

Peripartum CMP

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Disclosure
I have nothing to declare

Peripartum Cardiomyopathy

JACC State-of-the-Art Review

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ABSTRACT

Peripartum cardiomyopathy is a form of systolic heart failure affecting young women toward the end of pregnancy or in the months following delivery. Incidence is higher in African-American women and in women with older maternal age, hypertensive disorders of pregnancy, and multiple gestation pregnancies. Symptoms of heart failure mimic those of normal pregnancy, often resulting in a delay in diagnosis and preventable complications. Echocardiography showing decreased myocardial function is essential for the diagnosis. Medical management is similar to heart failure with reduced ejection fraction of other etiologies, but adjustments during pregnancy are necessary to ensure fetal safety. Variable outcomes include complete recovery, persistent heart failure, arrhythmias, thromboembolic events, and death. Subsequent pregnancy confers substantial risk of relapse and even death if there is incomplete myocardial recovery. Additional research about the etiology, optimal therapy including the use of bromocriptine, long-term outcomes, and duration of treatment after recovery are needed. (J Am Coll Cardiol 2020;75:207–21) © 2020 by the American College of Cardiology Foundation.

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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AHA SCIENTIFIC STATEMENT

Adverse Pregnancy Outcomes and Cardiovascular Disease Risk: Unique Opportunities for Cardiovascular Disease Prevention in Women

A Scientific Statement From the American Heart Association

ABSTRACT: This statement summarizes evidence that adverse pregnancy outcomes (APOs) such as hypertensive disorders of pregnancy, preterm delivery, gestational diabetes, small-for-gestational-age delivery, placental abruption, and pregnancy loss increase a woman's risk of developing cardiovascular disease (CVD) risk factors and of developing subsequent CVD (including fatal and nonfatal coronary heart disease, stroke, peripheral vascular disease, and heart failure). This statement highlights the importance of recognizing APOs when CVD risk is evaluated in women, although their value in reclassifying risk may not be established. A history of APOs is a prompt for more vigorous primordial prevention of CVD risk factors and primary prevention of CVD. Adopting

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2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

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Clinical update

Peripartum cardiomyopathy: current management and future perspectives

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Pregnancy is associated with marked physiological changes challenging the cardiovascular system. Among the more severe pregnancy associated cardiovascular complications, peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease emerging towards the end of pregnancy or in the first postpartum months in previously healthy women. A major challenge is to distinguish the peripartum discomforts in healthy women (fatigue, shortness of breath, and oedema) from the pathological symptoms of PPCM. Moreover, pregnancy-related pathologies such as preeclampsia, myocarditis, or underlying genetic disease show overlapping symptoms with PPCM. Difficulties in diagnosis and the discrimination from other pathological conditions in pregnancy may explain why PPCM is still underestimated. Additionally, underlying pathophysiologicals are poorly understood, biomarkers are scarce and treatment options in general limited. Experience in long-term prognosis and management including subsequent pregnancies is just beginning to emerge. This review focuses on novel aspects of physiological and pathophysiological changes of the maternal cardiovascular system by comparing normal conditions, hypertensive complications, genetic aspects, and infectious disease in PPCM-pregnancies. It also presents clinical and basic science data on the current state of knowledge on PPCM and brings them in context thereby highlighting promising new insights in diagnostic tools and therapeutic approaches and management.

Keywords

Peripartum cardiomyopathy • Heart failure • Pregnancy

Definition of peripartum cardiomyopathy

1. Heart failure secondary to left ventricular systolic dysfunction 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

Pathophysiology

- The etiology of PPCM is uncertain
- Combined 'two-hit' model including :

Systemic angiogenic imbalance / **host susceptibility**

- 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

Pathophysiology PPCMP

- **A complex disease with a quite heterogeneous and incompletely understood pathophysiology involving :**
- **angiogenic,**
- **metabolic,**
- **hormonal ,**
- **oxidative stress factors**

Predisposing factors for PPCM

- **Multiparity and multiple pregnancies,**
- **Family history,**
- **Ethnicity,**
- **Smoking,**
- **Diabetes,**
- **Hypertension,**
- **Pre-eclampsia,**
- **Malnutrition,**
- **Age of mother (with older mothers being at greater risk),**
- **Prolonged use of tocolytic beta-agonists**

PPCM should be suspected in all women with a delayed return to the pre-pregnancy state

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.

^aMay be considered depending on costs and local availability.

^bMay be considered depending on the clinical presentation and/or differential diagnoses.

Management

- 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.
- **Multidisciplinary TEAM** care includes cardiologists, intensivists, obstetricians, neonatologists, anaesthetists and cardiac surgeons
- **Timely diagnosis** and treatment are crucial.

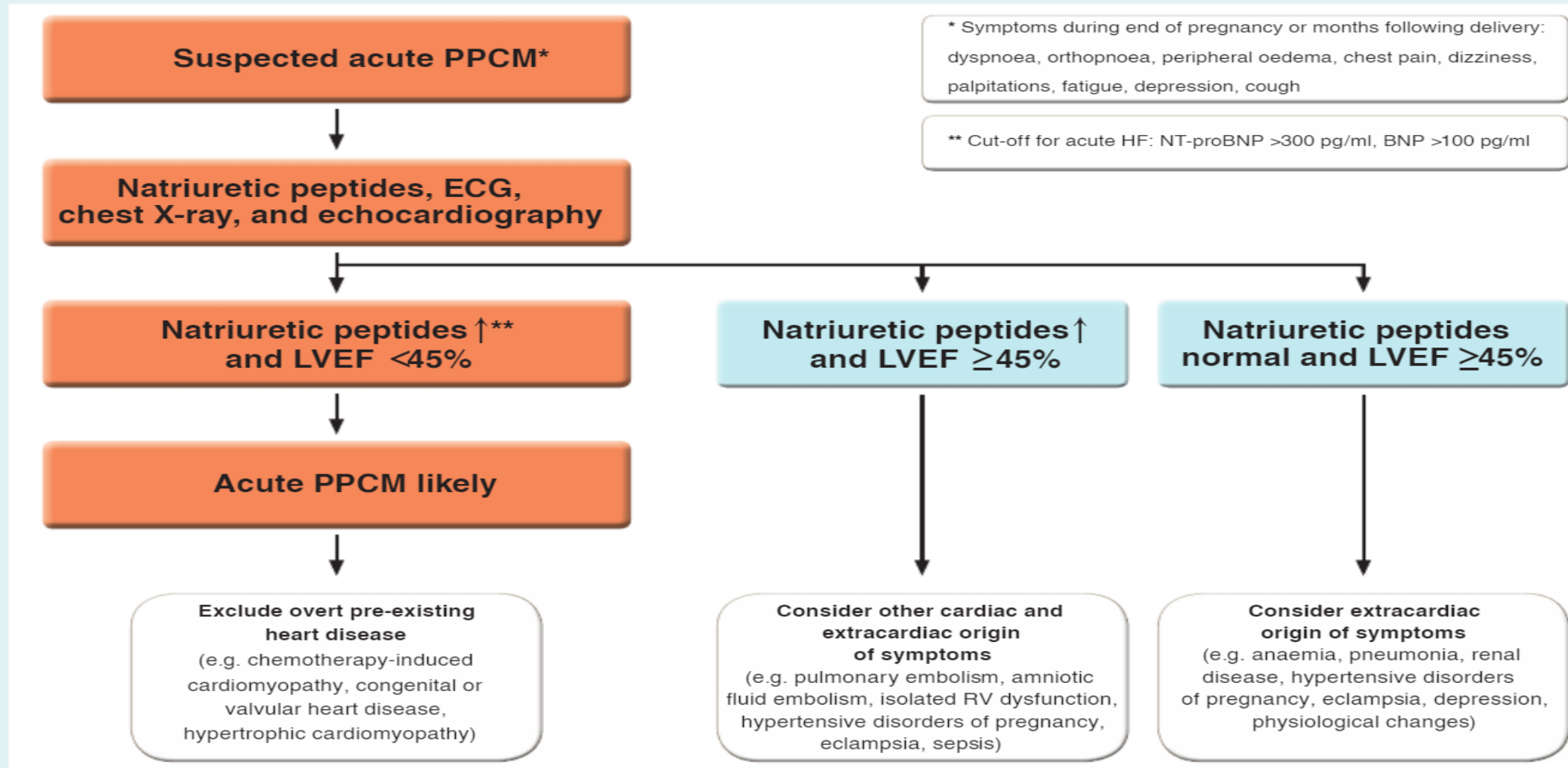


Figure 1 Diagnostic pathway in patients with suspected peripartum cardiomyopathy (PPCM). BNP, B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular.

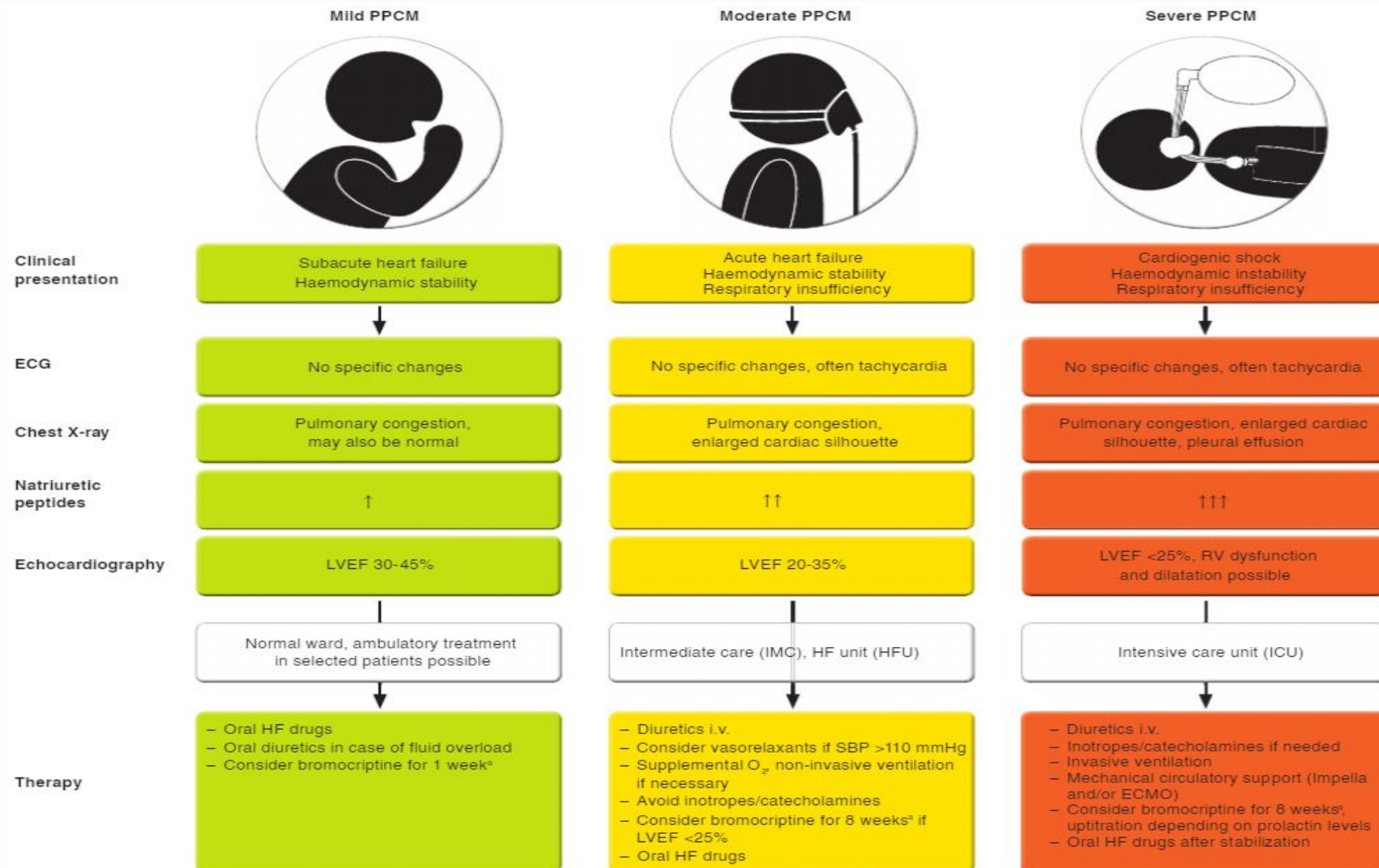


Table 3 Medications safety during pregnancy and lactation

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] (<i>limited data</i>). Potential reduction in placental blood flow but use is often unavoidable.	Use with caution (<i>limited data</i>). 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 (<i>contraindicated</i>) – ARBs are known to be fetotoxic [9]	Avoid (<i>no published data</i>), consider different feeding method for infant in discussion with mother or consider ACEI instead (<i>better established safety profile</i>).	—	—	—
Ivabradine	Avoid (<i>contraindicated</i>) – teratogenic.[24]	Avoid (<i>no published data</i>) or consider different feeding method for infant in discussion with mother.	—	—	—
Cardiac glycoside	Use with extreme caution only (<i>limited data</i>). ESC guidelines for the management of cardiovascular disease during pregnancy suggest to allow digoxin in atrial fibrillation if needed.[10]	Use with caution (<i>limited data</i>). 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] (<i>limited data</i>).	Use with caution (<i>limited data</i>). 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] (<i>limited data</i>).	Use with caution (<i>no data</i>).[8]	—	—	Observe for drowsiness, lethargy, poor feeding, flushing and weight gain.[6,8]
VKA	First trimester – avoid (<i>contraindicated</i>). Significant risk to foetus. Foetal/infant death or abnormalities in 37% of cases following first trimester exposure [11]. Consider LMWH instead	Use with caution (<i>limited data</i>). 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	Drugs with lactation safety data	Relative infant dose from breast milk	Infant monitoring
	Summary	Summary			
VKA	Second/third trimester – use with extreme caution[10] (<i>limited data</i>), 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 (<i>contraindicated</i>).[10]	Avoid. Small levels of rivaroxaban in breast milk in a single case study[37]	–	1.34%[6]	—
Unfractionated heparin	Use with caution[10] (<i>limited data</i>).	Use with caution (<i>limited data</i>). 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] (<i>limited data</i>).	Use with caution (<i>limited data</i>). 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 (<i>limited data</i>) unless allergy or adverse reaction to LMWH.[10]	Avoid (<i>no published data</i>) and/or consider LMWH instead (<i>better established safety profile</i>).	–	–	–

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

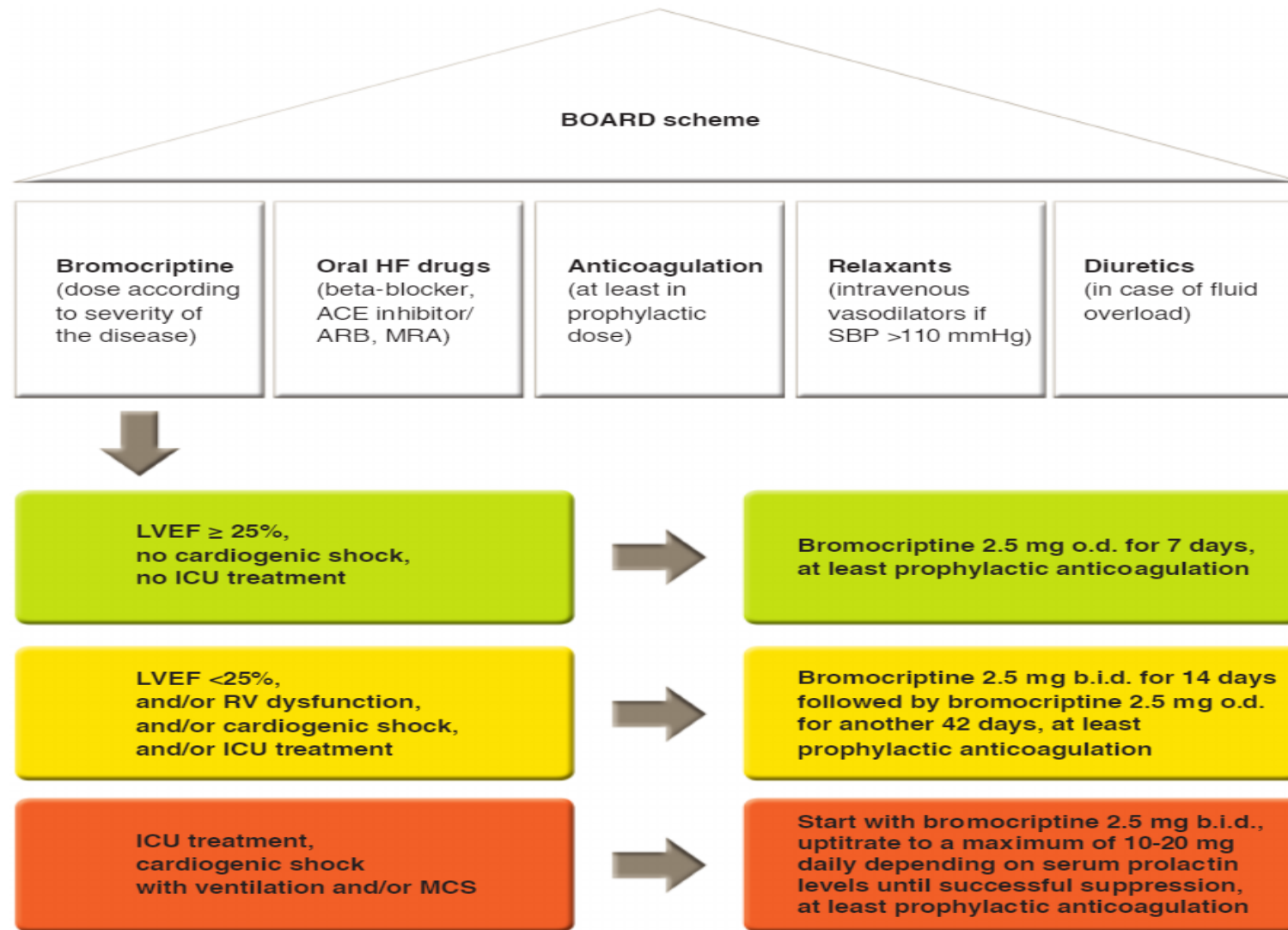


Figure 3 BOARD scheme for the therapy of patients with acute peripartum cardiomyopathy (PPCM). Of note, this scheme addresses patients after delivery who do not breastfeed. If bromocriptine treatment is considered (class IIb recommendation), different regimens are recommended according to disease severity. 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.

Peripartum Cardiomyopathy (PPCM)

Definition:

- Non-ischemic cardiomyopathy with reduced LVEF (<45%)
- Commonly presents in the first months postpartum or towards the end of pregnancy

Risk Factors:

- African-American race, preeclampsia, hypertension, multigestational pregnancies, age >30 years

Symptoms:

- Heart failure symptoms can be confused with common symptoms of normal pregnancy

Management Options for PPCM



During Pregnancy:

- Beta-blockers, loop diuretics, hydralazine/isosorbide dinitrate, digoxin, low-molecular-weight heparin
- (No ACE/ARB/aldosterone receptor antagonists)
- MCS for severe heart failure/cardiogenic shock
- Consider early delivery if unstable



Delivery:

- Plan ahead with a Cardio-Obstetrics Team
- If unstable, consider hemodynamic monitoring and optimization
- Caution for fluid overload, especially after delivery



After Pregnancy:

- Heart failure management. Beta-blockers, enalapril, and spironolactone are compatible with breastfeeding.
- Anticoagulation for LV thrombus; consider if severe LV dysfunction (LVEF <35%)
- Consider a wearable cardioverter/defibrillator if severe LV dysfunction
- Discuss Contraception

Outcomes

Worse prognosis with lower LVEF, dilated LV, African-American race, and delayed diagnosis.

Long-term Outcomes

- After recovery, optimal duration of medication treatment is unknown
- In the case of stopping medications, wean gradually and observe closely
- Continue surveillance after recovery

TABLE 1 Differential Diagnosis for Heart Failure During Pregnancy

Differential Diagnosis	Considerations
Takotsubo cardiomyopathy	Echocardiogram may show classic apical ballooning
Familial cardiomyopathy	Family history, genetic testing
Pre-existing cardiomyopathy	History of HF prior to pregnancy; prior echo studies with low LVEF before pregnancy
Recurrent peripartum cardiomyopathy	Ask about symptoms of HF that occurred after a prior pregnancy
Pre-eclampsia	Preserved systolic function on echocardiogram
Hypertrophic cardiomyopathy	Left ventricular hypertrophy, LVOT obstruction, preserved systolic function, genetic testing
Myocarditis	Consider if viral prodrome, histological diagnosis, fulminant presentation
Arrhythmogenic right ventricular cardiomyopathy	Consider with family history, genetic testing, echocardiographic findings
Left ventricular noncompaction	Echocardiographic and CMR findings
Chemotherapy-related cardiomyopathy	History of chemotherapy, particularly doxorubicin
Valvular heart disease	Echocardiographic findings; congenital aortic stenosis; mitral stenosis from rheumatic heart disease in endemic country. Patients with PPCM may also have valve disease, i.e., mitral regurgitation
Congenital heart disease	May be diagnosed for the first time during pregnancy by echocardiography
Tachycardia-arrhythmia mediated cardiomyopathy	Consider if specific underlying rhythm abnormality. Note that sinus tachycardia may be secondary to heart failure during pregnancy
Hypertensive heart disease	Left ventricular hypertrophy; less common in young people unless very longstanding history of hypertension
Ischemic heart disease	Cardiovascular risk factors; angina; prior CAD; consider SCAD and MINOCA diagnoses
Cardiomyopathy related to other systemic medical diseases	Consider in the appropriate context, i.e., systemic lupus erythematosus, antiphospholipid syndrome, hemochromatosis
Cardiomyopathy related to other acute conditions	May consider if patient has other conditions such as sepsis, treatment in intensive care unit, post-respiratory arrest
Pulmonary embolism	Dyspnea, tachycardia with preserved LVEF

CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; HF = heart failure; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MINOCA = myocardial infarction in non-obstructive coronary arteries; PPCM = peripartum cardiomyopathy; SCAD = spontaneous coronary artery dissection.

FIGURE 1 Heart Failure and Anticoagulant Medications: Indications and Safety in Pregnancy and During Lactation

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
HEART FAILURE MEDICATIONS				
Loop diuretics	Yes	Caution for hypovolemia or hypotension that may lead to decreased placental perfusion	For signs and symptoms of congestion and fluid overload.	Yes, but over-diuresis can lead to decreased milk production.
Beta blockers (metoprolol tartrate used most commonly)	Yes	IUGR; fetal bradycardia and hypoglycemia	For standard treatment of HF; consider treatment of women with subsequent pregnancy.	Yes
Hydralazine/nitrates	Yes	Caution with hypotension	Use for afterload reduction during pregnancy (instead of ACE-I/ARB) when needed.	Yes, but ACE-I/ARB typically chosen post-partum
Digoxin	Yes	No associated congenital defects	Can be used with symptomatic heart failure and/or systolic dysfunction during pregnancy, or afterwards per guidelines.	Yes
ACE-I/ARB	No	Anuria, oligohydramnios, fetal limb contractures, craniofacial deformation, pulmonary atresia, fetal hypocalvaria, intra uterine growth restriction, prematurity, patent ductus arteriosus, stillbirth, neonatal hypotension and death	Cannot use during pregnancy. After delivery, should be used as part of guideline-directed medical therapy for afterload reduction and LV remodeling.	Enalapril and captopril can be used
Aldosterone receptor antagonists	No	Spironolactone has been associated with antiadrenergic activity, feminization of male rat fetuses and permanent changes in reproductive tract in both sexes	As per guideline-directed medical therapy for heart failure.	Spironolactone can be used
Sacubitril-valsartan	No	Same as ACE-I/ARB	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
Ivabradine	Scant data in humans; would avoid due to concerns in animal studies	Scant data in humans, animal data suggest risk	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
ANTICOAGULANTS				
Low molecular weight heparin	Yes	Caution at time of delivery and with neuraxial anesthesia; does not cross placenta; consider the need for monitoring anti-Xa levels	For prevention and treatment of thromboembolic complications during pregnancy and as bridge to warfarin postpartum.	Yes
Warfarin	Avoid	Warfarin embryopathy and fetopathy	For prevention and treatment of thromboembolic complications postpartum.	Yes

Legend:

	Data or experience to support use
	Caution with using this medication
	Data is limited or inconclusive

Imaging findings that are associated with Unfavorable outcome :

- **LV end-diastolic diameter >60 mm,**
- **Severely depressed LV function (EF<30%),**
- **Right ventricular dysfunction at initial diagnosis**

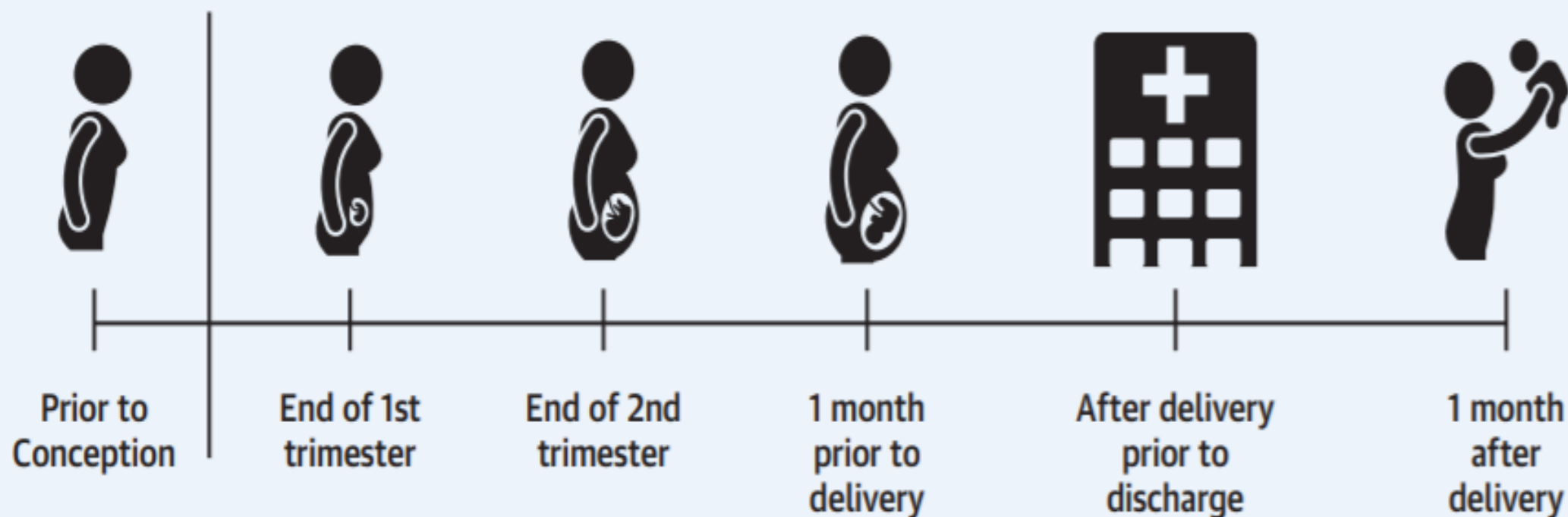
FIGURE 2 Counseling and Management of Subsequent Pregnancies in PPCM

 Subsequent Pregnancy	Recovered (LVEF $\geq$ 50%)	Nonrecovered (LVEF <50%)
Preconception or First Visit	Preconception risk counseling and follow-up planning. Clinical and LVEF reassessment off renin-angiotensin blocking agents for 3 months. Baseline echocardiogram and BNP/NT-proBNP level.	Preconception risk counseling including discussion of alternative ways to build a family. If pregnant and not considering termination: Close follow-up planning, stop renin-angiotensin blocking agents and switch to hydralazine/isosorbide dinitrate. Baseline echocardiogram and BNP/NT-proBNP level.
Maternal Risks	~20% have a relapse Severe deterioration is rare Mortality unlikely Rate of subsequent recovery is high	Higher risk of relapse ~50% show further deterioration in LV dysfunction Increased morbidity and mortality Premature delivery and abortion more common
Medications	Continue beta blocker therapy (metoprolol tartrate preferred). Yield of starting prophylactic beta blocker therapy unclear. Diuretics and hydralazine/isosorbide dinitrate in case of clinical or LV functional deterioration.	Continue beta blocker therapy (metoprolol tartrate preferred). Hydralazine/Isosorbide dinitrate for hemodynamic and symptomatic improvement. Consider digoxin. Consider anticoagulation if severe LV dysfunction (LVEF <35%).
Follow-up	Close monitoring of symptoms during pregnancy and the postpartum period with repeat echocardiographic assessment of LV function and BNP/NT-proBNP level at the end of the 1st and 2nd trimesters, 1 month prior to delivery, after delivery prior to hospital discharge, 1 month postpartum, and at any time if symptoms develop.	
Labor and Delivery	Multidisciplinary team for planning; patient involved. Spontaneous vaginal delivery preferred unless fetal or maternal instability. Monitor for volume overload in the first 48 hours after delivery in cases of recurrent LV dysfunction.	Multidisciplinary team for planning; patient involved. Spontaneous vaginal delivery preferred unless fetal or maternal instability. Early delivery if further decrease in LV function and hemodynamic deterioration. Consider hemodynamic monitoring for optimization prior to delivery and monitoring during and after delivery. Monitor for volume overload in the first 48 hours after delivery.

Risks of a subsequent pregnancy differ based on the pre-conception recovery status. There is higher risk with nonrecovered myocardial function and pregnancy should be discouraged. Peripartum management options depend on the clinical status and myocardial function. ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LV = left ventricular; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.

FIGURE 3 Serial Monitoring During a Subsequent Pregnancy

Clinical assessment, echocardiogram, and BNP should be performed at regular intervals and with any concerning symptoms:



Proposed outline for serial testing during a subsequent pregnancy. BNP = brain natriuretic peptide.

Thank You
Comment & Question