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Peripartum cardiomyopathy- can the link between prolactin and PAI-1 provide a clue?

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Peripartum cardiomyopathy (PPCM) is a rare but potentially lethal condition which develops during the last month of pregnancy or more commonly, in the early postpartum period, resulting in heart failure with reduced left ventricular (LV) function. It affects between 1 in 900 and 1 in 4000 women with live births and is more common in blacks, who also appear to have a worse outcome.[1]

Clinically, it can manifest with the spectrum of heart failure presentations, from mild dyspnoea to fulminant cardiac failure requiring mechanical circulatory support, transplant and even result in death from pump failure or fatal arrhythmias. Reported mortality rates range from 4% to 11% and recovery is unpredictable.[1] Although 50-80% of patients recover with normalisation of LV function, usually within 6 months, others may be left with long-term LV dysfunction.

Endomyocardial biopsies reveal an inflammatory state in PPCM, but whilst advancing maternal age and a history of pre-eclampsia are recognised risk factors, the precise pathophysiology remains unclear. In line with some cancer aetiologies, PPCM is thought to occur in line with Knudson's two-hit hypothesis, whereby individuals with a genetic susceptibility develop PPCM due to a second genetic mutation, possibly caused by the effects of pregnancy.

The concept of genetic predisposition is supported by recognition of familiar clustering of cases and the observation that subsequent pregnancies carry a risk of relapse, even after successful recovery of LV function. Furthermore, amongst PPCM patients, there is an increased frequency of mutations in TTN, the gene that encodes titin, and TTN variants overlap considerably with mutations known to cause dilated cardiomyopathy (DCM).[2]

However, in the last decade or so, increasing evidence has emerged that prolactin, a 23kDa protein secreted by the pituitary gland, also plays an important role in the pathogenesis of

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PPCM. In addition to stimulating lactation from the late stage of pregnancy, prolactin also has cytokine-like effects on tumour growth, differentiation and apoptosis, and influences hemopoiesis, angiogenesis and coagulation. In mice, the N-terminal fragment of prolactin (16kDa-PRL) inhibits tumour growth and promotes fibrinolysis by binding to and inhibiting the effects of plasminogen activator inhibitor 1 (PAI-1).[3] PAI-1 is a member of the family of endogenous serine protease inhibitors (serpins) that beyond inhibiting plasma fibrinolytic activity by blocking urokinase- and tissue- plasminogen activator (uPA and tPA, respectively), promotes tumour angiogenesis and growth.

Oxidative stress, well known to increase during pregnancy, has been linked to a number of pregnancy-related complications such as miscarriage, pre-eclampsia and pre-term labour. In addition, oxidative stress stimulates the expression of cathepsin D by cardiomyocytes,[3] which cleaves prolactin into the 16kDa-PRL fragment. This in turn inhibits angiogenesis and promotes endothelial apoptosis, resulting in heart failure.

In mice, cardiomyocyte-specific deletion of cardioprotective STAT3 (signal transducer and activator of transcription 3) was associated with enhanced oxidative stress and increased generation of 16kDa-PRL, which upregulates microRNA-146a (miR-146a),[4] resulting in inhibition of several pathways, culminating in cardiomyocyte hypertrophy and death.[5]

Recognition of these adverse effects of 16kDa-PRL led to evaluation of its inhibitor, bromocriptine, as a treatment for PPCM. Bromocriptine, a dopamine agonist that inhibits prolactin release, was historically used to suppress lactation. Whilst treatment with bromocriptine was able to completely reverse myocardial dysfunction in mice,[5] there is little convincing data in humans of definitive benefit. A randomised study in 20 African women with PPCM showed that bromocriptine improved LV function, but mortality in the control arm was surprisingly high.[6] A small observational registry showed that use of bromocriptine improved LV function, without affecting overall recovery.[7] A trial assessing 2 different

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bromocriptine regimens (without a placebo/control group), started 1-2 months post-partum, showed no difference in outcome.[8] So perhaps the role of prolactin in PPCM is not so clear after all.

We now have more answers, provided by an elegant study from Dr Ricke-Hoch and co-workers published in *Cardiovascular Research*.[9] They performed an observational cohort study of patients with PPCM and matched healthy post-partum controls, and in parallel performed studies in transgenic mice to provide mechanistic insight. They show that in PPCM patients, plasma levels of MiR-146a was 3.6-fold higher than in healthy post-partum controls and positively correlated with circulating PAI-1 level, which was also significantly elevated compared to controls. In baseline PPCM serum, 16kDa-PRL coprecipitated with PAI-1, which was associated with higher uPA receptor (uPAR)-mediated NF-kB activation in endothelial cells than that in healthy controls. At 6 months, LV function improved, and PAI-1 levels decreased, but were still significantly elevated compared to baseline in controls. The observed upregulation of circulating PAI-1 in PPCM patients was associated with higher PAI-1 mRNA level in cardiac biopsies and dermal fibroblasts compared to healthy controls. This was supported by the demonstration of increased cardiac PAI-1 expression in transgenic mice with PPCM induced by cardiomyocyte-specific-knockout of STAT3, compared to postpartum wildtype controls.

The role of PAI-1 is however, still not so clear. On the one hand, the association of PAI-1 with 16kDa-PRL and increased uPAR-mediated NF-kB activation in endothelial cells suggests a pathological or a bystander role. On the other hand, in an elegant mechanistic study, the authors show that systemic PAI-1-knockout mice exhibit accelerated peripartum cardiac fibrosis, inflammation, heart failure, and mortality, suggesting a possible cardioprotective or compensatory role for PAI-1.

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A challenge with PPCM is that it is rare and that it can be easily missed by the obstetric team until heart failure is advanced, with no easy early, specific diagnostic test. Delay in diagnosis, which is associated with adverse outcomes,[10] in combination with limited specific treatment for heart failure highlights the need to find specific markers of PPCM. Whilst there are no specific diagnostic biomarkers, NT-proBNP and troponin are often elevated in PPCM but not in the normal peri-partum period. Previous studies have shown that miR-146a may serve to differentiate PPCM patients from those with idiopathic DCM or those without cardiomyopathy.[4] LV size and function at the time of diagnosis are strongly predictive of recovery.[10]

The paper by Dr Ricke-Hoch *et al.* adds significantly to knowledge regarding the pathomechanism of PPCM (**Figure**).[9] The cohort of 63 patients with PPCM is large in relative terms, given the rarity of the condition. Yet, although the promoter combination 4G/4G; A-844/A-844 in PPCM patients was associated with the highest PAI-1 expression, this sample size did not allow the authors to draw solid conclusions regarding the impact of PAI-1 polymorphisms on heart failure severity and prognosis. Nevertheless, in PPCM patients, circulating and cardiac PAI-1 expression are upregulated, and circulating PAI-1 levels which correlate with plasma miR-146a levels, together with the uPAR-NF-kB activity, may be a useful diagnostic marker for PPCM. While circulating PAI-1 may induce vascular impairment via the uPAR/NF-kB/miR-146a pathway and exert pro-thrombotic effects, intra-cardiac PAI-1 expression may protect the PPCM heart from fibrosis, implying that reduction of PAI-1 may not necessarily be advisable. Further, given that obesity during pregnancy is increasingly prevalent and adipose tissue is one the main sources of circulating PAI-1, it would be interesting to consider the influence of body weight on PAI-1 plasma levels.[11,12]

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However, in the study reported here, all women with PPCM were diagnosed postpartum and only 3 had endomyocardial biopsy. Another limitation is that all those subjects in whom follow-up samples were obtained were all treated with BOARD (Bromocriptine, Oral heart failure therapies, Anticoagulants [here including low molecular weight heparin, LMWH], vaso-Relaxing agents, and Diuretics), in addition to standard heart failure medications. However, both bromocriptine and LMWH can supress PAI-1 expression, and PAI-1 levels may have been much higher had bromocriptine not been given. Further studies are now needed to prospectively validate these possible new biomarkers of PPCM, not only in women during pregnancy to see if we can identify those who are developing PPCM, but also to assess whether such markers can serve to predict response to treatment or recovery and to investigate potential pharmacological modulation of circulating and/or intracardiac PAI-1, including in those not routinely treated with BOARD medications.

Conflicts of Interest: None to disclose

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Figure. Schematic of postulated drivers of peripartum cardiomyopathy. In individuals with a genetic predisposition, the effects of oxidative stress in late pregnancy, when prolactin levels are high, lead to cathepsin D-mediated cleavage of normally 23kDa prolactin to release 16 kDa prolactin. The latter upregulates miR-146a resulting in cardiomyocyte hypertrophy and death. On the other hand, prolactin 16kDa interacts with PAI-1, which is associated with higher non-canonical uPAR- NF-kB activation promoting endothelial dysfunction. Since circulating PAI-1 levels correlate with plasma levels of miR-146a, combining, PAI-1 and miR-146a levels and uPAR- NF-kB activity may aid in the diagnosis of PPCM. Finally, PAI-1 is also found to be increased in cardiac tissue from PPCM subjects, and may play a cardioprotective role and attenuate PPCM-related extensive fibrosis.

miR = microRNA; NF-kB = nuclear factor-kappa B; PAI-1 = plasminogen activator inhibitor 1; PPCM = peripartum cardiomyopathy; STAT-3 = signal transducer and activator of transcription 3; uPAR = urokinase plasminogen activator receptor.

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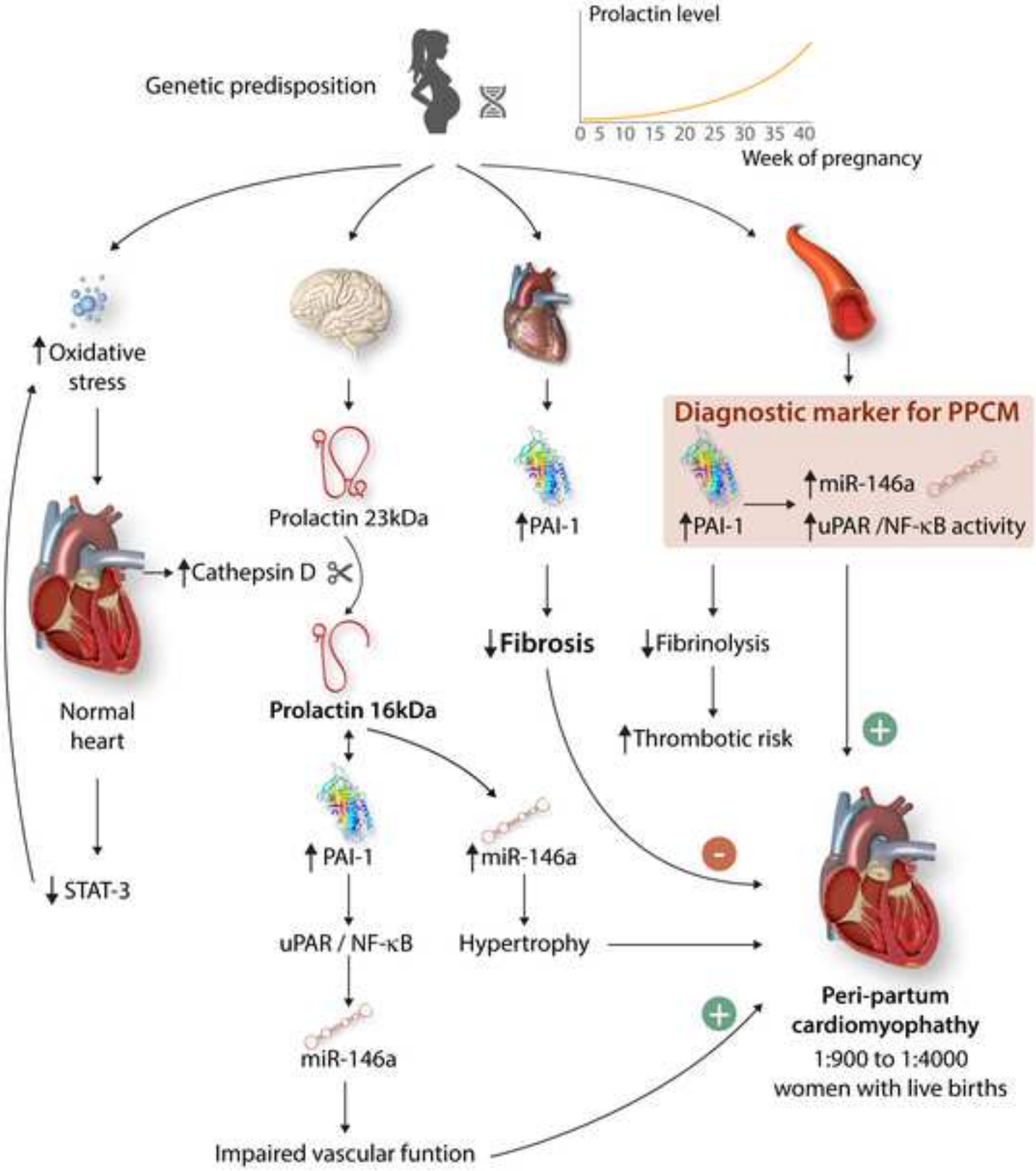
Figure(s)



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