Peripartum Cardiomyopathy

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KEYWORDS

• Peripartum cardiomyopathy • PPCM • Postpartum cardiomyopathy • Pregnancy • Heart failure

KEY POINTS

- Diagnosing peripartum cardiomyopathy (PPCM) requires a high degree of suspicion, because presenting signs and symptoms tend to mimic those of normal pregnancy and the early postpartum period.
- Guideline-directed medical therapy for heart failure, with special considerations for use during pregnancy and lactation, is recommended, although efficacy and optimal duration of therapy have not been established.
- Outcomes of both mother and child are generally good, although a subset of women experience chronic heart failure, transplant, and/or cardiac death.
- Subsequent pregnancy is not contraindicated in all women with history of PPCM, because risk of cardiac complications associated with future pregnancy varies according to degree of left ventricular recovery.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a form of heart failure with no known cause that occurs toward the end of pregnancy or in the months following pregnancy and is marked by left ventricular (LV) systolic dysfunction. Outcomes vary, because most women experience complete LV recovery, but a significant minority experience persistent cardiac dysfunction, transplant, or death.

CASE DEFINITION

The National Heart, Lung, and Blood Institute (NHLBI) and the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) Working Group (WG) on PPCM have both published definitions for PPCM[1,2] (**Box 1**). These 2 definitions differ in terms of timing of diagnosis and the cutoff for LV ejection fraction (LVEF). Further investigation is needed to determine potential differences between women diagnosed with PPCM using the NHLBI criteria and (1) women who present with previously undiagnosed cardiomyopathy before 1 month before delivery or greater than 5 months postdelivery, and (2) women who present with an initial LVEF greater than 45%, to determine whether or not pathophysiology and outcomes are similar. Having a clear and accurate definition of PPCM is crucial for determining optimal management strategies and prognosis and facilitating collaborative research.

EPIDEMIOLOGY

Estimates of PPCM incidence vary widely around the world, with many of the estimates coming from retrospective single-center cohort studies. **Fig. 1** presents selected incidence estimates from several countries. The highest reported rates occur in Nigeria, with 995 cases per

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Box 1
Current peripartum cardiomyopathy definitions.

NHLBI[1]

- Development of cardiac failure in the last month of pregnancy or within 5 months of delivery
- Absence of an identifiable cause for the cardiac failure
- Absence of recognizable heart disease before the last month of pregnancy
- LV systolic dysfunction identified by classic echocardiographic criteria, such as ejection fraction less than 45% or fractional shortening less than 30%, or both

European Society of Cardiology[2]

- Heart failure secondary to LV systolic dysfunction with an LV ejection fraction less than 45%
- Occurrence toward the end of pregnancy or in the months following delivery (mostly in the months following delivery)
- No other identifiable cause of heart failure

(*Data from* Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. Jama. 2000;283(9):1183-1188 and Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. European journal of heart failure. 2010;12(8):767-778).

100,000 deliveries, and Togo, with 781 cases per 100,000 deliveries.[3,4] In the United States, nationwide estimates vary from 18 to 103 per 100,000 live births or deliveries.[5–9] Risk factors associated with increased risk of developing PPCM include black African descent, hypertensive diseases of pregnancy (HDPs), multifetal pregnancies, and advanced maternal age.[6,7,10–13]

PATHOPHYSIOLOGY, GENETICS, AND RISK FACTORS

The cause of PPCM is not fully understood but is most likely multifactorial. Current research suggests that hormones of late pregnancy cause a vasculotoxic environment that, in susceptible women, leads to the development of PPCM.[14,15] High levels of prolactin are secreted from the pituitary gland and can be cleaved into the vasculotoxic, proinflammatory, and proapoptotic 16-kDa form.[16] At the same time, antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) is secreted from the placenta, inhibiting vascular endothelial growth factor and placental growth factor. Both the 16-kDa form of prolactin and sFlt-1 have been shown to cause PPCM in mouse models.[17,18] sFlt-1 levels are significantly increased in women with PPCM, and higher levels at diagnosis are associated with worse outcomes.[19] Women with preeclampsia also have significantly increased sFlt-1 levels, which may at least partially explain why HDP increases risk for PPCM.[20]

A small percentage of women with PPCM have a family history of dilated cardiomyopathy (DCM). Family clustering has also been observed.[21–26] Studies have also shown that a subset of women with PPCM have genetic mutations linked to DCM, predominantly in the TTN gene, which encodes the titin protein, which is critical to cardiac muscle structure.[27–29] The Investigations of Pregnancy Associated Cardiomyopathy (IPAC) study found that 1 TTN mutation genotype was associated with lower LVEF at 6 and 12 months, especially in black women, which may help explain why black women have worse outcomes compared with white women.[30] High frequencies of mutations in the TTN gene have also been found in women with preeclampsia, which may help to explain the increased risk of PPCM in women diagnosed with HDP.[31] However, only 15% to 20% of women with PPCM have TTN mutations, and greater than 90% of individuals in the general population that have TTN mutations never develop any form of cardiomyopathy,[27–29,32] so the significance of TTN mutations in women with PPCM remains unclear. Other factors that may increase susceptibility for PPCM include oxidative stress, inflammation, viral infection, and antiangiogenic molecules.[33]

DIAGNOSIS

Because the exact cause remains unknown and no single test currently exists to confirm the diagnosis, PPCM remains a diagnosis of exclusion. Women generally present with symptoms that are common to pregnancy (orthopnea, dyspnea on exertion, fatigue, edema, paroxysmal nocturnal exertion, and chest tightness), so the diagnosis of PPCM may be delayed or missed altogether. Late diagnosis has been linked to worse outcomes, including persistent cardiac dysfunction and increased mortality.[13,34–40]

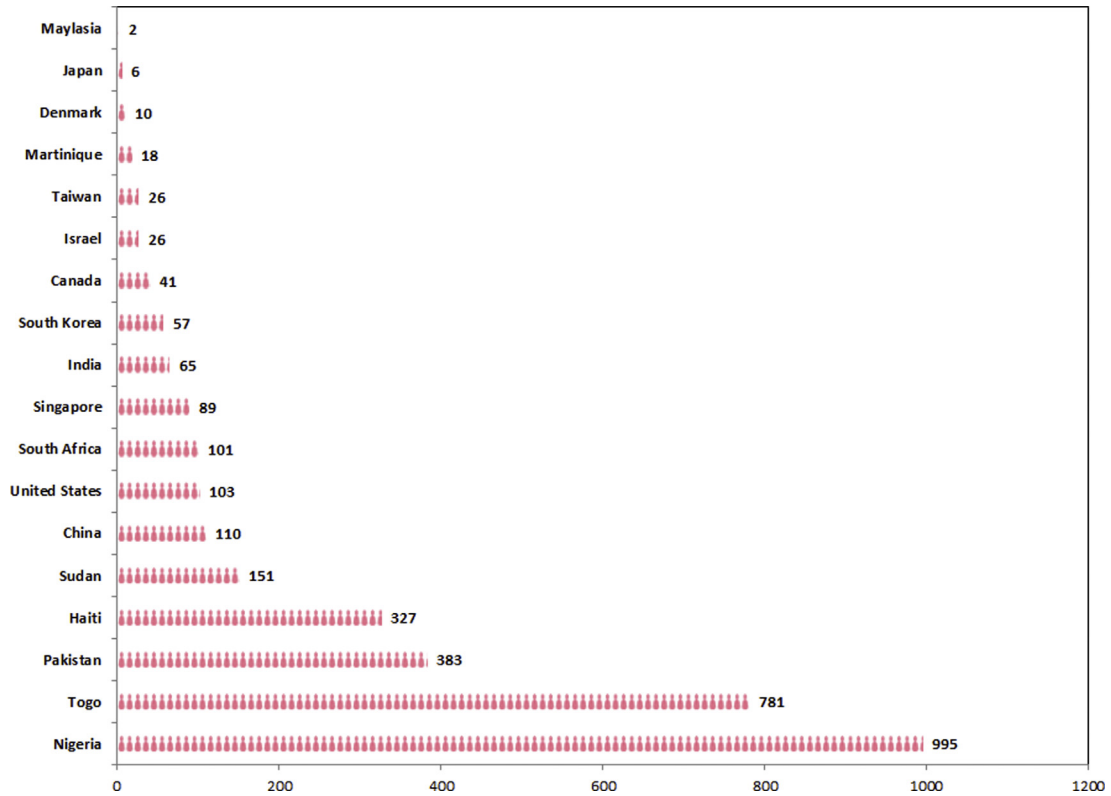

Fig. 1. Incidence of peripartum cardiomyopathy (per 100,000 live births or deliveries.) Measurements using live births: Haiti,[127] United States,[9] Singapore,[77] India,[128] Canada,[119] Martinique,[129] Japan,[130] Malaysia.[131] Measurements using deliveries: Nigeria,[3] Togo,[4] Pakistan,[132] Sudan,[133] China,[134] South Africa,[135] South Korea,[136] Israel,[118] Taiwan,[39] Denmark.[64] *Data from* Refs.[3,4,9,39,64,77,118,119,127–136]

Diagnostic Tests

Echocardiogram, electrocardiogram (ECG), chest radiograph, cardiac MRI, and laboratory testing may all be useful in the diagnosis of PPCM. Echocardiography is the most important imaging modality, because it is readily available in many health care centers and can easily and comprehensively assess cardiac structure and function. By the NHLBI definition, LVEF must be less than 45%.[1] The left ventricle is usually, but not always, dilated.[33–35,41] Assessment of right ventricular (RV) function is essential, because 3 recent articles have reported that many women with PPCM also have RV dysfunction and that these women are at higher risk for adverse outcomes.[42–44] Additional echocardiographic findings may include RV dilatation, mitral and/or tricuspid valve regurgitation, atrial enlargement, increased pulmonary pressures, and intracardiac thrombus.[33–35,41] Cardiac MRI may be useful for the evaluation of biventricular structure and function or when echocardiography is nondiagnostic, but gadolinium is not recommended for use during pregnancy.[43,45,46] Suggested diagnostic testing is outlined in **Table 1**.

BIOMARKERS

Many biomarker levels have been shown to be abnormal in women with PPCM and may thus be useful in diagnosing PPCM (**Table 2**). Markers of cardiac function such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), and cardiac troponin are likely the most clinically useful. No biomarkers can be used in isolation to confirm PPCM, because none are specific to this disease.

TREATMENT

Initial Management

Initial management strategies vary depending on pregnancy status (**Table 3**). A multidisciplinary team approach to management is recommended,

Table 1
Suggested evaluation for women with peripartum cardiomyopathy

Time Period[a]	History and Clinical Examination	Laboratory Tests[b]	Urinalysis[c]	Chest Radiograph	Chest CTA[d]	ECG	ECHO	Cardiac MRI[e]
Diagnosis	♥♥♥♥	♥♥♥♥	♥♥	♥♥♥♥	♥♥	♥♥♥♥	♥♥♥♥	♥
3 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥		
6 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
12 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
18 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
24 mo	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	
>24 mo[f]	♥♥♥♥	♥♥♥♥				♥♥♥♥	♥♥♥♥	

♥♥♥♥, highly recommended.
♥♥, recommended in certain circumstances.
♥, consider in certain circumstances.
Abbreviations: CTA, computed tomography angiography; ECG, electrocardiogram; ECHO, echocardiogram.
[a] Timing of follow-up may vary according to presentation and clinical course.
[b] Suggested laboratory tests include complete blood count, basic metabolic panel, and brain natriuretic peptide (BNP) or N-terminal prohormone of BNP (NT-proBNP) at all times points plus aspartate aminotransferase, alanine aminotransferase, cardiac troponin, and thyroid-stimulating hormone at baseline and during follow-up, if indicated.
[c] Urinalysis is especially important for women presenting with increased blood pressure during pregnancy or the first 6 weeks postpartum to assess for preeclampsia.
[d] Consider chest CTA to assess for pulmonary embolism in patients presenting during pregnancy or the first 6 weeks postpartum.
[e] Consider cardiac MRI if patient presents during the postpartum period and echocardiography results are inconclusive.
[f] Annual follow-up should occur indefinitely.

Table 2
Biomarkers in peripartum cardiomyopathy

Biomarkers of Cardiac Function		
NT-ProBNP	May be increased[29,138,154]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
BNP	May be increased[104]	Higher levels at diagnosis are associated with persistent LV dysfunction[104,138] Higher levels at 6 mo are associated with persistent LV dysfunction[104] Higher levels at 6 mo may predict mortality[89,138] Increased levels at 3 and 6 mo may predict persistent dysfunction[69] Lower levels at 3 and 6 mo are associated with faster recovery[69]
Cardiac troponin	May be increased[154]	Higher levels at diagnosis are associated with persistent LV dysfunction[156]
Biomarkers of Inflammation		
C-reactive protein	May be increased[95,138,154,157]	Higher levels at baseline may predict mortality[157] Higher levels at baseline are correlated with worse disease[95] Increased levels at 3 and 6 mo may predict persistent dysfunction[69]
IL-6	May be increased[138,157]	Higher levels at baseline may predict mortality[157]
Tumor necrosis factor alpha	May be increased[95,138,157]	Higher levels at baseline may predict mortality[157]
IL-1β	May be increased[138]	—
Interferon gamma	May be increased[138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Pregnancy and Nursing Hormones		
Relaxin-2	May be decreased[158,159]	Higher levels at diagnosis are associated with recovery at 2 mo[19]
Prolactin	May be increased[138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Vasculotoxic Cause–related Biomarkers		
Oxidized low-density lipoprotein	May be increased[16,138]	Failure to decrease levels by 6 mo is associated with persistent LV dysfunction[138]
Fas/apoptosis antigen 1	May be increased[95,138]	Higher levels at baseline may predict mortality[95]

sFlt-1	May be increased[18]	Higher levels at diagnosis are associated with more severe disease and major adverse events[19,60]
Asymmetric dimethyl arginine	May be increased[29]	—
PlGF	May be increased[159]	—
sFlt1/PlGF ratio	May be low[159]	—
Plasminogen activator inhibitor-1	May be increased[160]	—
MicroRNAs		
miR-146a	May be increased[29,161]	—
miR-1991	May be increased[162]	—
Biomarkers of Fibrosis and Remodeling		
Galectin-3	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Soluble ST2	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Cleaved osteopontin	May be increased[102]	High baseline levels are associated with poor outcomes[102]
Matrix-metallo-proteinase-2	May be increased[138]	—

Abbreviations: IL, interleukin; PlGF, placental growth factor.
(*Data from* Refs[16,18,19,29,60,89,95,96,102,104,138,154,156–160,162])

particularly if the woman is pregnant or in the early postpartum period.

Medical Therapy

Women diagnosed with PPCM should be treated with guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF), bearing in mind the safety of specific medications during pregnancy and breastfeeding. Recommended medications may include β-blockers, angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin receptor II blocker (ARBs), angiotensin receptor neprilysin inhibitor (ARNIs), hydralazine/nitrates, mineralocorticoid receptor antagonists (MRAs), and diuretics. Anticoagulation should be initiated if LV thrombus is present and may be considered in women with LVEF less than 35%.

Whether or not initiating GDMT for HFrEF is necessary in all women with PPCM remains unclear, because some women recover LV function quickly and completely while taking only minimal to low doses of heart failure medications. Note that there has never been a randomized clinical trial testing the efficacy and safety of any heart failure medications in women with PPCM. Information regarding specific medications and their compatibility with pregnancy and breast feeding is reviewed Karen L. Florio and colleagues' article, "Cardiovascular Medications in Pregnancy: A Primer," in this issue.

Bromocriptine

Bromocriptine, which inhibits the nursing hormone prolactin, has been proposed as a novel treatment of PPCM in response to the hypothesis that the development of PPCM is driven by the antiangiogenic and proapoptotic 16-kDa cleaved form of prolactin. A small proof-of-concept study with 20 women in South Africa found that the addition of bromocriptine led to greater recovery of LVEF and lower mortality at 6 months.[47] A second study in Burkina Faso showed that treatment with bromocriptine was associated with increased LVEF at 2 weeks and at 3, 6, and 12 months, as well as decreased mortality.[48] However, both studies had unusually high rates of mortality in the control groups, limiting the ability to generalize the results. A multicenter randomized study with no control group conducted in Germany compared 2 dosing regimens (1 week vs 8 weeks) of bromocriptine in addition to GDMT for heart failure.[49] Both study groups had similar outcomes, with no women undergoing heart transplant and

Table 3
Initial management of peripartum cardiomyopathy

	Hemodynamically Stable	Hemodynamically Unstable	Hemodynamically Stable	Hemodynamically Unstable
Consult Cardio-obstetrics specialist				
Consult High-risk obstetrics (maternal fetal medicine) specialist			—	—
Form multidisciplinary team to prepare delivery plan			—	—
Consider early delivery	—		—	—
Arrange for fetal monitoring during labor and delivery			—	—
Initiate selected oral heart failure medications (eg, diuretics, nitrates, hydralazine, digoxin)			—	—
Initiate oral GDMT for HFrEF (eg, β-blocker, ACE-I, ARB, ARNI, MRA, diuretics [modify if lactating])	—	—		(after stabilized)
Consider using inotropes	—		—	
Initiate anticoagulation if LV thrombus				

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Table 3
(*continued*)

	Hemodynamically Stable	Hemodynamically Unstable	Hemodynamically Stable	Hemodynamically Unstable
Consider anticoagulation if LVEF <35%	—	—		
Plan for vaginal delivery		—	—	—
Plan for probable cesarean delivery	—		—	—
Provide supplemental oxygen and/or noninvasive ventilation, if hypoxic		—		—
Intubate and ventilate if hypoxic despite noninvasive ventilation	—		—	
Consider advanced heart failure therapies[a] if failure to respond to medical therapy (and delivery)	—		—	
Discuss lactation preferences	—	—		—
Discuss contraception	—	—		

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

[a] Mechanical circulatory support/ventricular assist device/cardiac transplant.

no mortality in either group. The lack of a control group limits the applicability of these results in current clinical practice.

In addition to the lack of rigorous clinical research showing the efficacy of bromocriptine for treatment of acute PPCM, concern regarding potential serious adverse effects has limited routine administration of bromocriptine in clinical practice. Treatment with bromocriptine has been associated with stroke, myocardial infarction, and seizures and, as a result, it is no longer marketed for elective lactation suppression in the United States.[34] If bromocriptine is used, anticoagulation should be administered for the duration of therapy because women are already in a hypercoagulable state during the peripartum period and bromocriptine may further increase hypercoagulability.

Of particular importance, women treated with bromocriptine cannot breastfeed their infants. The World Health Organization recommends exclusive breastfeeding for 6 months and continued breastfeeding for at least 1 to 2 years because of the importance of breastfeeding to the health of both mother and infant. Not breastfeeding is associated with increased risk of diabetes, ovarian and breast cancer, and postpartum depression for mothers, and higher rates of mortality, infections, eczema, asthma, childhood obesity, type 2 diabetes, leukemia, and lower intelligence in children.[50,51] Results of the IPAC study and 2 retrospective cohort studies suggest that breastfeeding has no detrimental effect on outcomes for women with PPCM.[52–54]

The most recent statement on PPCM by the HFA ESC WG PPCM lists treatment with bromocriptine as a class IIb recommendation.[41] In contrast, the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) both recommend that bromocriptine should not routinely be used in the treatment of PPCM until more rigorous data that support the safety and effectiveness of its use are available.[35,55]

Chronic Management

Most experts agree that GDMT for HFrEF should be continued indefinitely in women with PPCM who have persistent cardiac dysfunction. The optimal duration of treatment of women who recover normal LV function is unknown. A 2016 AHA scientific statement on the diagnosis and treatment of dilated cardiomyopathies recommended indefinite continuation of treatment in women with PPCM, including those with recovered cardiac function, as well as yearly clinical follow-up and assessment of LV function even after recovery.[35] More recent articles suggest that treatment duration should be considered on a case-by-case basis, with changes to or discontinuation of any cardiac medications to be completed slowly using a stepwise approach with frequent clinical and echocardiographic monitoring and follow-up.[34,41] The HFA ESC WG PPCM has published recommendations for women diagnosed with PPCM who have recovered LV function (LVEF>55%) and are New York Heart Association (NYHA) functional class I as follows: continuation of all cardiac drugs for at least 12 to 24 months after full recovery and then discontinue them in a stepwise fashion (first MRA, second ACE-I/ARB/ARNI, and then β-blocker) with frequent monitoring of symptoms and LV function.[41] Thus, although both the AHA and HFA ESC WG PPCM guidelines agree that diuretics can be tapered and discontinued if there are no signs of fluid overload, there is no consensus regarding duration of other cardiac medications in individual women.

Several studies and case reports have shown that some women with PPCM who have recovered LV function can safely be tapered off medical therapy.[36,56–58] In 1 study, 5 women were tapered off all cardiac medications and none experienced deterioration of LV function over an average follow-up duration of 29 months (range, 5–63 months.)[58] Another report found that 2 women who had fully recovered LV function had deterioration of LVEF after discontinuation of all cardiac medications, with deterioration occurring at 24 and 34 months after diagnosis.[57] Two more recent studies found that women with LV recovery may have high rates of LV diastolic dysfunction and reduced exercise capacity[59] as well as ongoing angiogenic imbalance and residual myocardial injury,[60] suggesting that women who recover may benefit from long-term GDMT for HFrEF.

Long-term cardiology follow-up of women with history of PPCM who have recovered LV function is recommended regardless of whether or not LV recovery occurs and/or cardiac medications are discontinued (see **Table 1**).

Advanced Heart Failure Therapies

Women with PPCM who have severe myocardial disease may benefit from a wearable or implantable cardiac defibrillator, left ventricular assist device (LVAD), mechanical circulatory support (MCS), and/or transplant. Multiple factors affect the rates of each of these types of advanced heart failure therapy, including time to diagnosis, race, and availability. Rates of use of each of these advanced therapies in women with PPCM are difficult to discern, because studies often do not list

these therapies separately and have combined these outcomes differently for reporting. A nationwide study conducted in the United States reported that, between 2004 and 2011, 1.5% of patients with PPCM required MCS and 0.5% of patients underwent transplant.[9] Study specific rates in the United States vary between 0% and 7.8% for defibrillator implantation, 0% to 17.2% for MCS (intra-aortic balloon pump, LVAD, and extracorporeal membrane oxygenation), and 0% to 8.8% for transplant.[11,36,40,61–63] Rates in other countries vary widely, often depending on the availability of these advanced treatment options.[39,56,63–71]

OUTCOMES

Mortality

Women with PPCM tend to have lower mortalities than women with other forms of DCM.[72,73] Reported mortalities related to PPCM vary widely both within and between countries and within similar follow-up durations (**Table 4**). A recent systematic review and meta-analysis by Kerpen and colleagues[74] found the overall PPCM mortality to be 9%, with higher rates in developing countries (14%) compared with more advanced countries (4%). **Fig. 2**, which includes 9 countries in addition to the 13 included in the meta-analysis by Kerpen and colleagues,[74] shows a similar trend of higher mortalities in developing countries. The higher PPCM mortalities in developing countries are most likely related to the impact of social determinants of health, including reduced access to care in general and access to advanced heart failure therapies in particular.

Mortalities in Taiwan and the United States seem to be exceptions among advanced countries, whereas rates in The Philippines, China, and Singapore do not follow the trend among developing countries. Small sample sizes[75–77] and differences in methodologies and populations, particularly among the US reports,[7–9,11–13,36,38,40,43,58,61,62,72,73,78–87] may account for these variations.

Left Ventricular Recovery

Similar to mortality, women with PPCM tend to have higher rates of LV recovery than women with other forms of DCM.[72,73] Recovery rates differ between countries, from 28% in Haiti[88] to 43% in Israel,[71] 48% in Turkey,[89] 47% in Germany,[29] 55% in South Africa,[90] 63% in Japan,[67] and 67% in Denmark.[64] There is a wide variation in recovery rates within the United States as well, with reported rates ranging between 23% and 72%.[38,40,58,61,78,84,86,91,92] Lack of consensus in the definition of LV recovery (LVEF>45% vs 50%, vs 55%, or any recovery vs a specific percentage increase in LVEF) and follow-up time (6 months vs 12 months vs longer) contributes to the large range in reported LV recovery rates among studies across the globe.

Timing of LV recovery varies, with some women recovering in days to weeks, whereas other women require months to years. An article from Israel reported that 22% of women with PPCM achieved full recovery (LVEF $\geq$ 50%) within 2 weeks, a further 30.1% recovered by 1 year, and an additional 13.8% recovered between 1 and 10 years.[71] The mean time to recovery in a study of 44 women in the United States was 54 months.[86] In Haiti, reported recovery time ranged from 3 to 38 months and in Turkey from 3 to 42 months (mean, 19.3 months).[69,93] One study completed in the United States found that 83% of women who recovered did so after more than 6 months of follow-up, whereas another study reported that 25% of women who recovered did so between 2 and 8 years after diagnosis.[84,94] The wide range of time to LV recovery underlines the importance of long-term cardiac follow-up of women with PPCM.

Predictors of Outcome

Many factors have been evaluated for their potential to predict outcomes in PPCM, particularly the risks for persistent myocardial dysfunction and death. The most reliable predictor has been found to be LVEF at diagnosis, with studies consistently reporting that women with lower LVEF (particularly <30%) at diagnosis are less likely to recover and more likely to experience adverse outcomes, including death.[29,36,38,40,57,58,61,78,80,83,86,91,92,95,96] Studies have also reported that the degree of LV dilatation may be a useful predictor, with larger LV end-diastolic diameter (LVEDD) being associated with lack of LV recovery and death.[29,40,57,58,78,92,96,97] LV dilatation and LVEF were combined as predictors in the IPAC study, which found that 91% of women with LVEF greater than or equal to 30% and LVEDD less than 60 mm recovered.[40] The IPAC study also reported that LV global longitudinal strain at presentation was associated with clinical outcomes and may be useful for risk stratification in addition to LVEF.[98] RV fractional area change at diagnosis was shown to be a strong predictor of outcomes in the IPAC study,[44] whereas another study in the United States found that moderate to severe RV dysfunction was associated with more severe disease and higher risk of adverse outcomes.[43] T-wave abnormalities on

Table 4
Studies with greater than or equal to 50 subjects reporting mortality among women with peripartum cardiomyopathy

First Author	Follow-up Duration	Actual, Mean, Median	Country	Data Source	Study Years	Sample (n)	Mortality (%)
In Hospital							
Kolte et al,[9] 2014	NA	NA	United States	Nationwide Inpatient Sample database	2004–2011	34,219	0.0
Krisnamoorthy et al,[80] 2016	NA	NA	United States	Nationwide Inpatient Sample database	2009–2010	4871	0.0
Lee et al,[136] 2018	NA	NA	South Korea	Korean National Health Insurance Database	2010–2012	795	1.0
Masoomi et al,[8] 2018	NA	NA	United States	Nationwide Readmissions Database	2013	568	1.2
Kao et al,[11] 2013	NA	NA	United States	Inpatient administrative databases for 6 states	2003–2007	535	1.3
Mielniczuk et al,[7] 2006	NA	NA	United States	National Hospital Discharge Survey	1990–2002	16,269	1.9
1–6 mo							
Azibani et al,[102] 2020	6 mo	Actual	Germany	1 hospital	Missing	73	0.0
Dhesi et al,[119] 2017	6 mo	Actual	Canada	Multiple databases linked together covering all of Alberta	2005–2014	194	1.5

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Table 4
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First Author	Follow-up Duration	Actual, Mean, Median	Country	Data Source	Study Years	Sample (n)	Mortality (%)
Huang et al,[154] 2012	21.6 d	Mean	China	1 hospital	2007–2009	52	1.9
Tibazarwa et al,[90] 2012	6 mo	Actual	South Africa	1 hospital	2003–2008	78	3.8
Libhaber et al,[97] 2015	6 mo	Actual	South Africa	2 hospitals	Missing	206	12.6
Blauwet et al,[106] 2013	6 mo	Actual	South Africa	1 hospital	Missing	162	13.0
Azibani et al,[102] 2020	6 mo	Actual	South Africa	1 hospital	Missing	56	14.3
Sliwa 2006 et al,[95] 2006	6 mo	Actual	South Africa	1 hospital	Missing	100	15.0
7–12 mo							
Kamiya et al,[67] 2011	9.6 mo	Mean	Japan	Nationwide survey of medical locations	2007–2008	102	3.9
Isezuo et al,[3] 2007	9.7 mo	Mean	Nigeria	1 hospital	2003–2005	65	12.3
1–2 y							
Phan et al,[79] 2020	1 y	Actual	United States	Southern California Kaiser Healthcare System	2003–2014	333	0.3
Erbsoll et al,[64] 2017	10–14 mo	Actual	Denmark	Danish National Patient Register, Medical Birth Registry, Causes of Death Registry	2005–2014	61	1.6

McNamara et al,[40] 2015	1 y	Actual	United States	IPAC: nationwide cohort of 100 women	2009–2012	100	4.0
Goland et al,[12] 2013	1.6 y	Mean	United States	2 hospitals	1993–2000	156	7.1
Wu et al,[39] 2017	1 y	Actual	Taiwan	National health insurance database	1997–2011	742	7.3
Elkayam et al,[38] 2015	1.9 y	Mean	United States	Survey mailed to doctors nationwide and data from 1 hospital	Missing	100	9.0
Sliwa et al,[140] 2011	2 y	Actual	South Africa	1 hospital	Missing	60	36.7
>2 y							
Amos et al,[58] 2006	3.6 y	Mean	United States	1 hospital	1990–2003	55	0.0
Habli et al,[78] 2018	3.4 y	Mean	United States	2 hospitals	2000–2006	70	0.0
Li et al,[104] 2016	3.6 y	Mean	China	1 hospital	2004–2011	71	0.0
Moulig et al,[152] 2019	5 y	Actual	Germany	1 hospital	2006–2013	66	1.5
Gunderson et al,[13] 2011	3 y	Actual	United States	Northern California Kaiser delivery hospitals	1995–2004	110	1.8
Peters et al,[43] 2018	3.6 y	Median	United States	1 hospital	1992–2016	53	1.9
Brar et al,[81] 2007	4.7 y	Mean	United States	Southern California Kaiser Healthcare System	1996–2005	60	3.3
Ekizler et al,[163] 2019	5.6 y	Median	Turkey	1 hospital	2009–2017	82	7.3

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Table 4
(*continued*)

First Author	Follow-up Duration	Actual, Mean, Median	Country	Data Source	Study Years	Sample (n)	Mortality (%)
Pillarisetti et al,[84] 2014	2.9 y	Mean	United States	2 hospitals	1999–2012	100	11.0
Fett et al,[150] 2005	2.2 y	Mean	Haiti	1 hospital	2000–2005	98	15.3
Akil et al,[66] 2016	2.7 y	Mean	Turkey	3 hospitals	2002–2012	58	15.5
Harper et al,[62] 2012	7 y	Actual	United States	1 hospital	2002–20,030	85	16.5
Biteker et al,[69] 2020	3.4 y	Mean	Turkey	1 hospital	2005–2016	52	19.2
Mahowald et al,[61] 2019	6.3 y	Mean	United States	1 hospital	2000–2011	59	20.3
Mishra et al,[145] 2006	6.1 y	Mean	India	1 hospital	1995–2005	56	23.2

Abbreviation: NA, not available.
(*Data from* Refs.[3,7–9,11–13,38–40,43,58,61,62,64,66,69,78,79,81,84,90,95,97,102,104,106,119,136,140,145,150,152,154])

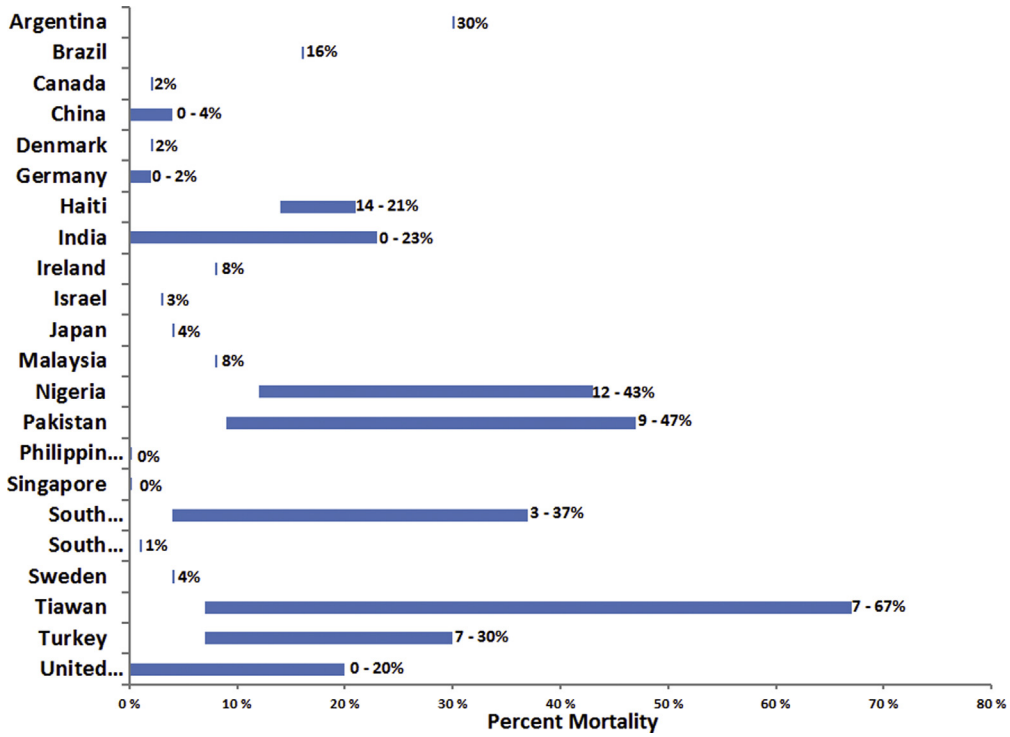

Fig. 2. Percentage mortality estimates for peripartum cardiomyopathy. Twenty-four countries are represented, 12 of which only had 1 estimate available, whereas each of the other 10 countries had between 2 and 25 estimates available. For countries with only 1 estimate available, that value is indicated. For the countries with multiple estimates available, ranges are presented showing the highest and lowest estimates for each country. *Data from* Refs.[7–9,11–13,36,38–40,42,43,47,56–58,61,62,64–70,73,75–87,95,97,99,102,106,119,131,136–155]

ECG have been suggested as a useful tool for predicting adverse outcome in PPCM, which could be advantageous in resource-poor settings in which echocardiographic evaluation may not be readily available.[90,99]

Other factors that also seem to affect outcomes include race, HDP, and body mass index (BMI). Studies in the United States show that, compared with nonblack women, black women have worse outcomes, including slower and less complete recovery of LV function and higher rates of defibrillator use, transplant, and mortality.[36,40,61,91,100–103] A recent meta-analysis found that studies with higher rates of African women tend to have higher mortalities.[74] History of HDP during index pregnancy may also be important, with multiple studies finding an association between HDP and improved rates of recovery and reduced mortality.[29,40,52,64,67,94,97,104] The IPAC study found that higher BMI is associated with less cardiac recovery at 6 and 12 months,[105] whereas a study including predominantly black African women in South Africa found that lower BMI was associated with a worse combined end point of death, LVEF less than 35%, or remaining in NYHA functional class III/IV at 6 months.[106] Women with multiple predictors of poor outcome may be at increased risk of persistent cardiac dysfunction and death, but this remains speculative because of limited data. Multiple biomarkers have been investigated for their potential usefulness in predicting which women are more likely to experience adverse outcomes, but none have been validated for clinical use (see **Table 2**).

SUBSEQUENT PREGNANCY

Many women with history of PPCM desire to become pregnant again. One recent study found that 74% of women diagnosed with PPCM desire to have more children and 1 in 4 women with PPCM who are sexually active were not using birth control.[107] All women with PPCM are at risk of declining LV function during subsequent pregnancy, but the risk is not necessarily prohibitive. Although some women experience worsening LV function or even death with subsequent pregnancy, others are able to complete a subsequent pregnancy without cardiac complications. Having

1 subsequent pregnancy without heart failure relapse does not ensure that a woman will not experience worsening heart function during a future subsequent pregnancy and vice versa.[83,108–110] At present, there is no clear method to identify with certainty which women will experience adverse cardiac events with subsequent pregnancies. The risk of heart failure relapse is highest in women who have persistent LV dysfunction at the onset of a subsequent pregnancy, with up to 50% having further decline in LV function during subsequent pregnancies.[111–114] Women with recovered LV function have an approximately 20% chance of heart failure relapse as defined in various studies by either experiencing heart failure symptoms and/or decrease in LVEF.[108,111–114]

The AHA, the CCS, and the HFA ESC WG PPCM stratify recommendations regarding subsequent pregnancy based on LV function, recommending that women with partial or fully recovered LV function be advised that they may consider subsequent pregnancy, whereas women with lack of LV recovery should be advised against subsequent pregnancy.[35,55,113] Despite these recommendations, studies show that only 59% to 75% of women diagnosed with PPCM report receiving counseling on the risk of subsequent pregnancy.[107,115] Importantly, qualitative studies have shown that women report feeling that the counseling provided tends to be limited, with women simply being told that they should not get pregnant again rather than engaging in an informed discussion with a health care provider.[116,117] These findings indicate that discussions regarding contraception and potential risks of subsequent pregnancy should occur with informed health care providers who can provide accurate information and are willing to participate in a shared decision-making process.

All women considering or undergoing subsequent pregnancy, regardless of cardiac function before conception, should be closely monitored by a multidisciplinary team from before conception through to several months postpartum in order to identify potential cardiac compromise as early as possible so as to optimize management and improve outcomes.[35,111,113] Recommended cardiac monitoring includes clinical evaluation, BNP or NT-proBNP, and echocardiogram either just before conception or within the first trimester, at 6 months' gestation, 9 months' gestation, before hospital discharge after delivery, and 1 month after delivery, with the timeline and type of follow-up adjusted according to the patient's clinical status.

ADDITIONAL CLINICAL CONCERNS

Infant Outcomes

The few studies of PPCM that include infant outcomes suggest that PPCM diagnosis in mothers is related to increased adverse outcomes in the infants, including higher rates of preterm and premature birth,[13,87,118,119] increased risk of being born small for gestational age,[13,118] increased rates of low birth weight,[13,87,118,119] and lower Apgar scores at both 1 and 5 minutes.[13,87,118] In women with PPCM, rates of premature birth (<37 weeks' gestation) vary between 25% and 60%[13,38,87,104,119] and are significantly increased compared with controls (25.4% vs 8.6% $P<.01$[119] and 27.9% vs 7.3%; $P<.001$[13]). Mean birthweight for infants born to mothers with PPCM ranged between 2378 and 3178 g,[38,56,64,71,76,78,84,87,118,119] and 2 studies with controls found that birth weights were significantly lower in infants born to mothers with PPCM (2697 vs 3165 g, $P<.002$[118]; and 3188 vs 3331 g, $P<.01$[119]).[13,38,56,64,71,78,84,87,118,119] Two studies that examined Apgar scores at 1 and 5 minutes found both to be significantly lower in infants born to mothers with PPCM compared with those born to mothers without PPCM.[13,118]

Premature birth, low birth weight, and lower Apgar scores are all known to be associated with greater risk of infant mortality and a variety of early and late developmental and other medical issues.[120] However, information regarding these outcomes in children of women with PPCM remains limited because infant outcomes in PPCM have only rarely been assessed in research studies.

Mental Health

Depression is a well-known risk factor for heart disease, and depression and anxiety are linked to worse outcomes in heart failure.[121,122] Women diagnosed with PPCM tend to be young mothers who were previously in the prime of their lives and now must juggle a diagnosis of heart failure while caring for a newborn, a household, and possibly other children. These stresses increase the risk for mood disorders. High levels of generalized anxiety, cardiac anxiety, and quality-of-life concerns are present in more than 50% of women with PPCM, and 56% of women with PPCM never return to their baseline emotional states after PPCM diagnosis.[115] Although only 3% to 7% of women with PPCM have a history of depression before PPCM diagnosis,[9,64,80] the rate of depression in women after diagnosis with PPCM has been reported to be 32.3%,[123] which is higher than the reported rate of 11.5% among

Box 2
Knowledge gaps in peripartum cardiomyopathy requiring further evidence-based investigation

Research questions

Diagnosis

- How can women who are susceptible to developing PPCM be identified before pregnancy?

Pathophysiology and genetics

- What is the exact pathophysiology/pathophysiologies of PPCM?
- To what extent to do genetic variations contribute to the development of PPCM and influence outcomes?

Diagnosis

- Is there a PPCM-specific biomarker, or set of biomarkers, that can be used to diagnose PPCM with a high degree of certainty?

Treatment

- Which, if any, typical heart failure medications are beneficial for treating all women with PPCM?
- How long should GDMT for HFrEF be continued in women with PPCM who have completely recovered LV function?
- Is bromocriptine safe and effective for treatment of acute PPCM?
- When is the use of wearable defibrillators indicated?
- When should an implantable cardioverter defibrillator be recommended?
- What is the most appropriate type and timing of follow-up in women who have recovered LV function versus those who have not?

Outcomes

- What are the best clinical predictors of outcome for women with PPCM that could be available in various health care resource settings?
- What are the very-long-term (ie, decades after diagnosis) outcomes for women with history of PPCM?
- Do women with history of PPCM have higher risk of developing other types of cardiac disease as they age?

Subsequent pregnancy

- What are the risks of cardiac deterioration and death with subsequent pregnancy with women with history of PPCM and those who have recovered LV function versus those who have not?
- Are there management strategies that are useful to reduce the risk of adverse outcomes in women during a subsequent pregnancy?

Infant outcomes

- What are the short-term and long-term health risks for infants born of mothers with PPCM?
- Are there strategies than can mitigate these risks?

Mental and emotional health

- Are there safe and effective strategies that can be used to decrease the burden of mental and emotional health issues affecting women with PPCM and their families?

Issues to be addressed in order for future research to adequately address knowledge gaps

- Global agreement on the definition of PPCM
- Global agreement on the definition of LV recovery
- Global agreement on the definition of relapse during subsequent pregnancy
- Funding for large, multicenter, well-designed, and well-adjudicated prospective registries and clinical trials

postpartum women in the United States.[124] Notably, there has been an association reported between depression and lower adherence to appointments for PPCM.[123] Qualitative studies suggest that an underlying issue for ongoing emotional and mental distress is lack of inclusion of the women and their partners in discussions and decisions related to the women's care and prognosis, with 35% of women in 1 study thinking that they had not been adequately counseled and another 33% thinking they were left with unaddressed questions.[115–117,123,125,126]

The HFA ESC WG PPCM and AHA both advise that each woman with PPCM be assessed and followed during subsequent pregnancy by a multidisciplinary team including cardiology, obstetrics, maternal-fetal medicine, neonatology, anesthesiology, and possibly other specialties.[35,113] Given the high incidence of mood disorders in women with history of PPCM, including mental health specialists or social workers on the multidisciplinary team to help address the long lasting emotional and psychological impact of PPCM would be beneficial, not only during subsequent pregnancy but after initial diagnosis as well.

SUMMARY

Although rare, PPCM can have a profound effect on previously healthy young women. Numerous advances have been made in understanding the cause, pathophysiology, and natural history of this disease, but many knowledge gaps remain (**Box 2**). Large prospective studies and randomized clinical trials are needed to address these knowledge gaps and to facilitate development of evidence-based guidelines regarding the diagnosis and management of PPCM. In addition, it is of utmost importance that management decisions regarding women with PPCM be formulated among a multidisciplinary team using a shared decision-making approach with the patients and their families in order to optimize diagnosis, treatment, and outcomes for all concerned.

CLINICS CARE POINTS

- Women diagnosed with PPCM benefit from evaluation and treatment by a multidisciplinary team including members from cardiology, maternal fetal medicine, obstetrics, social work, mental health and other specialties as indicated.
- Obtaining a complete patient and family cardiac history is important in order to establish the diagnosis of PPCM, as PPCM is a diagnosis of exclusion.
- Clinicians should have a low threshold for obtaining cardiac testing, including an ECG, echocardiogram, and B-type natriuretic peptide (BNP) or N-terminal proBNP, in pregnant/postpartum women who present with signs/symptoms suggestive of heart failure, even though the signs/symptoms may seem typical for women who are pregnant or postpartum.
- No biomarkers, including troponin T, troponin I, B-type natriuretic peptide (BNP) or N-terminal proBNP, are specific for the diagnosis or PPCM.
- Bromocriptine may be helpful for treatment of acute PPCM, particularly in postpartum women with severely depressed LVEF, but the safety and efficacy of this medication for treatment of PPCM has not yet been established.
- Clinicians must be cognizant of which of the guideline directed mediations for heart failure are safe to use during pregnancy and which are safe to use during lactation.
- Contraceptive counseling during the postpartum period and on a regular basis thereafter is imperative in order to prevent unplanned pregnancy.
- Women with history of PPCM should be counseled about the risk of subsequent pregnancy, bearing in mind that women who have recovered normal LV function are generally able to complete a subsequent pregnancy without significant complications.
- Screening women with PPCM for anxiety and depression in both in the acute and chronic care setting is essential for optimizing management of their mental and physical health.

DISCLOSURE

The authors have nothing to disclose.

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