Peripartum cardiomyopathy

Peripartum cardiomyopathy is a form of dilated cardiomyopathy of indeterminate aetiology occurring in late pregnancy or the months following delivery. This article reviews current knowledge of its pathophysiology, therapeutic strategies and prognosis, as well as new treatments and future directions.

Peripartum cardiomyopathy is a rare form of pregnancy-associated dilated cardiomyopathy of unknown aetiology causing systolic heart failure. Despite its rarity, it is important because of its high morbidity and mortality rates and its occurrence in young women.

According to the 2010 European Society of Cardiology definition, peripartum cardiomyopathy is '… an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found' (Sliwa et al, 2010a).

The true incidence of peripartum cardiomyopathy is unknown; current estimates are based primarily on case series from single centres and a limited number of population-based studies, and range between 18 per 100 000 and 333 per 100 000 births (Blauwet and Cooper, 2011). Striking geographical variability has been observed, with low incidence in Japan (1:20,000) and a higher incidence in the United States (1:540), while peripartum cardiomyopathy is relatively common in Haiti (1:300) and parts of Africa (1:100) (Capriola, 2013).

Risk factors

Identified risk factors for peripartum cardiomyopathy include increased maternal age, a history of hypertension complicating pregnancy (including pre-eclampsia), multiparity, multiple gestations, African descent, prolonged use of tocolytic drugs, poverty, malnutrition, and anaemia during index pregnancy (reviewed by Capriola, 2013). Many of these factors either predispose to oxidative stress or can exacerbate heart failure.

Pathogenesis

The underlying pathogenesis is still unknown. Despite various hypotheses, none has sufficient strong supporting evidence. It has been suggested that an unprotected increase in oxidative stress leads to an increased expression and proteolytic activity of cardiac cathepsin D. This may lead to the conversion of prolactin into an anti-angiogenic and pro-apoptotic 16kDa N-terminal fragment form which results in myocardial injury from the combined effects of hypoxaemia and apoptosis (Hilfiker-Kleiner et al, 2007). Halkein et al (2013) showed that this N-terminal prolactin fragment induces microRNA-146a (miR-146a) expression in endothelial cells, which attenuates angiogenesis and decreases myocardial metabolism. Prolactin may also result in breakdown of immune tolerance and autoimmunity (Shelly et al, 2012), leading to autoimmune myocarditis. A central role of prolactin in the pathogenesis may explain its predilection for late pregnancy and lactation when prolactin levels increase many-fold. Other potential mechanisms are discussed in *Table 1*. There have also been reports of familial (Morales et al, 2010; Van Spaendonck-Zwarts et al, 2010) and racial (Brar et al, 2007) predisposition.

Clinical manifestation and diagnosis

The onset of peripartum cardiomyopathy varies considerably but most patients develop symptoms within the first few months postpartum rather than during pregnancy. The most common presenting symptoms (dyspnoea, peripheral oedema and fatigue) are frequent complaints in normal pregnancy and the postpartum period, so awareness of the condition and a high index of suspicion are required.

The signs of peripartum cardiomyopathy are similar to those of heart failure caused by other factors (*Table 2*). Peripartum cardiomyopathy is a diagnosis of exclusion (*Table 3*). Work-up can be summarized as:

- Diagnosis of systolic heart failure and exclusion of alternative causes for the patient's symptoms
- Exclusion of other causes of systolic heart failure
- Assessment of the severity of heart failure.

Necessary diagnostic investigations are outlined in *Figure 1*. Useful biomarkers that help in making the diagnosis include serum troponins and natriuretic peptides. Troponins are useful in ruling out myocardial infarction. A slight elevation in troponins may be noted in patients with substantial myocardial injury, especially in the acute phase. It should be noted that natriuretic peptides increase nearly twofold in pregnant women compared with non-pregnant women in the first trimester but do not change significantly subsequently during pregnancy. In patients with peripartum cardiomyopathy, B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide values can increase up to fivefold higher than those in normal pregnancy. Likewise, serum inflamma-

Dr Sarah Grixti *is Foundation Year Doctor in the Department of Internal Medicine,* **Dr Caroline J Magri** *is Higher Specialist Trainee and* **Dr Robert Xuereb** *is Consultant Cardiologist in the Department of Cardiac Services and* **Professor Stephen Fava** *is Head of the Diabetes and Endocrine Centre, Department of Internal Medicine, Mater Dei Hospital, Tal-Qroqq, Msida MSD 2090, Malta*

Correspondence to: Dr CJ Magri (caroline.j.magri@gmail.com)

Table 1. Proposed pathogenic mechanisms for peripartum cardiomyopathy

Hypothesis	Mechanism
Excessive prolactin production	Low cardiac STAT 3 (signal transducer and activator of transcription 3) protein level with increased serum levels of activated cathepsin D and 16kD prolactin was noted in patients with peripartum cardiomyopathy (Hilfiker-Kleiner et al, 2007)
Viral myocarditis	Myocarditis was noted during endomyocardial biopsy in some patients with peripartum cardiomyopathy. Histology revealed dense lymphocytic infiltration with a variable amount of myocytic oedema, necrosis and fibrosis (Hilfiker-Kleiner et al, 2008)
Abnormal immune response	An abnormal immune response to fetal microchimerism (the introduction of fetal cells of haematopoietic origin into the maternal circulation) has been suggested (Ansari et al, 2002)
	Cardiac tissue autoantibodies have also been implicated (Warraich et al, 2005; Lamparter et al, 2007)
Abnormal haemodynamic response	Cardiac output increases by up to 50% during pregnancy
	Pregnancy is associated with transient left ventricular dysfunction that is maximal during the third trimester and resolves shortly after birth in a normal pregnancy
	Peripartum cardiomyopathy may be in part the result of an exaggerated decrease in the left ventricular function (Pearson et al, 2000)
Cytokine-mediated inflammation	An increase in serum markers of inflammation including high sensitivity C-reactive protein, interferon-γ and interleukin-6 have been noted in women with peripartum cardiomyopathy (Sliwa et al, 2006; Forster et al, 2008)
Prolonged tocolysis	The association between the use of β-sympathomimetic drugs for >4 weeks and heart failure appears unique to pregnancy (Lampert et al, 1993)
Genetic	Peripartum cardiomyopathy may be part of a spectrum of familial dilated cardiomyopathy, suggesting that peripartum cardiomyopathy may have a genetic cause (Anderson and Horne, 2010)
Cardiac angiogenic imbalance	Animal studies suggest that peripartum cardiomyopathy is mainly a vascular disease, caused by excess anti-angiogenic signalling in the peripartum period. The extent of cardiac dysfunction correlated with circulating levels of sFLT1 (soluble fms-like tyrosine kinase 1), a vascular endothelial growth factor inhibitor (Patten et al, 2012)

tory markers, including high sensitivity C-reactive protein and interferon-γ, as well as oxidized low-density lipoprotein, a marker for oxidative stress, are significantly elevated (Blauwet and Cooper, 2011). However, these latter investigations are not widely available and are not specific enough to be clinically useful.

A chest X-ray may show cardiomegaly, venous congestion, pulmonary oedema and pleural effusion. However, in pregnancy, the heart is pushed upward and laterally giving an erroneous impression of cardiomegaly. An electrocardiogram may show sinus tachycardia and non-specific ST segment and T-wave changes. Signs of increased voltage as a result of left ventricular hypertrophy and conduction abnormalities may also be present. Tibazarwa et al (2012) have demonstrated that major T-wave abnormalities on the baseline 12-lead electrocardiogram were associated with reduced left ventricular ejection fraction at baseline and at 6 months, while baseline ST segment elevation was also associated with lower left ventricular ejection fraction at 6 months.

Table 2. Signs of heart failure in peripartum cardiomyopathy

Signs of left heart failure	Tachypnoea
	Pulmonary crepitations
	Loud second pulmonary sound (P2)
	Third heart sound (S3) or gallop rhythm
	New systolic murmur (mitral and/or tricuspid regurgitation)
	Lateral and/or downward displacement of apex beat
Signs of right heart failure	Jugular venous distension
	Hepatojugular reflux
	Hepatomegaly
	Peripheral oedema
	Ascites

Table 3. Differential diagnoses of peripartum cardiomyopathy

Pregnancy-associated myocardial infarction
Sepsis
Pre-eclampsia
Pulmonary embolism
Amniotic fluid embolism
Valvular heart disease
Hypertensive heart disease
Unrecognized congenital heart disease
Thyrotoxicosis
Other forms of cardiomyopathy: idiopathic dilated cardiomyopathy, familial dilated cardiomyopathy, HIV/AIDS cardiomyopathy, alcoholic cardiomyopathy

Cardiac imaging is crucial in the diagnosis of peripartum cardiomyopathy. Transthoracic echocardiography has been the primary cardiac imaging modality used as it is non-invasive, poses no radiation risk and is widely available. Furthermore, it enables serial evaluation of cardiac function while excluding valvular heart disease. In peripartum cardiomyopathy, the left ventricular ejection fraction is generally <45%. Dilated heart chambers, especially the left ventricle, and pericardial effusions may also be noted. Doppler evaluation may show regurgitation at the mitral, tricuspid and pulmonary valves, and pulmonary hypertension. Assessment of diastolic function frequently reveals a restrictive pattern indicative of elevated left ventricular filling pressures.

Cardiac magnetic resonance imaging enables assessment of global and segmental contractility and identifies inflammatory processes. Furthermore, it is non-invasive and does not involve any ionizing radiation. However, it is still available in only a few centres and the administration of gadolinium during pregnancy is not recommended although it is acceptable in lactating females.

Endomyocardial biopsies can enable the clinician to distinguish between inflammatory and non-inflammatory aetiologies, allowing appropriate treatment to be delivered in inflammatory cases. However, no histological classification for the diagnosis of peripartum cardiomyopathy has been established, thus its role remains controversial.

Management

Patients with peripartum cardiomyopathy need to be managed in a multidisciplinary team including obstetricians, cardiologists, perinatologists and neonatologists. Management is complex and controversial in view of the lack of randomized controlled trials secondary to ethical constraints. There is much reliance on expert opinion. Therapeutic strategies are similar to standard treatment for other forms of heart failure, with the choice of treatment dependent on the severity of symptoms and severity of left ventricular dysfunction, while avoiding medications that lead to deleterious effects on the fetus or nursing infant. Therapeutic strategies aim to reduce preload and afterload while increasing cardiac inotropy. Medications should be continued until there is objective evidence of improved or resolving left ventricular dysfunction.

Antepartum management

There is a spectrum of presentation from acute pulmonary oedema to mild dyspnoea. In patients with peripartum cardiomyopathy presenting with overt pulmonary oedema and severe heart failure, maternal health should be given priority and delivery should ensue, irrespective of gestational age. Ideally, delivery is planned in the following 48 hours to optimize fetal outcome while preserving maternal life. However, if the mother's condition is critical, delivery of the fetus is expedited. Such patients need to be managed on an intensive care unit. In addition, supportive measures need to be provided including inotropic support, mechanical ventilation, intra-aortic balloon pump counterpulsation, left ventricular assist device and cardiac transplantation (*Table 4*). Left ventricular assist device implantation may be used as a bridge to recovery; in subjects where the left ventricular ejection fraction remains significantly impaired, left ventricular assist device implantation may be a useful bridge to transplantation. The outcome following cardiac transplantation in patients with peripartum cardiomyopathy is comparable to those transplanted for other aetiologies.

In mildly symptomatic patients, conservative management is indicated with a low sodium diet (max 2 g/

Figure 1. Diagnostic testing in evaluation of peripartum cardiomyopathy.

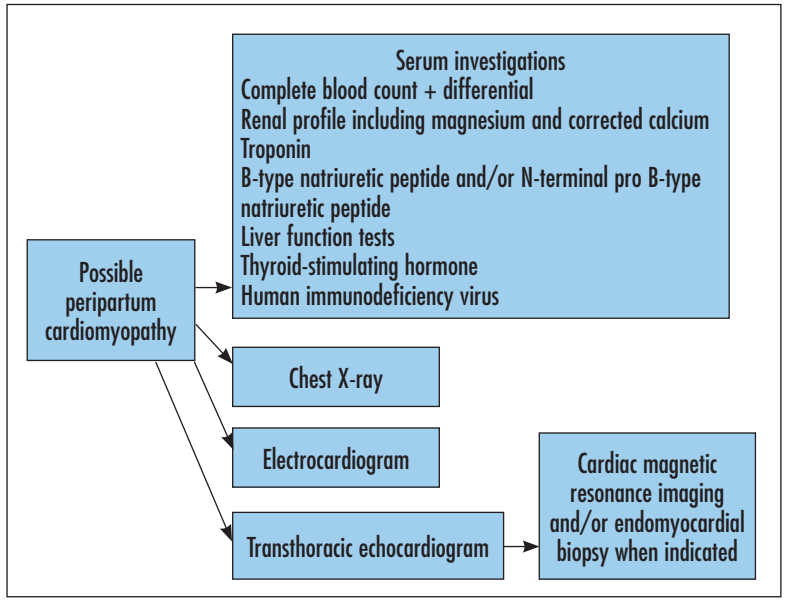

Table 4. Management of decompensated peripartum cardiomyopathy

Therapeutic strategy	Description
Airway protection	Prompt intubation is necessary to prevent complications in severe decompensated heart failure
Respiratory support	Includes supplemental oxygen, non-invasive ventilator support and mechanical ventilation as indicated
Diuretics	Intravenous furosemide; dose adjustments should be made on the basis of creatinine clearance
Vasodilators	Include nitroglycerin infusion and nitroprusside. Nitroprusside needs to be used with caution because of the toxic effects of thiocyanate on the fetus
Positive inotropic agents	Include milrinone, dobutamine and dopamine
Anticoagulation	Heparin should be considered in patients with left ventricular ejection fraction <35%
Device therapy	Includes intra-aortic balloon pump, left ventricular assist device and extracorporeal membrane oxygenation
Cardiac transplantation	Considered in patients refractory to medical treatment and mechanical circulatory support

day), fluid restriction (max 2 litres/day), light daily exercise and pharmacological therapy. A combination of hydralazine and nitrates may be used to decrease afterload. Loop diuretics may be used with caution since a rapid reduction in blood supply may decrease blood supply to the fetus. β-blockers, such as carvedilol or extended release metoprolol, have been approved for use in peripartum cardiomyopathy and can improve survival (Moioli et al, 2010). However, they can decrease perfusion in the acute decompensated phase of the disease and should thus be avoided in the early stages of peripartum cardiomyopathy. Although β-blockers may cause fetal bradycardia, growth retardation and fetal hypoglycaemia, maternal health remains the priority for treatment and thus they should be considered under medical guidance.

Patients with peripartum cardiomyopathy are at increased risk of thromboembolic complications, including deep vein thrombosis, pulmonary embolism, and left ventricular thrombus if left ventricular function is severely impaired. It is suggested that patients with left ventricular ejection fraction <35% receive anticoagulation (Blauwet and Cooper, 2011), preferably with low molecular weight heparin, during the first trimester and before delivery. Warfarin can be administered in the second and third trimester, particularly at doses <5 mg daily, since it is less teratogenic than during the first trimester and at low doses. However, low molecular weight heparin may be preferred in view of lower incidence of fetal adverse effects, at the expense of a higher risk of maternal thromboembolic complications.

In patients with peripartum cardiomyopathy with mild to moderate left ventricular dysfunction presenting before 32 weeks' gestation, pregnancy should be allowed to continue until a gestational age is reached where fetal outcome is good, provided left ventricular function is monitored weekly by echocardiography. If peripartum cardiomyopathy presents after 32 weeks, delivery is recommended to ensure recovery of left ventricular function.

Labour and delivery

In subjects with significant haemodynamic compromise not responding to treatment, termination of pregnancy should be considered urgently to safeguard the mother's life since it often results in improvement in left ventricular function (reviewed by Sliwa et al, 2010a). An instrumental vaginal delivery, under close monitoring, is preferable once the patient has been optimized from a haemodynamic point of view and with an apparently healthy fetus. Caesarean section should be performed for obstetric reasons or because of maternal instability requiring inotropic treatment or mechanical support. Continuous invasive haemodynamic monitoring of the mother is essential together with early fetal heart rate monitoring as abnormalities in fetal heart rate tracings are common when maternal oxygenation and circulation are compromised.

An experienced anaesthesiologist should be consulted early on. The preferred mode of analgesia during a vaginal delivery is epidural since it stabilizes cardiac output. For caesarean section, continuous spinal anaesthesia and combined spinal and epidural anaesthesia have been recommended. Ergometrine is contraindicated (Sliwa et al, 2010a).

Postpartum management

In the postpartum period, the mainstay of treatment is drugs, mainly angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, while aldosterone antagonists may be used when angiotensin-converting enzyme inhibitors are not tolerated. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers must be avoided during pregnancy to prevent potential adverse effects on fetal renal function. Aldosterone antagonists may also cause antiandrogenic effects on the fetus and should thus be avoided in the antepartum period.

Patients with persistent left ventricular dysfunction despite optimal medical treatment are at risk of sudden death from ventricular arrhythmias. There are no guidelines regarding the use of implantable cardioverter-defibrillator implantation and cardiac resynchronization therapy specific for patients with peripartum cardiomyopathy. The decision regarding implantable cardioverter-defibrillator implantation must be carefully weighed against the possibility that left ventricular function recovers within 6 months; it requires extensive consultation between the physician and the patient to ensure informed consent. Patients with persistent New York Heart Association (NYHA) functional class III or IV symptoms despite optimal medical treatment, and whose left ventricular ejection fraction remains <30%, may be candidates for implantable cardioverter-defibrillator implantation for primary prevention of sudden death. Cardiac resynchronization therapy may be considered in patients with peripartum cardiomyopathy with persistent NYHA functional class III or IV symptoms in the chronic setting despite optimal medical treatment if they have left ventricular ejection fraction <35% and QRS duration ≥120 ms. Further studies are needed to evaluate the role of implantable cardioverter-defibrillator and cardiac resynchronization therapy in these patients.

Prevention of complications

Novel targeted therapies for peripartum cardiomyopathy include pentoxyfylline and bromocriptine. Pentoxyfylline is a tumour necrosis factor inhibitor; it has been reported to result in improved outcome in a small series of South African women (Sliwa et al, 2002). Bromocriptine reduces prolactin production by dopamine agonist actions and thus prevents formation of the 16kDa prolactin fragment that causes myocardial damage. It has been studied in a small group of patients with peripartum

cardiomyopathy and has been associated with a significantly larger rate of left ventricular recovery, a decreased rate of mortality and symptomatic heart failure at 6 months (Sliwa et al, 2010b). Bromocriptine might also improve left ventricular diastolic function, as reported by Ballo et al (2012). Further studies are needed.

Prognosis

There is significant variation in reported mortality rates, from 28% (Sliwa et al, 2000) to 2.1% (Mielniczuk et al, 2006). Death is usually secondary to severe pulmonary oedema, cardiogenic shock, arrhythmias and thromboembolic events. The risk of death increases with older age, worsening left ventricular function (left ventricular ejection fraction <25%), multiparity, African American ethnicity and delayed diagnosis. Biomarkers of worsened outcome include increased levels of N-terminal pro-B-type natriuretic peptide, troponin T, and markers of inflammation and apoptosis (Blauwet and Cooper, 2011).

There are conflicting data on duration of recovery of left ventricular function and whether the initial severity of left ventricular dysfunction is predictive of outcome. Studies from the United States have shown an improvement in left ventricular function of at least 50% in patients with peripartum cardiomyopathy, mostly occurring within 2–6 months after the diagnosis (Sliwa et al, 2004). However, Biteker et al (2012) have shown that full recovery of left ventricular systolic function requires an average time of 19.3 months after initial diagnosis. Patients with complete recovery were more likely to have a higher left ventricular ejection fraction and smaller left ventricular end-systolic dimensions at baseline. In keeping with this, Blauwet et al (2013) have shown that increased left ventricular end-systolic dimension and older age are independent predictors of poor outcome in patients with peripartum cardiomyopathy, together with lower body mass index and lower serum cholesterol. Both the obesity paradox and cholesterol paradox have emerged as novel predictors of poor outcome of peripartum cardiomyopathy for the first time; nonetheless, further studies are required.

Subsequent pregnancies

Patients with peripartum cardiomyopathy who have subsequent pregnancies are at increased risk of recurrent heart failure, even with normal resting left ventricular function. However, the risk does not appear to be the same for all patients. In 61 patients with peripartum cardiomyopathy with subsequent pregnancy, Fett et al (2010) showed that subjects with left ventricular ejection fraction ≥55% before subsequent pregnancy had a 17% chance of clinical relapse compared with 46% of women whose left ventricular ejection fraction remained <55%. Similarly, Elkayam et al (2001) showed that subjects with initial left ventricular ejection fraction <50% exhibited decreased risk of developing recurrent heart failure in subsequent pregnancies than those with baseline left ventricular ejection fraction >50% (21% *vs* 44%).

In a retrospective study of 70 patients with peripartum cardiomyopathy, subjects with left ventricular ejection fraction ≤25% at first diagnosis had an increased risk of persistent left ventricular dysfunction and subsequent need for cardiac transplantation whether or not they had a subsequent pregnancy (Habli et al, 2008). It is thus reasonable to suggest that women with left ventricular ejection fraction ≤25% at diagnosis as well as those with failure of normalization of left ventricular function are at highest risk and should be strongly advised to avoid subsequent pregnancies.

Patients with milder forms of the disease should still be advised that the risk of subsequent pregnancies is not minimal and careful monitoring will be needed both during pregnancy and the postpartum period. An echocardiogram should be repeated 2 months following delivery. If the left ventricular function has not yet returned to normal, 6-monthly clinical visits and echocardiography are advisable, or more frequently as indicated by new symptomatology. Dobutamine stress echocardiography may allow further risk stratification by enabling identification of women who will go on to develop heart failure with the haemodynamic stress of a subsequent pregnancy. Thus, Dorbala et al (2005) have demonstrated a good correlation between the mean left ventricular ejection fraction at maximal inotropic contractile reserve and the left ventricular ejection fraction at 6-month follow-up; however, the study was limited by the small number of patients (n=7).

Conclusions

Peripartum cardiomyopathy is a heterogenous condition that affects previously healthy women. Whereas the clinical and echocardiographic status improves rapidly in some patients with complete return to pre-pregnancy levels, in others the outcome is worse with progression to decompensated heart failure and persistent left ventricular dysfunction. Comprehensive heart failure treatment should be provided; this might involve non-pharmacological agents including device implantation and cardiac transplantation.

Studies are needed for better understanding of the pathophysiology; this may eventually result in targeted therapy and identification of females who are at increased risk of peripartum cardiomyopathy in future pregnancies. The role of bromocriptine also requires further evaluation. It is expected that the Peripartum Cardiomyopathy Registry of the European Society of Cardiology and the Investigation in Pregnancy Associated Cardiomyopathy study in the USA will result in better insight regarding the aetiology, epidemiology, diagnosis and management of peripartum cardiomyopathy, thus possibly improving the prognosis of this condition. **BJHM**

Conflict of interest: none.

Anderson JL, Horne BD (2010) Birthing the genetics of peripartum cardiomyopathy. *Circulation* **121**: 2157–9 (doi: 10.1161/CIRCULATIONAHA.110.956169)
Ansari AA, Fett JD, Carraway RE, Mayne AE, Onlamoon N, Sundstrom JB (2002) Autoimmune mechanisms as the basis for human peripartum cardiomyopathy. *Clin Rev Allergy Immunol* **23**: 301–24
Ballo P, Betti I, Mangialavori G, Chiodi L, Rapisardi G, Zuppiroli A (2012) Peripartum cardiomyopathy presenting with predominant left ventricular diastolic dysfunction: efficacy of bromocriptine. *Case Rep Med* **2012**: 476903 (doi: 10.1155/2012/476903)
Biteker M, Ilhan E, Biteker G, Duman D, Bozkurt B (2012) Delayed recovery in peripartum cardiomyopathy: an indication for long-term follow-up and sustained therapy. *Eur J Heart Fail* **14**(8): 895–901 (doi: 10.1093/eurjhf/hfs070)
Blauwet LA, Cooper LT (2011) Diagnosis and management of Peripartum Cardiomyopathy. *Heart* **97**: 1970–80 (doi: 10.1136/heartjnl-2011-300349)
Blauwet LA, Libhaber E, Forster O et al (2013) Predictors of outcome in 176 South African patients with peripartum cardiomyopathy. *Heart* **99**(5): 308–13 (doi: 10.1136/heartjnl-2012-302760)
Brar SS, Khan SS, Sandhu GK et al (2007) Incidence, mortality, and racial differences in peripartum cardiomyopathy. *Am J Cardiol* **100**: 302e4
Capriola M (2013) Peripartum Cardiomyopathy: A review. *Int J Women's Health* **5**: 1–8 (doi: 10.2147/IJWH.S37137)
Demakis JG, Rahimtoola SH (1971) Perparitum cardiomyopathy. *Circulation* **44**: 964–8
Dorbala S, Brosenza S, Zeb S et al (2005) Risk stratification of women with peripartum cardiomyopathy at initial presentation: a dobutamine stress echocardiography study. *J Am Soc Echocardiogr* **18**: 45–8
Elkayam U, Tummala PP, Rao K et al (2001) Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med* **344**: 1567–77
Fett JD, Fristoe KL, Welsh SN (2010) Risk of heart failure relapse in subsequent pregnancy among peripartum cardiomyopathy mothers. *Int J Gynaecol Obstet* **109**(1): 34–6 (doi: 10.1016/j.ijgo.2009.10.011)
Forster O, Hilfiker-Kleiner D, Ansari AA et al (2008) Reversal of IFN-gamma, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. *Eur J Heart Fail* **10**: 861–8 (doi: 10.1016/j.ejheart.2008.07.005)
Habli M, O'Brien T, Nowack E, Khoury S, Barton JR, Sibai B (2008) Peripartum Cardiomyopathy: prognostic factors for long-term maternal outcomes. *Am J Obstet Gynecol* **199**: 415e1–5 (doi: 10.1016/j.ajog.2008.06.087)
Halkein J, Tabruyn SP, Ricke-Hoch M et al (2013) MicroRNA-146a is a therapeutic target and biomarker for peripartum cardiomyopathy. *J Clin Invest* **123**(5): 2143–54 (doi: 10.1172/JCI64365)
Hilfiker-Kleiner D, Kaminski K, Podewski E et al (2007) Acathepsin D-cleaved 16kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* **128**: 589–600
Hilfiker-Kleiner D, Silwa K, Drexler H (2008) Peripartum cardiomyopathy: recent insights in its pathophysiology. *Trends Cardiovasc Med* **18**: 173–9 (doi: 10.1016/j.tcm.2008.05.002)
Lamparter S, Pankuweit S, Maisch B (2007) Clinical and immunologic characteristics in peripartum cardiomyopathy. *Int J Cardiol* **118**: 14–20
Lampert MB, Hibbard J, Weinert L, Briller J, Lindherimer M, Lang RM (1993) Peripartum heart failure associated with prolonged tocolytic therapy. *Am J Obstet Gynecol* **168**: 493–5
Mielniczuk LM, Williams K, Davis DR et al (2006) Frequency of peripartum cardiomyopathy. *Am J Cardiol* **97**: 1765–8
Moioli M, Valenzano Menanda M, Bentivoglio G, Ferrero S (2010) Peripartum cardiomyopathy. *Arch Gynecol Obstet* **281**: 183–8 (doi: 10.1007/s00404-009-1170-5)
Morales A, Painter T, Li R et al (2010) Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. *Circulation* **121**: 2176–82 (doi: 10.1161/CIRCULATIONAHA.109.931220)
Patten IS, Rana S, Shahul S et al (2012) Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. *Nature* **485**(7398): 333–8 (doi: 10.1038/nature11040)
Pearson GD, Veille JC, Rahimtoola S et al (2000) Peripartum Cardiomyopathy: National Heart, Lung and Blood institute and Office of Rare disease (National Institutes of Health) workshop recommendations and review. *JAMA* **283**: 1183–8
Shelly S, Boaz M, Orbach H (2012) Prolactin and autoimmunity. *Autoimmun Rev* **11**(6-7): A465-70 (doi: 10.1016/j.autrev.2011.11.009)
Sliwa K, Skudicky D, Bergermann A, Candy G, Puren A, Sareli P (2000) Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma level of cytokines and Fas/Apo-1. *J Am Coll Cardiol* **35**: 701–5
Sliwa K, Skudicky D, Candy G, Bergemann A, Hopley M, Sareli P (2002) The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. *Eur J Heart Fail* **4**: 305–9
Sliwa K, Forster O, Zhanje F, Candy G, Kachope J, Essop R (2004) Outcome of subsequent pregnancy in patients with documented peripartum cardiomyopathy. *Am J Cardiol* **93**(11): 1441–3, A10
Sliwa K, Forster O, Libhaber E et al (2006) Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J* **27**: 441–6
Sliwa K, Hilfiker-Kleiner D, Petrie MC et al, Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy (2010a) Current state of knowledge on aetiology, diagnosis, manamgment and therapy of perpipartum cardiomyopathy. *Eur J Heart Fail* **12**: 767–78 (doi: 10.1093/eurjhf/hfq120)
Sliwa K, Blauwet L, Tibazarwa K et al (2010b) Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation* **121**: 1465–73 (doi: 10.1161/CIRCULATIONAHA.109.901496)
Tibazarwa K, Lee G, Mayosi B, Carrington M, Stewart S, Silwa K (2012) The 12-lead ECG in peripartum cardiomyopathy. *Cardiovascular J Afr* **23**: 322–9 (doi: 10.5830/CVJA-2012-006)
Van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ et al (2010) Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. *Circulation* **121**: 2169–75 (doi: 10.1161/CIRCULATIONAHA.109.929646)
Warraich RS, Sliwa K, Damasceno A et al (2005) Impact of pregnancy-related heart failure on humoral immunity: clinical relevance of G3-subclass immunoglobulins in peripartum cardiomyopathy. *Am Heart J* **150**: 263–9

KEY POINTS

- Peripartum cardiomyopathy is a form of dilated cardiomyopathy of unclear aetiology occurring in late pregnancy or within a few months of delivery.
- Hypotheses for the underlying pathophysiology including excessive prolactin production and/or excessive production of its 16KDa N-terminal fragment, viral myocarditis, abnormal immune response, abnormal haemodynamic response, cytokine-mediated inflammation, cardiac angiogenic imbalance as well as genetic susceptibility.
- Patients may present with signs of left and/or right heart failure. Peripartum cardiomyopathy is thus a diagnosis of exclusion; serum biomarkers and cardiac imaging are crucial in making the correct diagnosis.
- The prognosis of peripartum cardiomyopathy is variable. Associated complications include severe pulmonary oedema, cardiogenic shock, arrhythmias, thromboembolic events and rarely death.
- Therapeutic regimens are similar to standard treatment for other forms of heart failure while avoiding medications that are deleterious to the fetus or newborn. Implantable cardioverter defibrillator and cardiac resynchronization therapy requires further evaluation.
- It is expected that the Peripartum Cardiomyopathy Registry of the European Society of Cardiology and the Investigation in Pregnancy Associated Cardiomyopathy study in the USA will result in better insight regarding the aetiology, epidemiology, diagnosis and management of peripartum cardiomyopathy.