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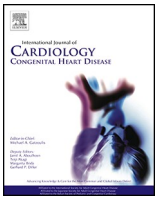

Diagnosis and management of peripartum cardiomyopathy and recurrence risk

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ABSTRACT

Peripartum cardiomyopathy (PPCM) is a rare, but serious condition, with a non-negligible risk of adverse events. Several risk factors for PPCM have been individuated over the years, including Afro-American ethnicity, pre-eclampsia, advanced maternal age, genetic predisposition, multiparity, twin pregnancy, obesity, smoking and diabetes. However, PPCM pathophysiology is still poorly understood, thus making it challenging to develop disease specific therapies. At present, Bromocriptine is the only targeted drug, but further evidence is needed to establish indication and timing of administration. Therefore, these patients are mainly treated following general heart failure guidelines. Even though in most patients left ventricular ejection fraction recovers during follow-up, cases of persistent left ventricular dysfunction are not uncommon. Moreover, all patients detain a certain risk of recurrence after subsequent pregnancies, which is difficult to estimate due to the dearth of long-term prospective data.

In this manuscript, we aim to provide an updated review of current evidence about PPCM pathophysiology, diagnosis, treatment and recurrence risk. In addition, we discuss the gaps in knowledge that should be addressed by future research.

1. Background: Epidemiology, risk factors, pathophysiology

Peripartum cardiomyopathy (PPCM) is a form of heart failure (HF) defined as new onset of left ventricular ejection fraction (LVEF) reduction (<45 %) occurring towards the end of pregnancy or in the months after delivery in the absence of other identifiable causes of HF or recognizable pre-existing structural heart disease [1]. According to the initial definition, the PPCM onset period ranged from the last month of pregnancy to the 5th month postpartum [2]. Nonetheless, the documentation of similar cases presenting before or after this timeframe [3,4] has led to broaden the definition, which is now time-independent.

The global estimated incidence of PPCM is around 1 every 2000 deliveries [5], with wide regional differences ranging from 1 in 100 births in Nigeria [6] to 1 in 20,000 in Japan [7]. In Western Countries, reported incidence is between 1 in 1000 and 1 in 5000 [8–10], significantly higher in women of African ancestry than in Caucasians [11]. In fact, state-wide studies conducted in the United States reported that African Americans are 3–16 times more likely to develop the disease in comparison to white women, probably due to polygenic predisposition [11,12].

Other than ethnicity, several other risk factors for PPCM have been detected over the last few decades (Graphical Abstract). Patients with gestational hypertension or pre-eclampsia present a three-fold increased risk of PPCM [10]. Furthermore, a recent meta-analysis of 22 studies with 979 cases of PPCM reported that preeclampsia was present in 22 % and other hypertensive disorders in 97 % [13].

Multiple gestations are strongly associated with PPCM, being reported in 7 %–14.5 % of cases [10,13]. Advanced maternal age is

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another relevant risk factor for PPCM, more likely from 30 years of age onwards, independently from the presence of age-associated comorbidities, including hypertension [10]. In addition, a study by at Kolte et al. showed a 10-fold increased risk in women over 40 in comparison to those under 20 [8]. The recent rise of medium maternal age has been considered one of the possible explanations to the continuing PPCM uptrend rate during the last few decades [14].

Other conditions deemed to be predisposing to PPCM are multiparity, twin pregnancy, obesity, smoke, diabetes, anaemia, asthma, malnutrition and prolonged tocolytic therapy [10,13,15–20].

Even though a growing body of research has led to greater knowledge and awareness of this condition, PPCM pathophysiology still remains not fully understood, but it is almost certainly multifactorial.

Pregnancy-related hemodynamic stress has been the first proposed mechanism. However, the main circulatory changes occur during the second trimester, whereas PPCM mostly manifests itself after delivery [10]. Studies conducted in rodent models have suggested a possible role of prolactin-induced vascular dysfunction [21]. This hypothesis is also endorsed by the typical hematic increase in women with PPCM of the soluble fms-like tyrosine kinase 1, an antagonist of the vascular endothelial growth factor, secreted by the placenta during the last months of pregnancy and proved to lead to PPCM in mice [22]. This molecule is also elevated in preeclampsia and multiple gestations, thus partially explaining the association between these conditions and PPCM [16]. Conversely, secretion of relaxin-2, a pregnancy-associated vasculoprotective hormone, is suppressed in PPCM [23]. The fact that all pregnant women undergo similar hemodynamic and hormonal changes but very few of them develop PPCM, suggests that genetic predisposition could be particularly important. Heterozygous loss-of-function genetic variants in one of several genes associated with nonischaemic dilated cardiomyopathy have been encountered in almost 15 % of PPCM cases [24]. In fact, pregnancy and partum have been recognised as potential triggers fostering the overt manifestation of a genetic cardiomyopathy [24,25]. Interestingly, a genome-wide association study also highlighted polymorphisms in regions supposed to regulate vascular homeostasis [26]. However, genetic anomalies are not detected in the majority of cases, suggesting that either most of them have not been detected yet or that epigenetic and environmental factors strongly contribute to disease onset. Among these, the possible role of viral infections has been described [25,27].

2. Clinical presentation and diagnosis

Women with PPCM typically present with symptoms and signs of heart failure, including fatigue, dyspnoea, orthopnoea, nocturnal paroxysmal dyspnoea, chest tightness, tachycardia, tachypnoea, elevated jugular venous pressure, and pulmonary oedema [16]. In some cases, PPCM onset may be confused with expected pregnancy-related symptoms, thus delaying the diagnosis with negative prognostic implications [28]. Rarely, PPCM presents with cardiogenic shock, arrhythmias or thromboembolic events [29].

Noteworthy, PPCM is adiagnosis of exclusion, which should be considered when a new LVEF <45 % is identified in pregnant women during the peri-partum period in the absence of structural heart disease [16] (Fig. 1). LV dilation is usually present, but is not a diagnostic criterion, as a certain degree of cardiac chambers enlargement may be a physiological adaptation to pregnancy [16]. Differential diagnoses that should be explored include pre-existing structural heart disease, pulmonary embolism, preeclampsia-induced pulmonary oedema without LV dysfunction, spontaneous coronary artery dissection, myocarditis, Takotsubo syndrome, myocardial infarction, aortic dissection with acute aortic regurgitation, alcohol abuse and chemotherapeutic agents [25].

Electrocardiography (ECG) may show non-specific abnormalities, including sinus tachycardia and ST segment alterations [5]. However, it is important to underline that a normal ECG does not exclude PPCM and that some ECG changes may be detected also in uncomplicated pregnancies, such as left axis deviation, transient ST/T abnormalities, inverted T waves in the anterior leads and Q waves in the inferior leads [16]. Conversely, ECG may be particularly useful to rule out ST segment elevation myocardial infarction.

Serum brain natriuretic peptide and its N-terminal portion are usually elevated in PPCM [30], while their levels are typically normal

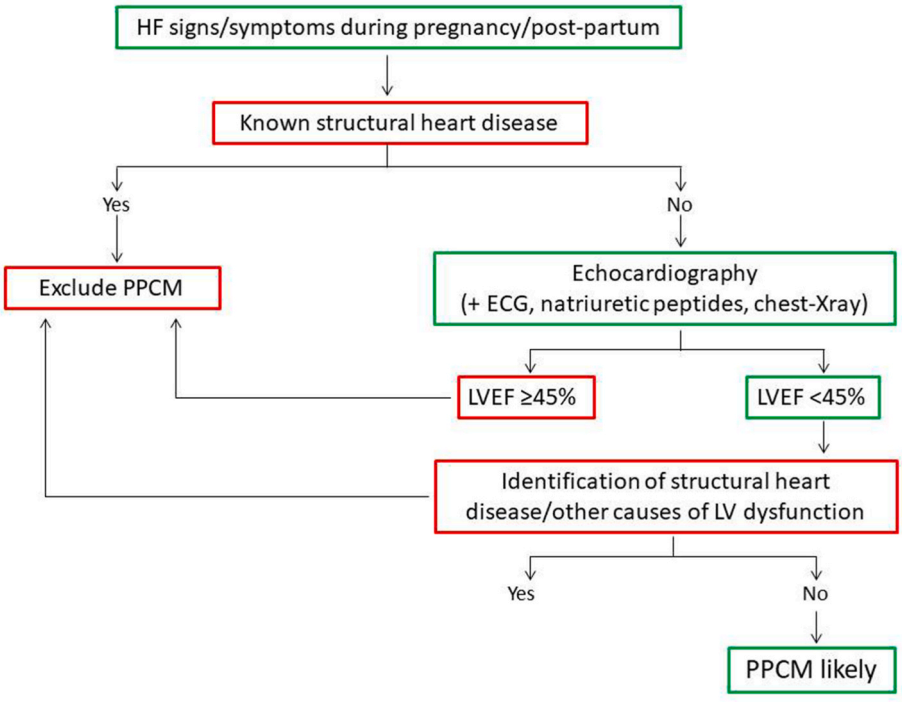

Fig. 1. Legend: Flow chart of peripartum cardiomyopathy diagnosis. Abbreviations: ECG: electrocardiography; LVEF: left ventricular ejection fraction; HF: heart failure; PPCM: peripartum cardiomyopathy.

during pregnancy or only slightly elevated in case of pre-eclampsia. Even cardiac troponin may be increased in PPCM, with persistently high levels been associated with poorer outcomes [31]. The possible diagnostic and prognostic role of additional biomarkers, such as soluble fms-like tyrosine kinase 1 [23] and specific micro-ribonucleic acids [32], need further investigation [33].

PPCM diagnosis is usually performed by means of echocardiography [16], which allows not only to assess the degree of LV dysfunction, but also to explore right ventricle (RV) involvement, cardiac chambers dimensions, functional mitral or tricuspid regurgitation, and to rule out LV apical thrombosis, which should always be excluded in case of severe LVEF reduction.

Cardiac magnetic resonance can be considered in case of suboptimal echocardiographic windows, but gadolinium administration is not advised in pregnancy [16] andshould be considered in the post-partum period.

Imaging modalities using ionizing radiations should be avoided during gestation, unless deemed essential. Even though the risks for the fetus are reduced in the third trimester when PPCM typically occurs, ionizing radiation levels should be kept “as low as reasonably achievable” [16]. Chest X-ray may be useful to assess the degree of pulmonary congestion, even though lung ultrasound should always be preferred when possible. Computed tomography could be necessary to rule out specific differential diagnoses, including pulmonary embolism and aortic dissection [25].

Endomyocardial biopsy is not required in the vast majority of cases [16], and may be considered only when other pathologies requiring a completely different management are highly suspected, such as giant cell myocarditis.

3. Acute phase management

PPCM clinical presentation is extremely variable. The European Society of Cardiology Study group on PPCM described three possible clinical scenarios [33]: i) mild PPCM, characterised by subacute HF and hemodynamic stability, LVEF 30–45 %; ii) moderate PPCM, with overt HF symptoms but preserved hemodynamic stability, LVEF 20–35 %; iii) severe PPCM, with cardiogenic shock, hemodynamic instability and respiratory failure, LVEF <20 %. PPCM therapeutic management according to disease severity is summarised in Fig. 2.

Patients with mild PPCM do not require admission in intensive care and, in selected cases, follow up in dedicated outpatient clinics may be considered [33]. Oral HF drugs may be useful, in particular beta-blockers as they are effective and safe in pregnancy [33]. In contrast, antagonists of the renin-angiotensin-aldosterone axis are not recommended during gestation due to their teratogenic potential [34]. In their place, the combination of hydralazine-nitrate should be considered during pregnancy [16]. Oral diuretics may be useful for symptom relief in case of pulmonary congestion [35]. Vaginal delivery is advised in the absence of obstetric contraindications and there should be no restrictions to lactation [33].

Patients with moderate and severe PPCM require hospital admission, respectively in HF and intensive care units [33]. Acute phase management should be conducted according to the guidelines for acute HF(35). The possible teratogenic effects of inotropes and vasopressors in humans are still largely unknown, but this should not halt their use when needed. If intravenous vasodilators are required, nitroglycerine should be preferred over nitroprusside for the possible cyanide toxicity [36].

Patients with PPCM seem to be particularly prone to the side effects of beta-adrenergic stimulation, therefore drugs like dobutamine should be avoided [37]. In case inotropic support is required, norepinephrine is the preferred option. Recent small studies have demonstrated that

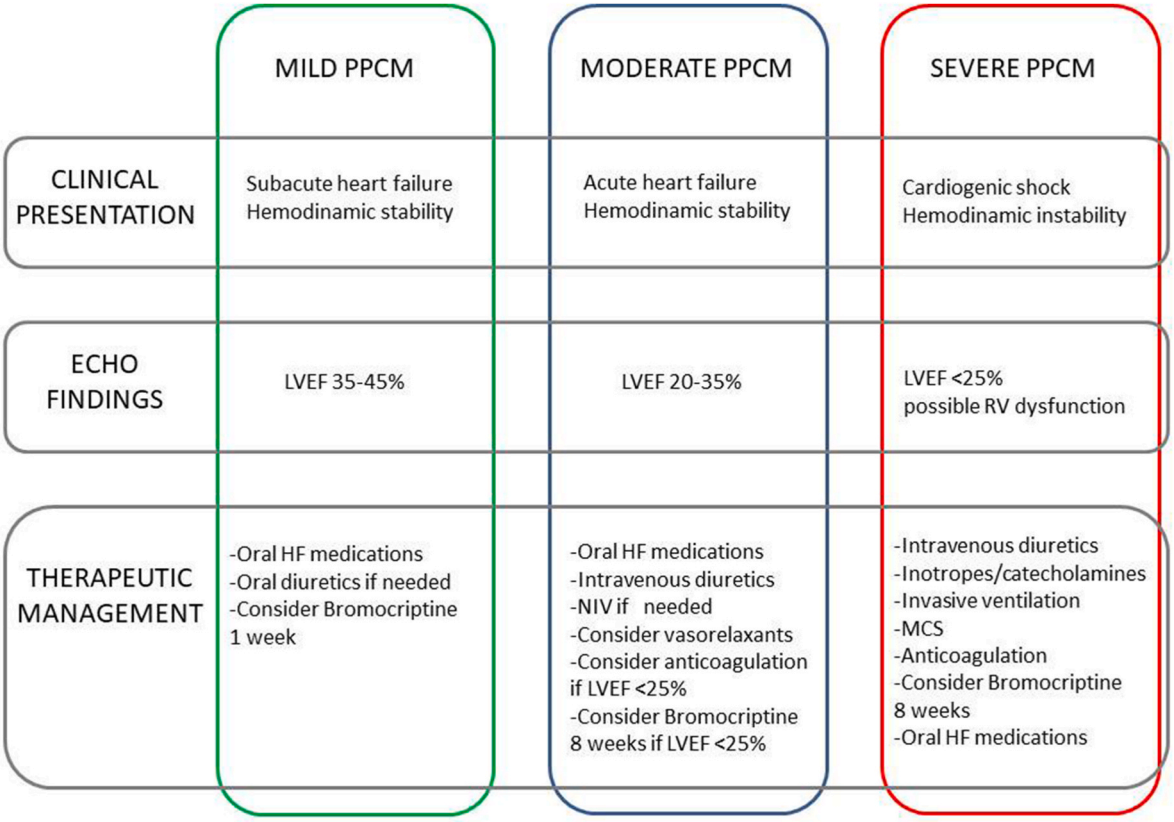

Fig. 2. Legend: Peripartum cardiomyopathy management according to disease severity. Abbreviations: LVEF: left ventricular ejection fraction; HF: heart failure; MCS: mechanical circulatory support; NIV: non-invasive ventilation; PPCM: peripartum cardiomyopathy.

levosimendan, however safe, did not provide substantial benefits [38], but stronger data from larger trials are warranted. Due to the poor tolerance to beta-adrenergic agents in PPCM, in case of inotrope-dependent HF mechanical circulatory support may be considered with a lower threshold than in similar cases due to the different pathology [33]. Long-term support with left or biventricular assist devices are required in up to 7 % of PPCM [29] and may be used as a bridge to recovery or to transplantation. As LV function improvement may occur after several months from symptom onset and heart transplantation in PPCM has worse outcomes than in HF of other aetiologies, organ transplantation should be delayed as much as possible [33]. Similarly, the possibility of a late recovery should be considered when evaluating an implantable cardioverter device placement. However, considering the increased risk of cardiac arrest during the months following PPCM diagnosis [39], wearable cardioverters/defibrillators may be considered in selected cases as bridge to recovery or definite indication to intracardiac/subcutaneous device implantation [33]. In case of hemodynamic instability despite optimal therapy, early delivery or pregnancy termination if prior to fetal viability should be performed. The option of therapeutic abortion may also offered to selected patients with severe PPCM without hemodynamic instability and discussed together with their family.

As pregnancy is a pro-thrombotic condition, patients with PPCM and severe LVEF are at increased risk of apical thrombosis. Therefore, current European [16] and American guidelines [40]suggest anticoagulation in case of LVEF $<$35 % or $<$30 %, respectively, even in absence of other indications. As anticoagulation strategy, low-molecular-weight heparin subcutaneous administration is preferred during pregnancy as it does not cross as opposite to warfarin, which may be considered only during the second trimester in patients with mechanical heart valves. During lactation, both low-molecular-weight heparin and warfarin may be used. In opposite, direct oral anticoagulants are contraindicated both during pregnancy and breastfeeding due to the absence of safety studies. In patients requiring mechanical circulatory support, unfractioned heparin is recommended with careful activated partial thromboplastin time monitoring.

Vaginal delivery is preferred in case of hemodynamic stability provided epidural anaesthesia is administered to avoid sudden blood pressure increase [33]. In case of hemodynamic instability, emergency caesarean section should be performed [33].

Post-partum major hemodynamic changes occur and must be carefully monitored especially in patients with PPCM. For instance, the removal of caval compression by the fetus and the autotransfusion due to uterine contractions can on one hand improve cardiac output due to increase in venous return, but on the other may cause fluid overload and pulmonary oedema.

Breastfeeding is deemed safe in patients with mild and moderate PPCM(33), even though the available data are limited. As regards patients with severe PPCM, preventing lactation may be considered due to breastfeading-related high metabolic demands. However, decisions about whether to inhibit or continue lactation should be taken carefully jointly with the patient on a case-by-case basis [33].

Bromocriptine, a drug inhibiting prolactin secretion, is the only targeted therapy available at present for PPCM. However, due to the dearth of evidence from randomised trials, indication to its use is not particularly strong. In moderate and severe PPCM, bromocriptine 2.5 mg twice daily administration should be considered for 8 weeks according to European guidelines [16] and may be considered according to the American ones [40]. In mild cases, the same therapeutic scheme may be considered for one week [33]. The main concern regarding bromocriptine is its prothrombotic effect, which makes the association with at least prophylactic anticoagulation necessary [41]. In addition, bromocriptine suppresses lactation, therefore, the potential benefits of this drug should be weighed against the well-known favourable effects of breastfeeding for both the mother and the child.

As recently suggested [33], the acronym “BOARD” encloses the main pharmacological therapies that should be specifically considered in PPCM according to disease severity, namely Bromocriptine, Oral HF drugs, Anticoagulants, intravenous venous Relaxants and Diuretics. As regards novel HF drugs, including sacubitril/valsartan and sodium-glucose cotransporter 2 inhibitors, there is a dearth of studies assessing their pros and cons in this peculiar clinical setting.

4. Long term management and prognosis

Out of the acute phase, PPCM patients may require chronic HF treatment [35]. Most of conventional HF medications are safe during breastfeeding [36]. As mentioned above, safety data about novel HF therapies are still insufficient, but their use after delivery is increasing.

Patients with persistent LV dysfunction require life-long medical therapy [33]. In the absence of congestive symptoms, diuretics can be stopped; concerning patients with recovered LV function (LVEF $\geq$50 %), the indications are less clear. There is evidence that a subtle LV longitudinal dysfunction persists in this subgroup and cases of further LVEF impairment over time have been reported, even without subsequent pregnancies [42]. If HF medications discontinuation is contemplated, careful de-escalation rather than abrupt interruption should be employed [33]. Close clinical and echocardiographic follow-up is clinically necessary. LVEF recovers in most cases (~76 %) [10], generally within the first 6 months after delivery [29], even though later improvement is possible [43]. Of note, pre-eclampsia is associated with a higher likelihood of LVEF normalisation [10,13], but also with lower 1-year survival [13]. Recently, Jackson et al. elaborated a registry aimed to predict recovery likelihood [44], including baseline LVEF, baseline LV end-diastolic diameter, human development index, duration of symptoms, QRS duration and pre-eclampsia; however promising, external validation is needed [44].

Among Afro-American women, recovery rates are markedly lower (~45 %) [45] and mortality is higher than in other ethnicities, reported in up to 11 % of cases in a population composed of 96 % Afro-Americans [46] vs 4 % in a study group with less significant racial differences [29]. Overall, the risk of mortality and re-hospitalisation is 12-times and 3-times higher in patients with PPCM than in controls [10]. In addition, children born to women with PPCM have a 5-fold increase in mortality rates and a 3-times higher incidence of cardiac disease at long-term follow up as compared to off-springs with healthy mothers [10].

5. Recurrence risk and maternal counselling for future pregnancies

The most complex task for cardiologists when assessing patients with PPCM is, probably, to provide adequate counsel about the individual patient risk of subsequent pregnancies (SSPs). In general, there is a relapse risk for all cases, albeit variable. PPCM relapse has been variously defined either as a decrease of LVEF $<$45 % in patients with LVEF $>$50 % or an absolute decrease in LVEF by $>$10 % in patients with LVEF $<$50 % [47] or an absolute decrease by $>$20 % independent of baseline LVEF [48]. In addition, adverse cardiovascular events are not rare in these patients. However, short- and long-term outcomes are still largely unknown due to limited prospective data. The majority of evidence, indeed, comes from retrospective observational studies, which often lack in data (i.e. LVEF of index pregnancy, cardiac dimensions, left and right ventricular function at onset of the SSP, etc.) and have a small sample sizes, hence it is not possible to draw a definitive conclusions. However, as many women are young at the time of index PPCM, and likely to desire more children it is paramount to provide them and their partner with as much information as possible to help them make conscious decisions. Patient education and involvement in this setting is key [49,50], as well as the provision of dedicated multidisciplinary team to provide all support necessary and minimise risks of SSP(49).

Several factors contribute to PPCM relapse (Graphical Abstract) (Table 1). Current data suggest that pre-pregnancy LVEF is the strongest

Table 1
Studies evaluating outcomes of patients with peripartum cardiomyopathy following subsequent pregnancies.

First author	Year	Patientsnumber	Post-index pregnancy LVEF		Reduced LVEF post-SSP		Maternal adverse events		Miscarriage/Fetal adverse events	
			Recovered	Unrecovered	Total	Unrecovered	Total	Unrecovered	Total	Unrecovered
Pachariyanon[55]	2023	45	30	15	13	7	13	7	9	6
Elkayam[56]	2001	44	28	16	–	–	13	7	–	–
Goland[59]	2022	34	23	11	4	3	NA	NA	–	–
Fett[60]	2010	61	35	26	18	12	–	–	–	–
Codsi[61]	2018	25	24	1	5	1	NA	NA	20	–
Hilfiker-Kleiner[62]	2017	34	18	16	19	11	4	4	4	–
Yaméogo[63]	2018	29	13	16	–	–	14	9	14	–

Abbreviation: LVEF: left ventricular ejection fraction.

known predictor of outcome in PPCM patients having SSPs. In fact, the vast majority of studies report worst maternal and fetal prognosis in case of persistently reduced LVEF. Of note, as the cut-off for defining LV systolic function recovery in PPCM patients who desire SSPs is not strict, some studies have considered as recovered LVEF ≥55 % and others ≥50 %. Therefore, results coming from different groups may be difficult to compare.

Goland et al. [51] prospectively enrolled 45 PPCM who had SSPs and defined LVEF as recovered when ≥55 %. A slight reduction in LVEF was recorded in most patients, mainly occurring in the third trimester and more prominent in patients with LVEF <55 % prior to SSP. In patients with LVEF ≥55 %, mean LVEF was mildly reduced but remained within normal range. A relapse was observed in the 25 % of women with pre-pregnancy LVEF <55 %, but no death occurred.

Fett et al. [52] described relapses of PPCM in 29 % of cases, with a significantly higher rate (46 %) in women with LVEF <55 % compared to 17 % in women with LVEF ≥55 %.

Codsi et al. [53]reported a PPCM relapse rate of 21 % after a SSP in a group of 25 PPCM patients, of which only one had recovered LV systolic function (defined as LVEF ≥50 %).

Elkayam et al. described of reduction >20 % in LVEF in 21 % of the cohort with LV recovery with no mortality cases and in 44 % of pregnancies with persistent LV dysfunction with a high mortality rate (19 %) in this latter group.

A multicentre study from Germany, Scotland, and South Africa by Hilfiker-Kleiner et al. [54] included 34 women with SSP and demonstrated a high risk of relapse (defined as LVEF <50 %) in women with persistent LV dysfunction. In addition, death occurred in up to 25 % of PPCM patients with persistently reduced LVEF prior to a SSP, while no death was recorded in the group with recovered LV function [54]. Worse outcomes in patients with persistently reduced LVEF have also been reported by Yameogo et al. [55].

In a review including 93 women with persistent LV dysfunction, almost 50 % had further decrease of LVEF, which persisted in 39 %, whereas 16 % of patients died [56].

As mentioned above, fetal outcomes seem to be worse among women with persistent LV dysfunction, with higher rates of stillbirth, abortion, and pre-term delivery [48].

In light of these data, current guidelines discourage women with unrecovered LVEF (<50–55 %) to have SSPs [16].

However, it is important to underline that recovered LVEF does not guarantee uncomplicated subsequent pregnancy. In fact, although the mortality rate is generally low, these patients may develop LVEF impairment, PPCM relapse and even serious complications such as cardiac arrest, cardiogenic shock, ventricular arrhythmias, and even need of temporary LV mechanical assist devices [56]. Moreover, a recent study by Pachariyanon [47] et al. reported that, even though five-year adverse outcomes and all-cause mortality were higher in the group with unrecovered LVEF compared to the group with LVEF recovery, at a median followup of 8 years no significant differences were reported between the two groups. As this is at present the study with the longer follow-up, there is the possibility that adverse events in PPCM patients with SSPs may occur later in life, and this needs to be discussed with the patient. Clearly, long-term follow-up of all patients with PPCM is warranted.

In order to improve risk stratification, the additional prognostic role of indices of subtle left ventricular dysfunction has been investigated, including global longitudinal strain and contractile reserve. In a study by Suguahara et al., significantly reduced global longitudinal strain was associated with worse outcomes, even after adjusting for LVEF [57]. Similarly, reduced contractile reserve, examined either with exercise [52]or dobutamine [58]stress test, has been proven to predict adverse events occurrence in PPCM. However, there is lack of data regarding the prognostic role of these indices in PPCM patients with SSPs.

Other than LV function, additional factors that have been associated to higher risk of PPCM relapse and/or poor outcomes after SSPs include Afro-American descendance [48,55], low socio-economic background [48], lower LVEF during the index pregnancy [55,56]and obesity [59]. Furthermore, loss from followup is another adverse prognostic factor [47]. In fact, as previously discussed, patients with PPCM need life-long follow up even in cases of recovered LVEF. This is even more relevant when SPPs are contemplated. If the patient is still on pharmacological therapy, discontinuation of possibly teratogenic drugs is mandatory before attempting a SSP. In particular, renin-angiotensin-aldosterone axis antagonists must be gradually down-titrated and finally stopped; close follow-up during in this weaning process is advisable and LVEF stability over at least three months should be documented before trying to conceive. Prophylactic therapy with beta-blockers has been suggested and may be considered in case of SSPs, even though data is lacking. Bromocriptine administration during the index pregnancy was associated with better outcomes of SSPs both in African and Caucasian patients [54], albeit more data from larger studies need to confirm this.

In women with PPCM who do not desire or have been discouraged to have SSPs, safe contraception should be discussed and provided in a timely fashion [49]. Combined contraceptive pills should be avoided due to the high thrombogenic and hypertensive action of the oestrogenic components. Progesterone-only pills, intrauterine contraceptive devices or progesterone cutaneous implants are the preferred alternatives [49]. Barrier methods should not be used alone for their low efficacy. Surgical methods, such as vasectomy and hysteroscopic tubal occlusion, may also be considered and discussed with both the patient and her partner.

6. Gaps in knowledge and future perspectives

PPCM remains a poorly understood condition affecting young women, who often desire further pregnancies.

The diagnosis is clinical and echocardiographic and should prompt HFmedical therapy and other support as required. Patients should be given time to record recovery and the degree of cardiovascular residual involvement, if any. The only targeted therapy in the acute phase, at present, appears to be bromocriptine, albeit relevant data is weak for general recommendation. There is an ongoing Randomized Evaluation of Bromocriptine in Myocardial Recovery Therapy for Peripartum Cardiomyopathy (REBIRTH) trial involving 200 women randomly assigned

to bromocriptine or placebo (ClinicalTrials.gov number, NCT05180773), completion in 2026, which may shed light on safety and efficacy of this drug.

Future research should investigate the patho-physiological mechanism/s leading to PPCM to allow for aetiologic therapeutic targets, whereas longer prospective studies may refine risk stratification regarding relapse and adverse events in patients with PPCM contemplating further pregnancies.

All patients with PPCM warrant life-long follow-up, including those who make a full recovery of LV function in the medium term. We present herewith individual risk factors predisposing to adverse outcome and PPCM relapse with SSPs, to facilitate counselling of women who desire further pregnancies.

CRediT authorship contribution statement

Giulia Iannaccone: Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Francesca Graziani:** Writing – review & editing. **Polona Kacar:** Writing – original draft. **Pietro Paolo Tamborrino:** Writing – original draft. **Rosa Lillo:** Visualization. **Claudia Montanaro:** Supervision. **Francesco Burzotta:** Visualization. **Michael A. Gatzoulis:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper other than two of them (CM and MAG) serving as IJCCHD Editorial Board Members, but not involved with the handling of the paper.

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none.

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