REVIEW ARTICLE

Peripartum Cardiomyopathy; an overview of the diagnosis, management and prognosis.

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Abstract

Normal gestation leads to profound physiological adaptations to the cardiovascular system. A rare but important condition is peripartum cardiomyopathy a form of cardiomyopathy which presents in the latter stages of gestation or in the first few months postpartum. Clinical signs and symptoms (fatigue, shortness of breath, pedal oedema) are often attributed to pregnancy and diagnosis. The aetiology of this condition is poorly understood however numerous hypotheses have been made. Management is complex and requires a multidisciplinary approach. Long term prognosis is variable but there is a substantial morbidity and mortality burden as well as subsequent important implications for future pregnancies. This article provides an overview of our current understanding of peripartum cardiomyopathy.

Introduction

Diagnosing abnormalities of cardiac function can be challenging and in pregnancy the situation is even more complex because of the need to differentiate physiological adaptation from serious pathology. During gestation, pregnancy leads to changes in the mother's cardiovascular system to deal with the increased demands of the foetus. This includes an increase in blood volume and cardiac output and a decrease in systemic vascular resistance. Plasma volume may increase by 40% and cardiac output increases to up to 50% (Table 1). The chambers of the heart may increase in size by up to 30% partly due to dilatation although there is limited data on diastolic and systolic function (1).

At present it is estimated that cardiovascular disease may affect up to 4% of pregnancies in western industrialised countries (1). The spectrum of cardiovascular disease includes both congenital and acquired disease and both chronic and acute presentations. Cardiomyopathies make up a small but important proportion of cardiovascular disease in pregnancy. Of the cardiomyopathies, peripartum

cardiomyopathy (PPCM) is the most common (2).

Parameter	Healthy Pregnancy	PPCM
CO	Increases by 30-50%	no data
LVEF	No change	Reduced to less than 45%
Plasma Volume	Increases by up to 40%	No data
Blood Pressure	Initial fall by second trimester (10mmHg) Normalises to non-pregnant values in third trimester	No data

Table 1: Reported physiological changes during pregnancy compared to changes in PPCM

Definition and Incidence

In 2000, the definition of the Workshop held by the National Heart Lung and Blood Institute and the Office of Rare Diseases (2) stated that it must develop during the last month of pregnancy or within 5 months of delivery. Recognising that strict time criteria may lead to under-diagnosis, in 2010 a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy defined PPCM as:'an idiopathic cardiomyopathy presenting with heart failure (HF) secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. It is a diagnosis of exclusion. The LV may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%' (3).

Reported incidence of PPCM varies greatly across the world from 1:40322 Malaysia (4) to 1:100 in Nigeria (5).

Risk Factors

Traditional risk factors include increased maternal age, history of cardiovascular disease affecting pregnancy (hypertension, pre-eclampsia), multiparity, African descent, prolonged use of tocolytics. The strongest evidence appears to be for African descent, advanced maternal age, hypertensive disease and multiple gestation pregnancy (6).

The highest incidence of PPCM appears to be in populations of African descent. The high incidence observed in Nigeria (7) relates to the Hausa and Fulani tribes. This is postulated to be related to a form of lake salt ingested in the immediate postpartum

period which leads to significant volume overload (8).

Whilst PPCM is thought to be prevalent in woman of high parity it is important to note that a 24-37% of cases present during the first pregnancy (9). Elkayam et al., (10) demonstrated in the USA that PPCM is not limited to black women and almost 40% of cases occurred in primigravid women and >50% within the first 2 pregnancies. There was additionally increased incidence of PPCM in women ≥30 years of age and hypertensive disease was more prevalent. Mean parity in this study was 2.1 +/- 1.7. A study in Japan demonstrated similarly high rates of PPCM in primigravid woman (54%) as well as increased prevalence of hypertensive disease in these patients (11). Mean parity in this study was 1.62±1.17 for females with hypertensive disease and 1.67±0.78 for those without.

Diagnosis and Clinical Manifestation

The diagnosis of PPCM is often challenging due to its variable presentation and difficulty in distinguished from normal symptoms of pregnancy and physiological adaptations. The complex but normal physiological changes which females undergo during pregnancy, and in the early postpartum period, can lead to vey common symptoms that may unfortunately mimic the presenting features of a PPCM, including pedal oedema, exertional dyspnoea, paroxysmal nocturnal dyspnoea and orthopnoea. Further symptoms that may be experienced in PPCM such as abdominal discomfort secondary to abdominal congestion, palpitations and pre-syncopal features may be attributed to the pregnancy, fatigue or anaemia and could potentially lead to further delayed diagnosis (3).

The majority (>75%) of patients present with symptoms in the first 4 months after delivery, with only 9% presenting in the last month of pregnancy. The remaining 13% present either earlier than 1 month prior to delivery or more than 4 months after delivery (12). The most frequent initial presentation is with New York Heart Association functional class III or IV symptoms but this may vary (13).

Physical examination may identify signs of volume overload such as a raised jugular venous pressure, tachypnoea, pulmonary wheeze, third heart sound (S3), new systolic murmur or peripheral oedema. Unfortunately, some women present in cardiogenic shock or with malignant arrhythmias. It is a recognised cause of fulminant acute heart failure and some of the morbidity/mortality is with new mothers needing MCS and transplant.

<u>Clinical assessment and Investigations</u>

These include measurement of physiological parameters. Whilst these may be non-specific (tachypnoea, tachycardia) they can alert clinicians to the severity of a patient's illness (for example in severe hypotension) and guide the timing of future investigations. It is normal practice to perform a urine dip for proteinuria as this is one of the key features of preeclampsia.

There are unfortunately no specific ECG findings that help diagnose PPCM however only 4% of woman have been shown to have a completely normal ECG (14). Common ECG changes are sinus tachycardia, ST-T segment depression, T-wave inversion, P-wave abnormalities and QRS-axis deviation (14). ECG changes should prompt clinicians to undertake further cardiological investigations.

Aside from the basic blood profile most patients will undertake as part of their routine monitoring (full blood count with differential, renal profile with magnesium, bone profile, liver profile, thyroid function, virology), other serum tests not routinely performed but relevant in suspected PPCM include troponin and B-type natriuretic peptide (BNP). Troponin assays are useful in ruling out an acute myocardial infarction and should be interpreted within the clinical context. BNP whilst not specific for PPCM is elevated in heart failure and a study by Forster et al., (15) demonstrated that patients with PPCM had higher baseline NT-proBNP levels compared to control (988.7–3077.7fmol/ml compared to 184.6–715.6fmol/ml; $p<0.0001$). A normal BNP level effectively rules out heart failure.

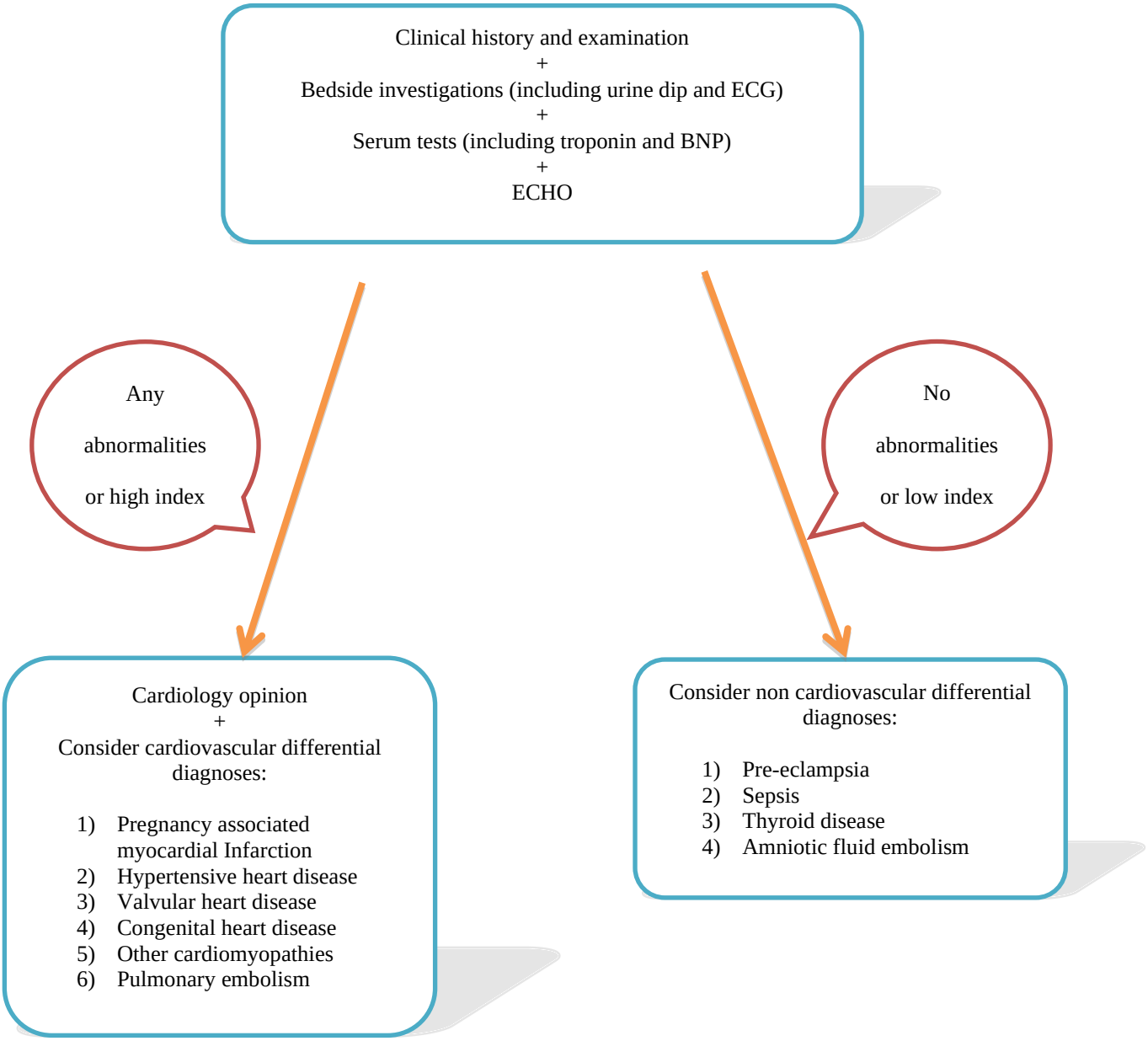
Imaging

A chest X-Ray may demonstrate evidence of decompensated heart failure (pulmonary oedema, pleural effusions, pulmonary congestion, upper lobe blood diversion) as well as cardiomegaly. It is important to note that the heart maybe displaced upwards and laterally as a result of the growing foetus complicating interpretation of radiographs further (16).

The most important imaging modality in diagnosing PPCM is echocardiography. Left ventricular ejection fraction (LVEF) is almost always reduced (2, 6). Elkayam et al. (10) reported a mean LVEF at baseline of 29% in 93 women presenting with PPCM. Echocardiography is relatively straightforward to perform, globally available, provides immediate results and, lacking ionising radiation, is safe for both mother and foetus. It also allows for serial monitoring of cardiac function and identifies any valvular abnormalities.

Cardiovascular magnetic resonance imaging allows for accurate assessment of cardiac function, structure and contractility whilst also identifying inflammatory processes. It is non-invasive and does not use ionizing radiation however it is not globally available. Late gadolinium enhancement is recognised as a bad prognostic marker however the contrast agent can cross the placenta and should therefore be avoided in the antenatal period.

Figure 2: Assessment of peripartum cardiomyopathy in a breathless patient based on current guidance (3).



Pathophysiology

This pathophysiology leading to PPCM is not fully understood and is likely to be multifactorial. Potential aetiologies postulated however include various viral infections (EBV, CMV, HHV-6 and parvovirus B19), stress-activated cytokines and inflammatory cascades, autoimmune processes and more recently 16-kDa prolactin (17). Furthermore, there is likely to an underlying genetic susceptibility and perhaps some overlap with dilated cardiomyopathy (DCM) as there is often a family history of DCM.

Management

Patients with PPCM should be managed in a multidisciplinary setting including obstetricians, cardiologists and intensivists. Management of PPCM is complex and difficult during the antenatal period given the limitations of using specific drugs such as ACEi to the foetus however thankfully it is rare for women to present during this period. In the postpartum period management is individualised guideline-based heart failure treatment.

In the acute phase, management is similar to that of acute HF of any cause as defined by ESC guidelines (18). Essentially this involves oxygen therapy including where necessary non-invasive ventilation, intravenous nitrates, intravenous diuretics and inotropic agents in patients with a low output state as indicated by signs of hypoperfusion.

Antenatal management

Antenatal management of PPCM is challenging given the limitations of drug therapy in the current situation as well as the ethical complexities of undertaking trials in this patient cohort. As discussed earlier presentation at this stage is highly variable and often overlaps with normal physiological changes. Timely delivery of the foetus is ideal and any therapeutic interventions should consider maternal and foetal health. Vaginal delivery is the preferred method but if an emergency caesarean section is required then this is recommended to be performed under general anaesthetic with a cardiac anaesthetist.

Angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin-II receptor blockers (ARB) are contraindicated because of their effect on the developing renal system and neural tube defects. Hydralazine and long-acting nitrates are thought to be safe during pregnancy. Beta-blockers have not been shown to have a teratogenic effect and b-1 selective drugs are preferred rather than b-2 receptor blockers given their theoretical anti-tocolytic effect. Diuretics can cause reduced placental perfusion with potential

harm to the fetus and should be used in the lowest dose possible (9). Aldosterone antagonists are thought to have an anti-androgenic effect and are therefore avoided.

Patients with a LVEF <35% are at increased risk of thromboembolic disease and anticoagulation should therefore be given (19). Given the fetotoxic effects of warfarin especially in the first trimester treatment with low molecular weight heparin is recommended.

Postpartum management

Following delivery of the foetus, patients with PPCM should receive individualised full heart failure treatment as determined through recent guidance to include beta blockers, enalapril and captopril for ACEi and spironolactone. Whilst the initial guidance has been to avoid breastfeeding there is some evidence that in women who breastfeed there were higher rates of recovery (20). Moreover, most heart failure medications can be given safely during breastfeeding. Discussions on the appropriateness of contraception to prevent subsequent pregnancies should be initiated given the risk of recurrence.

Other drug therapy

Bromocriptine leads to dopaminergic inhibition of prolactin secretion. Given our current understanding of overexpression of the 16kDa prolactin fragment in PPCM this presents a potential therapeutic target. In an open-label randomized trial, patients were given bromocriptine 2.5mg orally twice a day for 2 weeks followed by 2.5mg orally once a day for 6 weeks on top of usual medical therapy compared to medical therapy alone. Twenty patients were included and in the bromocriptine arm, patients had a significant reduction in combined all-cause death, NYHA functional class or LEVF <35% at 6 months. These patients displayed greater recovery of LVEF (27% ±8 at baseline to 58% ±11 at 6 months; P=0.012) compared to control (27% ±8 at baseline to 36% ±11 at 6 months) and importantly no thromboembolic events were recorded and no intracardiac thrombi could be detected using cardiac magnetic resonance at 4-6 months (21). Newborn growth in mothers who had lactation suppression was similar to the control group. Although these findings suggest a potential role for bromocriptine, it is not currently approved for this purpose.

Prognosis and subsequent pregnancies

Data on long term prognosis of PPCM varies greatly. Mortality rates range from 2.1% to 28% (13, 22) and appear to differ across the world. Recent improvements in mortality are thought to be due to better management of heart failure (6). Mortality

is usually due to ventricular arrhythmias, severe decompensated heart failure or thromboembolic sequelae (23). In a study by Goland et al., (24) of 182 patients, adverse events occurred in 25% with the majority of these occurring in the first 6 months postpartum. In this study a baseline EF of ≤25% and non-Caucasian race were predictors of major adverse events.

What is perhaps more consistent however is the proportion of patients whose LV systolic function returns to baseline. Studies in the United States have suggested that at least 50% of patients show an improvement in LV function within 2-6 months after diagnosis (3). Patients with a higher baseline EF and smaller LV end-systolic dimensions were more likely to show a full recovery (25). Mean time to recovery was 19.3 months and 4 of 42 patients showed late deterioration. In view of the long time to recovery, possibility of late deterioration in some patients and lack of consensus on appropriate duration of treatment in patients with PPCM, close follow-up is indicated not only for those patients who have failed to recover but also for those with recovering LV systolic function.

Women with PPCM are evidently at increased risk of redeveloping or exacerbating their condition with subsequent pregnancies and therefore careful preconception counselling cannot be overemphasised. In a study by Elkayam et al., (26) of 44 women with a total of 60 subsequent pregnancies, women with a LVEF <50% had a 44% chance of developing symptoms of heart failure compared to 21% in those whose LVEF was >50%. Moreover in the group with reduced EF, 3 of 16 women died after the first subsequent pregnancy compared to none in those whom had a normal EF.

Guidance from the Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy (3) suggests that women with PPCM need careful counselling about family planning, due to the "high risk of relapse in subsequent pregnancies and terminating pregnancy may not prevent the onset of PPCM"

Conclusion

Peripartum cardiomyopathy is a rare and complex condition that carries significant morbidity and mortality on previously healthy women. Its incidence varies throughout the world and woman typically present in the early postpartum period with symptoms of heart failure. Whilst multiparity is a risk factor for its development at least half of patients are primigravid and otherwise well leading to

a misinterpretation of their symptoms as being part of the normal puerperal process. Management is complex and poorly investigated in the antepartum phase. In the postpartum period this follows general heart failure guidance. Increased awareness and understanding of this condition has prompted further research in this field. Whilst the majority of patients have improvements in their heart function 6 months post event, in others this is not the case and severe heart failure ensues. Already large clinical registries on PPCM (ESC EUROOBS program) have been set up (27) and this should provide information on the nature of the disease, its management and prognosis.

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