

Peripartum Cardiomyopathy

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Abstract

Peripartum cardiomyopathy (PPCM) is a low frequent, but potentially fatal disease, that manifests with heart failure and reduced ejection fraction, with no other identified cause, and related to the puerperal pregnancy cycle. It is a global disease with different clinical manifestations and prognosis. Known risks include preeclampsia, advanced maternal age, multifetal gestation, and African ascendance. Genetic tests have shown that up to 20% of women with PPCM have an identifiable variant of cardiomyopathy. The etiopathogenesis of PPCM, although still unclear, is characterized by endothelial dysfunction caused by anti-angiogenic agents in the placenta, and prolactin degradation products.

Clinical manifestation of PPCM does not differ from that of heart failure in other cardiomyopathies, with symptoms varying from mild to cardiogenic shock. Mortality rates in PPCM patients vary widely, and are related to cardiogenic shock, thromboembolism, and complex arrhythmias. The disease may progress rapidly to severe HF, with indication for mechanical circulatory support or cardiac transplant.

The treatment of PPCM during gestation is distinct due to potential adverse effects of drugs to pregnancy. However, a careful selection of beta-blockers, diuretics and vasodilators has achieved therapeutic success for the mother and the fetus. Although the treatment meets traditional guidelines developed for nonpregnant adults, the use of bromocriptine (ergot alkaloid) and cabergoline (dopamine D2 receptor agonist) has shown favorable results in ventricular recovery in patients with LVEF < 35% when treated with optimized treatment for heart failure.

Introduction

Peripartum cardiomyopathy (PPCM) is a low frequent, but potentially fatal disease, that manifests with heart failure (HF) with reduced ejection fraction (HFrEF), with no other identified cause, and related to the puerperal pregnancy cycle. So far, there is no specific biomarker for PPCM, and hence its diagnosis has been challenging, and made by exclusion, based on similarity of common symptoms at the end of pregnancy and HF symptoms. Silwa et al.¹ proposed

a diagram (Figure 1) highlighting particularities of PPCM that will be discussed in this paper.

Definition

According to the updated definition, PPCM is defined as a cardiomyopathy presenting with HFrEF $\leq 45\%$ (in some cases, a left ventricular ejection fraction between 45% and 50%), during the final month of pregnancy through the months after delivery without any other known cause of HF.²

Epidemiology

Ambiguity in the diagnosis and variability among notification standards are limiting factors for determining the epidemiology of PPCM.³ In Nigeria, for example, the incidence is estimated to be 1 in 102 deliveries, and in Japan, 1 in 15,000 deliveries. In the USA, the estimated incidence of PPCM is 1 in 938 deliveries; according to the inpatient registry, the number of patients in the age range 36 to 54 years was more than twice that of patients in the age range 15-35 years, and the prevalence of PPCM in black patients was three times higher.⁴ Advanced maternal age, African-American race, hypertensive disorders of pregnancy, and multiple pregnancies are among the main risk factors for PPCM. The most common comorbidities were arterial hypertension (36.2%), deficiency anemia (23.65), obesity (17.6%), smoking (17.2%), chronic pulmonary disease (11.8%), diabetes mellitus (6.3%), and abuse of illicit drugs (3.9%).⁵

Global registries of cohorts of patients with PPCM, such as the IPAC (Investigations of Pregnancy Associated Cardiomyopathy)⁶ and the EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology (ESC) Study Group on PPCM,⁷ have shown consistent results on the prevalence and adverse prognosis of PPCM in black people. Disparities in the incidence and prognosis of PPCM in African descendants are explained by multifactorial aspects including pathophysiological mechanisms, genetic substrate and socioeconomic conditions.^{8,9}

Risk factors

The main risk factors for the development of PPCM are hypertensive disorders of pregnancy, advanced maternal age, multifetal gestation, multiparity, *in-vitro* fertilization, and African ascendance.^{7,9} The marked association between preeclampsia and PPCM suggests a common pathophysiological mechanism. The meta-analysis by Bello et al.¹⁰ reported a prevalence of preeclampsia of 22% among women with PPCM, *i.e.*, four times the mean global estimate (5%). In the ESC registry, the prevalence of hypertensive

Keywords

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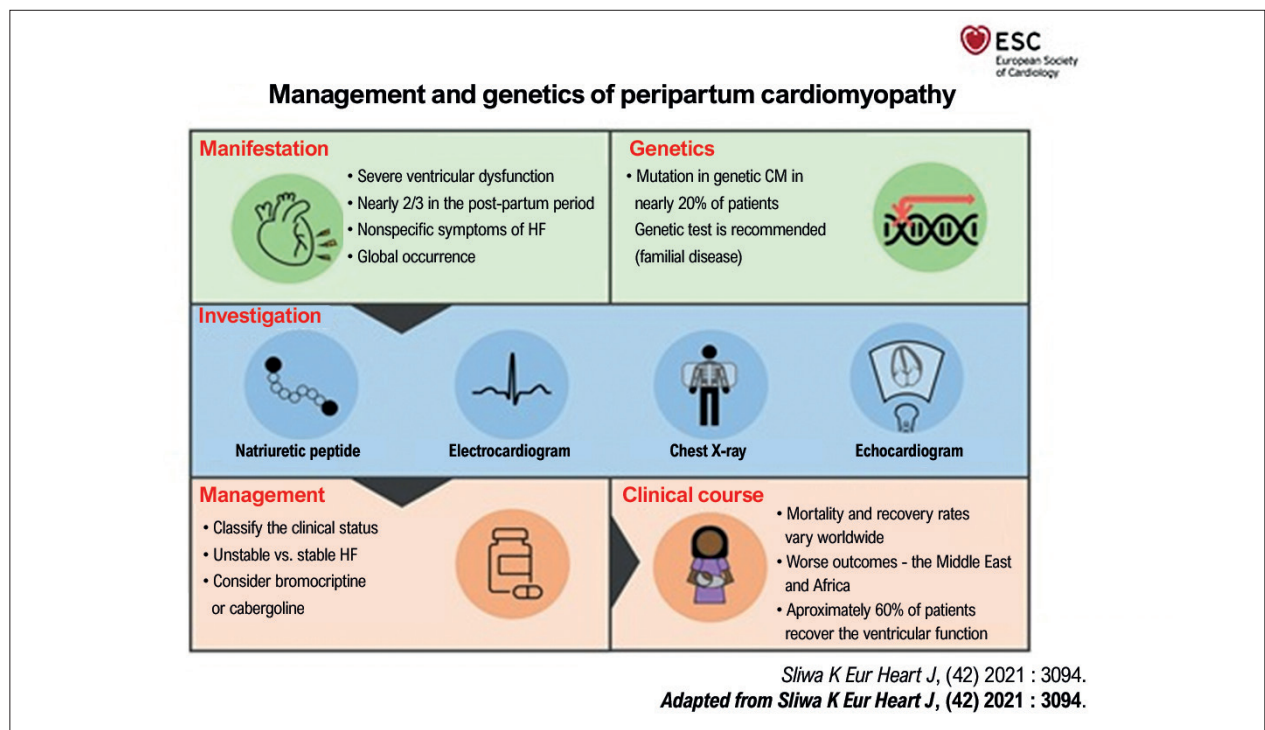


Figure 1 – Highlights of peripartum cardiomyopathy (CM); HF: heart failure.

disorders in PPCM patients was 39%, and the frequency of preeclampsia in these cases was 25%. A comparative study of three groups: (i) women without hypertension (PPCM-noHTN); (ii) women with hypertension but without preeclampsia (PPCM-HTN); (iii) women with preeclampsia (PPCM-PE) showed that women with PPCM-PE had more severe symptoms of both PE and HF, including acute lung edema. The study also showed that clinical manifestation of disease occurred predominantly during delivery and for the first 10 days thereafter. However, the PPCM-PE group showed greater likelihood of left ventricular recovery.¹¹

Genetic aspects

Precision medicine has highlighted the important role of genetics in the pathophysiology of cardiomyopathies, showing that up to 20% of women with PPCM has an identifiable variant.¹² Although PPCM is a distinct clinical entity, the overlapping with familial dilated cardiomyopathy (DCM) indicates that a subgroup of patients present the clinical and genetic spectrum of familial DCM.¹³ The genetic test applied for cardiomyopathies should be offered for PPCM patients, mainly in cases of close relatives, in attempt to anticipate disease prognosis and family screening. Women with a family history of cardiomyopathy may present symptoms of myocardial dysfunction caused by cardiocirculatory and hormonal overload in the end of pregnancy or after or in the postpartum period. In this context, a model called ‘multiple hit’ has been proposed, in which accumulation of risk factors (genetic, environmental, among others), boosted by pregnancy-related stress, lead to the development of PPCM.¹

The study by Goli et al.¹⁴ provided the first genetic and phenotypic landscape of PPCM and demonstrated that predisposition to HF is an important risk factor for PPCM. This indicates that specific genetic therapies for DCM may also be applied to PPCM. Recently, a high proportion of pathogenic variants of the titin (TTN) gene, mostly titin-truncating variants (TTNtrvs) has been identified as the key point in the pathogenesis of PPCM and also in DCM. It is believed that 15-20% of DCM patients share the same titin-truncating variants of PPCM.¹⁵

The emergence of next-generation sequencing (NGS) platforms has confirmed that truncating variants in TTN were the predominant genetic substrate in cohorts of patients with PPCM. Other rarer truncating variant (i.e., frameshift, nonsense, essential splice site) in the sarcomeric TTN and in the *FKTN*, *RBM20*, *LMNA* and *DSP* genes were found in patients with PPCM and family members with DMC. The gene *PTHLH rs258415* can affect cardiac function and predispose to PPCM, similar to the *GNB3 c.825C>T* polymorphism, particularly the homozygous TT allele, which is associated with a worse prognosis and is more prevalent in patients of African ethnicity.¹⁶

The small heat shock protein 20 (HSP20), also known as HspB6, is a class of molecular chaperones that play a protective role against cellular stress and maintenance of cellular proteostasis. Metabolic and contractile demands of the heart require protein quality control, and the HSPs play an important cardioprotective role in the regulation of cardiac response to stress, as occur in the gestational period. Recent genetic investigations have demonstrated that HSPs

are involved in the pathogenesis of PPCM, and HSPB6 mutations seem to induce the lethal form of the disease, with a nearly 100% mortality rate.¹⁷

Etiopathogenesis

The etiopathogenesis of PPCM has not been elucidated yet, and encompasses inflammatory, autoimmune and viral mechanisms, dietary selenium deficiency, excessive salt intake, and heredity.^{2,18} Inflammation and autoimmune reactions seem to have a potential to induce and promote PPCM. In this context, circulating cytokine levels, including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF α), C reactive protein (CRP) and gamma interferon γ (INF- γ) have a correlation with the severity of HF in PPCM patients.¹⁹

Recent studies have suggested that PPCM is a disease characterized by endothelial dysfunction caused by antiangiogenic agents of placenta, and by prolactin (PRL) degradation products that have two biological roles – the first as a hormone, and the second as an immune system modulator. Experimental studies with female mice in which the transcription factor STAT3 was deleted in cardiomyocytes developed PPCM. The absence of STAT3 led to increased reactive oxygen species, which, by still poorly understood mechanisms, led to the inappropriate secretion from the myocytes of peptidases, mainly cathepsin D, which in turn, cleaves PRL into a 16-KDa-PRL fragment.²⁰

The 16-KDa fragment is an antiangiogenic agent that causes apoptosis of endothelial cells induces the expression of microRNA (miR)-146a, which is in turn taken up by cardiomyocytes,²¹ leading to vascular damage and HF. This complex process occurs due to changes in the signaling and metabolism of the tyrosine kinase receptor 4 (ErbB4 or HER4).²² Circulating levels of microRNA146a are dramatically increased, and this molecule may serve not only as a biomarker but also as a therapeutic target in PPCM.^{23,24}

Inhibition of PRL release by dopamine D2-receptor (D2R) agonists, such as bromocriptine and cabergoline, has shown good results in the recovery of myocardial function in PPCM patients.²⁵⁻²⁹ Cabergoline, which has a selective agonistic effect on D2R, seem to have a dual advantage over bromocriptine, due to its higher affinity for D2R (leading to greater PRL inhibition) and a prolonged effect (14-21 days) from the initial use³⁰ (Figure 2).

Prognosis and diagnosis

The prognosis of PPCM depends on the recovery of ventricular function, which is related not only to genetic, ethnic and environmental factors, but also to early diagnosis, and immediate, optimized treatment of HF. Possible predictive variables of ventricular function recovery (or not) have been investigated, notably black ethnicity, advanced age, and echocardiographic and natriuretic peptide measurements during the acute phase of the disease (Table 1).³¹ Mortality rates in patients with PPCM have varied widely, from 7% to 50%, and been related to cardiogenic shock, thromboembolism, and arrhythmias.^{2,3}

Clinical manifestation of PPCM is not different than that of HFrEF in other cardiomyopathies, varying from mild symptoms to cardiogenic shock, which occurs in less than 5% of patients. The disease may progress rapidly to severe HF, with indication for mechanical circulatory support or cardiac transplant. More severe cases require intensive therapy in intensive care units (ICUs), and the association with PE indicates greater severity and high readmission rates with severe clinical conditions in the postpartum. The differential diagnosis from other cardiomyopathies that present with HF during pregnancy are described in Figure 3.³²

Complementary tests

The diagnosis of PPCM should follow the traditional steps consisting of personal and family history, clinical

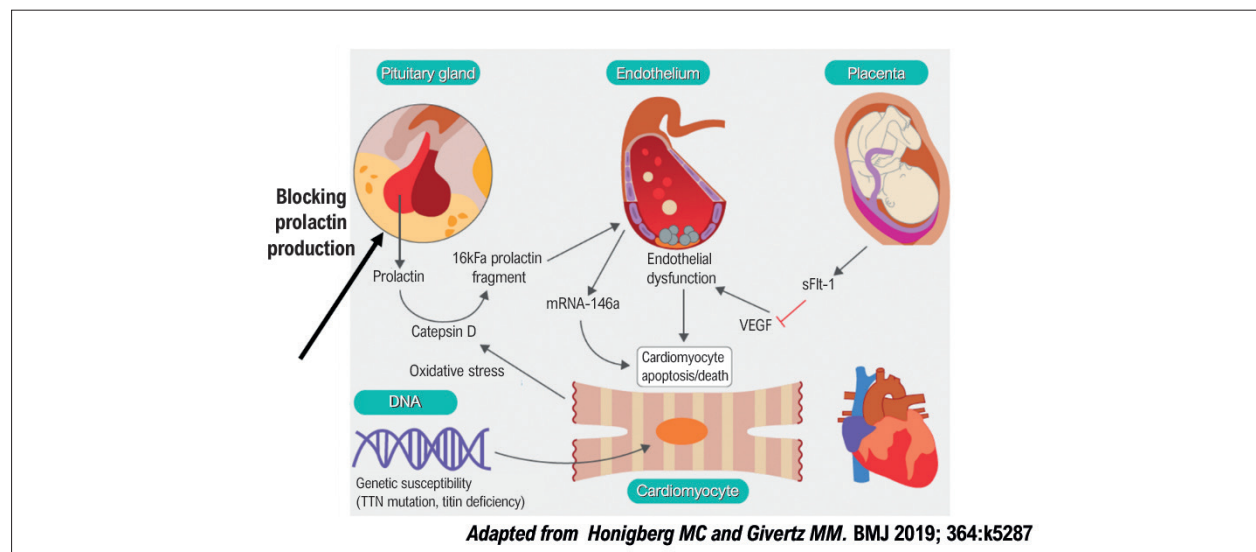


Figure 2 – Etiopathogenic mechanisms of peripartum cardiomyopathy – role of bromocriptine and cabergoline; sFlt-1: soluble fms-like tyrosine kinase-1; VEGF: vascular endothelial growth factor.

Table 1 – Analysis of predictors of left ventricular systolic dysfunction in peripartum cardiomyopathy

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
LVEF< 34%	5	2.34-10.68	<0.001	3.17	1.38-7.30	0.007
FS<16%	3.31	1.61-6.80	0.001	0.57	0.15-2.09	0.396
LVEDD>64mm	3.82	1.86-7.85	<0.001	1.394	0.586-3.316	0.452
BNP>1860 pg/mL	4.74	2.11-10.63	<0.001	2.87	1.18-6.99	0.020
CRP>21 pg/mL	1.88	0.86-4.08	0.113	0.792	0.326-1.927	0.608

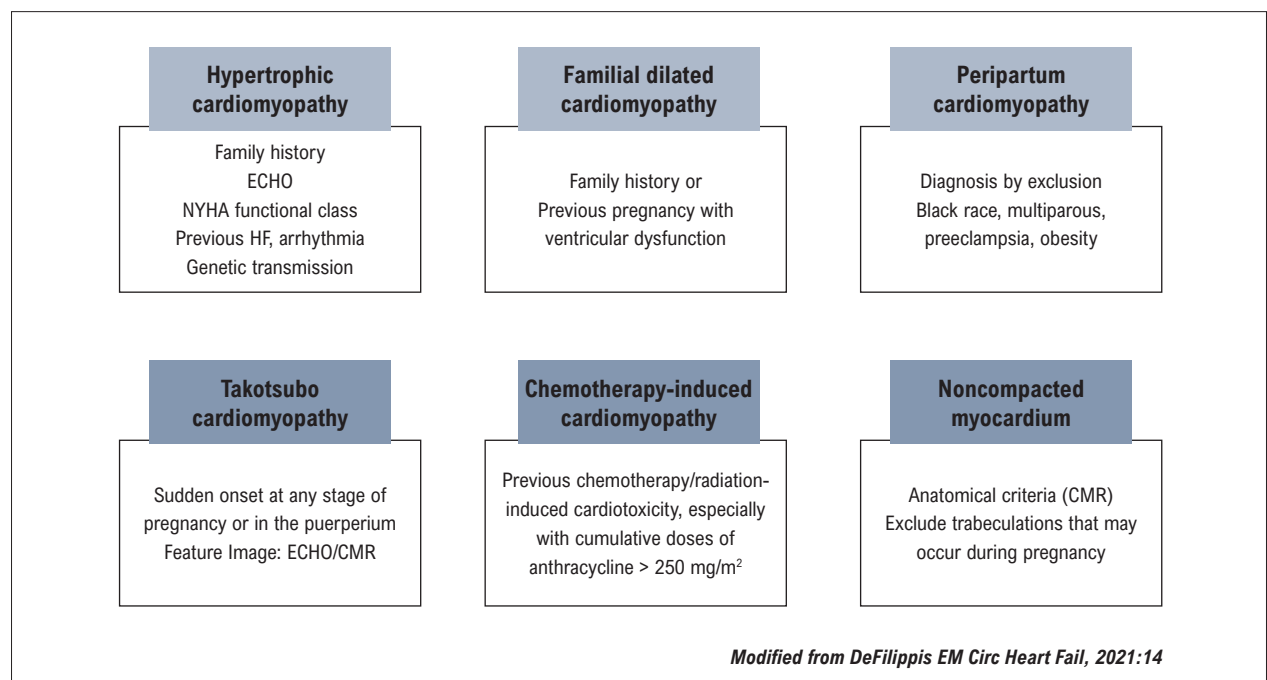
LVEF: left ventricular ejection fraction; FS: fractional shortening; LVEDD: left ventricular end-diastolic diameter; BNP: B-type natriuretic peptide; CRP: C-reactive protein. Li et al.¹

features of HF, measurement of natriuretic peptide levels – B-type natriuretic peptide (BNP), N-terminal pro-B-Type natriuretic peptide (NT-pro-BNP) – and transthoracic echocardiogram (Figure 4).³³

The electrocardiogram (ECG) is usually abnormal, with findings of sinus tachycardia, ventricular repolarization, QT interval prolongation, and left ventricular overload. The EURObservational Research Programme showed that sinus tachycardia, left ventricular hypertrophy, QRS width greater 120 ms and left bundle branch block were more common in patients with LVEF < 35% (59.0% vs. 43.8% - p = 0.005).^{34,35} Chest x-ray reveals increased heart area and/or pleural effusion and diffuse pulmonary infiltration.

Transthoracic Doppler echocardiography is the most used imaging method in the diagnosis of PPCM due to

its noninvasiveness and easy use. The test confirms the diagnosis of PPCM by systolic dysfunction with LVEF,45%, or between 45% and 50% in patients with HF of uncertain cause. Although left ventricular systolic dysfunction is the diagnostic criterion for PPCM, it has been hypothesized that LVEF may be preserved in some stages of disease.³⁶ A study on global longitudinal strain (GLS) and global circumferential strain (GCS) showed that GLS and GCS with cutoffs of 10.6% and 10.1% at presentation, respectively, were associated with unfavorable outcomes including death, heart transplantation, ventricular assist device implantation and persistent left ventricular dysfunction over 12 months after delivery.³⁷ It is worth remembering that three-dimensional echocardiography can provide additional information to the identification


Figure 3 – Differential diagnosis of cardiomyopathies. HF: heart failure; CMR: cardiac magnetic resonance imaging; ECHO: echocardiogram.

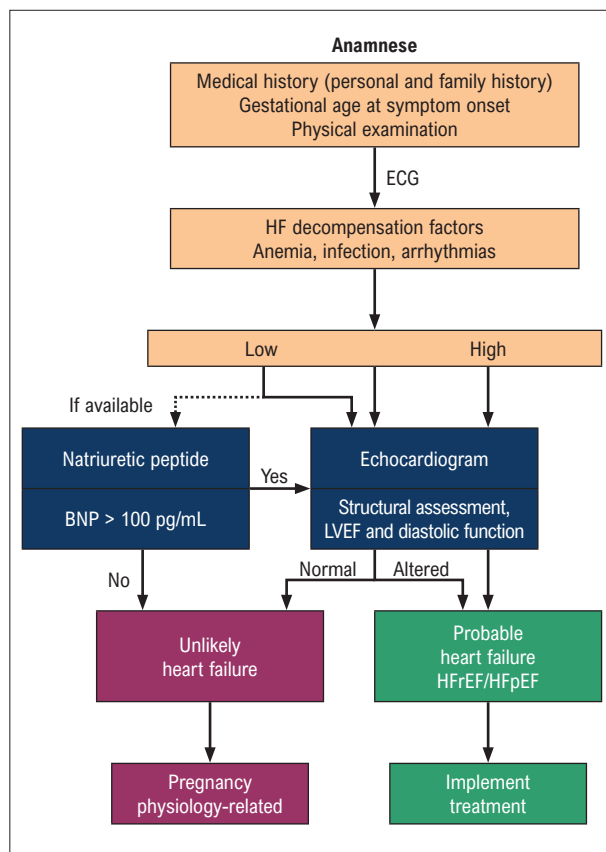


Figure 4 – Diagnostic steps in peripartum cardiomyopathy; ECG: electrocardiogram; HF: heart failure; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction. adapted from Avila et al.³³

of intracavitary thrombi in cardiac chambers.

Cardiac magnetic resonance (CMR) imaging is superior to echocardiography for cardiac detecting intracavitary thrombi, particularly in case of mural or smaller thrombi. The detection of late gadolinium enhancement by CMR has an important prognostic value in quantifying the presence and the magnitude^{38,39} of myocardial fibrosis, fundamental for the prognosis of PPCM. With respect to the other imaging tests, chest tomography plays a distinct role in the diagnosis of pulmonary thromboembolism, which is common in the puerperium.

Although there is currently no specific marker of PPCM, natriuretic peptides are an excellent laboratory resource in the diagnosis of HF in PPCM. Also, these peptides are predictive of event-free survival and FEVE recovery and hence useful in risk stratification of these patients. NT-proBNP levels are proportionally higher with the severity of HF in PPCM and considered the main predictive factors of death and readmission within one year after delivery.^{40,41}

Treatment of HF in PPCM during pregnancy

During pregnancy, the treatment of HF in PPCM differs from that of HFrEF in non-ischemic cardiomyopathies

due to the possible adverse effects to the mother and conceptus. Table 2 describes the main characteristics of medications in the treatment of HF during pregnancy and lactation.^{42,43} The β 1-selective beta blockers, bisoprolol and metoprolol, do not affect uterine activity; metoprolol succinate has an advantage over metoprolol tartrate because of the fractionated doses (25mg, 50mg and 100mg), and carvedilol, although widely used, has not been adequately studied during pregnancy. Diuretics should be used in HF and with caution due to the risk of reducing placental perfusion.

Treatment of HF in PPCM in the puerperium

The treatment of HFrEF in the postpartum meet traditional guidelines developed for nonpregnant adults. However, an important difference is the use of dopamine agonists like bromocriptine (ergot alkaloid) and cabergoline (dopamine D2 receptor agonist) that have shown favorable results in ventricular recovery in patients with LVEF < 35% when treated with optimized treatment for HF.²⁵⁻²⁹ Doses and duration of bromocriptine and cabergoline should be determined based on clinical severity and LVEF values (Table 3).^{29,43} Research groups on PPCM have suggested the inclusion of the BOARD (bromocriptine, oral HF drugs, anticoagulants, relaxants, and diuretics)⁴⁴ regimen to recommendations for treatment of acute HF in PPCM to standardize treatment and obtain more robust results and evidence of a better disease diagnosis.⁴⁵

Low-molecular-weight heparin should be indicated at prophylactic dose for patients with severe systolic dysfunction, treated or not with dopamine agonists. The combination of reduced LVEF, prothrombotic activity in the end of pregnancy and puerperium, and the use of bromocriptine/cabergoline leads to a very high risk of thromboembolism, which is considered one of the main causes of death in PPCM. In Brazil, cabergoline was registered and approved by ANVISA, and was included in the periodic review of the Ministry of Health clinical protocols and therapeutic guidelines and covered by the Brazilian unified health system since October 2020.

In summary, the management of PPCM patients under optimized treatment for HF should consider: 1) Serial Doppler echocardiography every six months; 2) if recovery of left ventricular function, discontinuation of diuretics and continuation of HF drug therapy – beta-blocker, angiotensin converting enzyme inhibitor (ACEI); angiotensin receptor blocker (ARB), and spironolactone in the following six months; 3) discontinuation of spironolactone in six to 12 months of treatment, and continuation of beta-blocker, ACEI/ARB; 4) gradual reduction until permanent discontinuation of ACEI/ARB after 12 months and maintenance of beta-blocker in the following six months; 5) consider discontinuation of beta-blocker beyond the 18 month-period of treatment if ventricular function recovery is confirmed by transthoracic echocardiography and CMR.

Table 2 – Pharmacotherapy for heart failure in pregnancy and lactation – peripartum cardiomyopathy

Drug	Use during pregnancy	Possible adverse effects	Use during lactation
Loop diuretics (furosemide)	Allowed	Hypovolemia and maternal hypotension; uterine hypoperfusion	Allowed (when in excess, it may reduce milk supply)
Betablockers (β 1-selective), Bisoprolol, carvedilol, and metoprol	Not allowed	Bradycardia and/or hypoglycemia (dose dependent)	Allowed
ACEIs and ARBs	Not allowed	Renal agenesis, oligoamnion, malformation fetal loss	Allowed (captopril, enalapril)
Mineralocorticoid receptor antagonists	Not allowed	Feminization of male fetus	Allowed
Sacubitril-valsartan	Not allowed	Similar to ACEIs and ARBs	Unknown
Hydralazine/nitrates	Allowed	Uteroplacental hypoperfusion	Allowed
Ivabradine	Not allowed	Unknown	Unknown
Digoxin	Allowed	Low birthweight	Allowed
Heparin (UFH and LMWH)	Allowed	Do not cross the placental barrier	Allowed
Warfarin	Avoid – teratogenic risk	Warfarin embryopathy (skeletal abnormalities intracranial hemorrhage, spontaneous abortion, fetal losses)	Allowed
DOACs (rivaroxaban, apixaban, edoxaban, dabigatran)	Not allowed	Limited data; possible malformations, intrauterine growth restriction	Unknown

ACEIs: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; UFH: unfractionated heparin; LMWH: low-molecular-weight heparin; DOACs: direct oral anticoagulants. Ávila et al.³³ e Halpern et al.⁴²

Table 3 – Bromocriptine and cabergoline regimen in the treatment of acute heart failure in peripartum cardiomyopathy

LVEF $\geq$ 25%, without cardiogenic shock, without ICU treatment	➡	Bromocriptine 2.5mg/day ➡ 7 days Or Cabergoline 1 mg	At least, prophylactic anticoagulation
LVEF < 25%, and/or RV dysfunction and/or cardiogenic shock and/or ICU treatment	➡	Bromocriptine 2.5mg/2x day ➡ 14 days Followed by 2,5mg/day ➡ 42 days Or Cabergoline 1 mg/week ➡ 2 weeks Followed by 0.5mg/week ➡ 6 weeks	At least, prophylactic anticoagulation
ICU treatment, cardiogenic shock with invasive ventilation and/or MCS	➡	Bromocriptine 2.5mg/2x day, progressively increase to 10-20mg/day Or Cabergoline 1 mg/week - 4.5mg/week ➡ Until prolactin suppression	At least, prophylactic anticoagulation

Koenig T. et al. Card Fail Rev. 2018; 46. Pfeffer TJ. ESC Heart Fail. 2023; 465. LVEF: left ventricular ejection fraction; ICU: intensive care unit, RV: right ventricular; MCS: mechanical circulatory support.

Treatment of acute HF in PPCM

Respiratory assistance and ventricular assist device should be employed as soon as the diagnosis of cardiogenic shock is confirmed, and an emergency cesarean section should be considered. The objective is to restore hemodynamic conditions as early as possible to prevent irreversible

damage to the mother and fetus. Pregnant women should be monitored in ICUs and followed according to the ESC protocol^{46,47} (Figure 5).

The following recommendations must be considered:
 1) keep oxygen saturation $\geq$ 95%; if necessary, noninvasive

ventilation with final positive expiratory pressure of 5 – 7.5 cmH₂O; 2) intravenous diuretic in pulmonary congestion; intravenous nitroglycerin at doses from 10-20 to 200 µg / min when systolic arterial pressure > 110 mmHg; 4) use of inotropic agents (dobutamine and levosimendan) in cases of low cardiac output (hypoperfusion, vasoconstriction, acidosis, renal failure, liver dysfunction, and sensorial impairment), and persistent pulmonary congestion despite administration of vasodilators and/or diuretics. Mechanical circulatory support devices should be early considered as a rescue therapy for patients that persist with hemodynamic instability and, in many cases, as temporary support for left ventricular assist device implantation (HeartMate) or cardiac transplantation.⁴⁸

Obstetric care in PPCM

In general, the choice of delivery type depends on obstetric indication. However, cesarean delivery should be considered in severe cases only, for unstable patients or with cardiogenic shock. Vaginal delivery is the preferred type in uncomplicated cases, clinically stable patients, and without fetal compromise. Most anesthesiologists prefer general anesthesia due to important pre- and post-load variations consequent to the type of blockage (peripheral, epidural or combined).³⁸

Contraception of PPCM women with or without ventricular function should be effective, well accepted, and with no thromboembolic risk. In this regard, contraception prescription should be based on the World Health Organization eligibility criteria, which consider progestogen as the most appropriate contraceptive in PPCM patients (Table 6).

Subsequent pregnancy of patients with PPCM

The elucidation about genotype-phenotype associations and possible epigenetic alterations implies the implementation of genetic counseling. However, studies are needed to clarify the role of genetic variants identified in the context of PPCM. Left ventricular function seems to be determinant of progression and prognosis for a “new” gestation in women with history of PPCM.⁴⁹⁻⁵¹ Figure 6 presents a brief proposal of reproductive counseling in family planning of PPCM women and risk stratification for a “new” pregnancy.

Final considerations

PPCM is a not a common disease but has intriguing features. Points that should be considered essential are the prompt diagnosis of the disease, provide optimized

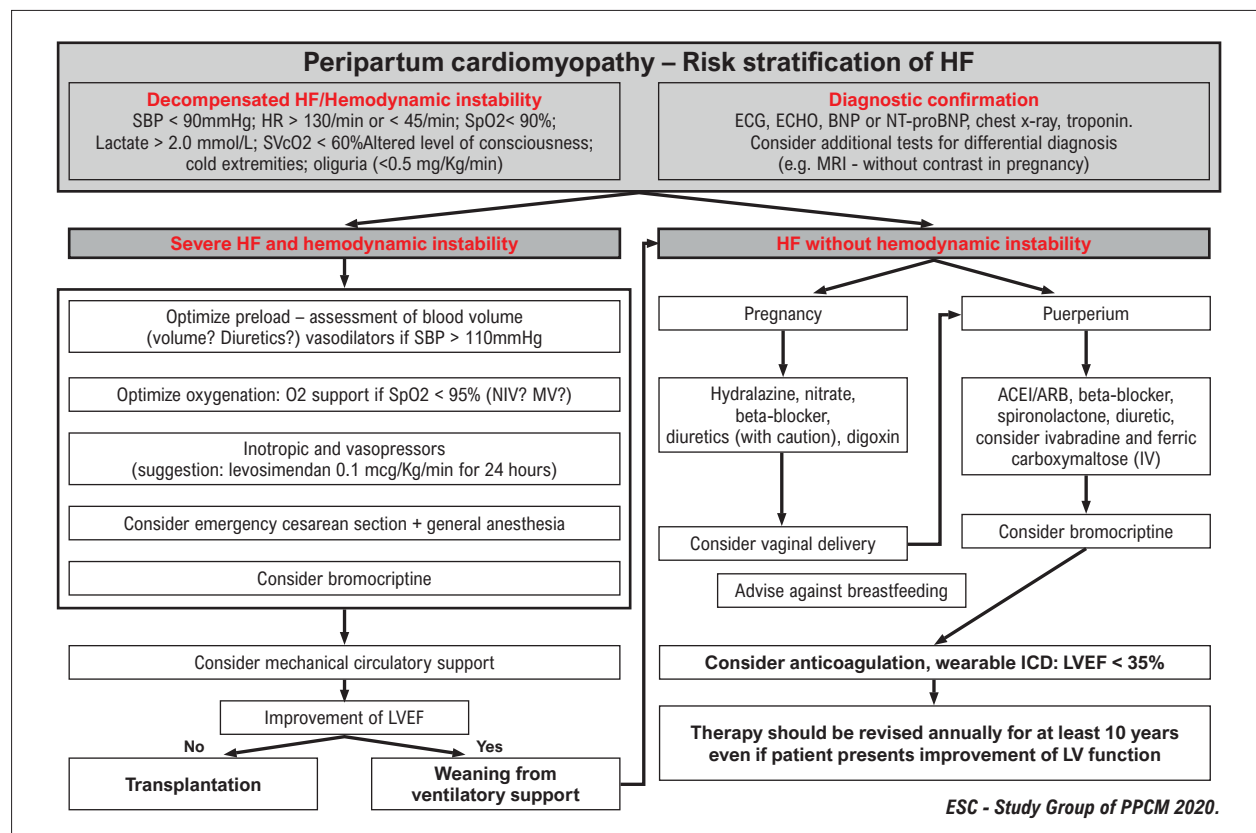


Figure 5 – Peripartum cardiomyopathy – risk stratification of heart failure. SBP: systolic blood pressure; HF: heart failure; SpO₂: oxygen saturation; ScvO₂: central venous oxygen saturation; HR: heart rate; LVEF: left ventricular ejection fraction; MV: mechanical ventilation; ICD: implantable cardioverter-defibrillator; ECG: electrocardiography; ECHO: echocardiography, BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-Type natriuretic peptide; MRI: magnetic resonance imaging; IV: intravenous.

Table 4 – Contraceptive options in peripartum cardiomyopathy

Progestogens alone – failure < 1% WHO eligibility criteria – Categories 1 and 2 Cardiovascular disease
Progestogen-only pill (POP) Desogestrel 75 mcg - Cerazette® norethindrone acetate 0.35mg - Micronor® - indicated during lactation
Injectable every three months Medroxyprogesterone acetate - 150 mg - Depoprovera® Contracep®
Transdermal implant Implanon® - Etonogestrel 68 mg – 3 years
Intrauterine devices - Levonorgestrel-releasing intrauterine system (LNg-IUS) Mirena® (52mg/20mcg) or Kyllena® (19.5mg) – 5 years

WHO: World Health Organization. Avila et al.³³

treatment as early as possible, and a strict long-term follow-up focusing on cardiac function preservation and recovery in a young, previously healthy woman.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Ávila WS, Carvalho RCM.

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Ethics approval and consent to participate

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

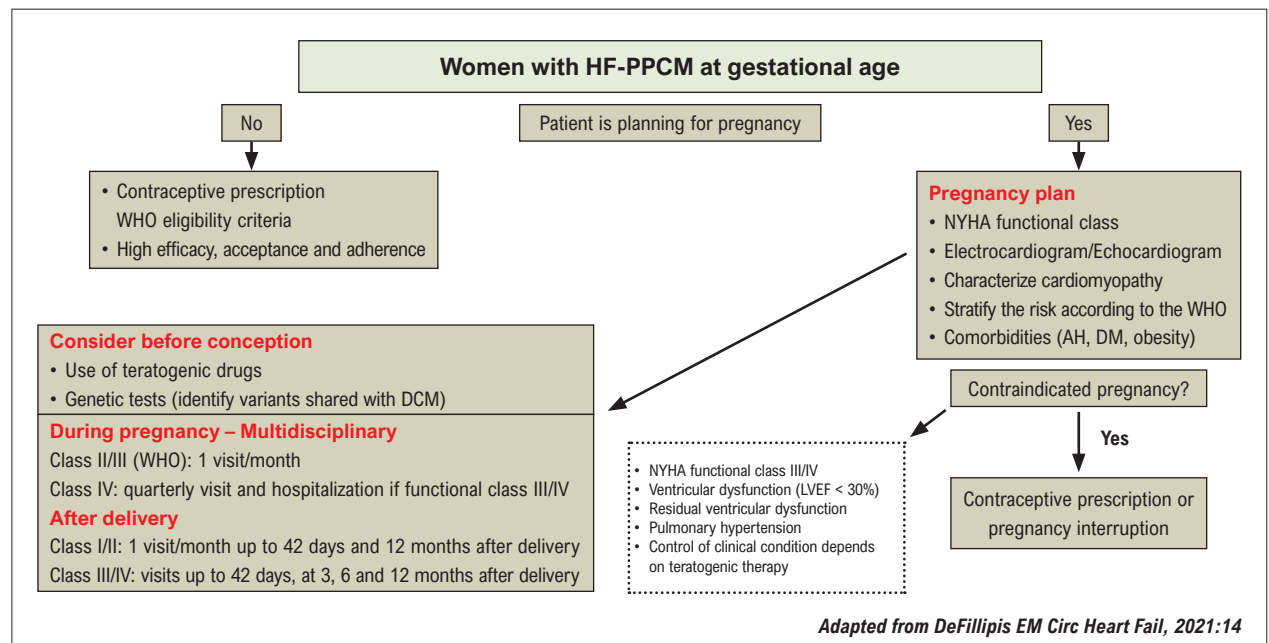


Figure 6 – Family planning – risk assessment – pregnancy and contraception. WHO: World Health Organization; AH: arterial hypertension; DM: gestational diabetes; CMD: cardiomyopathy; LVEF: left ventricular ejection fraction; HF: heart failure; PPCM: peripartum cardiomyopathy. DeFillippis et al.³²

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