Education in Heart

Title: Peripartum cardiomyopathy: diagnosis and management

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Learning objectives

1) Become familiar with the mortality and cardiac recovery rates from PPCM
2) Consider the therapeutic strategies in PPCM
3) Learn what is known of the pathogenesis of PPCM

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Introduction

In 2010 the European Society of Cardiology's Peripartum Cardiomyopathy (PPCM) Working Group defined PPCM as "an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion"[1] (Figure 1). It is important to appreciate that not all heart failure during pregnancy is due to PPCM. Other cardiovascular conditions can present during pregnancy; for example, pre-exisiting cardiomyopathies or previously undiagnosed congenital or valvular heart disease.

How common is peripartum cardiomyopathy?

The incidence of PPCM varies between countries and between races within countries. In Africa, amongst predominantly black populations, the incidence is around 1 in 1000 live births[1]. There are a few countries where PPCM appears to be much more common. For example, in Nigeria and Haiti an incidence of 1 in 100 and 1 in 300 pregnancies respectively has been reported[2,3]. In the United States, the incidence in predominantly white populations is between 1 in 1000 and 1 in 4000, but in African-American populations it is between 1 in 1000 and 1 in 2000. The incidence in Europe and Australasia is as yet unstudied. The incidence does appear to be increasing – possibly due to increased awareness and diagnosis[4].

It is striking that PPCM is usually recognised when patients are very sick with severe myocardial dysfunction[5]. It seems very likely that less severe forms of PPCM go undiagnosed, with symptoms being ascribed to the stresses around the arrival of a new child or alternative diagnoses. To establish the true incidence of PPCM, a prospective, multicentre, international initiative monitoring thousands of women starting normal pregnancies would be necessary. This might be achievable if cardiac biomarkers are identified as a gateway to further investigation (see later discussion of potential biomarkers).

What causes PPCM?

A number of potential factors have been associated with the development of PPCM. Environmental factors might be important in some regions. For example, in Nigeria mothers consume more salt around the time of birth. Viruses, dietary deficiencies and inflammation have been reported to be associated with PPCM, but no strong evidence points to a causative role[6].

Risk factors that have been associated with PPCM include increasing age, multiple births, black and Asian race[7] and hypertension/pre-eclampsia[8]. Whether or not pre-eclampsia is a distinct entity or an over-lapping condition is the subject of debate. The most important clinical issue is to identify and treat hypertension, heart failure and left ventricular dysfunction if present.

Two mechanisms have recently been proposed as likely causes of PPCM. One involves the pituitary hormone prolactin and the other placental soluble fms-like tyrosine kinase 1 (soluble-Flt1).

Elegant animal models have demonstrated that, during pregnancy, excessive oxidative stress can lead to prolactin being cleaved by cathepsin D into an abnormal 16kDa form which can damage the heart and blood vessels (e.g. through apoptosis of endothelial cells)[9,10]. In murine models, treatment with bromocriptine (which suppresses prolactin) reverses experimental PPCM. The 16kDa prolactin-

mediated damage has been shown to involve micro-RNA 146a. Levels of this are elevated in patients with PPCM, emphasising the relevance of this in humans. Discovery of the 16kDa prolactin pathway has led to bromocriptine being advocated as a treatment for patients with PPCM. Bromocriptine as a therapy will be discussed later in this article. Micro-RNA 146a might also represent a diagnostic biomarker tool and could conceivably also be a therapeutic target.

Soluble-Flt 1 is secreted by the placenta and acts by inhibiting vascular endothelial growth factor (VEGF) signalling leading to endothelial dysfunction and causing angiogenic imbalance. Soluble-Flt 1 plasma levels are higher towards the end of pregnancy in patients with PPCM[11]. Increased levels of soluble-Flt1 are associated with worse clinical outcomes[12]. That both 16kDa prolactin and soluble-Flt1 are elevated in patients at the time when PPCM manifests suggests a role for both these pathways in the development of PPCM. It may also provide a link between pre-eclampsia and PPCM.

A potentially beneficial hormone in PPCM is relaxin-2. Relaxin is produced in the ovaries, breast and placenta with receptors in the heart, smooth muscle and connective tissue. It has a variety of haemodynamic effects, including increased cardiac output and decreased systemic vascular resistance, as well as anti-inflammatory and anti-fibrotic properties. Higher levels of relaxin-2 are associated with increased rates of myocardial recovery[13]. A recent trial of relaxin in acute heart failure (not in PPCM) reported no reduction in cardiovascular death or worsening heart failure[14]. The roles of soluble-FLt1, 16kDa prolactin and relaxin-2 are summarised in Figure 2.

Familial occurrence has been described in PPCM, suggesting a possible role for a genetic pre-disposition. However, pregnancy may also unmask a previously undiagnosed familial cardiomyopathy [15]. PPCM shares similar genetic findings with patients with dilated cardiomyopathy of other mechanisms[16]. A recent study found that 15% of individuals have a pathogenic genetic mutation, most commonly truncating variants in the titin (TTN) gene. As this field evolves, we will hopefully find out which patients have a primary genetic cardiomyopathy and how many have PPCM with a genetic pre-disposition.

Presentation of PPCM

PPCM most commonly presents post-partum and most commonly in the week after birth[1718]. The European Society of Cardiology PPCM Working Group removed the artificial time cut offs that had been a feature of previous definitions[1]. A sizeable proportion does present pre-partum.

Symptoms and signs of PPCM

Distinguishing symptoms of PPCM from those of normal pregnancy is not easy. Shortness of breath, fatigue and ankle oedema are not specific to PPCM. When a woman reports orthopnoea, paroxysmal nocturnal dyspnoea or marked ankle swelling, PPCM should be suspected. The non-specific nature of presenting complaints, as well as lack of awareness of the condition, often results in delayed diagnosis. Persistent cough, palpitations or right hypochondrial pain should raise suspicion. Women can present with symptoms of thromboembolic complications of PPCM, for example unilateral leg swelling (deep venous thrombosis), stroke or acute limb ischaemia (arterial embolisation). Around 6% of patients with PPCM experience thromboembolic complications[4]. Signs of PPCM can include those normally found in patients with heart failure, but basal crackles are less

common (as they are in other cohorts of young versus older patients with heart failure[19]). Tachycardia, elevated jugular venous pressure, a third heart sound and displaced apex beat are common.

Investigations

The diagnostic approach to suspected PPCM is illustrated in Figure 3. When PPCM is suspected, an electrocardiogram, natriuretic peptide measurement and echocardiogram should be performed urgently. Cardiological review should follow any abnormal results. A chest x-ray is not diagnostic in the assessment of PPCM as heart size cannot be determined accurately. However, a chest x-ray may be required to investigate the cause of breathlessness if unclear. Chest x-ray in pregnancy should be considered safe, with a negligible radiation dose. Differentiating PPCM from other cardiovascular and non-cardiovascular causes of symptoms during pregnancy is often challenging. The major differential diagnoses are listed in Table 1. BNP and NT-proBNP are not elevated in normal pregnancy so can be useful to diagnose PPCM[20]. There is a suggestion that microRNA 146a might prove to be a biomarker specific for PPCM, but this is not yet validated sufficiently to be recommended in clinical practice[10]. The most common finding on an electrocardiogram is a sinus tachycardia. ST segment and T wave changes are also common[21]. Echocardiography in PPCM is characterised by left (and often right) ventricular dilatation and dysfunction. As left ventricular systolic function is normal or even hyperdynamic in pregnancy, any quantitatively- or qualitatively-reported impairment of left ventricular systolic function should prompt further assessment. Secondary mitral regurgitation is common. Left ventricular thrombus is common. There are no specific features of PPCM on cardiac magnetic resonance imaging, but it can complement the information provided by echocardiography (e.g. it is more sensitive for detecting thrombus) and is considered to be safe in pregnancy. Gadolinium contrast agent is usually avoided as its safety in pregnancy is unknown.

Delivery of a patient with PPCM

When PPCM is diagnosed pre-partum, an urgent assessment by a multidisciplinary team involving cardiologists, obstetricians, neonatologists and anaesthetists is necessary. Involvement of cardiac surgeons (if it is felt likely that mechanical circulatory support may be required) should also be considered. Timing, mode and location of delivery should be the focus of discussion between the clinical team and the patient as early as possible, and should take into account the patient's wishes. Women with PPCM should be delivered in a high-risk obstetric or cardiac unit by a specialist multidisciplinary team with expertise in managing pregnancy in women with cardiac disease. There should be access to level 3 intensive and neonatal intensive care units. Clinical status of the mother, severity of left ventricular dysfunction, and growth of the foetus are all markers that are used to guide when and how a woman with PPCM delivers. Spontaneous vaginal delivery is often possible, but Caesarean section is preferred if the mother is critically ill. Steroids should be given before delivery for neonatal lung maturity.

Outcomes of PPCM

Death

PPCM had the lowest mortality of all causes of dilated cardiomyopathy in one large series[22]. The only major study of in-hospital mortality of PPCM reported that 1.3% of women with PPCM died[23]. Studies from different countries report widely varying mortality rates. The 6-month mortality rate was reported to be around 15-30% in most series enrolling in the 1990s or early 2000s[243], although most of these studies were conducted in Africa or Haiti. Recent studies have reported markedly lower death rates. The IPAC (Investigation of Pregnancy-Associated Cardiomyopathy) multicentre study of 100 patients in the Unites States of America reported a 1-year mortality rate of 4%[25]. Low mortality rates have been reported in Pakistan (0% at 6 months), Japan (4% at 6 months) and Germany (2% at 6 months)[262728]. Mortality rates appear to be higher in black compared to white populations[1], and higher mortality rates are reported from South Africa and Turkey[293031]. Although late deaths have been reported in the literature, few studies have examined long-term mortality rates.

Myocardial recovery

The common question that follows a diagnosis of PPCM is: can cardiac function recover? Certainly, PPCM is the sub-type of cardiomyopathy with the greatest rate of myocardial recovery. Older studies, predominantly from Africa, reported that by 6 months around 30% of patients displayed evidence of myocardial recovery. The recent IPAC study reported much greater recovery rates than had been previously; 72% had an ejection fraction of greater than 50% and 52% greater than 55% at 1 year[25].

Can we predict myocardial recovery?

Those who present with the lowest ejection fraction are the least likely to recover[25]. Those with low NT-proBNP or troponin levels are more likely to recover[32]. There are no accurate predictors of whether or not myocardial recovery will occur. The lack of ability to predict recovery makes clinical decision-making difficult as a patient with initially low ejection fraction may recover; therefore the use of implanted cardioverter defibrillators, ventricular assist devices or transplantation may have been unnecessary if used too early.

Maternal/ child bonding and psychology

Being diagnosed with PPCM is traumatic for the mother, father and family. Every effort should be made to allow for the mother and child to be together. Remote baby monitors can be used. Formal psychological support should be offered to the family.

Breast-feeding

The advantages and disadvantages of breast-feeding should be discussed with the mother[33]. Although there are few hard data, angiotensin converting enzyme (ACE) inhibitors, beta-blockers and spironolactone are generally considered safe in breastfeeding[34]. Most guidance does, however, recommend avoiding ACE inhibitors in the first few weeks after delivery, particularly in pre-term infants due the risk of neonatal hypotension. The amount of beta-blocker and spironolactone present in breast milk is negligible. The use of warfarin is also considered safe. If bromocriptine is used, breast-feeding is suppressed. Involving a pharmacist in prescribing is wise. There have been concerns about the impact of breastfeeding on maternal health in women with heart failure

(especially women who are critically ill), but also the impact of withholding breastfeeding on bonding and child health.

Treatment

There are as yet no specific treatments for PPCM, but marked progress in understanding pathogenetic mechanisms may lead to targeted treatments. Current pre-delivery, post-delivery and long-term management is summarised in Figure 4.

Pharmacological therapy

Before delivery

Before delivery, patients with symptomatic PPCM should receive diuretics. Although patients are commonly given advice about fluid and salt restriction, there is a lack of evidence to support this recommendation. Diuretics result in improved symptoms and clinical status. It has been proposed that diuretics reduce placental flow, but this is not the experience in clinical practice (in fact placental flow is likely to be improved with improved haemodynamic status). ACE inhibitors and angiotensin receptor blockers are not recommended during pregnancy as they are associated with a diverse range of congenital abnormalities. The combination of hydralazine and nitrates is thought to be safe. Beta-blockers can be used with caution if the patient is stable and euvolaemic, although foetal growth screening is recommended. Mineralocorticoid receptor antagonists and ivabradine are not recommended during pregnancy due to lack of safety data.

After delivery

After delivery, standard pharmacological treatment for heart failure due to left ventricular dysfunction should be started.

Anticoagulation

Treatment dose anticoagulation should be used if there is left ventricular thrombus or atrial fibrillation. As pregnancy and heart failure are both pro-coagulant conditions, and the frequency of thromboembolic events is in the region of 6%, anticoagulation should be considered in all patients after diagnosis. Heparin is used to anticoagulate pre-partum and low molecular weight heparin or warfarin is used postpartum. Some countries choose to use prophylactic dose low molecular weight heparin only, while others use treatment dose. There is no consensus as to how long to continue anticoagulation after delivery. Some argue that, as the pro-coagulant effects of pregnancy are low after 6 weeks, anticoagulation should be stopped. Others continue until 6 months or until substantial recovery in cardiac function is seen. Confidence in stopping anticoagulants is increased if cardiac function improves.

Inotropic support

A very small randomised placebo-controlled trial of levosimendan against placebo did not demonstrate benefit[35]. The management of acute severe PPCM-related heart failure has recently been reviewed by the European Society of Cardiology's Heart Failure Association's PPCM Working Group. Recommendations for inotropes are essentially the same as other causes of acute heart failure with the exception of a recommendation to avoid catecholamines if possible[36] (Figure 5).

Should bromocriptine be used to treat PPCM?

As described above, there is good evidence that the abnormal 16kDa prolactin fragment pathway is associated with the pathogenesis of PPCM. Given that bromocriptine suppresses the production of prolactin, this has been proposed as a treatment (but it means a mother cannot breastfeed). In 2010, a randomised trial of bromocriptine therapy was published[37]. 20 patients were randomised to placebo or bromocriptine. Bromocriptine was associated with greater recovery of left ventricular function. 4 of 10 patients died in the placebo arm and 0 of 10 died in the bromocriptine arm. Bromocriptine was also associated with greater recovery in left ventricular function in a non-randomised study of 96 patients in Germany[28]. A randomised trial is nearing completion in Germany and is eagerly awaited (Clinicaltrials.gov NCT00998556). However, data from the initial randomised trial of 20 patients suggested that the growth curves of the children of mothers randomized to bromocriptine or standard care were normal compared to World Health Organization standard curves[37]. Bromocriptine use in the USA is subject to a black box warning due to increased thromboembolic risk. Its use varies due to the lack of strong evidence, with only 1% of the IPAC USA cohort receiving the drug compared to 57% in the cohort from Germany[25].

Should medical therapy be withdrawn in patients whose hearts recover after PPCM?

Women who have echocardiographically-recovered myocardial function after PPCM are usually keen to stop their medical therapy. There are limited data to guide this decision. One study of 15 patients found no deterioration in left ventricular function after 2 years off therapy[38]. Some patients with apparently normal left ventricular function have abnormal contractile reserve on stress echocardiography[39]. Anecdotally, some women do have deterioration in cardiac function after withdrawal of therapy. Withdrawal decisions should be discussed with the patient and family and sequential withdrawal of treatment seems reasonable with monitoring of cardiac function.

Implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy (CRT)

It is a concern when patients with PPCM are about to be discharged with on-going (often very severe) severe left ventricular dysfunction. In observational cohorts, sudden death is commonly reported as the mode of death, with 38% of deaths reported as sudden in one study from the USA[40]. There are few data of the efficacy of ICDs in cohorts with PPCM. It is tempting to consider implanting an ICD. As with all causes of heart failure, guidelines suggest a period of best medical therapy before considering ICD implantation. Since most patients with PPCM show some recovery of left ventricular function, it is wise to wait until at least 6 months after diagnosis. A similar argument can be made for delaying CRT for around 6 months.

Wearable cardioverter defibrillators

To “bridge” the gap between severe left ventricular dysfunction and potential myocardial recovery, some have advocated wearable cardioverter defibrillators. In one single-centre observational cohort from a tertiary referral centre, 7 patients were provided wearable cardioverter defibrillators and 3 had appropriate therapies for ventricular dysrhythmias[41]. Another retrospective study of 107 patients reported no shocks in a cohort of 107 patients wearing cardioverter defibrillators[42]. A multicentre trial would be valuable to establish if these devices are beneficial.

Mechanical circulatory support and cardiac transplantation

Around 5% of patients with PPCM receive a left ventricular assist device (LVAD) or undergo cardiac transplantation[1]. Some have reported that LVADs are associated with recovery of left ventricular function in PPCM, although explantation of LVADs is not common. Care should be taken to ensure that these devices are necessary and that the patient would not recover with optimal pharmacological therapy alone. Outcomes of patients with PPCM undergoing LVAD implantation do appear to be better than general cohorts with dilated cardiomyopathies[43]. Cardiac transplantation is sometimes necessary in those who struggle despite optimal management. Outcomes of patients with PPCM appear worse than other aetiologies undergoing cardiac transplantation, with higher rates of rejection and mortality[44]. Some patients do undeniably present in extremis and warrant short-term mechanical circulatory support.

Contraception and further pregnancy

Patients must be counselled with regard to contraception and the potential risk of future pregnancies. This counselling should take place before discharge and, ideally, a contraceptive solution be provided. Counselling about future pregnancy risk will need to be reassessed as the patient progresses and should involve both a cardiologist with expertise in cardiac obstetrics and an obstetrician.

Contraception

Progesterone-only coils, implants/injectables or progesterone-only pills are the preferred mode of contraception. Oestrogen-containing combined oral contraceptives are not recommended, both because they are pro-thrombotic and because they increase fluid retention, which may exacerbate cardiac disease. Barrier methods are not sufficiently reliable[1].

Future pregnancies

Historically patients with PPCM were advised not to have further pregnancies. Women should now be offered careful assessment and pre-pregnancy counselling by a combined cardiac obstetric team to help them and their partner decide how they wish to proceed in terms of future pregnancy. If left ventricular function has recovered there is a risk of recurrent heart failure of around 25% during a subsequent pregnancy[45]. The risk of dying is very low if myocardial recovery has occurred. Not surprisingly, if left ventricular function has not recovered, the risk of subsequent pregnancy is higher. Mortality seems to be around 16%, with the risk of recurrent heart failure around 50%[45]. Future pregnancies should be managed by a multidisciplinary cardiac and obstetric team. Ideally, patients should have a period off pharmacological therapy before conception to ensure that left ventricular function does not deteriorate. Stress testing (preferably exercise stress echocardiography) can be useful prior to conception to assess myocardial reserve and guide decision-making[46]. Patients should be monitored closely with serial assessments of cardiac function and natriuretic peptides.

The Heart Failure Society of the European Society of Cardiology's PPCM Registry

The sparsity of data regarding PPCM prompted the Heart Failure Society of the European Society of Cardiology's PPCM Registry[47]. This aims to collect comprehensive data on baseline characteristics, treatment and outcomes in 1000 women with PPCM. As of January 2017, over 525 patients have been entered. Patients who have presented within the last 6 months with PPCM are eligible for inclusion (for further details and to join the registry e-mail: eorp@escardio.org).

The future

Increased awareness of PPCM is the primary aim of the coming years. New specific diagnostic techniques may emerge from improved understanding of the pathological pathways. Perhaps groups of patients with PPCM have different responsible pathological processes which would warrant tailored therapeutic approaches. Better prognostic scores or tools would allow treatment of those who are likely to benefit and avoidance of unnecessary therapies in others. Early recognition and focussed management in combined cardiology and obstetric teams should lead to even better outcomes.

Summary and conclusions

PPCM is uncommon, but not rare. The pathogenesis is increasingly understood and involves hormonal and vascular processes which damage the cardiovascular system. These pathways have the potential to be used to develop novel diagnostic and therapeutic approaches. Mortality rates are lower than were historically reported and myocardial recovery rates are improving, but there remains a need for improved outcomes in this cohort of young patients. Contraceptive advice and counselling about the risk of subsequent pregnancies should be offered to all patients.

Learning objectives

PPCM should be suspected in women towards the end of pregnancy or in the months following delivery if they have symptoms or signs of heart failure.

Investigations for suspected PPCM should include an electrocardiogram, BNP or NT-proBNP and an echocardiogram.

Most women with PPCM recover to normal cardiac function over 12 months on conventional medical therapy for heart failure. Mortality has fallen to <10% at 1 year.

Women with PPCM must be advised about contraception to avoid unplanned conception on teratogenic drugs for heart failure.

Women should be counselled with respect to the potential risk of future pregnancies.

Patients should be managed by a team involving cardiologists, anaesthetists and obstetricians.

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Figure 1 – European Society of Cardiology PPCM Working Group defintion of PPCM

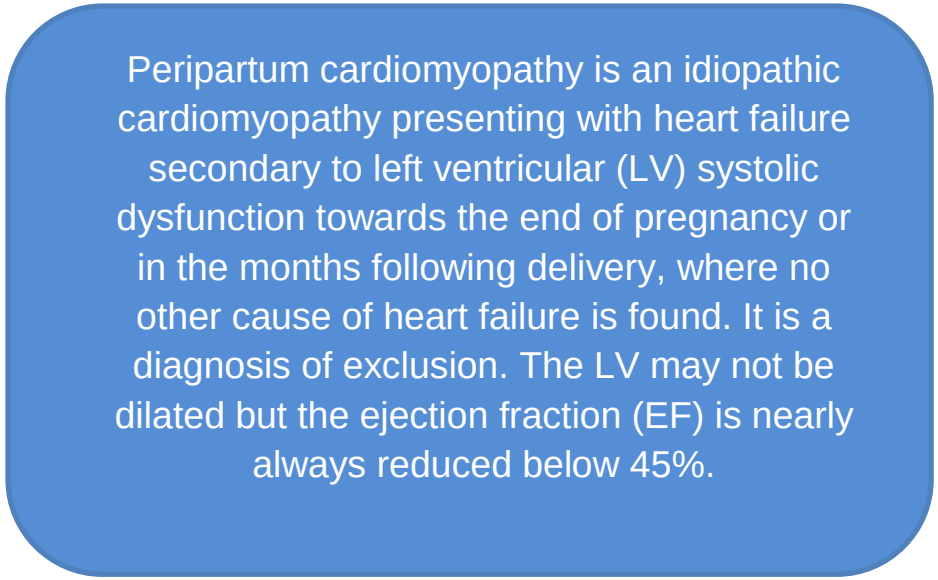
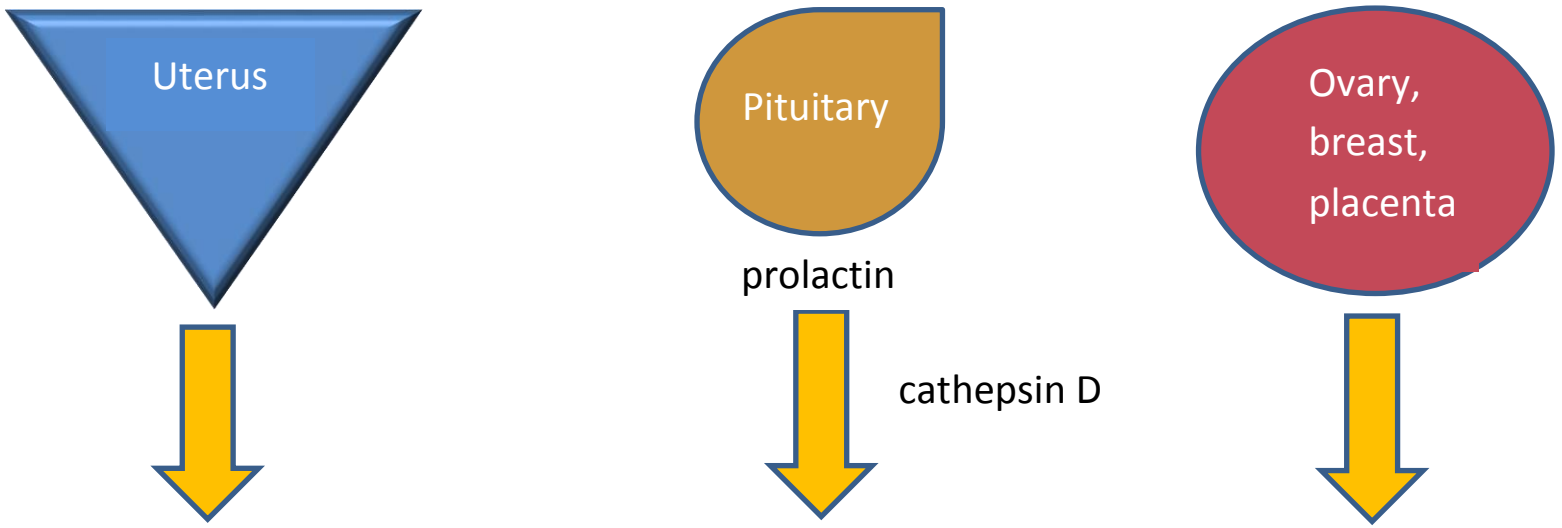


Figure 2 – Pregnancy hormones in PPCM



soluble-Flt 1
- angiogenic imbalance
- endothelial dysfunction
- myocardial damage

Possible therapy
- vascular endothelial growth factor analogues

16kDa prolactin
- endothelial damage
- cardiomyocyte damage

Possible therapy
- bromocriptine
- antagomirs

relaxin-2
- increased cardiac output
- decreased vascular resistance

Possible therapy
- relaxin

Figure 3 – Diagnostic approach to suspected PPCM

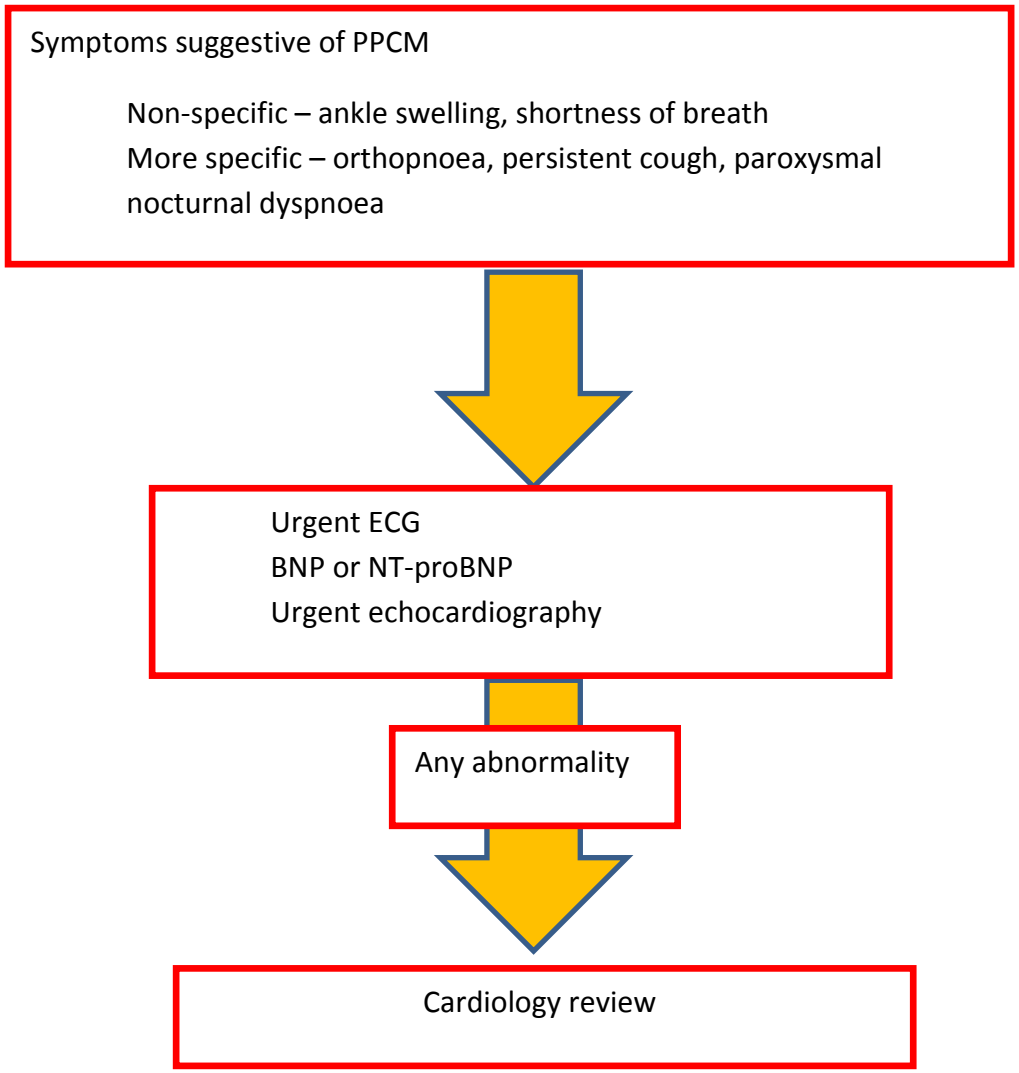


Table 1 – Differential diagnosis of PPCM

	Distinguishing features
Cardiovascular conditions	
Pre-existing idiopathic or familial DCM unmasked by pregnancy	• PPCM most commonly presents towards the end of pregnancy or post partum whereas DCM usually presents by the 2nd trimester
Pre-existing valvular heart disease unmasked by pregnancy	• PPCM most commonly presents towards the end of pregnancy or post partum whereas valvular heart disease usually presents by 2nd trimester
Pre-existing congenital heart disease	• PPCM most commonly presents towards the end of pregnancy or post partum whereas congenital heart disease usually presents by 2nd trimester
Pre-eclampsia	• Pre-eclampsia usually presents during pregnancy and is associated with proteinuria and hypertension
Pregnancy associated myocardial infarction	• History and electrocardiogram +/- coronary angiography should distinguish
Pulmonary embolus	• History / ECG / CXR
Non-cardiovascular conditions	
Anaemia	• Low haemoglobin
Depression, lack of fitness	• These should be distinguishable following history and examination, such as weight gain

DCM – dilated cardiomyopathy; PPCM – peripartum cardiomyopathy

Figure 4 – PPCM management

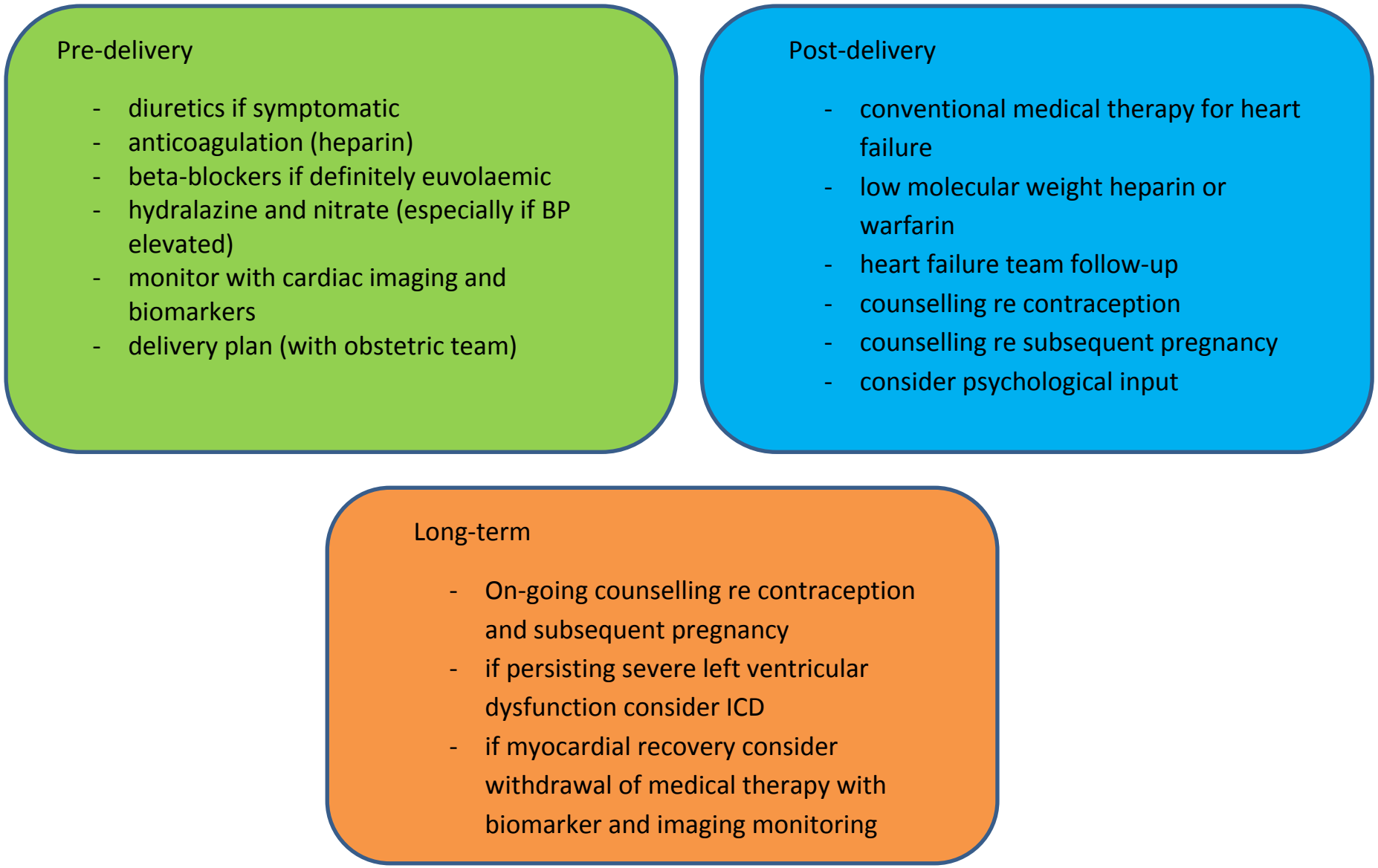


Figure 5 – Management of severe acute PPCM (adapted from the HFA ESC Study Group on PPCM guidelines for the management of severe acute PPCM)