Review Article on Cardiovascular Diseases in Low- and Middle-Income Countries

Detection and management of arrhythmias in peripartum cardiomyopathy

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Abstract: Peripartum cardiomyopathy (PPCM) is an idiopathic dilated cardiomyopathy, in which previously healthy women present with heart failure secondary to left ventricular (LV) systolic dysfunction during the last months of pregnancy or up to 5 months postpartum. PPCM occurs worldwide. The incidence seems to be increasing, possibly due to increasing awareness of the condition and diagnosis thereof. Women diagnosed with PPCM present with symptoms and signs of heart failure, thromboembolism or arrhythmia. Although the incidence of arrhythmias in this condition is not well documented, patients with PPCM often have rhythm disturbances. Indeed, life-threating arrhythmias contribute significantly to sudden cardiac death (SCD) in this population, especially when patients have poor systolic function. In this review, we summarize the evidence on atrial and ventricular arrhythmias in PPCM, as detected by various diagnostic modalities. Furthermore, we summarize the management of arrhythmias in PPCM, as recommended by contemporary guidelines.

Keywords: Ambulatory electrocardiographic monitoring (AECG); arrhythmia; cardioverter-defibrillator; electrocardiogram (ECG); peripartum cardiomyopathy (PPCM)

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Introduction

Peripartum cardiomyopathy (PPCM) is a rare, idiopathic dilated cardiomyopathy, presenting with heart failure secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or up to five months postpartum (1). PPCM occurs worldwide. However, the incidence of PPCM varies between countries as well as between ethnic groups (2-5). Incidence seems to be increasing, possibly due to increased awareness of the condition and the diagnosis thereof (6).

Even though the exact pathophysiology of PPCM is unknown, various mechanisms have been proposed to contribute to the pathogenesis. These include nutritional factors, viral infections, inflammatory and autoimmune processes, as well as a familial and genetic predisposition (7). Recent studies suggest that the nursing hormone prolactin is crucially involved in the pathogenesis of PPCM (8).

LV recovery in PPCM remains markedly heterogenous and differs significantly between countries and ethnicities. Recent reports suggest that approximately 45–75% of all affected women recover their LV function after 6 to 12 months. However, lower rates of recovery have been reported in developing countries (9). Although LV recovery predominantly occurs within the first 6 months after diagnosis, it has been shown to continue beyond

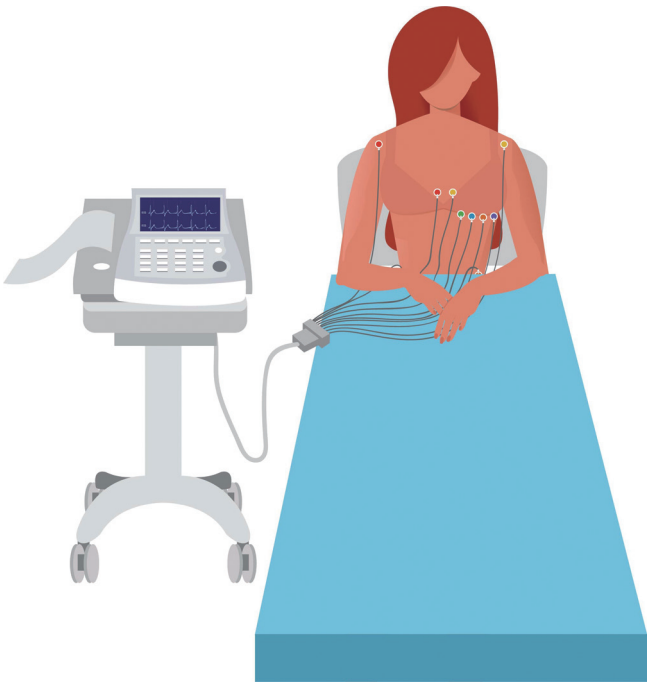

Figure 1 The 12-lead electrocardiogram forms part of the routine work-up of all patients who are diagnosed with peripartum cardiomyopathy. The test is non-invasive, widely available, inexpensive and easily performed.

12 months (10). African ethnicity seems to have an impact on the outcome of patients with PPCM, as it has been shown that women of African ethnicity present with a more severely reduced LV ejection fraction (LVEF) and recover less frequently than their non-African counterparts (11).

Sudden cardiac death (SCD), which is often the result of a preceding episode of a ventricular tachyarrhythmia, is responsible for about one-third of deaths in non-ischaemic cardiomyopathies (NICM) (12). In PPCM, SCD contributes to 25–39% of all-cause mortality (13,14), suggesting that arrhythmias are not uncommon in this population (15). Indeed, in a retrospective analysis of 9,841 hospital admissions for PPCM in the USA, arrhythmias were reported to have occurred in 18.7% of cases. In this study, ventricular tachycardia (VT)—seen in 4.2% of patients—was the most common arrhythmia, followed by atrial fibrillation (1.3%) and ventricular fibrillation (VF) (1%) (16). However, literature on the exact underlying mechanisms of SCD in the course of PPCM is scarce, particularly that pertaining to the burden of malignant ventricular arrhythmias. Nevertheless, studies show that reduced LVEF in the early stages of PPCM is accompanied by a high risk of life-threatening ventricular arrhythmias, which may lead to SCD if left untreated (17,18). In this regard, Goland *et al.* estimated that in the USA 1 in 4 women with PPCM suffer cardiac arrest secondary to ventricular tachyarrhythmia (14).

In this review, we explore the methods of detecting and diagnosing arrhythmias in PPCM, which may ultimately assist in the risk stratification and in decision of appropriate therapy. We also summarise the management of arrhythmias in PPCM, as recommended by contemporary guidelines.

12-lead electrocardiogram (ECG)

The 12-lead ECG (*Figure 1*) is an inexpensive, easily performed and widely available clinical investigation, which forms part of the routine work-up of patients who present with cardiovascular disease (*Table 1*). Indeed, the ECG is recommended in all patients who present with a suspected diagnosis of PPCM (27). The 12-lead ECG is invaluable for the analysis of waveform abnormalities that are associated with chamber enlargement (such as atrial dilatation or ventricular hypertrophy), conduction delays (such as bundle branch blocks) and repolarization abnormalities (such as T wave inversion and prolonged QT intervals) (28). The 12-lead ECG is also indispensable as a diagnostic modality of brady- and tachyarrhythmias.

Although there is no specific electrocardiographic abnormality that is pathognomonic of PPCM, women with PPCM rarely have a normal ECG (19,20). The most common waveform abnormalities seen on the 12-lead ECG include non-specific T wave changes (i.e., T wave inversion) and prolongation of the QTc interval (*Table 2*) (19-21,29,33). T wave inversion at the time of diagnosis is associated with poor systolic function (LVEF <35%) (20). Furthermore, an upright T wave in lead aVR has recently been shown to be a predictor of adverse outcome in PPCM (31). In another prospective study, QTc prolongation (i.e., corrected QT interval >460 ms) on the initial ECG was shown to be an independent predictor of poor long-term outcome in PPCM. In fact, all patients who died in this study initially presented with a prolonged QTc interval (20). Care should therefore be taken when treating patients with PPCM to avoid drugs that are associated with QT prolongation.

Despite the QRS complex of patients with PPCM being marginally wider than that of a healthy population (21), it is typically narrow (i.e., QRS <110 ms) (20,22,29). As opposed to other forms of dilated cardiomyopathy where bundle branch blocks are encountered in 25–30% of patients (34,35), bundle branch blocks are seldom found in

Table 1 Comparison of devices used to diagnose arrhythmias, with supporting evidence of the atrial and ventricular arrhythmias found in PPCM

	ECG	Ambulatory ECG monitoring		Cardioverter-defibrillator devices	
	12-lead ECG	Continuous monitoring (e.g., Holter ECG)	Intermittent monitoring (e.g., implantable loop recorder)	Wearable cardioverter-defibrillator (WCD)	Implantable cardioverter-defibrillator (ICD)
Length of recording	10 seconds	Usually 24 or 48 hours, though newer devices can monitor up to 60 days	Up to three years (depending on the battery leave of the device)	As long as wearable cardioverter-defibrillator is worn	As long as battery life of implanted cardioverter-defibrillator lasts
Purpose of device	Diagnostic	Diagnostic	Diagnostic	Therapeutic, but also provides diagnostic information	Therapeutic, but also provides diagnostic information
Application	Non-invasive	Non-invasive	Invasive	Non-invasive	Invasive
Arrhythmias diagnosed	Whereas sinus tachycardia is common at time of diagnosis, sinus arrhythmia becomes more prevalent at follow up (19-21). While sinus tachycardia is associated with poor outcome, sinus arrhythmia predicts freedom of death and readmission to hospital (20). Prolonged QTc at time of diagnosis is associated with poor outcome (thought to be related to increased risk of ventricular arrhythmias) (20). Atrial fibrillation and LBBB, which are more prevalent in other forms of non-ischaemic dilated cardiomyopathy, seem to be uncommon in PPCM (20,22,23). AV block SVT and VT are rarely diagnosed by 12-lead ECG in PPCM (19-21)	Literature confined to a single study on 19 patients: sinus tachycardia found in 89% and non-sustained ventricular tachycardia in 21% of patients (24)	To the best of our knowledge, there is no literature available on external or implantable loop recorders in PPCM	WCD for primary prevention of SCD used in patients with LVEF <35%: though Saltzberg *et al.* (25) detected no arrhythmias, Duncker *et al.* (17,18) reported in two studies that the WCD could detect non-sustained ventricular tachycardia and ventricular fibrillation, which were successfully aborted by the WCD	ICD for primary prevention of SCD used in patients with LVEF <35%. A single study reports that 37% of patients had appropriate shocks (26)

ECG, electrocardiogram; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; PPCM, peripartum cardiomyopathy; QTc, corrected QT interval; SCD, sudden cardiac death; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Table 2 Summary of prospective and retrospective studies diagnosing arrhythmias in PPCM

Author	Year	Country	N	Main finding about arrhythmias in PPCM	Arrhythmias diagnosed with				
					ECG	Holter	ILR	WCD	ICD
Prospective studies									
Diao *et al.* (24)	2004	Senegal	19	24-hour Holter found sinus tachycardia in 89% of patients, non-sustained VT in 21%		X			
Duncker *et al.* (17)	2014	Germany	12	9 of 12 patients had LVEF <35%; in 3 of 7 patients with WCD, ventricular tachyarrhythmias were detected and successfully treated by the device				X	
Duncker *et al.* (18)	2017	Germany	49	All patients had LVEF <35% and fitted with WCD. Of these 12% had ventricular tachyarrhythmias with appropriate therapy by the device				X	
Hoevelmann *et al.* (20)	2019	SA	66	Prolonged QTc and sinus tachycardia were independent predictors of poor outcome. Sinus arrhythmia was associated with event-free survival	X				
Honigberg *et al.* (29)	2019	USA	88	Left atrial enlargement on ECG predicted poor long-term outcome	X				
Karaye *et al.* (21)	2016	Nigeria	54	54 patients with PPCM were compared with 77 healthy controls. QTc prolongation was found in almost 25% of those with PPCM	X				
Ntusi *et al.* (23)	2015	SA	30	30 patients with PPCM were compared to 53 patients with hypertensive heart failure of pregnancy. Atrial fibrillation was found in 10% of patients with PPCM	X				
Pillarisetti *et al.* (30)	2014	USA	100	2 patients died from arrhythmia-related causes (unspecified)	?				
Saltzberg *et al.* (25)	2012	USA	107	107 patients with PPCM were compared with 109 other non-dilated ischaemic cardiomyopathies. None of the patients with PPCM experienced any arrhythmic events				X	
Sliwa *et al.* (22)	2017	SA	411	Left bundle brunch block occurred in 9.3% of patients with PPCM	X				
Tibazarwa *et al.* (19)	2012	SA	78	Sinus tachycardia was found in 45% of PPCM patients, left bundle branch block in 5%, PVC in 4%	X				
Retrospective studies									
De Benedetti Zunino *et al.* (26)	2014	USA	19	ICD for primary prevention: 37% of patients had appropriate shocks					X
Ekizler *et al.* (31)	2019	Turkey	82	An upright T wave in lead aVR on ECG was associated with poor outcome	X				
Goland *et al.* (14)	2009	USA	46	15% had ventricular tachyarrhythmias requiring ICD; 7% had bradyarrhythmias requiring pacemakers	?				
Laghari *et al.* (32)	2013	Pakistan	45	6.6% of patients presented with ventricular tachycardia	?				
Li *et al.* (33)	2016	China	71	QTc prolongation was found in 47% of PPCM patients	X				
Mallikethi-Reddy *et al.* (16)	2017	USA	9841	Arrhythmias were present in 18.7% of hospitalized PPCM cohort. 4.2% had VT, 2.2% had sudden cardiac death	?				

ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; ILR, implantable loop recorder; LVEF, left ventricular ejection fraction; PPCM, peripartum cardiomyopathy; PVC, premature ventricular complex; QTc, corrected QT interval; VT, ventricular tachycardia; WCD, wearable cardioverter-defibrillator; SA, South Africa; USA, the United States of America.

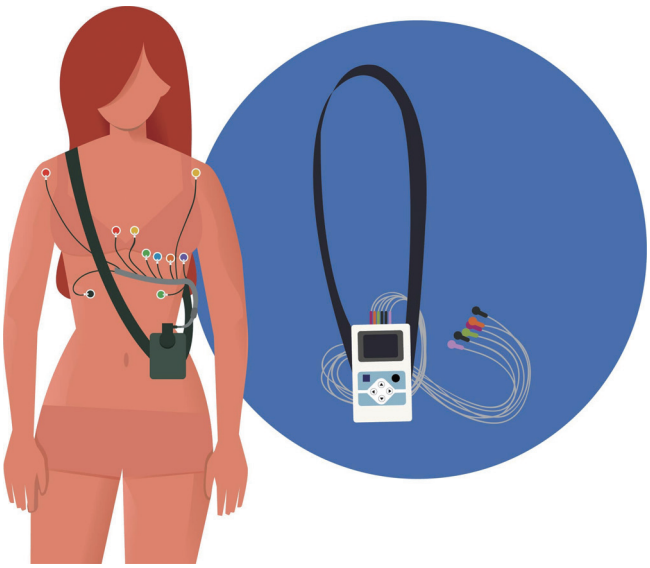

Figure 2 The Holter ECG is a form of continuous ambulatory ECG monitoring, which typically records data for 24 to 48 hours. The Holter ECG has a good yield of arrhythmias, but only if they occur frequently. ECG, electrocardiogram.

PPCM (20,22). Though the literature on bradyarrhythmias in PPCM is scarce, it has been reported that up to 7% of patients require permanent pacing (14).

The majority of patients with PPCM present with sinus rhythm. Though sinus tachycardia (i.e., sinus rhythm with heart rate >100 beats per minute) is frequently found at the time of diagnosis, there seems to be a significant reduction in heart rate between the initial presentation with PPCM and subsequent follow-up visits (20,22). Sinus arrhythmia (i.e., sinus rhythm with variable RR intervals), which occurs in about one third of patients at the time of their PPCM diagnosis, becomes more prevalent at long-term follow-up (20). Whereas sinus tachycardia at the time of diagnosis has been shown to be an independent predictor of poor long-term outcome in PPCM, sinus arrhythmia seems to be associated with event-free survival (i.e., no death or readmission to hospital) (20).

Although atrial fibrillation is more prevalent in PPCM than in hypertensive heart failure of pregnancy (23), it remains relatively uncommon (20,31). Supraventricular and ventricular tachycardia are rarely are rarely recorded by the 12-lead ECG in patients with PPCM (16,20,29). However, as the 12-lead ECG usually only records a 'snapshot' of 10 seconds, it is thought that the true incidence of these brady- and tachyarrhythmias is underestimated by studies that include the 12-lead ECG as the only method of diagnosing arrhythmias in PPCM.

Ambulatory ECG monitoring

Ambulatory electrocardiographic monitoring (AECG) is essential in the work-up of arrhythmias, especially when arrhythmias and/or symptoms are paroxysmal (36). Because ambulatory ECG monitoring extends the recording time significantly from the 10-second long 12-lead ECG, it allows for a more accurate characterization of cardiac activity during ordinary daily activities and increases the yield of arrhythmias (36,37).

AECG devices can be categorized according to whether they record continuously (over a shorter period of time) or intermittently (with brief recordings over an extended period of time) (37). Continuous AECG monitoring is commonly referred to as "Holter" ECG monitoring (*Figure 2*). Holter monitors are non-invasive and are usually worn for a period of 24 to 48 hours (38,39), though newer technology allows monitoring for up to 60 days (40). Holter monitoring is more likely to detect arrhythmias if symptoms and/or arrhythmias occur frequently. However, intermittent AECG monitoring allows for longer periods of surveillance. Intermittent AECG devices include external loop recorders (i.e., an adhesive electrode that is usually worn for up to two months) and implantable loop recorders (ILR) (i.e., a monitoring device that is implanted subcutaneously) (*Figure 3*). Due to recent advances, newer ILR devices are smaller in size and have improved algorithms for arrhythmia detection (*Figure 4*) (41). Although loop recorders are worn continuously, they only record when the device detects an arrhythmia or when patients activate the device when symptomatic. Because of their extended monitoring, loop recorders are more likely to detect intermittent or infrequent arrhythmias (40).

Literature on ambulatory ECG monitoring in PPCM is limited to a single study by Diao *et al.*, who prospectively studied the detection of arrhythmias by 24-hour Holter in a cohort of 19 patients with PPCM (24). Though infrequent symptoms impede the detection rate of arrhythmias by Holter monitoring (38), the 24-hour Holter recorded VT in 4 of 19 the patients (21%) in this cohort (24).

Similarly, the 12-lead ECG does not often record premature atrial or ventricular contractions in PPCM (20), but these were more frequently diagnosed by Holter monitoring, i.e., premature atrial contractions in 21% and

premature ventricular contractions in 36.8% of patients in the study by Diao *et al.* (24). The significance of detection of premature complexes by AECG in PPCM has not yet been studied.

In addition to the detection of arrhythmias, Holter monitoring also provides useful information regarding heart rate. The ambulatory monitoring device's software typically provides the average heart rate over the monitoring period, as well as the minimum and maximum heart rates, and the time spent in bradycardia and tachycardia over the period that the Holter ECG was worn by the patient (36,40). In their study, Diao *et al.* demonstrated that Holter monitoring was more sensitive at diagnosing sinus tachycardia: the 24-hour Holter detected sinus tachycardia in 89.4% of patients with PPCM, whereas the 12-lead ECG recorded sinus tachycardia in only 68.4% of patients from the same cohort (24). Diagnosing sinus tachycardia may have implications on risk stratification of patients with PPCM, as sinus tachycardia on the 12-lead ECG has been shown to be associated with poor long-term outcome (20).

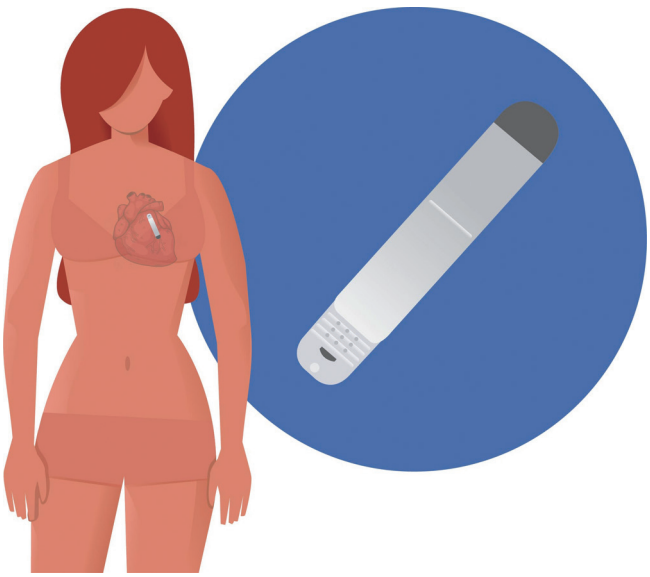

Figure 3 The implantable loop recorder (ILR) is a form of intermittent ambulatory ECG monitoring, which is implanted subcutaneously and can record up to 3 years' data. ILRs should be considered when arrhythmias are thought to occur infrequently and when the Holter ECG is non-revealing. ECG, electrocardiogram.

As SCD significantly contributes to mortality in PPCM, and recognizing the shortage of literature on ECG monitoring beyond that of the 12-lead ECG, future research should include AECG in prospective studies to establish the true incidence of arrhythmias in PPCM. At present, there is an ongoing study with an ILR for the early identification of patients with PPCM at risk for arrhythmic events.

Prevention and treatment of arrhythmias in PPCM

The management of arrhythmias in PPCM requires the concurrent treatment of systolic heart failure. The essential therapies for acute PPCM can be summarized with the acronym 'BOARD' (Bromocriptine, Oral heart failure therapies, Anticoagulants, vasoRelaxing agents, and Diuretics) (42). As outlined in the European Society of Cardiology (ESC) Guidelines (43), therapeutic management

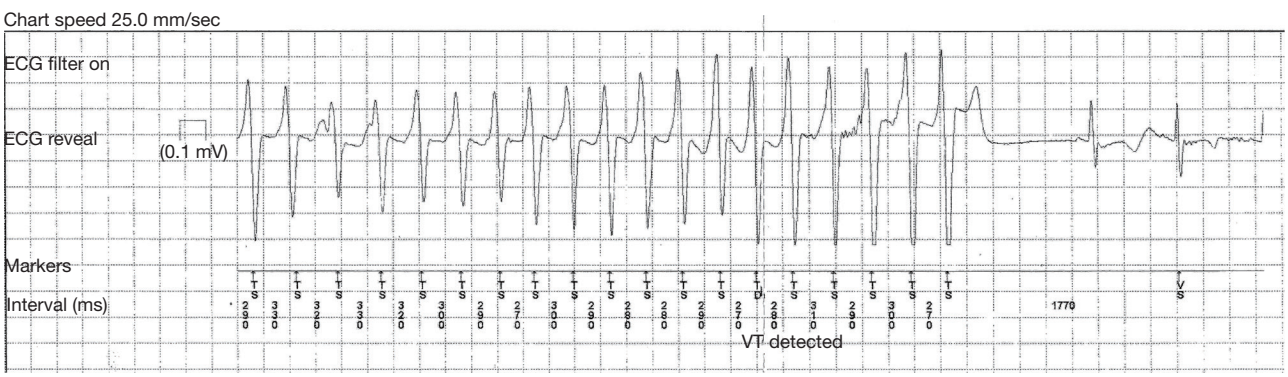

Figure 4 An episode of non-sustained ventricular tachycardia (VT) as recorded by an implantable loop recorder in a patient with peripartum cardiomyopathy. The non-sustained VT is recognised by the wide QRS complexes with short RR intervals (on the left). The last two beats (on the right) represent sinus rhythm with narrow QRS complexes.

of acute PPCM differs depending on the severity of heart failure, and whether the patient presents during the antepartum or postpartum period.

In the antepartum period, patients with PPCM are best co-managed by a team consisting of cardiologists and obstetricians to ensure the health of the mother and the foetus. Due to the risk of fetotoxic side-effects, treatment such as angiotensin converting enzyme inhibitors (ACE-i), angiotensin II receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI) and mineralocorticoid receptor antagonists (MRA) should rather be avoided during pregnancy. However, hydralazine and nitrates have been shown to be safer in the antepartum period instead. Loop diuretics could be considered for the treatment of pulmonary congestion and vaginal delivery should be pursued in patients without cardiopulmonary distress. Beta-blockers (i.e., metoprolol as preferred agent) could be initiated but the doses should be titrated with caution (27,43).

After delivery, treatment of PPCM should be aligned with contemporary acute and chronic heart failure guidelines (27,44-46). First-line therapy should consist of a combination of beta-blockers, ACE-i/ARBs, an MRA and diuretics. The benefits of using digoxin in addition to first-line therapy remains controversial (47). The use of the prolactin-blocker, bromocriptine, should be considered, and should be accompanied by anticoagulants to reduce the risk of thromboembolic events (27).

As sinus tachycardia is associated with adverse outcome in PPCM, ivabradine may be considered in addition to first-line therapy in patients with an increased resting heart rate who are not pregnant or breastfeeding (27,43). However, evidence supporting the use of ivabradine in this setting is currently limited to a single retrospective observational study (48).

When a patient with PPCM develops atrial fibrillation, beta-blockers and/or digoxin could be considered. Because amiodarone is associated with foetal side effects, it should be reserved for emergency situations. Electrical cardioversion is only indicated in the setting of haemodynamic instability (43,49).

Patients with PPCM who present with sustained VT or VF should be electrically cardioverted or defibrillated without delay (43,50). Intravenous amiodarone may be considered in patients with refractory VT (43,50).

Implantable cardioverter-defibrillator (ICD)

Patients with severely impaired systolic function (LVEF <35%) are at high risk of life-threatening ventricular arrhythmias, which could result in SCD (51,52). The current ESC guidelines on acute and chronic heart failure therefore recommend ICD implantation as primary prevention in patients with severely reduced ejection fraction (i.e., LVEF <35%) despite optimal medical therapy (OMT) and as secondary prevention in patients with a documented or survived episode of ventricular arrhythmias (44). Indeed, in a retrospective analysis of 19 patients with PPCM that received ICDs for primary prevention of SCD, 36.8% received appropriate shocks (26). However, given the high LV recovery rate associated with PPCM, the decision to implant an ICD should be made with caution. Early implantation of ICDs is often not justifiable in this young population and it has therefore been suggested that, in PPCM, they should be reserved for patients without LV recovery (27,43).

Wearable cardioverter-defibrillator (WCD)

A WCD (LifeVest®, Zoll, Pittsburgh, PA, USA) is a safe and non-invasive device, which can protect from SCD during a suspected, vulnerable period for arrhythmic events. The vest continuously analyzes the heart rhythm and delivers biphasic shocks once a life-threatening arrhythmia is detected (53). Although these devices primarily have a therapeutic indication, they also offer important diagnostic information. A recent study from Germany evaluated the use of a WCD for prevention of SCD in PPCM in PPCM (*Figure 5*). During a cumulated wearing time of 932 days, four adequate shocks were delivered by the WCD for VF to the seven patients with newly diagnosed PPCM and severely reduced ejection fraction (LVEF <35%) who opted to wear the WCD (17). In a subsequent study on 49 patients with newly diagnosed PPCM and severely reduced ejection fraction (LVEF <35%), the WCD recorded ventricular arrhythmias in six patients (12%), i.e., five episodes of VF, two sustained VTs and one non-sustained VT. All episodes of VF were terminated by a WCD shock and no inappropriate shocks occurred during the study period. These ventricular arrhythmias occurred between 40 and 165 days after the diagnosis of PPCM was made and the WCD was fitted (18).

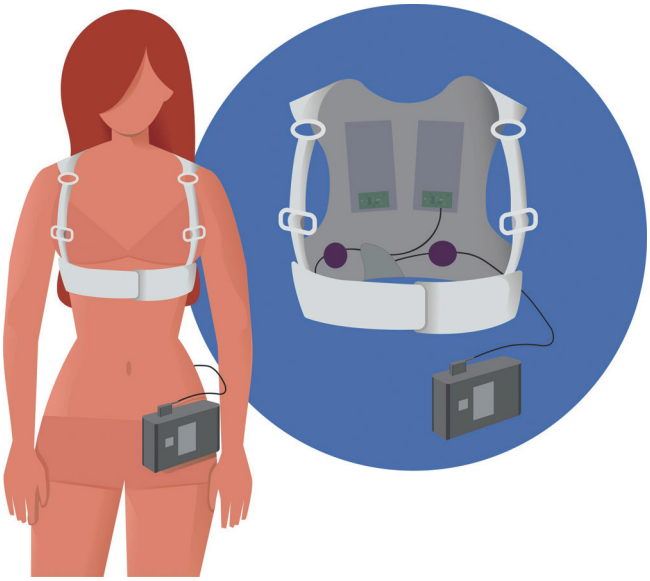

Figure 5 The wearable cardioverter-defibrillator (WCD) is a non-invasive device that is worn by patients with LVEF <35%. The WCD is able to deliver biphasic shocks when a life-threatening arrhythmia is detected and could be used as a 'bridging' strategy during the first 6 months of vulnerability to sudden cardiac death in PPCM, before a final decision towards implantable cardioverter-defibrillator (ICD) is made. PPCM, peripartum cardiomyopathy; LVEF, left ventricular ejection fraction.

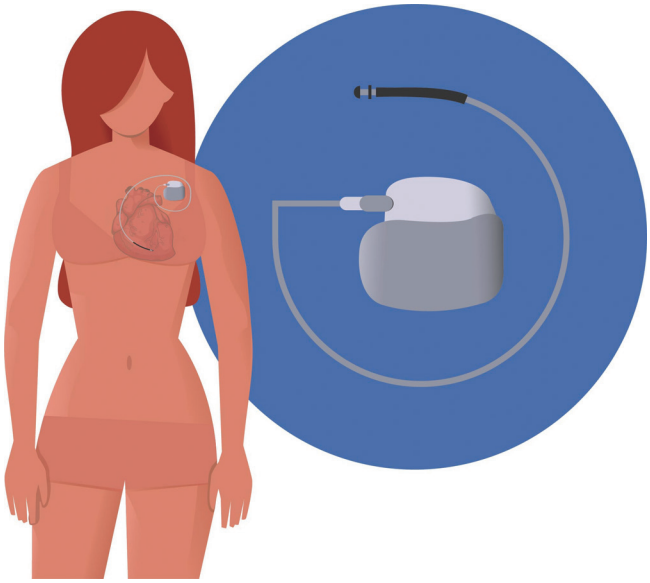

Figure 6 The implantable cardioverter defibrillator (ICD) delivers shocks when life-threatening arrhythmias are detected. In PPCM, ICD therapy is best reserved for patients without LV recovery (usually LVEF <35%) at follow-up. PPCM, peripartum cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction.

Despite the limited evidence on WCD in PPCM, the current European and American guidelines suggest consideration of these devices for high-risk patients with LVEF ≤35% as a 'bridging strategy' to LV recovery (27,43). Bearing in mind that a WCD could save the life of a young mother, the high costs of the vest could be justifiable; especially given its reusability. ICD implantation (*Figure 6*) and cardiac resynchronization therapy (CRT) [for patients with LBBB (left bundle branch block) and QRS duration ≥130 ms] should be reserved for patients with persistent LV dysfunction (LVEF <35%) despite OMT at 6 to 12 months after presentation (43,54).

Conclusions

The 12-lead ECG commonly shows repolarisation changes such as T wave inversion and QT prolongation. However, arrhythmias other than sinus tachycardia are infrequently detected by the 12-lead ECG. Though there is limited literature on ambulatory ECG monitoring in PPCM, it has been shown that life-threatening ventricular arrhythmias might be relatively common in the early phase of the condition. Because LV recovery is common in PPCM, the decision to insert an ICD in a patient who initially presents with an LVEF <35% could be delayed, and a WCD could be considered instead. The WCD could be used as 'bridging therapy' until the LVEF is re-evaluated at follow up. ICDs are best reserved for patients with PPCM without LV recovery after 6 months.

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