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Peripartum cardiomyopathy: from genetics to management

Karen Sliwa [1,2]*, Johann Bauersachs [3], Zolt Arany [4], Timothy F. Spracklen[1], and Denise Hilfiker-Kleiner [3,5]

[1]Cape Heart Institute, Faculty of Health Sciences, University of Cape Town, South Africa; [2]Department of Medicine, Division of Cardiology, Groote Schuur Hospital, University of Cape Town, South Africa; [3]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; [4]Cardiovascular Institute, University of Pennsylvania, Philadelphia, PA, USA; and [5]Medical Faculty of the Philipps University Marburg, Marburg, Germany

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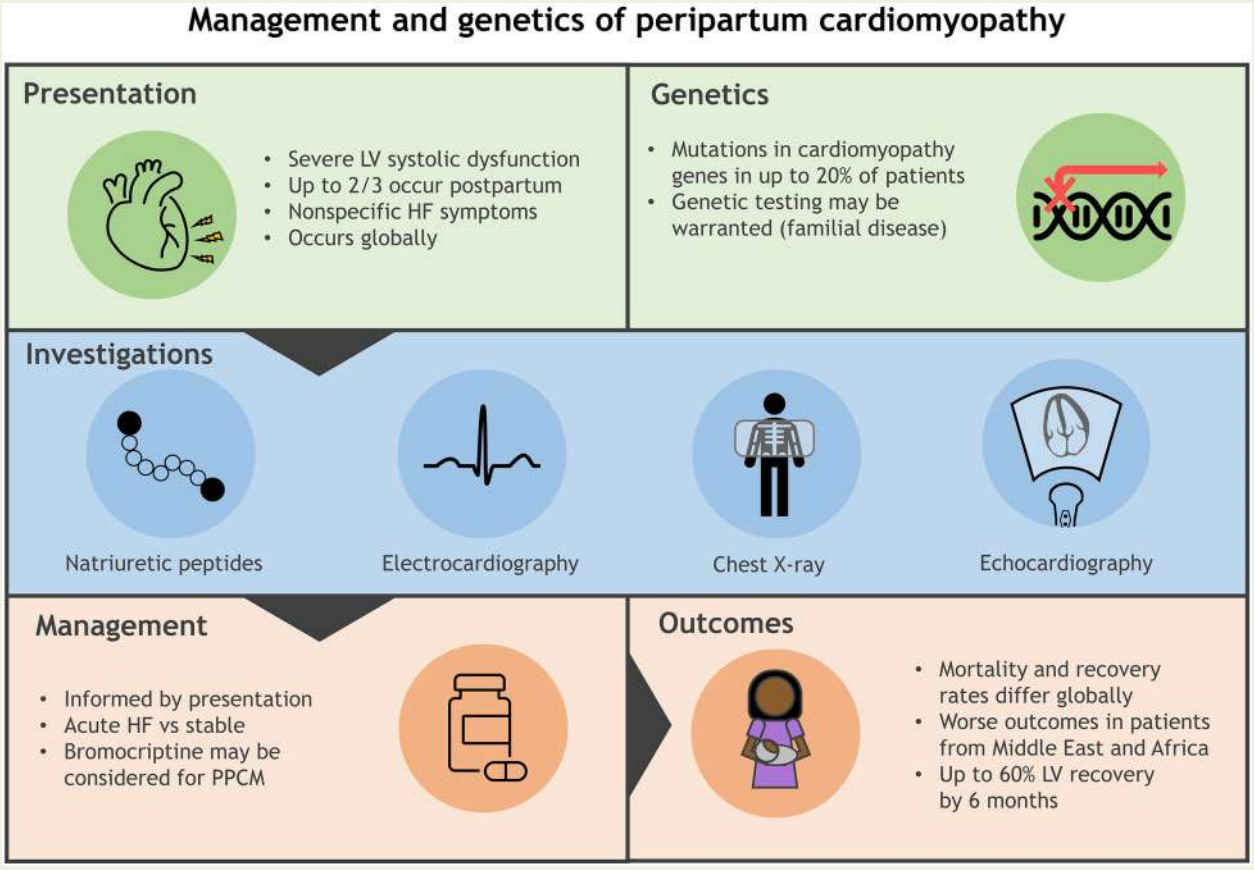
Peripartum cardiomyopathy (PPCM) is a disease that occurs globally in all ethnic groups and should be suspected in any peripartum women presenting with symptoms and signs of heart failure, towards the end of pregnancy or in the months following delivery, with confirmed left ventricular dysfunction. After good history taking, all women should be thoroughly assessed, and alternative causes should be excluded. Urgent cardiac investigations with electrocardiogram and natriuretic peptide measurement (if available) should be performed. Echocardiography follows as the next step in investigation. Patients with abnormal cardiac investigations should be urgently referred to a cardiology team for expert management. Referral for genetic work-up should be considered if there is a family history of cardiomyopathy or sudden death. PPCM is a disease with substantial maternal and neonatal morbidity and mortality. Maternal mortality rates range widely, from 0% to 30%, depending on the ethnic background and geographic region. Just under half of women experience myocardial recovery. Remarkable advances in the comprehension of the pathogenesis and in patient management and therapy have been achieved, largely due to team efforts and close collaboration between basic scientists, cardiologists, intensive care specialists, and obstetricians. This review summarizes current knowledge of PPCM genetics, pathophysiology, diagnostic approach, management, and outcome.

* Corresponding author. Tel: +27 21 4066358, Email: karen.sliwa-hahnle@uct.ac.za

Graphical Abstract



Keywords Peripartum cardiomyopathy • Heart failure • Pregnancy • Genetics

Introduction

Peripartum cardiomyopathy (PPCM) is increasingly recognized as an important medical condition that can complicate pregnancy. It is a life-threatening cardiomyopathy, characterized by acute or slowly progressing left ventricular (LV) dysfunction—late in pregnancy, during delivery, or in the first postpartum months—in women with no previously known cardiac disease.[1,2] Over the past two decades a substantial amount of new knowledge on this condition has been published, including better understanding of the pathophysiology, the genetic predisposition for a portion of patients, on diagnostic tools, management and outcome. The Heart Failure Association of the European Society of Cardiology (ESC) Working Group on PPCM initiated the largest prospective global cohort study, under the umbrella of the EURObservational Research Programme (EORP), with >700 PPCM patients, providing novel data on presentation in various ethnic groups, as well as maternal and Foetal outcome.[3]

This review provides an update on new findings from genetics to management (*Graphical abstract*).

Presentation

Women often present with non-specific symptoms of heart failure late in pregnancy, during delivery or in the postpartum months, to medical professionals of various disciplines. The ESC EORP PPCM study has shown that the majority of women present postpartum in Africa (75%), Europe (69%), the Middle East (66%), and Asia-Pacific (57%) (*Figure 1*). At that stage, these women are usually no longer under obstetric care and present with their symptoms and signs to general practitioners or to the medical emergency services. Also, midwifes may be the first to be addressed by postpartum women with symptoms and/or signs of heart failure. They should be aware of the potential presence of PPCM and trigger appropriate diagnostic clarification.

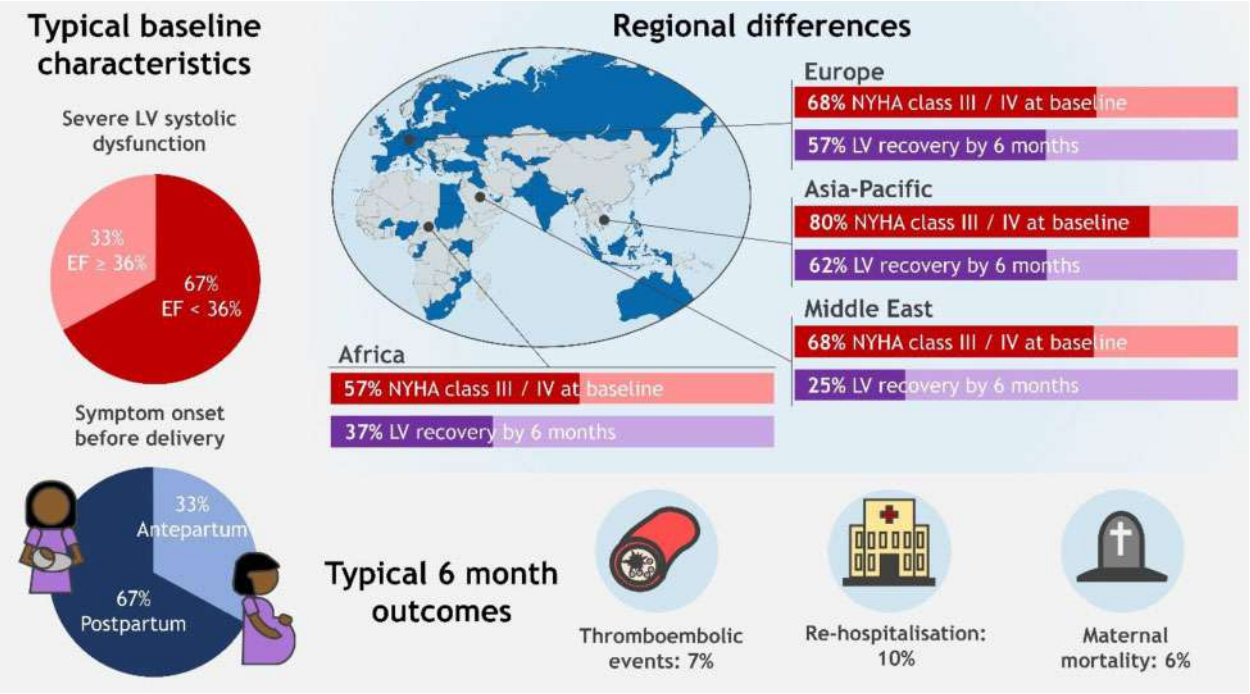


Figure 1 Baseline characteristics, 6-month outcomes, and regional differences observed in the peripartum cardiomyopathy (PPCM) EURObservational Research Programme (EORP). Analysis of 739 PPCM patients from 49 countries. In the map, countries in blue are those included in the EORP registry (countries not included in the illustration: Argentina, Canada, Honduras, Nicaragua, and the USA). EF, ejection fraction; LV, left ventricular; NYHA, New York Heart Association.

Distinguishing signs and symptoms of PPCM, from the spectrum of normal pregnancy or the common fatigue post-delivery, can be challenging. However, a low threshold of suspicion of heart failure is crucial in a woman with suggestive clinical features. A substantial proportion of women that present postpartum have few physical signs, despite substantial cardiac dysfunction (*Figure 1*). Shortness of breath, fatigue and mild ankle swelling are less specific symptoms of heart failure during pregnancy, whereas orthopnoea and paroxysmal nocturnal dyspnoea are more specific. The majority of women with PPCM present with severe symptoms (New York Heart Association class III or IV).[4] PPCM is generally viewed as a diagnosis of exclusion. However, in a previously healthy woman presenting during the last month of pregnancy, or in the months after delivery, with signs and symptoms of heart failure, the diagnosis of PPCM is likely if an echocardiogram reveals significantly reduced LV ejection fraction (LVEF). A clearly detailed medical history is essential to exclude other conditions that may cause a dilated cardiomyopathy (DCM), including viruses, alcohol, LV non-compaction cardiomyopathy, and medications (particularly cardiotoxic chemotherapy). Hypertensive disorders complicate as many as 5–10% of pregnancies worldwide, with pre-eclampsia in ~3%.[5] The prevalence of hypertensive disorders in women with PPCM is higher, with >20% having been reported to develop pre-eclampsia during the index pregnancy.[6] The relationship between hypertensive disorders of pregnancy and PPCM is not well understood. Pathological pathways resulting in angiogenic imbalance and endothelial dysfunction have been identified in both conditions, suggesting that overlap may exist.[7]

Genetics

A role for genetics in the development of PPCM has been supported by multiple reports, with a genetic cause of disease identified in up to 20% of studied patients. The most notable example of this is mutations in the sarcomeric gene titin (*TTN*), a well-established disease gene for DCM. Several rare truncating (i.e. nonsense, frameshift, or splice site) mutations in *TTN* were reported in PPCM patients from European and American populations.[8,9] These mutations comprised ~10–15% of a PPCM cohort, which was a similar *TTN* mutation yield to the 17% observed in a corresponding cohort of nonischaemic DCM patients.[9]

Combined with other discoveries of DCM gene mutations in PPCM patients,[10–12] this suggests a substantial overlap in genetic susceptibility between PPCM and inherited forms of cardiomyopathy. Indeed, a number of PPCM patients have reported a positive first-degree family history for heart failure and cardiomyopathy, including those with cardiomyopathy-associated mutations.[8,11,12] There have also been limited reports of PPCM occurring amongst carriers of X-linked forms of DCM, such as Duchenne muscular dystrophy and Danon disease.[13–15]

A recent large study from the Arany group of 469 PPCM patients from around the world lent further weight to the notion that PPCM and DCM bear significant genetic overlap. The study confirmed a ~10% prevalence of pathogenic truncating variants in these women with PPCM, a ~20-fold higher prevalence than in control cohorts.[16] In addition, statistically significantly enriched truncating variants were

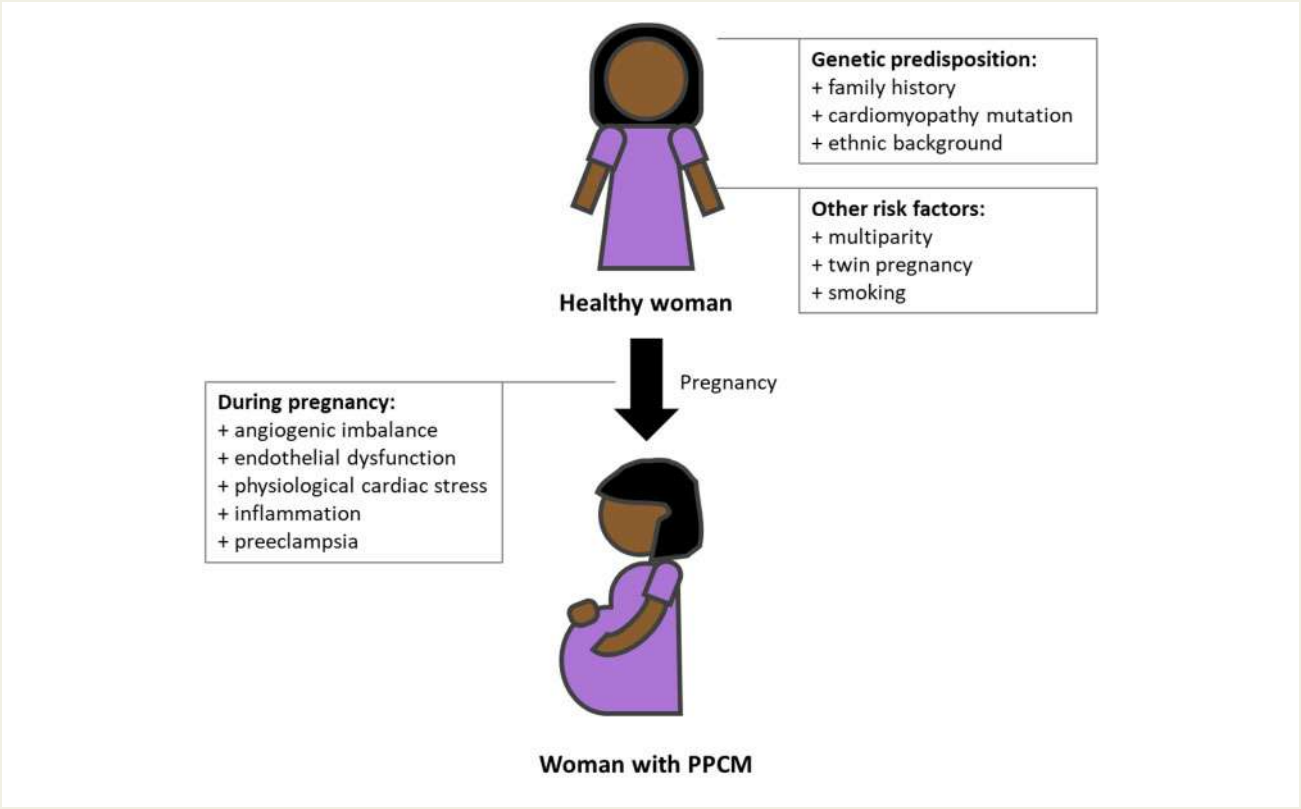


Figure 2 The 'multiple hit' model of peripartum cardiomyopathy (PPCM). Genetic predisposition, physiological changes during pregnancy, and other risk factors may act cumulatively to induce PPCM in otherwise healthy women. These include individuals with a family history of cardiovascular disease or carriers of cardiomyopathy-causing mutations, who do not manifest cardiomyopathy until late in pregnancy or shortly after delivery.

identified in the genes *DSP*, *FLNC*, and *BAG3*. The relative prevalence of truncating mutations in these four genes in women with PPCM (*TTN*: ~10%; *DSP* and *FLCN* ~1%; *BAG3*: ~0.2%) was nearly identical to the prevalence in cohorts with DCM, strongly supporting the idea that there is a high degree of genetic similarity between PPCM and DCM.

How these genetic mutations predispose to PPCM is unclear. The proteins encoded by these four genes have very different roles in the cardiomyocyte, including roles in the sarcomere (*TTN*), desmosome (*DSP*), intercalated discs (*FLNC*), and autophagy (*BAG3*). One possible explanation posits a 'multiple hit' model, in which accumulation of risk factors (genetic and environmental) increases the likelihood of disease (*Figure 2*). Consistent with this idea, a high prevalence of *TTN* mutations has also been seen in alcohol-induced and oncotherapy-induced cardiomyopathies.[17,18] Also, consistent with this idea of strong genetic/environment interaction, recent work has shown that 95% of people with truncating mutations in *TTN* show no evidence of cardiac disease, i.e. the penetrance of *TTN* truncations mutations is very low, indicating that cardiac function is preserved in the absence of additional cardiac stressors.[19] The hemodynamic and vasculo-hormonal stressors of pregnancy or parturition likely represent such a stressor.[1]

In addition to rare deleterious mutations, PPCM may be influenced by common variants, although fewer data are available to address this possibility. A small study of 97 patients suggested that the C825T polymorphism in the gene *GNB3* may be associated with poorer outcomes, and may explain the increased prevalence of PPCM amongst individuals of African ancestry.[20] A similarly small genome-wide association study of 41 PPCM patients identified a single-nucleotide polymorphism in the parathyroid hormone-like hormone gene (*PTHLH*) that was significantly associated with risk of PPCM.[21] Independent replication in larger studies will help elucidate the roles of these variants.

Genetic predispositions to PPCM may also be shared with other diseases. For example, the Hilfiker-Kleiner group suggested an enhanced risk for cancer in PPCM patients (16-fold), compared to age-matched women.[22] The incidence of cancer occurred both prior to and after PPCM. Some of these patients carried known pathogenic or likely pathogenic variants, as classified according to the American College of Medical Genetics criteria, in genes associated with an increased cancer risk including *ATM*, *ERCC5*, *NBN*, *RECQL4*, and *SLX4*. Interestingly, all these genes are related to the DNA damage response (DDR) pathway,[22] suggesting the possibility that mutations within the DDR pathway concomitantly increase the risks for cancer and for cardiotoxicity due to anticancer treatment and/or pregnancy. These findings will benefit from independent replication and may be limited to some demographic cohorts, as for example a review of the case records of a large South African cohort of >176 PPCM

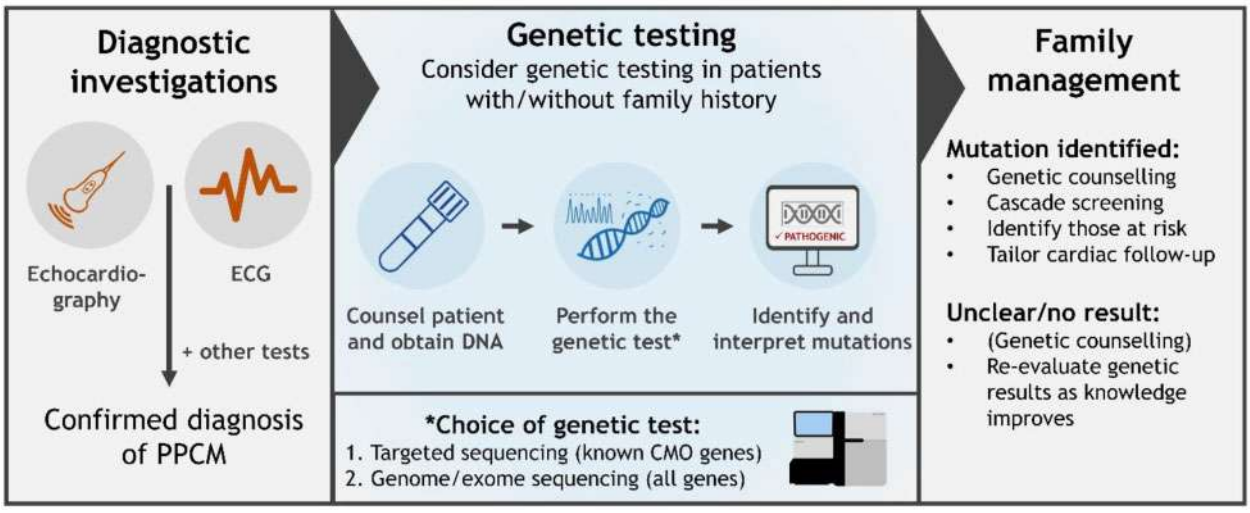


Figure 3 Overview of the genetic testing process. After a diagnosis of peripartum cardiomyopathy, genetic testing should be considered in healthcare settings that offer it. Patients should be counselled before a DNA sample is obtained. Genetic tests include targeted sequencing of known cardiomyopathy genes and genome or exome sequencing. Once the results are interpreted, they should be reported to the patients and appropriate steps taken. In the event of a positive genetic result, cascade screening of her relatives may identify at-risk individuals who may require cardiac follow-up. CMO, cardiomyopathy; ECG, electrocardiography.

patients[23] did not detect any cases with cancer prior, or concomitant to, PPCM diagnosis (unpublished data).

The significant burden of identifiable genetic mutations in women with PPCM has implications for clinical care. Currently, there are no recommendations for genetic testing in women with PPCM. Initial observations suggest that mutations in TTN herald a worse prognosis,[9] but more research is needed. In contrast, mutations in *FLNC* and *DSP* are associated with malignant arrhythmias in DCM and warrant aggressive anti-arrhythmic management. Moreover, in cases where a likely pathogenic variant is identified, testing of family members can provide reassurance or indicate closer monitoring. Genetic testing of patients with DCM, and of at-risk family members, is currently recommended.[24] In healthcare systems, which offer it, genetic testing may be considered in cases of PPCM, especially in cases of familial aggregation of cardiomyopathies, for prognosis and to facilitate family screening.

Inflammation, neurohormones, and cardiac signalling

PPCM is considered as a distinct entity of unknown aetiology,[1,2] probably resulting from multiple pathomechanisms initiating and driving the disease. This also seems to be reflected by the variable cardiac presentation and risk factor profiles observed in PPCM patients and the different animal models that develop PPCM.

Amongst these are inflammation and autoimmune reactions with elevated levels of various circulating cytokines as potential factors inducing and driving PPCM.[25] Interleukin-6 (IL-6), tumour necrosis factor-α (TNFα), C-reactive protein (CRP), and interferon-gamma (IFNγ) were found to be elevated and correlated with the severity of cardiac failure.[26–28] Anti-inflammatory strategies, for example with pentoxifylline, a xanthine-derived agent known to reduce the release of TNFα and IL-6, improved the outcome of PPCM patients in an African cohort.[26] The origin of enhanced inflammation in PPCM patients is unclear and may be pathogen driven, or the result of autoimmune processes. In fact, several smaller studies reported elevated levels of autoantibodies (AABs), specifically against cardiac troponin I (TnI) and myosin heavy chain 7, which correlated with more severe LV dysfunction.[25] AABs against β1-adrenergic receptors (β1 R) and the M2-muscarinic receptor (M2-R) were also described in PPCM patients.[29] These reports suggest that PPCM patients without AABs had a favourable outcome.[30] Respectively, plasmapheresis may improve cardiac function in PPCM patients.[31] However, data are limited and it is unclear whether AABs are contributing to the pathogenesis of PPCM, or are a consequence of the disease.

An interesting aspect will also be the impact of the current COVID-19 pandemic on patients with PPCM, specifically because pregnancy suppresses the immune system, thus allowing viral infections to spread more efficiently. Moreover, after the delivery, the immune system is strongly activated, a feature that may, in view of the COVID-19 disease, be beneficial or may lead to an overactivation of the immune system with damaging effects.

However, there is accumulating evidence that several pathomechanisms in PPCM converge on a common pathway, which involves unbalanced oxidative stress and the generation of the anti-angiogenic 16-kDa prolactin.[32] Along this line, experimental and clinical observation suggests central roles for protection of the maternal heart from oxidative stress by specific activation of major signalling pathways, including the signal transducer and activator of transcription 3 (STAT 3), the peroxisome proliferator-activated receptor γ coactivator 1α

and phosphoinositid-3-kinase (PI3) and protein kinase B (AKT) as summarized by Hilfiker-Kleiner *et al.*[32] and Ricke-Hoch *et al.*[33] Deregulation of any of these pathways is associated with increased oxidative stress, which promotes the cleavage of the nursing hormone prolactin, a hormone rising during pregnancy and, periodically, released from the pituitary gland during nursing, into shorter N-terminal 16-kDa prolactin fragment (16-kDa prolactin). The 16-kDa prolactin induces endothelial dysfunction and damage and subsequently leads to heart failure. Blocking prolactin with the dopamin D2 receptor agonist, bromocriptine, has emerged as a potential disease-specific therapy for PPCM, and it has been added to the ESC guidelines on cardiovascular diseases in pregancy as a therapeutic option that should be considered.[34]

More recently, impairment in neurohormonal signalling, specifically lower circulating levels of serotonin, has also been reported in PPCM patients.[35] Levels of the depression-associated microRNA-30e, a microRNA that impairs the function of the serotonin receptor 5-HT1AR, are elevated in PPCM patients.[35] These alterations were associated with an increased prevalence for major depressive disorders, post-traumatic-stress-disorder, and panic-disorder in PPCM patients, compared with postpartum women without a PPCM diagnosis.[35] However, it remains unknown if this observation is related to the severe stressors, these women undergo due to having severe heart failure linked to their pregnancy.

Diagnostic assessment

Urgent diagnostic assessment with prompt referral to a specialist is indicated in any peripartum woman with signs or symptoms of heart failure. Once a diagnosis of PPCM is reached, additional tests can be considered to allow more sophisticated phenotyping and prognostication.

The electrocardiogram (ECG) is a widely available and powerful diagnostic tool in any cardiac condition. It should form the basis of clinical work-up in all women with a potentially cardiac-related complaint and, particularly, in those with suspected PPCM. To a varying degree, at the time of diagnosis the ECG is abnormal in almost all women with PPCM. In a prospective study of women with PPCM in South Africa, >90% had at least one electrocardiographic abnormality and almost 50% had a significant electrocardiographic abnormality (e.g. Q-wave abnormality, ST-segment depression, T-wave inversion, bundle branch block, second- or third-degree atrioventricular block, frequent ectopy, or brady- or tachyarrhythmia).[36] The recently published paper on ECG abnormalities in >400 patients included in the EORP PPCM study confirmed this observation.[37]

Chest X-rays can identify alternative causes for breathlessness or hypoxia, such as infection, effusion, or pneumothorax, but can be normal in PPCM, while commonly showing cardiomegaly and/or features of pulmonary congestion.

Echocardiography is the main diagnostic modality used to confirm the presence of cardiac dysfunction in PPCM and quantify severity. Furthermore, it excludes alternative causes of heart failure, such as congenital heart disease, primary valvular disease, and a number of inherited or acquired cardiomyopathies. LV end-diastolic and end-systolic volumes are commonly pathologically enlarged. The mean LVEF at the time of diagnosis in the global study on PPCM was around 30% in all ethnic groups.[3] Commonly coexisting findings are functional mitral regurgitation and right ventricular dysfunction. Part of the routine echocardiogram must be a comprehensive assessment of the right heart, as a reduced baseline right ventricular function has been shown to be an independent predictor of a worse outcome.[38,39]

Echocardiography is also an important tool in the identification of heart failure sequelae, such as intracardiac thrombi.

Access to cardiac magnetic resonance imaging (MRI) is often prohibited by cost and geographical location and, as such, it is not widely used as a standard investigation in the diagnosis of PPCM. Cardiac MRI can be useful to exclude other aetiologies, such as myocarditis, LV non-compaction cardiomyopathy, or infiltrative diseases, and to supplement information provided by echocardiography.

Routine haematological and biochemical testing can provide information on potentially reversible contributory factors, such as clinically significant anaemia, and help to establish the presence of end organ damage. Natriuretic peptide levels (where available) should be measured in women with suspected PPCM.

Although not currently routine medical practice, genetic testing may also be considered, especially in cases of familial aggregation of cardiomyopathies (*Figure 3*). Because PPCM frequently presents as acute heart failure (AHF), genetic testing may be secondary to more urgent clinical investigations that should take priority. However, the identification of disease-causing genetic mutations will be of clinical relevance to the patient and her family, including her offspring, who may be at the risk of genetic cardiomyopathy themselves. Patients would need to be counselled before performing genetic testing and, in the event that a positive result is obtained, on the methods of genetic testing and the potential implications of a positive result. Because genetic testing typically involves sequencing all well-established cardiomyopathy genes for mutations, identification of a pathogenic mutation in a PPCM patient should be followed by cascade screening of her relatives to determine other mutation carriers. Any mutation carriers may then require cardiological follow-up and routine screening for signs of deterioration in cardiac function.

Risk stratification

Risk stratification should be immediately performed to identify the appropriate level of care. The strongest parameters in identifying patients at risk of complications at the time of diagnosis are non-Caucasian race, ECG QT-interval prolongation, LVEF <30%, LV end-diastolic diameter of >60 mm, biventricular dysfunction, and delay of diagnosis. Other parameters including age >40 or <20 years, ante-partum diagnosis, haemodynamic parameters at presentation, and cardiac biomarkers might help refine the risk stratification.[40] Patients with a history of a previous diagnosis of PPCM have a particularly high risk of poor outcome and careful history taking must always be part of the first assessment.[41] In all women with PPCM and a subsequent pregnancy, the key parameter is pre-pregnancy LVEF, since the risk of deterioration and even death is significant in cases of persistent LV dysfunction before subsequent pregnancies. However, even patients with recovered LV functions are still at risk for relapse.

PPCM is associated with substantial morbidity and mortality. Most of the life-threatening complications, including severe heart failure,

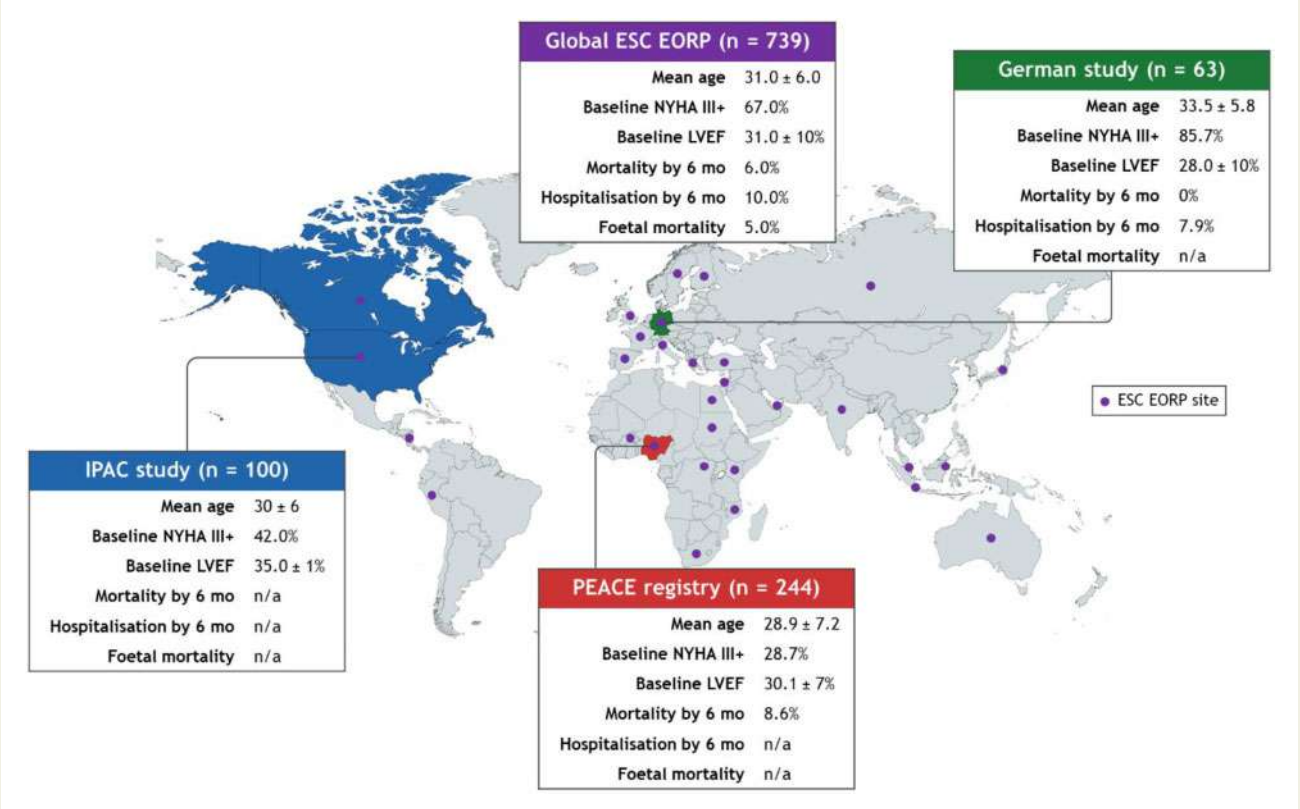


Figure 4 Comparison of clinical presentation and outcome of multi-centre peripartum cardiomyopathy studies. Data are taken from the North American Investigations of Pregnancy Associated Cardiomyopathy study,[53] PEripArtum Cardiomyopathy in NigEria registry,[54] a German multi-centre bromocriptine clinical trial,[51] and the European Society of Cardiology EURObservational Research Programme global peripartum cardiomyopathy registry.[3] Data that are not reported are marked n/a. LVEF, left ventricular ejection fraction; mo, month; n/a, not available; NYHA, New York Heart Association.

cardiogenic shock, arrhythmias, thromboembolic complications, and death, can be prevented by early referral to a centre with expertise in managing AHF and by appropriate use of medical and non-pharmacological therapy.[2]

Management

The management of PPCM differs according to the clinical scenario in which the patient presents; especially whether the patient is still pregnant or post-delivery, and whether the patient is stable or suffering from acute decompensated heart failure. A dedicated pregnancy heart team/task force for pregnant patients with AHF should be installed in all larger centres to ensure rapid decision-making processes regarding the best supportive care for mother and child, including (urgent) delivery, stopping lactation, and potential mechanical circulatory support (MCS) for patients in cardiogenic shock.[1,34]

Mild heart failure may be treated with standard heart failure drugs on a normal ward, or even on an outpatient basis if regular follow-up visits can be ensured. Haemodynamically stable patients with respiratory insufficiency at rest will be treated with intravenous diuretics and oxygen supplementation on an intermediate care/heart failure unit, whereas women with severe forms of acute PPCM leading to cardiopulmonary instability and cardiogenic shock are often in need of intubation and ventilation, as well as inotropic treatment and MCS implantation in an intensive care unit. Practical recommendations for treating AHF in the setting of PPCM are based on recent data and clinical experience.[1,42–44]

To ensure optimal treatment according to current evidence and best experience, patients with severe distress should be transferred early to an experienced centre whenever possible. If hemodynamic instability persists despite medical treatment, implantation of temporary MCS should be considered early. As the probability of at least partial recovery of ventricular function is higher than in other cardiomyopathies, implantation of a durable ventricular assist device or cardiac transplantation is only rarely necessary.

In patients with stabilized heart failure not in need of, or weaned from, inotropics and vasopressors, standard drug treatment proven to ameliorate LV remodelling and clinical outcomes in heart failure with reduced ejection fraction should be installed and titrated to maximum guideline-based dosages.

Clearly, during pregnancy, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and angiotensin receptor-neprilysin inhibitors (ARNIs) are contraindicated because of foetal toxicity and hydralazine and nitrates may be used instead. Mineralocorticoid receptor antagonists (MRAs) should be avoided

during pregnancy and lactation but should be started postpartum in symptomatic women—especially in women with LVEF <35%.

Despite an increased risk of foetal growth restriction, beta-blockers are indicated in all stable patients with marked systolic dysfunction while pregnant, and in all patients postpartum.[43] Dosages of diuretics should be adapted to control the symptoms or signs of congestion but avoiding higher doses when possible.

Breastfeeding is controversial in peripartum women presenting with heart failure.[45] The 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy suggests that preventing lactation may be considered in patients with severe heart failure to avoid the high metabolic demands of lactation and breastfeeding and to enable safe treatment with all established heart failure drugs.[34] There are, however, few published data that directly address the question of breastfeeding in PPCM. Only two small observational studies have directly addressed the question, and both have concluded that breastfeeding is not contraindicated in women with PPCM.[46,47] The decision of whether to breastfeed with PPCM, in particular in women with moderate LV dysfunction, must also consider at least two other factors: (i) the benefit of breastfeeding to the infant, in particular in developing countries, where undernutrition accounts for most of childhood mortality,[48] and (ii) the safety of medications used to treat PPCM during lactation. A detailed description of medication safety during pregnancy and lactation is given in table 3 in Bauersachs *et al.*[1]

Thromboembolic events

Around the time of PPCM diagnosis, the rate of peripheral arterial and venous thromboembolic events is rather high (7% in the first 30 days after delivery in the PPCM worldwide registry).[3,4] Thus, the suspicion for thromboembolism must be high, and an appropriate diagnostic procedure performed. Initial anticoagulation in prophylactic dose should be considered in all patients with PPCM, whereas therapeutic anticoagulation is firmly recommended in patients with intracardiac thrombus, evidence of systemic thromboembolism, or paroxysmal or persistent atrial fibrillation.

Arrhythmias and ECG abnormalities

There is no specific ECG pattern for PPCM. However, the ECG is rarely normal in patients presenting with PPCM and sinus tachycardia, as well as repolarization abnormalities, are common.[1] In the EORP PPCM worldwide registry, ECG abnormalities have been analysed, including regional and ethnic differences and their correlation with echocardiographic features. Sinus tachycardia at baseline was associated with poor systolic function (LVEF <35%), whereas wide QRS, left bundle branch block and LV hypertrophy were associated with LV dilatation.[37]

In a South African cohort, a poor outcome (defined as death, re-admission, NYHA class III/IV or LVEF ≤35% at 6- and 12-month follow-up) was independently predicted by a prolonged QTc interval or tachycardia at baseline.[36]

PPCM patients are at risk for sudden cardiac death (SCD) in the months after diagnosis, especially when LVEF is <35%. As early implantation of an implantable cardioverter-defibrillator (ICD) is not necessary in most patients, given the high likelihood of ejection fraction improvement after several months of heart failure drug treatment, a wearable cardioverter-defibrillator may be useful to prevent SCD due to ventricular fibrillation.[1,49] Only in women with severe LV dysfunction >6 months after diagnosis despite optimal medical therapy, implantation of an ICD or cardiac resynchronization therapy should be considered.

Bromocriptine

Bromocriptine suppresses prolactin production and was used for many years to stop lactation postpartum. In a small proof-of-concept study on acute PPCM, the addition of bromocriptine to standard heart failure medical therapy was associated with improved LVEF and mortality.[50] A recent multi-centre randomized study comparing two different bromocriptine dosages (2.5 mg daily for one week vs. 5 mg daily for 2 weeks, followed by 2.5 mg daily for 6 weeks) in severe PPCM patients observed a high LV recovery rate at 6 months with no mortality, use of assist device or heart transplantation, indicating a beneficial association between the use of bromocriptine in acute PPCM and clinical outcome.[51] The improvement in LVEF was similar in the short-term (one week) and long-term (eight weeks) bromocriptine groups, albeit a trend, not statistically significant, for more patients reaching full recovery at 6 months was found in the long-term group. Based on these data, the 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy states that bromocriptine may be considered in women with newly diagnosed PPCM.[34] Bromocriptine treatment should always be accompanied by anticoagulation at least at prophylactic dose, to reduce the thromboembolic risk.

To gain more evidence for bromocriptine treatment in PPCM, the North American Bromocriptine trial with funding from the NIH will randomize PPCM patients to 8 weeks of bromocriptine or placebo.

Long-term drug treatment/drug cessation

ARNI or ACE inhibitors, beta-blockers, and MRAs should probably be given in guideline-based dosages and not discontinued during the first year after complete recovery of LV function. Stepwise discontinuation of heart failure therapy might be considered if both complete recovery of ventricular function and normal exercise response are achieved. Since relapses have been observed after recovery in patients presenting with heart failure, tapering of the disease-modifying heart failure drugs should be performed under close observation of LV function.[1,32] Diuretics should be tapered if patients no longer have symptoms or signs of congestion.

Outcome

Although the prognosis of PPCM patients is more favourable compared to other cardiomyopathies, outcomes (particularly recovery of LV function and mortality) significantly differ globally.[2,41] *Figure 4* summarizes the clinical presentation, 6-month maternal outcome including rehospitalization and death in four recently conducted PPCM cohort studies.[3,51–53]

The highest maternal mortality was found in the 244 patients entered into the Nigerian PEACE study, with a median death of 18% within 17 months, and a 6-month mortality of 8%.

Mortality rates of PPCM patients range widely depending on geographical regions. The EORP global registry on PPCM, the largest

study to date, investigates clinical presentation, management and outcome of PPCM patients.[55] A total of 743 patients from > 40 countries in Europe, Africa, Asia-Pacific, and the Middle East were enrolled over a 6-year period. Initial results showed low mortality rates 1 month after the diagnosis (2.4% overall, 3.4% in ESC countries, and 1.4% in non-ESC countries).[4] However, the 6-month mortality was 6%, with 42% due to heart failure and 30% due to sudden death.[3]

Mortality rates from other studies reported substantially higher mortality ranges such as 15–30% in Turkey[56] and 12–28% in South Africa.[57,58]

Early mortality in the acute phase is often due to AHF, malignant arrythmia, cardiogenic shock, and thromboembolic events.[43,49] Later mortality is mainly due to deterioration of LV function, leading to heart failure.

Until recently it was thought that women with African ethnicity always experience worse outcome.[59–61] However, data from the global ESC EORP demonstrated a worse outcome in women from Middle East compared to African patients.[3] Currently, it is unknown if different genetic background plays a key role in defining the prognosis, or if the main determinants are also influenced by access to healthcare systems and heart failure therapy.

Most studies in patients with PPCM have only reported on the LV function at 6-month follow-up. Full recovery (mostly defined as LVEF >50–55%) ranges widely depending on racial background and geographic region. Data from China, Japan, Turkey, the USA, and Germany demonstrate recovery rates between 44% and 63% after 6 months.[41,62–66] Women in Pakistan, the Philippines, Nigeria, and South Africa display a lower chance of full recovery rates ranging from 21% to 36%.[23,27,41,67,68]

Prospective studies and registries that include patients with a follow-up ≥12 months demonstrate relatively high rates of LV recovery in PPCM patients. The multi-centre IPAC (Investigation of Pregnancy-Associated Cardiomyopathy) study analysed 100 American women with PPCM.[53] LV recovery was observed in 72% of women after 12 months. In a Turkish study, LV recovery was present in 47.6%.[62] It is important to note that >50% of patients who recover did so beyond 12 months after initial diagnosis.

Only very few prospective data report on the long-term follow-up of PPCM patients beyond 5 years after initial diagnosis. A German study prospectively investigated outcome of 67 patients, with a mean follow-up of 63 ± 11 months.[69] The LV function improved from 26% at initial diagnosis to 50% after 12 months and 54% after 5 years. The number of patients experiencing full recovery was 48% after 6 months, further rising to 60% and 72% after 1 and 5 years, respectively.

Conclusion

PPCM is a global disease that is often associated with a delayed diagnosis, leading to significant morbidity and mortality. It is an important contributor to early (<42 days) and late (up to 1 year) postpartum maternal death. The reported 1-year mortality ranges from 5% to 25%.

In the last two decades, remarkable advances in the comprehension of the pathogenesis and the improvement in patient management and therapy have been achieved, including a disease-specific therapeutic option, namely bromocriptine, which should be considered. This is largely due to team-effort and close collaboration between basic scientists, cardiologists, intensive care specialists and obstetricians. Recent data suggest that referral for genetic work-up should be considered for patients with a family history of a cardiomyopathy or sudden death.

With increasing awareness and better diagnostic tools the disease has moved from 'rare' to a 'relatively frequent' pregnancy complication, thereby raising research interest in this field.

Under the umbrella of the Heart Failure Association of the ESC, a PPCM Working Group was established in 2009, which led to several research projects advancing the knowledge about this condition.[70]

Despite ongoing research, numerous uncertainties regarding the incidence, pathophysiology, treatment, and prognosis of PPCM patients persist, indicating the need for further investigation. The need is to create more awareness about this condition globally, but also to understand differences in mode and presentation.

The establishment of the international registry on PPCM, funded by the ESC under the umbrella of the EORP, which recruited >700 patients from >40 countries will conclude its follow-up in 2021. Many more lessons will be learned from this program but also from other studies, such as the multi-centre Nigerian PEACE PPCM registry[54,71] and the large clinical service dedicated to women with PPCM in Iraq.[72]

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