriptine, given its increased risk of thromboembolism, stroke and myocardial infarction.[60] There are no established data on whether therapeutic or prophylactic anticoagulation should be used. Unfractionated and low-molecular-weight heparin can be used during pregnancy and lactation. Warfarin should not be used during pregnancy but is safe with lactation.[71] The novel anticoagulants are currently avoided as they have not been sufficiently studied during pregnancy or lactation.

Labor and Delivery

Multidisciplinary coordination by a cardio-obstetrics team of experts, including obstetrics, cardiology, maternal fetal medicine, anesthesiology, and nursing, is essential in timing and mode of delivery.[35,72] It is recommended that hemodynamically stable patients are safe to continue pregnancy with a preference for vaginal delivery. According to American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines, cesarean delivery may be considered in cases of acute heart failure, but is associated with increased risks of thromboembolism, infection, and hemorrhage.[60,73] Invasive hemodynamic monitoring during labor and in the early post-partum period should be considered in patients with unstable hemodynamics.[22]

Lactation

Most medications required for treatment of PPCM can be given safely with breastfeeding. The 2010 European Society of Cardiology statement on PPCM recommended against breastfeeding due to the postulated link between prolactin and PPCM.[3] However, subsequent IPAC data have not shown breastfeeding to be associated with adverse outcomes and a small study from the United States suggests breastfeeding may be associated with a higher chance of recovery.[24,74] Given this and the known benefits of breastfeeding to the infant, many experts recommend breastfeeding in those stable enough to do so.[75–77]

Sudden Death Prevention

Both cardioversion and defibrillation are safe in pregnancy and should be performed as indicated in any patient.[78] Fetal monitoring can be considered in non-emergent settings to assess for secondary fetal arrhythmias.[79] Early implantation of an ICD is usually discouraged as most patients recover to an LVEF ≥ 35% within 6 months.[60] Both the AHA and ESC recommend consideration of wearable cardioverter defibrillators (WCDs) in these patients as they could also be used to bridge to an ICD in patients that do not recover.[53,55,60,80] A recent study examining the use of WCDs in pregnancy found that arrhythmia detection remained excellent despite the altered anatomy and physiology, but since no shocks were delivered in these patients, the efficacy of these devices remains unclear.[81]

Contraception

Contraception should be discussed with all women with PPCM prior to discharge and should be emphasized by the patient's cardiologist and obstetrician.[82] Estrogen-containing contraceptives should be avoided if possible in the early postpartum setting given the risk of thromboembolism in the setting of systolic dysfunction. Safe and effective choices include progesterone-releasing subcutaneous implants or the Mirena intrauterine device, with tubal ligation and vasectomy as options for those not considering future pregnancy.

Subsequent Pregnancies

Patient counseling regarding subsequent pregnancies is essential. LVEF before a subsequent pregnancy is the strongest predictor of outcomes, with substantially worse outcomes in women whose ventricular function fails to normalize (LVEF ≥50%) (Figure 2).[83,84] Prior to pregnancy, teratogenic heart failure medications should be discontinued for at least 3 months and systolic function reassessed to ensure it remains normal prior to determining a patient as having recovered ventricular function. Even with normalized systolic function, subsequent pregnancies carry risk of relapse and persistent

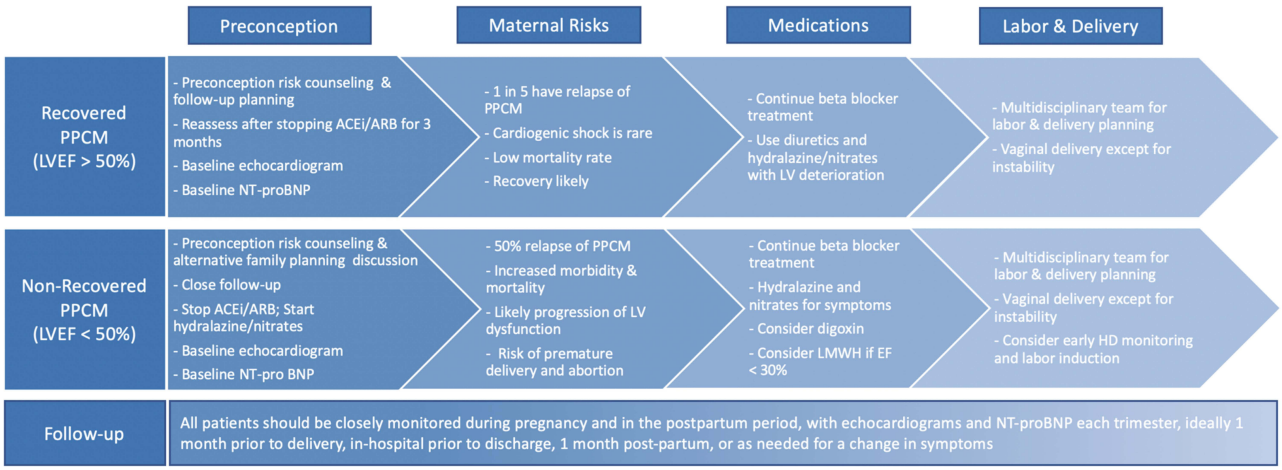

Figure 2 Subsequent pregnancy for patients with history of PPCM. The risks and recommendations vary based on the patient's LVEF recovery status. The risks are much higher in those with non-recovered PPCM (LVEF <50%) and pregnancy should be discouraged in these patients.

Abbreviations: PPCM, peripartum cardiomyopathy; LV, left ventricle; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; NT-pro BNP, N terminal pro-brain natriuretic peptide.

cardiac dysfunction.[84] Assessing for subclinical ventricular dysfunction with stress testing and echocardiographic strain imaging may help identify patients at higher risk for relapse.[85–88] Although there is not enough data, prophylactic use of beta-blockers during subsequent pregnancies should be considered in women with recovered systolic function. Women should be thoroughly counseled about the risks of subsequent pregnancy. Those choosing to become pregnant should be closely monitored during pregnancy and for 6 months postpartum with serial echocardiograms and clinical exams by a cardiologist.[22,89]

Conclusion

PPCM should be considered in any pregnant or postpartum patient with symptoms concerning for heart failure. Although uncommon, it is a serious medical condition that affects women of childbearing age throughout the world. The etiology of PPCM is not fully understood, but both genetic susceptibility and hormonal influences play major role. In patients with clinical symptoms and an elevated NT-pro-BNP level, an echocardiogram is essential for assessment of systolic function. Multidisciplinary collaboration within a cardio-obstetrics team is necessary for prompt treatment, delivery planning, and postpartum care, and may prevent adverse outcomes. Development of more specific diagnostic criteria such as specific imaging findings, serum biomarker level, and/or genetic markers could help clinicians initiate more timely treatment. Given the rarity and underdiagnosis of PPCM, research collaboration among multiple centers is needed to answer important questions and define optimal management strategies. Significant gaps in knowledge remain, including the optimal anticoagulation strategy, timing of ICD implantation, frequency of imaging as well as more precise evaluation with strain imaging and stress testing for women who recover their systolic function, management of subsequent pregnancy, and long-term medical management after myocardial recovery.

Disclosure

The authors report no conflicts of interest in this work.

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