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Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy

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Peripartum cardiomyopathy (PPCM) is a potentially life-threatening condition typically presenting as heart failure with reduced ejection fraction (HFrEF) in the last month of pregnancy or in the months following delivery in women without another known cause of heart failure. This updated position statement summarizes the knowledge about pathophysiological mechanisms, risk factors, clinical presentation, diagnosis and management of PPCM. As shortness of breath, fatigue and leg oedema are common in the peripartum period, a high index of suspicion is required to not miss the diagnosis. Measurement of natriuretic peptides, electrocardiography and echocardiography are recommended to promptly diagnose or exclude heart failure/PPCM. Important differential diagnoses include pulmonary embolism, myocardial infarction, hypertensive heart disease during pregnancy, and pre-existing heart disease. A genetic contribution is present in up to 20% of PPCM, in particular titin truncating variant. PPCM is associated with high morbidity and mortality, but also with a high probability of partial and often full recovery. Use of guideline-directed pharmacological therapy for HFrEF is recommended in all patients

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respecting contraindications during pregnancy/lactation. The oxidative stress-mediated cleavage of the hormone prolactin into a cardiotoxic fragment has been identified as a driver of PPCM pathophysiology. Pharmacological blockade of prolactin release using bromocriptine as a disease-specific therapy in addition to standard therapy for heart failure treatment has shown promising results in two clinical trials. Thresholds for devices (implantable cardioverter-defibrillators, cardiac resynchronization therapy and implanted long-term ventricular assist devices) are higher in PPCM than in other conditions because of the high rate of recovery. The important role of education and counselling around contraception and future pregnancies is emphasised.

Introduction

The aetiology of cardiomyopathies occurring de novo in association with pregnancy is diverse. Cardiomyopathies are not very common diseases, but may cause severe complications, making a substantial contribution to maternal morbidity and mortality during pregnancy, in the immediate peripartum period, and up to months later.[1] Peripartum cardiomyopathy (PPCM) has to be differentiated from other causes of heart failure. The ongoing international PPCM registry in the EURObservational Research Programme (EORP) has recruited over 750 patients and will be the largest dataset to provide important novel information on PPCM.[2,3] It is unclear in what percentage PPCM persists to chronic, stable heart failure as patients with non-specific symptoms around pregnancy may remain undiagnosed and are only identified months or years later. How often heart failure in younger women is caused by PPCM will not be determined until there is a large pregnancy cohort study which includes monitoring of cardiac function.

Heart failure due to PPCM provides a challenge for treating physicians as PPCM presentation may vary from subtle signs and symptoms to severe acute heart failure, pulmonary oedema and/or cardiogenic shock.[4,5] Moreover therapeutic interventions need always to consider both the health of the mother and the foetus or baby. While evidence-based data from randomized clinical trials are scarce, in this position statement we summarize the current knowledge about pathophysiology and clinical best practice in the management of PPCM patients.

Definition and epidemiology

In 2010, the Study Group on peripartum cardiomyopathy of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) defined PPCM as an idiopathic cardiomyopathy occurring towards the end of pregnancy or in the months following delivery, abortion or miscarriage, without other causes for heart failure, and with a left ventricular (LV) ejection fraction (EF) $< 45\%$[5] (see Box). Given the fact that there are some patients with typical features of PPCM and a clear impairment of LVEF, also patients with an EF value between 45% and 50% may occasionally be diagnosed with PPCM. Since no specific test to confirm PPCM exists, it remains a diagnosis of exclusion, and differential diagnoses need to be considered. In particular, aggravation of a pre-existing heart disease by pregnancy-mediated haemodynamic changes should be

differentiated from PPCM. Cases of acute Takotsubo syndrome during the final trimester or following emergency delivery have been reported, and these require careful assessment to differentiate from PPCM.[6,7]

Definition of peripartum cardiomyopathy
1. Heart failure secondary to left ventricular systolic dysfuntion with a LVEF $< 45\%$
2. Occurrence towards the end of pregnancy or in the months following delivery (mostly in the month following delivery)
3. No other identifiable cause of heart failure

The incidence of PPCM differs widely depending on the ethnic/racial and regional background of women. Africans and African Americans are at a higher risk for developing PPCM, with an estimated incidence of 1:100 pregnancies in Nigeria and 1:299 in Haiti whereas incidences in Caucasian populations range from 1:1500 pregnancies in Germany to 1:10 000 in Denmark.[5,8–13] In a large US cohort of well-phenotyped patients, African American women were diagnosed with PPCM at a younger age and later in the postpartum period, and were more likely to present with a LVEF $< 30\%$ compared with non−African American women.[10] In the USA, an increasing incidence was described over the past years.[8] In a Japanese cohort the incidence was as low as 1:20 000,[14] however, these data should be interpreted with caution due to methodological aspects and possible underreporting. In contrast, an analysis that appears more representative of the Asian population was published recently from a nationwide database and estimated the incidence of PPCM in South Korea at 1:1741.[15,16]

Predisposing factors for PPCM seem to be multiparity and multiple pregnancies, family history, ethnicity, smoking, diabetes, hypertension, pre-eclampsia, malnutrition, age of mother (with older mothers being at greater risk), and prolonged use of tocolytic beta-agonists.[15,17−25]

Pathophysiology

The aetiology of PPCM is uncertain. A combined 'two-hit' model including systemic angiogenic imbalance and host susceptibility

(predisposition) is thought to be crucial in the pathophysiology of PPCM.[26,27] Possible factors leading to PPCM include genetic predisposition, low selenium levels, viral infections, stress-activated cytokines, inflammation, autoimmune reaction, pathological response to haemodynamic stress, unbalanced oxidative stress and induction of antiangiogenic factors.[17−19,23,26,28−32] Particularly, the oxidative stress-mediated cleavage of the hormone prolactin into a smaller antiangiogenic subfragment, 16-kDa prolactin, may drive PPCM by inducing endothelial damage.[29,33] Release of endothelial microparticles loaded with active compounds such as microRNAs, whose release into the circulation is also induced by 16-kDa prolactin, may subsequently impair cardiomyocyte metabolism and further contribute to the manifestation of PPCM.[13,27,29,33,34] The link between vascular pregnancy complications (e.g. pre-eclampsia) and PPCM was strengthened by the observation that women with PPCM had high levels of soluble fms-like tyrosine kinase 1 (sFlt-1), a potent vascular endothelial growth factor inhibitor, which has been implicated in the pathogenesis of pre-eclampsia, suggesting an overlap between these conditions. Indeed, pro-angiogenic therapies could rescue the PPCM phenotype in experimental models. In conclusion, PPCM is a complex disease with a quite heterogeneous and incompletely understood pathophysiology involving angiogenic, metabolic, hormonal and oxidative stress factors.

Genetic aspects

Genetically transmitted dilated cardiomyopathy (DCM) may manifest during early adulthood, and is sometimes difficult to distinguish from PPCM.[17,19,35,36] Indeed, recent observations support the notion that around 15−20% of patients with peripartum heart failure carry mutations known to induce cardiomyopathies, i.e. in genes like titin, beta-myosin heavy chain, myosin-binding protein C (MYBPC3), lamin A/C or sodium voltage-gated channel alpha subunit 5 (SCN5A).[17,19,35,36] One theory is that in gene-positive, phenotype-negative women without clinical symptoms prior to pregnancy, the physiological stress of pregnancy and delivery may unmask concealed DCM.[37] Further investigation is needed regarding mutations or polymorphisms in genes regulating metabolism, oxidative stress response, angiogenesis and the immune system as well as the higher frequency of PPCM in women of African ancestry.[10,13,27,38] Genetic testing may be considered in PPCM, in particular in those patients with a positive familial history.

Clinical presentation and (differential) diagnosis

While the majority of patients with PPCM present in the early postpartum period, there should also be a high index of suspicion towards the end of pregnancy.[3] The differential diagnoses differ according to stage of presentation – pre- vs. postpartum. *Table 1* summarizes differential diagnoses of PPCM and features of history, onset, biomarkers and echocardiography that help in the differentiation from PPCM.

An important differential diagnosis in patients presenting with acute heart failure at the end of pregnancy or directly post-delivery is severe (pre-)eclampsia leading to pulmonary oedema mainly due to diastolic dysfunction. In a South African cohort comparing hypertensive heart failure of pregnancy (HHFP) and PPCM,[39] PPCM was more often associated with twin pregnancy, smoking, cardiomegaly with lower LVEF, left atrial hypertrophy, QRS abnormalities, T-wave inversion and atrial fibrillation. By contrast, HHFP patients were more likely to have a family history of hypertension, hypertension and pre-eclampsia in a previous pregnancy, tachycardia at presentation, and LV hypertrophy. Mortality was 17% in PPCM compared to 0% among HHFP. Those data suggest significant differences in presentation and outcome of those two conditions that impact the long-term management, prognosis and advice about subsequent pregnancy.

In case of cardiogenic shock, pregnancy-associated myocardial infarction, pulmonary embolism and amniotic fluid embolism should be considered.[4] In the post-delivery situation, PPCM often presents with slowly developing heart failure with non-specific symptoms like shortness of breath, fatigue, chest pain, cough and abdominal discomfort leading to late diagnosis.[40] PPCM should be suspected in all women with a delayed return to the pre-pregnancy state. *Table 2* summarizes the diagnostic tests that are recommended for the diagnosis of PPCM at initial diagnosis and at follow-up visits.

In general, PPCM has to be differentiated from other causes of heart failure such as (pre-existing) DCM, adult congenital heart disease, toxic cardiomyopathy after e.g. chemotherapy, and Takotsubo syndrome.[5,7,13,27] Particularly after a very stressful labour or emergency due to foetal complications, high maternal catecholamine levels as well as uterotonic or tocolytic drugs with catecholaminergic properties may trigger Takotsubo syndrome.[7]

In a recent analysis of the worldwide EORP PPCM registry, characteristics and risk factors of PPCM patients with different ethnicities (including Asians) were reported.[3] Despite the huge differences in ethnic and socio-economic backgrounds among regions of the world, the baseline characteristics and mode of presentation of PPCM patients were remarkably similar.

Figure 1 summarizes the diagnostic pathway in patients with suspected PPCM including electrocardiogram (ECG), determination of natriuretic peptides, X-ray and echocardiography (according to local availability not all four have to be performed in all patients). *Figure 2* provides an overview of different clinical scenarios in patients with PPCM according to clinical severity with typical results from diagnostic tests and recommended monitoring and treatment.

Electrocardiogram

An ECG should be performed in all patients with suspected PPCM because it is safe, inexpensive and may help distinguish PPCM from other causes of symptoms. Although there is no specific ECG pattern for PPCM, at initial evaluation, the ECG is rarely normal and repolarization abnormalities are common.[41−43] Left bundle branch block may be an indirect sign for cardiomyopathy

Table 1 Differential diagnoses of peripartum cardiomyopathy

	History	Onset	Biomarkers	Echocardiography/cardiac MRI	Differentiation from PPCM
PPCM	No known cardiac disease, no HF signs and/or symptoms prior pregnancy	Towards the end of pregnancy and the months following delivery	Elevated natriuretic peptides	Reduced systolic LV function, LVEF <45%	–
Myocarditis	Prior viral infection (e.g. respiratory)	Acute or subacute onset after viral infection	Elevated troponin, elevated CRP	Normal or reduced systolic LV function, typical myocardial late gadolinium enhancement pattern, pericardial effusion	Cardiac MRI (LE pattern), myocardial biopsy
Pre-existing idiopathic/familial dilated or acquired cardiomyopathy	HF signs and/or symptoms and/or known heart disease prior pregnancy	During second trimester of pregnancy	Elevated natriuretic peptides	Reduced systolic LV function, RV dysfunction possible, typical myocardial LE pattern (DCM)	History, echocardiography, cardiac MRI (LE pattern)
Takotsubo syndrome	Chest pain, very stressful delivery or emergency due to foetal complications	Acute onset, during delivery or immediately after delivery	Elevated natriuretic peptides	Regional wall motion abnormalities with typical anatomical patterns	History, echocardiography
Pregnancy-associated myocardial infarction	Chest pain, epigastric pain	Acute onset, during pregnancy or immediately after delivery	Elevated troponin	Regional wall motion abnormalities, ischaemic myocardial scar	History, ECG, coronary angiography, cardiac MRI (LE pattern)
Pulmonary embolism	Chest pain, unilateral leg swelling, acute dyspnoea	Acute onset during pregnancy or after delivery	Elevated natriuretic peptides and/or troponin, elevated D-dimer	RV dysfunction, RV dilatation, LV function usually normal	Computed tomography, VQ scan
Amniotic fluid embolism	Chest pain during/immediately after delivery, acute dyspnoea	Acute onset during delivery or immediately after delivery	Elevated natriuretic peptides possible	Reduced RV systolic function, RV dilatation	History, echocardiography
Hypertensive heart disease/severe pre-eclampsia	Pre-existing or new-onset hypertension, proteinuria	During second trimester of pregnancy	Elevated natriuretic peptides	LV hypertrophy, diastolic dysfunction, transient LV dysfunction	History, echocardiography
Hypertrophic cardiomyopathy	Familial predisposition	During second trimester of pregnancy	Elevated natriuretic peptides	LV hypertrophy, typical myocardial late enhancement pattern, LVOTO (HOCM)	History, echocardiography, cardiac MRI (LE pattern)
HIV/AIDS cardiomyopathy	HIV infection, AIDS	During second trimester of pregnancy	Elevated natriuretic peptides	Reduced systolic LV function, LV/RV often not dilated	HIV serology/test
Pre-existing (unknown) congenital heart disease	HF signs and/or symptoms prior pregnancy, known heart disease, prior cardiac surgery	During second trimester of pregnancy	Elevated natriuretic peptides	(Corrected) congenital heart defects, cardiac shunts	History, echocardiography
Pre-existing valvular heart disease	HF signs and/or symptoms prior pregnancy, known heart disease	During second trimester of pregnancy	Elevated natriuretic peptides	Valvular stenosis or regurgitation, prosthetic heart valves	History, echocardiography

AIDS, acquired immunodeficiency syndrome; CRP, C-reactive protein; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HOCM, hypertrophic obstructive cardiomyopathy; HF, heart failure; HIV, human immunodeficiency virus; LE, late enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MRI, magnetic resonance imaging; PPCM, peripartum cardiomyopathy; RV, right ventricular; VQ, ventilation–perfusion.

Table 2 Diagnostic tests that are recommended for the diagnosis of peripartum cardiomyopathy at initial diagnosis and at follow-up visits

	Clinical examination	ECG	Natriuretic peptides	Echocardiography	Chest X-ray	Cardiac MRI	CT scan	Coronary angiography
Diagnosis of PPCM	X	X	X	X	X	(X)[b]	(X)[b]	(X)[b]
4-6 weeks after diagnosis	X	X	X	X				
3 months after diagnosis	X	X	X[a]	X				
6 months after diagnosis	X	X	X[a]	X		(X)[b]		
12 months after diagnosis	X	X	X[a]	X				
18 months after diagnosis	X	X	X[a]	X				
Annually for at least 5 years after diagnosis (especially if not fully recovered)	X	X	X[a]	X				

Generally, an individual approach is recommended depending on the severity of the disease and/or potential differential diagnoses.
CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; PPCM, peripartum cardiomyopathy.
[a]May be considered depending on costs and local availability.
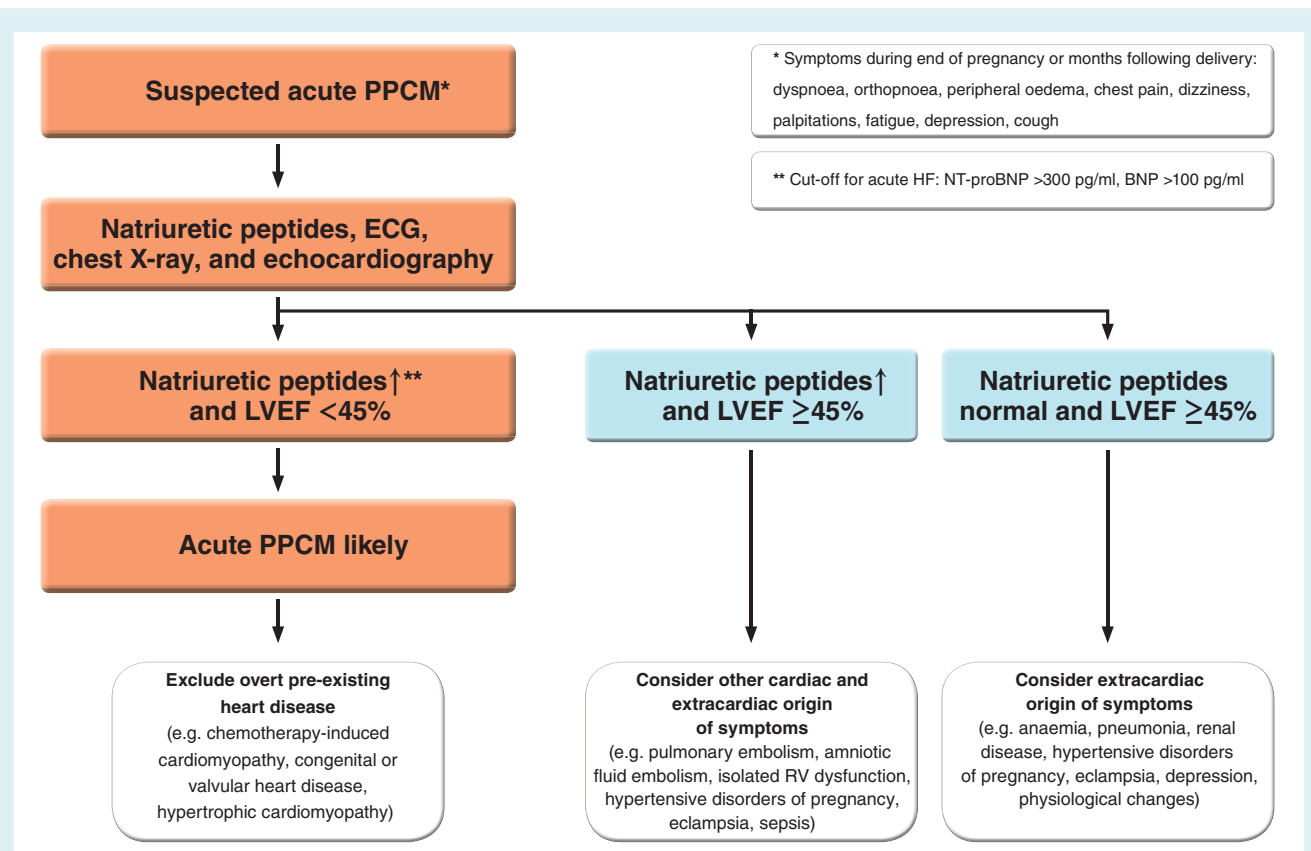[b]May be considered depending on the clinical presentation and/or differential diagnoses.

Figure 1 Diagnostic pathway in patients with suspected peripartum cardiomyopathy (PPCM). BNP, B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular.
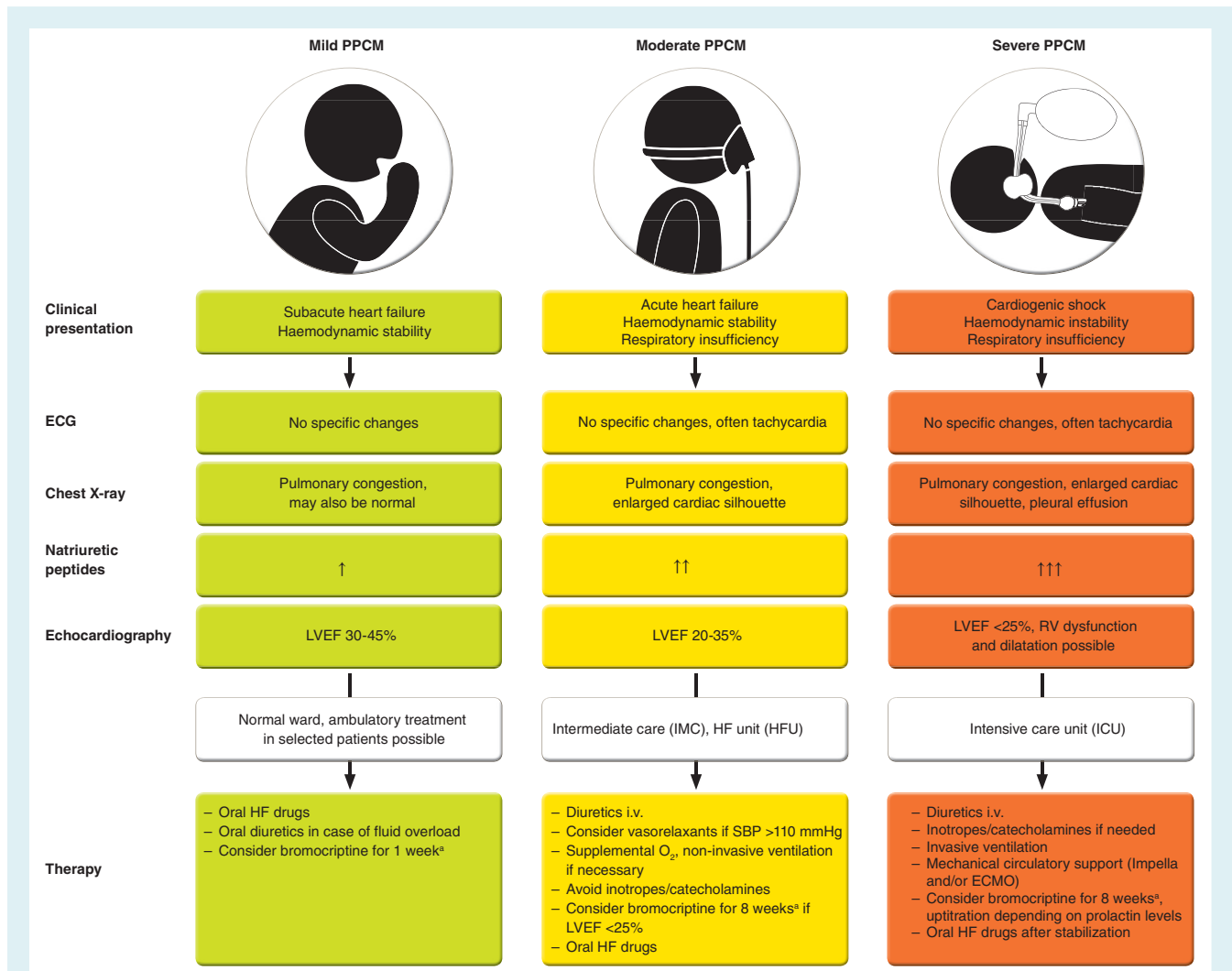
Figure 2 Overview of different clinical scenarios in patients with peripartum cardiomyopathy (PPCM). Typical results from diagnostic tests and recommended monitoring/treatment options are depicted according to disease severity. ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; HF, heart failure; HFU, heart failure unit; ICU, intensive care unit; IMC, intermediate care unit; LVEF, left ventricular ejection fraction; RV, right ventricular; SBP, systolic blood pressure. [a]Bromocriptine may be considered in PPCM patients (class IIb recommendation) and should be accompanied by at least prophylactic anticoagulation.

and structural heart disease should be ruled out in these women.[44] A recent study identified a long QTc interval at baseline which was found in almost 50% of the patients, and tachycardia as predictors of poor outcome in PPCM.[45]

Biomarkers

Concerning diagnostic properties of natriuretic peptides, one should keep in mind that B-type natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP) levels are not or only slightly elevated in normal pregnancy.[46] By contrast, patients with acute PPCM have consistently elevated plasma concentrations of natriuretic peptides, BNP or NT-proBNP.[5,11] The most important role of natriuretic peptides is to rule out heart failure (with a threshold < 100 pg/mL for BNP and < 300 pg/mL for NT-proBNP

can be ruled out with high probability), and they should not be used solely to establish the diagnosis of PPCM. Although one study demonstrated plasma BNP levels > 1860 pg/mL as an independent factor for persistent LV dysfunction, prognostic properties of natriuretic peptides remain uncertain.[47,48] Serum troponin concentrations measured at baseline may predict persistent LV dysfunction after 6 months.[49] More specific biomarkers would be helpful to allow a faster and more reliable diagnosis of PPCM, but these are yet to be adequately defined. Candidates involve 16 kDa-prolactin, interferon-gamma, asymmetric dimethylarginine (ADMA) and microRNA-146a.[11,29,32] There is controversy on the impact of imbalanced angiogenesis. Recently, high placenta growth factor (PlGF) and/or low sFlt-1/PlGF were suggested to be useful to diagnose PPCM. More research in this field is needed before any recommendations can be made.[50]

Cardiac imaging

Echocardiography is indicated as soon as possible in all cases of suspected PPCM to confirm the diagnosis, assess concomitant or pre-existing cardiac disease, exclude complications of PPCM (e.g. LV thrombus) and obtain prognostic information (for example LVEF and pulmonary hypertension). After stabilization, magnetic resonance imaging may provide a more accurate evaluation of cardiac structure and function, and can sometimes be helpful if there is high suspicion for another diagnosis such as arrhythmogenic right ventricular cardiomyopathy and myocarditis. The incremental value of cardiac magnetic resonance imaging in addition to echocardiography is uncertain. Administration of gadolinium to assess late enhancement should be avoided until after delivery due to the increased risk of stillbirth, neonatal death, and rheumatological, inflammatory, or infiltrative skin conditions.[51]

Endomyocardial biopsy

Endomyocardial biopsy adds limited diagnostic or prognostic information in PPCM. It may be used to exclude acute myocarditis after delivery, reveal significant viral presence, and exclude rare autoimmune myocarditis, storage or metabolic disease.[52] Whether or not myocarditis can be a mechanism of PPCM or whether myocarditis is a distinct entity is unclear. Myocarditis has been identified occasionally in patients thought to have PPCM.[53] Routine endomyocardial biopsy is not recommended in patients with suspected PPCM.

Management

Acute heart failure

In cases when PPCM presents with acute, decompensated heart failure (see *Figure 2*, clinical scenario acute heart failure/cardiogenic shock), the guidelines for the management of acute heart failure apply.[54,55] For rapid diagnosis and decision making in all pregnant women with acute heart failure, a pre-specified management algorithm and the establishment of a multidisciplinary team is crucial.[4,56,57] Multidisciplinary care includes cardiologists, intensivists, obstetricians, neonatologists, anaesthetists and cardiac surgeons (see *Figure 1* in ref. 4). Timely diagnosis and treatment are crucial. A recommended treatment algorithm for patients with acute PPCM is given in *Figure 2* in ref. 4. Clearly, the initial treatment of patients with severe forms of acute PPCM is different to those of stable patients (*Figure 2*).

If a patient is in cardiogenic shock/dependent on inotropes, she should be transferred immediately to an advanced heart failure centre where mechanical circulatory support (MCS), ventricular assist devices (VAD), and transplant consult teams are available.[4,55] Experimental data and a study in PPCM patients indicated that patients with PPCM may be especially sensitive to toxic effects of beta-adrenergic receptor stimulation which should be avoided whenever possible.[25] Norepinephrine is indicated to restore blood pressure, and levosimendan may be considered, however the only (small) randomized clinical trial in PPCM patients

did not show a beneficial effect on outcome.[4,58] The teratogenic effects of inotropic support and vasopressors in humans are unknown but their use may be necessary. In PPCM patients with severely reduced LV function and/or cardiogenic shock, VAD implantation as bridge to recovery or transplantation can be necessary (2–7% of PPCM patients).[4,9,11] It is important to note, however, that a significant proportion of PPCM patients improve or normalize their LV function over the first 6 months after diagnosis, which must be considered when decisions are made.[4] Short-term assist devices, e.g. microaxial pump, Centrimag or venoarterial extracorporeal membrane oxygenation (ECMO), may be required.[59] Long-term assist devices with left VAD or biventricular VAD can be implanted and some have been explanted after recovery.[60,61] Due to the toxic effects of beta-adrenergic agonists specifically in PPCM, MCS may be considered with a lower threshold than in other patients with inotrope-dependent cardiogenic shock.[25]

Heart transplantation in peripartum cardiomyopathy

Early cardiac transplantation should be reserved for patients with refractory severe heart failure where MCS is not possible or not desirable for individual reasons, mainly for cases with biventricular failure or severe initial right ventricular dysfunction.[62] Patients with PPCM appear to have higher rates of graft failure and death after heart transplantation, which may be partly explained by higher allosensitization, higher pre-transplant acuity, and increased rejection.[63] As late recovery beyond 6–12 months is possible[64] and outcomes with heart transplantation in PPCM are worse than in other causes of heart failure, delaying heart transplantation as long as possible is desirable.

Stabilized/chronic heart failure

For treatment of stabilized/chronic heart failure, the pregnancy status of the patient is important. Women who present with PPCM during pregnancy require joint cardiac and obstetric care.[4,57] Possible adverse effects on the foetus must be considered when prescribing drugs. Drugs for heart failure that can and cannot be used during pregnancy are described in *Table 3*. During pregnancy, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor–neprilysin inhibitors (ARNI), ivabradine and mineralocorticoid receptor antagonists (MRAs) are contraindicated because of concerns of teratogenicity and foetotoxicity.[13,56] Hydralazine, e.g. 25 mg every 6 h, and nitrates, e.g. isosorbide dinitrate 20 mg once daily with up-titration as tolerated, can be used during pregnancy instead of ACE inhibitors/ARBs for afterload reduction. Beta-blocker treatment is indicated for all patients with PPCM whether or not the patient is pregnant or after delivery. These drugs should only be started in patients who are euvolaemic and clinically stable. Diuretics should be used if patients have symptoms or signs of congestion whether or not they are pregnant, despite concerns about placental blood flow.

Table 3 Medications safety during pregnancy and lactation

Drug class	Use in pregnancy Summary	Use in lactation Summary	Drugs with lactation safety data	Relative infant dose from breast milk	Infant monitoring
ACEI	Avoid (*contraindicated*) – teratogenic.[1]	Use with caution (*limited data*). Clinically insignificant levels of captopril and enalapril found in breast milk.[2–5]	Enalapril (most data) Captopril	0.02–0.2%[6]	Observe for oedema, hypotension, weight gain, lethargy, pallor, and poor feeding, especially pre-term infants and those under 2 months.[6–8]
ARB	Avoid (*contraindicated*) – fetotoxic.[9]	Avoid (*no published data*) and/or consider ACEI instead (*better established safety profile*).	–	–	–
Beta-blocker	Use with caution[10] (*limited data*). Beta-blockers can cause intrauterine growth restriction.[11] If used near delivery, newborn infant should be closely monitored for 24–48 h for signs and symptoms of beta-blockade, such as hypotension and bradycardia, regardless of breastfeeding.[11]	Use with caution (*limited data*). Metoprolol is present in small levels in breast milk, with some transfer into infant serum; No adverse reactions in breastfed infants have been observed.[12–18] No detectable levels of bisoprolol were also found in breast milk in a single case study.[19]	Metoprolol (most data) Bisoprolol	1.4%[6]	Observe for signs or symptoms of beta-blockade, such as hypotension and bradycardia.[6–8]
MRA	Avoid (*not recommended*) – feminisation of rat fetus and limited data in humans[11,20]	Use with caution (*limited data*). All diuretics may theoretically suppress milk supply and mothers should be monitored for this. Clinically insignificant levels of canrenone (spironolactone active metabolite) found in breast milk.[21] Single case report of no harm with breastfeeding and spironolactone.[22]	Spironolactone	2–4.3% [extrapolated from canrenone (spironolactone active metabolite) data][6]	Observe for fluid loss, dehydration, feeding/weight gain and lethargy.[6–8]
Loop diuretic	Use with caution[10] (*limited data*). Potential reduction in placental blood flow but use is often unavoidable.	Use with caution (*no data*). All diuretics may theoretically suppress milk supply and mothers should be monitored for this. High protein binding and short half-life should limit passage into breast milk.[6–8]	–	–	Observe for fluid loss, dehydration, feeding/weight gain and lethargy.[6–8]

Table 3 Continued

Drug class	Use in pregnancy — Summary	Use in lactation — Summary	Drugs with lactation safety data	Relative infant dose from breast milk	Infant monitoring
Thiazide diuretic	Use with caution[10] (limited data). Potential reduction in placental blood flow but use is often unavoidable.	Use with caution (limited data). All diuretics may theoretically suppress milk supply and patients on high doses may need to monitor this. Small levels of hydrochlorothiazide were found in breast milk and were undetectable in infant serum in a single case study.[23]	Hydrochlorothiazide	1.68%[6]	Observe for fluid loss, dehydration, feeding/weight gain and lethargy.[6–8]
ARNI	Avoid (contraindicated) – ARBs are known to be fetotoxic.[9]	Avoid (no published data), consider different feeding method for infant in discussion with mother or consider ACEI instead (better established safety profile).	–	–	–
Ivabradine	Avoid (contraindi-cated) – teratogenic.[24]	Avoid (no published data) or consider different feeding method for infant in discussion with mother.	–	–	–
Cardiac glycoside	Use with extreme caution only (limited data). ESC guidelines for the management of cardiovascular disease during pregnancy suggest to allow digoxin in atrial fibrillation if needed.[10]	Use with caution (limited data). Small levels of digoxin in breast milk, undetectable levels in infant serum (other than in very high doses) and no observed adverse effects in the nursing infants.[25–29]	Digoxin	2.7–2.8%[6]	No special requirements
Vasodilators	Use with caution[10] (limited data).	Use with caution (limited data). Small levels of hydralazine in breast milk and infant serum and no observed adverse effects in the nursing infants.[30,31]	Hydralazine	1.2%[6]	No special requirements
Nitrates	Use with caution[10] (limited data).	Use with caution (no data).[8]	–	–	Observe for drowsiness, lethargy, poor feeding, flushing and weight gain.[6,8]
VKA	First trimester – avoid (contraindicated). Significant risk to foetus. Foetal/infant death or abnormalities in 37% of cases following first trimester exposure.[11] Consider LMWH instead	Use with caution (limited data). No detectable levels of warfarin in breast milk (at usual therapeutic doses), no warfarin activity in breastfed infants and no observed adverse effects in the nursing infants.[33–36]	Warfarin	–	No special requirements

Table 3 Continued

Drug class	Use in pregnancy	Use in lactation			
	Summary	Summary	Drugs with lactation safety data	Relative infant dose from breast milk	Infant monitoring
VKA	Second/third trimester – use with extreme caution[10] (*limited data*), only in cases with compelling indication(s). Foetal/infant death or abnormalities in 16% of cases following second trimester exposure and 27% in third trimester exposure.[11] Risk to foetus is dose-dependent, with doses >5 mg/day related to worse outcomes.[32] Consider LMWH as potential alternative after assessing individual thrombotic risk profile of the mother and dose of VKA needed and indication(s) for anticoagulation.[10] Good communication and joint decision making with the patient are vital.				
NOAC	Avoid (*contraindicated*).[10]	Avoid. Small levels of rivaroxaban in breast milk in a single case study[37]	–	1.34%[6]	–
Unfractionated heparin	Use with caution[10] (*limited data*).	Use with caution (*limited data*). Due to very high molecular weight, it would not be expected to be present in breast milk.[6,7] Also likely to be rapidly destroyed in infant gastric contents.[6]	–	–	No special requirements
LMWH	Use with caution[10] (*limited data*).	Use with caution (*limited data*). Little or no levels detectable in breast milk.[38,39] Oral adsorption unlikely.[6] No anti-Xa activity observed in breastfed infants.[40]	Dalteparin, Enoxaparin	–	No special requirements
Synthetic pentasaccharide (fondaparinux)	Avoid (*limited data*) unless allergy or adverse reaction to LMWH.[10]	Avoid (*no published data*) and/or consider LMWH instead (*better established safety profile*).	–	–	–

Green: may be used, use with caution; yellow: use with extreme caution; red: should be avoided/contraindicated.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ESC, European Society of Cardiology; LMWH, low molecular weight heparin; MRA, mineralocorticoid receptor antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.
Numbers in square brackets are references, which can be found online in the supplementary *Appendix S1*.

Post-delivery whether or not a woman is breastfeeding should be established when considering the choice of drug therapy for heart failure. For those who are breastfeeding, the drugs that can and cannot be used are also described in *Table 3*; it should be acknowledged that there are limited data to guide these recommendations. The risks of drugs during lactation cannot be described clearly but our expert-based recommendations attempt to balance the likely pros of therapy for heart failure against potential cons. Many drugs, including ACE inhibitors, beta-blockers and MRAs, pass into human breast milk but this is often at clinically insignificant levels. A summary of previously published guidance in national and international guidelines (including from the World Health Organization) is included in the online supplementary *Table S1*. These prior guidelines illustrate a lack of definitive data as they are frequently discordant both with each other and sometimes even within the same document.

For those not breastfeeding, heart failure should be treated according to guidelines on acute and chronic heart failure including ACE inhibition, beta-blockade and MRAs, and then replacing ACE inhibitors and ARBs with ARNI[13,54] (*Table 4*). As high resting heart rate is a predictor of adverse outcome, treatment with ivabradine might be useful in PPCM patients with high heart rate in sinus rhythm on top of beta-blockade.[65,66]

All patients should remain on a combined drug regimen for heart failure until they experience complete myocardial recovery and for at least 12–24 months after full recovery of LV function.[13] Following complete recovery, how long medical therapy should continue is unknown. Many clinicians recommend that all patients with PPCM remain on long-term therapy to avoid the potential decline in cardiac function which is a risk on stopping pharmacological therapy for heart failure.[67] Others believe that drugs can be gradually withdrawn under careful surveillance with serial cardiac imaging and biomarker measurement. A full discussion between patient, family and clinicians is necessary where the pros and cons of stopping or continuing therapy are carefully considered. Data to guide these decisions are limited. In a small cohort with recovered LV function post-PPCM who stopped their drug therapy, none experienced worsening of LV function; but this is not definitive evidence for the safety of withdrawing drug therapy in patients who have PPCM.[68] In those patients with an identified genetic contribution, indefinite continuation of heart failure therapy is recommended.[69] When a patient wishes to consider a subsequent pregnancy (following a fully informed decision-making process) drug therapy can be withdrawn under close monitoring for around 6 months before embarking on conception and pregnancy.

Pro-coagulant activity is increased during and early after pregnancy.[70] In the context of reduced EF in PPCM, initial treatment with low molecular weight heparin or oral anticoagulation at least in prophylactic dose is recommended because of the high rate of peripheral arterial and venous embolism (7% in the first 30 days after delivery, data from the PPCM worldwide registry).[3] Therapeutic anticoagulation is firmly recommended in patients with intracardiac thrombus detected by imaging or evidence of systemic embolism, as well as in patients with paroxysmal or persistent atrial fibrillation.

Delivery

Vaginal delivery is always preferable if the patient is haemodynamically stable and there are no absolute obstetric indications for caesarean delivery. Close haemodynamic monitoring is required. Epidural analgesia is preferred. Urgent delivery irrespective of gestation duration should be considered in women with advanced heart failure and haemodynamic instability despite optimal heart failure treatment.[4] In these cases, caesarean section is recommended with central neuraxial anaesthesia. To prevent abrupt pressure or volume changes, epidural anaesthesia might be the method of choice but should be carefully titrated, guided by an expert anaesthetic team.[4,56,57] If MCS may become necessary, the patient should be delivered by appropriate teams in hospitals capable of providing such care.

Breastfeeding

Breastfeeding in patients with heart failure is controversial. According to the 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy,[56] in patients with severe heart failure preventing lactation may be considered due to the high metabolic demands of lactation and breastfeeding (class IIb recommendation). These guidelines state that stopping lactation enables safe treatment with all established heart failure drugs. Normal growth percentiles and no adverse outcome for infants were observed in a collective of PPCM patients in South Africa where breastfeeding was terminated.[71] However, breastfeeding is tolerated by many women with PPCM with respect to their heart failure status. Additionally, many drugs for heart failure are also not contraindicated in breastfeeding mothers (see above and *Table 3*). Breastfeeding may also confer important benefits to infants and mothers, especially in developing countries. Numerous national and international guidelines, including from the World Health Organization, advise that many heart failure drugs are compatible with breastfeeding if used with caution (see online supplementary *Table S1*). Data on infant safety with breastfeeding is very limited however, and often involves older therapeutic agents and tiny patient numbers. Many drugs, including ACE inhibitors, beta-blockers and MRAs, pass into human breast milk but this is often at clinically insignificant levels (see online supplementary *Table S1*). Most studies often also involve single agents, rather than combinations of drugs. Breastfeeding may also confer important physical and psychological benefits to infants and mothers, especially in developing countries.[72]

Decisions on whether to inhibit lactation, terminate breastfeeding or continue breastfeeding with caution should be taken jointly with the patient on a case-by-case basis, taking into consideration both the health of the mother and the risk:benefit ratio of breastfeeding to the infant. Good counselling and shared decision-making are key. Online supplementary *Table S1* summarizes the current literature around lactation safety and heart failure drugs and may help guide clinicians, should mothers wish to continue breastfeeding.

Bromocriptine treatment

Based on the above-mentioned pathophysiological pathway of 16kD-prolactin-mediated PPCM, a small (*n* = 20) prospective

Table 4 Chronic drug treatment in peripartum cardiomyopathy patients after delivery

Drug	Persisting heart failure and absence of complete LV recovery	Complete and sustained recovery (LVEF > 55% and NYHA functional class I)
Beta-blocker	Essential for all patients in standard or maximally tolerated dosages	Continue all drugs (beta-blocker, ACEI/ARB/ARNI, MRA) for at least 12–24 months after full recovery, individual approach/discuss with patient. Discontinue stepwise and monitor symptoms and LV function: 1. MRA 2. ACEI/ARB/ARNI 3. Beta-blocker
ACEI	Essential for all patients in standard or maximally tolerated dosages	
ARB	Recommended in patients who do not tolerate ACEI	
ARNI	Recommended in patients with LVEF < 40% who are symptomatic despite maximal dosages of beta-blocker, ACEI/ARB and MRA	
MRA	Recommended in patients with LVEF < 40%, preferably eplerenone due to less hormonal side effects and less blood pressure reduction compared to spironolactone	
Ivabradine	Recommended in patients in sinus rhythm with a persisting heart rate > 70 b.p.m. at rest despite maximal tolerated beta-blocker up-titration	Discontinue if heart rate < 50 b.p.m. and/or in case of complete recovery
Diuretics	Recommended in patients with fluid overload	Taper dose/discontinue if no signs of fluid overload, maintain only if part of antihypertensive therapy

Please note that initiation of all heart failure drugs is only possible in patients who do not breastfeed (see also Table 3 and online supplementary *Table S1* for a more comprehensive summary of compatibilities with breastfeeding).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

randomized pilot study supported the hypothesis that the addition of the prolactin-blocker bromocriptine to standard heart failure therapy has beneficial effects on LVEF and mortality in women with severe acute PPCM.[71] Furthermore, in the German PPCM registry, standard heart failure plus bromocriptine treatment was associated with low mortality.[11] The randomized prospective German bromocriptine study compared short- and long-term bromocriptine treatment in patients with severe PPCM (EF < 35%).[73] Both high and low doses were associated with low mortality (there was no placebo arm). A Canadian study reported a greater LV recovery in PPCM patients treated with bromocriptine.[74] Treatment with bromocriptine may especially be considered in patients with right ventricular involvement.[75] A bromocriptine treatment scheme has been suggested: bromocriptine (2.5 mg once daily) for at least 1 week may be considered in uncomplicated cases, whereas prolonged treatment (2.5 mg twice daily for 2 weeks, then 2.5 mg once daily for another 6 weeks) may be applied in patients with EF < 25%, right ventricular involvement, intensive care treatment, and/or cardiogenic shock (*Figure 3*).[76]

There is no consensus as to whether or not bromocriptine should be used in PPCM. Some believe that as acute heart failure due to PPCM can have a poor prognosis in some patients and there are no evidence-based drug treatments, bromocriptine should be used.
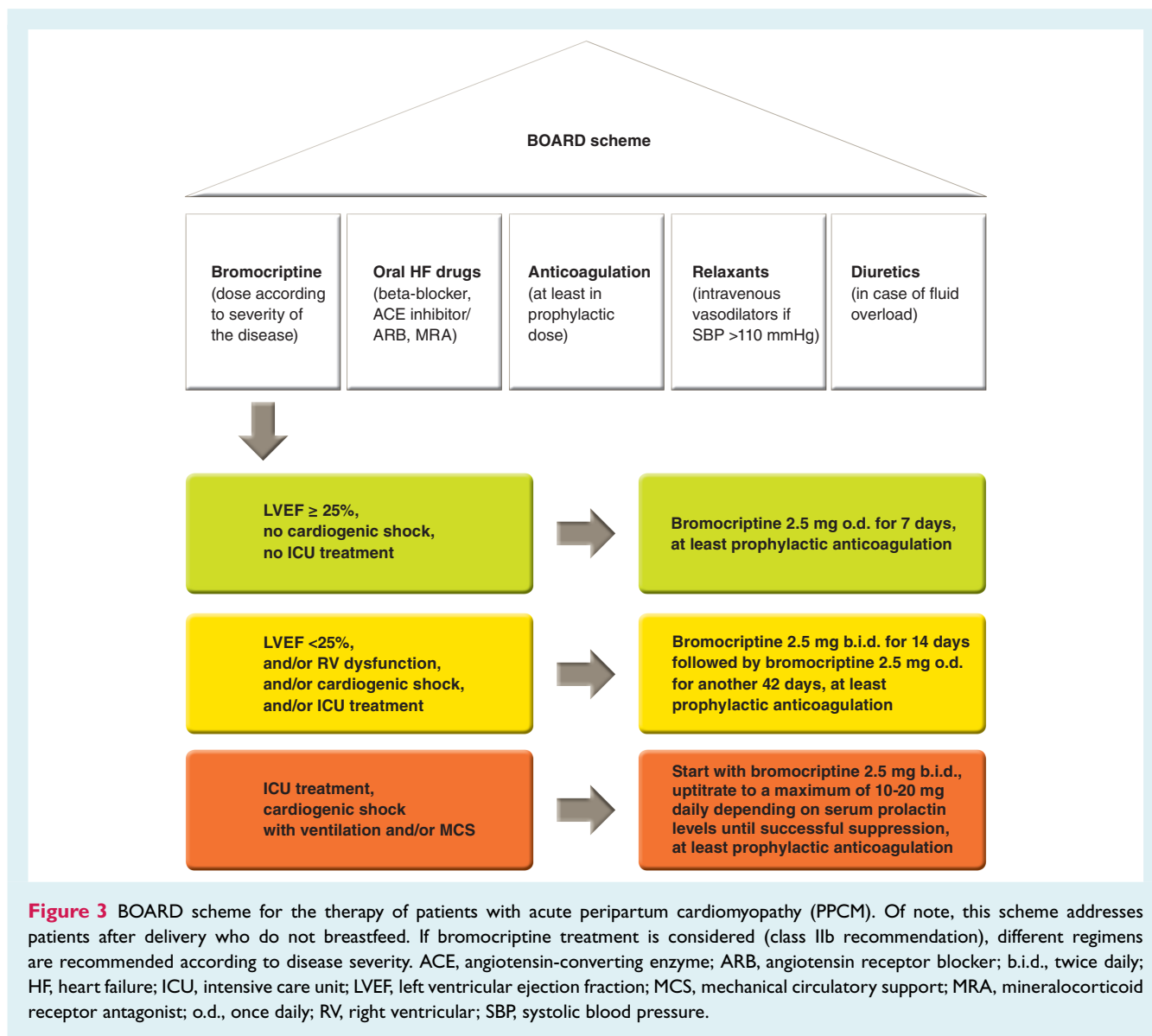
Data on bromocriptine treatment in PPCM patients with cardiogenic shock are scarce. Elevated prolactin levels have been associated with poor outcome in patients receiving ECMO support.[77] Individualized bromocriptine treatment with dose up-titration until successful prolactin suppression is achieved is a possible therapeutic option in these highly selected cases.[59] The safety profile seems reasonable when at least prophylactic anticoagulation is administered.[59]

International variations in the use of bromocriptine are large: in the USA bromocriptine is rarely used[9] whereas in Germany and non-EU countries in the worldwide PPCM registry, treatment with bromocriptine is common.[3] There are no large, randomized, placebo-controlled trials of bromocriptine in PPCM. A small (n = 60) bromocriptine vs. placebo trial is underway in Canada. Considerably larger, international placebo-controlled trials would be necessary to establish firm proof of clinical benefit, however, a truly placebo-controlled trial will not be possible as the placebo arm would continue lactation and therefore blinding would not be achievable.

To date, bromocriptine may be considered in patients with PPCM (class IIb recommendation).[56] As thromboembolic events have been reported during the use of bromocriptine (albeit mostly at higher dosages), bromocriptine treatment should always be accompanied by anticoagulation at least in prophylactic dosages. Therapies for patients with acute PPCM have been proposed under the BOARD label: Bromocriptine, Oral heart failure therapies, Anticoagulants, vasoRelaxing agents, and Diuretics.[78]

If bromocriptine is not available, cabergoline may be used as an alternative to bromocriptine, however apart from two reports[12,79] data are lacking regarding LV recovery with cabergoline in PPCM.

Figure 3 BOARD scheme for the therapy of patients with acute peripartum cardiomyopathy (PPCM). Of note, this scheme addresses patients after delivery who do not breastfeed. If bromocriptine treatment is considered (class IIb recommendation), different regimens are recommended according to disease severity. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; b.i.d., twice daily; HF, heart failure; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; o.d., once daily; RV, right ventricular; SBP, systolic blood pressure.

Prevention of sudden cardiac death and device therapy

Given the high rate of improvement of LV function during optimal heart failure drug therapy, early implantation of an implantable cardioverter-defibrillator (ICD) in patients with newly diagnosed PPCM is generally not advisable. Wearable cardioverter-defibrillators (WCDs) have been proposed as a mechanism to prevent sudden cardiac death during the first 3–6 months after diagnosis until a definitive decision about ICD implantation can be made.[4,41,80,81] In a German registry of patients with severe PPCM, several appropriate shocks were delivered for ventricular fibrillation within the first months.[41,80] No randomized trials of WCDs in PPCM have yet been started.

For women presenting with severe LV dysfunction > 6 months following first presentation despite optimal medical therapy, implantation of an ICD as well as cardiac resynchronization therapy (CRT) are recommended according to current ESC guidelines.[54] Although in non-ischaemic cardiomyopathy the necessity of ICD has been questioned in older patients,[82] young patients with severe LV dysfunction despite optimal medical therapy may still derive benefit from ICD implantation.[83] Subcutaneous ICDs represent an alternative to transvenous systems, although they neither provide anti-tachycardia pacing nor post-shock pacing, but can be more easily extracted if cardiac function recovers.

Prognosis, counselling, subsequent pregnancies

The HFA of the ESC Study Group on PPCM published in 2018 a practical guidance paper on the long-term prognosis, subsequent pregnancy, contraception and overall management of patients diagnosed with PPCM.[64]

Current evidence for long-term outcome is based mostly on retrospective data or on single-centre prospective studies or small registries covering only 6–12 months postpartum with a wide variation in reported mortality rates, ranging from 2% in Germany[11] to 12.6% from 206 patients with PPCM from South Africa.[66] African American women were more likely to worsen after initial diagnosis, had a lower chance to recover despite apparent adequate treatment.[10] Even after full recovery of LVEF, subtle diastolic dysfunction and reduced maximal exercise capacity (peak oxygen uptake) was reported recently in a Danish PPCM cohort compared to women with previous severe pre-eclampsia and previous uncomplicated pregnancies.[84] Residual cardiac impairment was also shown by assessing echocardiographic tissue Doppler imaging and speckle tracking for myocardial strain imaging.[85] Imaging findings that are associated with an unfavourable outcome include LV end-diastolic diameter > 60 mm, severely depressed LV function (< 30%) and right ventricular dysfunction at initial diagnosis.[9,86]

All patients with a previously diagnosed PPCM and their partners should receive careful counselling (class I recommendation) about the longer-term prognosis and undergo a risk stratification if further pregnancies are considered (see *Figure 1* in ref. 64). Based on a recent publication reporting on the outcome of women with PPCM and a subsequent pregnancy in cohorts from Germany, Scotland and South Africa,[76,87] women with an impaired systolic function are at substantial risk of relapse and death, and should therefore be strongly advised against pregnancy. As any subsequent pregnancy in a woman with PPCM entails a substantial risk, those women should be monitored by an experienced multi-disciplinary team throughout pregnancy and for at least 1 year postpartum.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Table S1. Summary of national and international guidance and guideline recommendations on the safety of breastfeeding and heart failure drug therapy.
Appendix S1. References of *Table 3*.

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