Acute heart failure: is it peripartum cardiomyopathy or not?

Katrin Bachelier-Walenta MD*, Denise Hilfiker-Kleiner MD† and Karen Sliwa MD PhD‡

*Department of Medicine, Cardiology, Angiology and Internal Intensive Care, Homburg/Saar, Germany; †Department of Cardiology and Angiology, Medical School Hannover, Hannover, Germany; ‡Department of Medicine, Medical School, Hatter Institute for Cardiovascular Research in Africa, Groote Schuur Hospital and University of Cape Town, Anzio Road, Observatory, Cape Town 7925, South Africa

Summary: Peripartum cardiomyopathy (PPCM) is a potentially life-threatening disease that occurs in women of child-bearing age.

Keywords: heart failure, HELLP syndrome, pregnancy, pre-eclampsia, peripartum cardiomyopathy

The development of heart failure (HF) in late pregnancy or the early puerperium, particularly in association with pre-eclampsia, is a rare and potentially life-threatening complication. The differential diagnosis in this setting includes Peripartum CardioMyopathy (PPCM). Data on the incidence of PPCM are limited with variable ranges reported from different geographic regions with high incidences in Africa and Haiti.^{1–3} For western societies only retrospective questionnaires for the USA are available which report one in 2500–4000 pregnancies.^{4,5} To date, no data on the frequency of the disease in Europe exist at all.

Recently a position paper by the Working Group on PPCM from the Heart Failure Association of the European Society of Cardiology⁶ proposed a revised definition of PPCM: (1) PPCM is an idiopathic cardiomyopathy presenting with 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.

(2) It is a diagnosis of exclusion with an ejection fraction (EF) nearly always reduced below 45% frequently but not always associated with LV dilation.

Although PPCM patients have a higher rate of spontaneous recovery of LV function compared with patients with other forms of non-ischaemic cardiomyopathy,⁷ normalization of LV function at six months has been reported to occur in only 23–54% of patients.^{2,3,8–11} Factors predicting poor outcome in case series include degree of LV systolic dysfunction and LV dilation on presentation, presence of LV thrombus, as well as increase markers of inflammation and apoptosis.^{5,12}

Research performed over recent years has achieved decisive advances in understanding aspects of the underlying molecular cascades that are dysregulated in PPCM. Among those, elevated pro-inflammatory serum markers such as sFas/Apo1, C-reactive protein, interferon gamma and interleukin 6, point to pro-inflammatory processes involved in the induction and the progression of PPCM and possibly impact on the prognosis.^{6,12} Recent work^{13,14} points to a possible involvement of a pathophysiological circuit involving unbalanced oxidative

stress and subsequent enhanced cleavage of prolactin into an angiostatic and pro-apoptotic 16k Da subfragment which leads to massive endothelial damage and myocardial dysfunction. An important role of endothelial damage is further supported by the recent work of Walenta *et al.*¹⁵ who demonstrated that endothelial microparticles are significantly increased in acute PPCM reflecting apoptosis with subsequent impaired microcirculation (Figure 1) and by Arany *et al.* who showed that angiogenic imbalance in PPCM may depend on multiple factors including sFlt-1 and 16k Da prolactin.¹⁶ In addition, genetic factors may contribute to a higher susceptibility to PPCM in patients with positive familial history of cardiomyopathy, who typically follow a more severe course of disease.^{17,18}

PPCM from different ethnic groups or geographic regions might have different aetiologies and inducing factors. This is supported by the different prevalence of co-morbidities and their impact on outcome in our PPCM collectives. For example, concurrent hypertensive conditions such as gestational hypertension, pre-eclampsia and/or haemolysis, elevated liver enzymes, low platelet syndrome (HELLP) were frequent in PPCM patients in the USA,⁹ in Europe and in Japan¹⁹ but rarely present in African PPCM patients.^{6,12} The African cohort studies, in fact, excluded patients with hypertension and pre-eclampsia as the researchers felt poorly managed hypertension leading to transient diastolic overload and flash pulmonary oedema associated with LV dysfunction was a separate entity. However, in western countries, pregnancy-associated hypertensive complications are frequently treated during pregnancy but are still associated with a higher risk of developing PPCM, suggesting additional pathomechanisms are present. Recent published experimental and clinical studies reported compelling evidence that pre-eclampsia may be a risk factor for PPCM by providing an extremely antiangiogenic environment.¹⁶

In this edition of *Obstetric Medicine*, Basak *et al.* report on a patient with acute HF who also had severe pre-eclampsia.²⁰ The patient was an overweight primigravida and chronic smoker, who developed new onset hypertension in the third trimester and presented at 38 weeks gestation with a blood pressure (BP) of 180/110 mmHg. She also had significant proteinuria and headaches and a diagnosis of severe pre-eclampsia

Correspondence to: Karen Sliwa
Email: sliwa-hahnlek@mdh-africa.org

Figure 1 Representative Acute heart failure in pregnant women dot plots of microparticles in plasma from one patient with peripartum cardiomyopathy (A) and from one healthy pregnant woman (B)

was made. Transthoracic echocardiography shortly after delivery showed poor LV function. The authors do not report on parameters such as functional mitral regurgitation or parameters of diastolic dysfunction. The LV dysfunction had normalized on echocardiography six weeks postpartum.

The authors suggest that the presence of marked systolic dysfunction represents an intrinsic failure of the ventricular contractility as seen in PPCM rather than impairment of LV response to increased afterload, i.e. the combination of increased systemic vascular resistance and contracted blood volume characteristic of cardiac failure secondary to pre-eclampsia. However, the remarkably rapid normalization of LV function would be more suggestive of HF secondary to hypertensive disease of pregnancy. A reliable distinction is not possible from the available data.

DOES THIS DIAGNOSTIC DISTINCTION MATTER TO THE MANAGING CLINICIAN OR THE PATIENT?

Acute onset PPCM with or without hypertension/pre-eclampsia requires intense management using intravenous diuretics, inotropic support, possibly including levosimendan and potentially mechanical assist devices.⁶ On the basis of the mechanisms described above, preliminary data support the use of bromocriptine in combination with anticoagulation therapy in patients with PPCM, demonstrating improved survival and recovery of LV function.^{14,21} Standard HF therapy should be commenced including beta-blockers and angiotensin converting enzyme inhibitors. Chronic resynchronization, which is sometimes referred to as 'biventricular pacing,' is a form of therapy for congestive heart failure and should be considered in patients with symptoms consistent with New York Heart Association Functional Class (III/IV), LVEF<35% and widened QRS/left bundle branch Block.²²

Ongoing experimental research by several investigators around the world and the newly initiated registry on PPCM in all European Cardiac Society affiliated member countries

via the ECS EUROOBS program (www.escardio.org) will hopefully contribute to increasing knowledge in this condition.

REFERENCES

- Desai D, Moodley J, Naidoo D. Peripartum cardiomyopathy: experiences at King Edward VIII Hospital, Durban, South Africa and a review of the literature. *Trop Doct* 1995;**25**:118–23
- Fett JD, Christie LG, Carraway RD, et al. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. *Mayo Clin Proc* 2005;**80**:1602–6
- Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. *Lancet* 2006;**368**:687–93
- Brar SS, Khan SS, Sandhu GK, et al. Incidence, mortality, and racial differences in peripartum cardiomyopathy. *Am J Cardiol* 2007;**100**:302–4
- Mielniczuk LM, Williams K, Davis DR, et al. Frequency of peripartum cardiomyopathy. *Am J Cardiol* 2006;**97**:1765–8
- Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2010;**12**:767–78
- Cooper LT, Mather PJ, Alexis JD, et al. Myocardial recovery in peripartum cardiomyopathy: prospective comparison with recent onset cardiomyopathy in men and nonperipartum women. *J Card Fail* 2012;**18**:28–33
- Duran N, Gunes H, Duran I, et al. Predictors of prognosis in patients with peripartum cardiomyopathy. *Int J Gynaecol Obstet* 2008;**101**:137–40
- Elkayam U, Akhter MW, Singh H, et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation* 2005;**111**:2050–5
- Goland S, Bitar F, Modi K, et al. Evaluation of the clinical relevance of baseline left ventricular ejection fraction as a predictor of recovery or persistence of severe dysfunction in women in the United States with peripartum cardiomyopathy. *J Card Fail* 2011;**17**:426–30
- Goland S, Modi K, Bitar F, et al. Clinical profile and predictors of complications in peripartum cardiomyopathy. *J Card Fail* 2009;**15**:645–50
- Forster O, Hilfiker-Kleiner D, Ansari AA, et al. Reversal of IFN-gamma, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. *Eur J Heart Fail* 2008;**10**:861–8
- Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* 2007;**128**:589–600
- Sliwa K, Blauwet L, Tibazarwa K, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation* 2010;**121**:1465–73

- 15 Walenta K, Schwarz V, Schirmer SH, *et al.* Circulating microparticles as indicators of peripartum cardiomyopathy. *Eur Heart J* 2012;**33**:1469–79
- 16 Patten IS, Rana S, Shahul S, *et al.* Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. *Nature* 2012;**485**:333–8
- 17 Morales A, Painter T, Li R, *et al.* Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. *Circulation* 2010;**121**:2176–82
- 18 Van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen D, *et al.* Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. *Circulation* 2010;**12**:2169–75
- 19 Kamiya CA, Kitakaze M, Ishibashi-Ueda H, *et al.* Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. Results from the Japanese Nationwide survey of peripartum cardiomyopathy. *Circ J* 2011;**75**:1975–81
- 20 Basak S, Rudra P. Acute onset peripartum cardiomyopathy in women with severe pre-eclampsia: a diagnostic dilemma. *Obstet Med*, 2012 (in press)
- 21 Hilfiker-Kleiner D, Meyer GP, Schieffer E, *et al.* Recovery from postpartum cardiomyopathy in 2 patients by blocking prolactin release with bromocriptine. *J Am Coll Cardiol* 2007;**50**:2354–5
- 22 Mouquet F, Kara MM, Lamblin N, *et al.* Unexpected and rapid recovery of left ventricular function in patients with peripartum cardiomyopathy: impact of cardiac resynchronization therapy. *Eur Heart J* 2012 (in press)

(Accepted 9 October 2012)