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The global landscape of peripartum cardiomyopathy: morbidity, mortality, recovery and inequity

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This article refers to 'Outcomes at one year in women with peripartum cardiomyopathy: findings from the ESC EORP PPCM Registry' by A.M. Jackson et al., published in this issue on pages X-Y.

Peripartum cardiomyopathy (PPCM) is a complex, potentially life-threatening and poorly understood cardiovascular complication of pregnancy, characterised by left ventricular (LV) systolic dysfunction (ejection fraction<45%), presenting as heart failure (HF) for which no other aetiology is identified.[1]

The estimates of incidence vary greatly by geographical region, ranging from 1:300 pregnancies in Haiti, 1:800 in the USA and 1:10,000 in Denmark.[2-4] These are likely underestimates as milder PPCM presentations, with breathlessness, mild fluid overload and fatigue, are often misinterpreted as physiological symptoms of pregnancy and of the postpartum period, with only the most severe cases being recognised and investigated.[5] The nature of this geographical variation is unclear. It might relate to differences in prevalence of underlying risk factors or socioeconomic characteristics that are intrinsically or culturally related to geography, it may be driven by biological or genetic differences across ancestral groups, or, more likely, a combination of both.

There is accumulating evidence that the incidence of PPCM is rising.[3] Women of African ancestry are at higher risk and other predisposing factors include multiparity, multifetal pregnancies, family history, smoking, diabetes, hypertension, pre-eclampsia and increasing maternal age.[6] The global rise in the prevalence of some of these risk factors might explain the increasing reported incidence of PPCM.

Many potential causes of PPCM have been proposed, including myocarditis, nutritional deficiencies, angiogenic imbalance, autoimmunity, inflammation and a pathological response to hemodynamic stresses.[2] From a mechanistic perspective, the oxidative stress-mediated cleavage of the hormone prolactin into a cardiotoxic fragment (16-kDa prolactin), induces endothelial damage and impairs cardiomyocyte metabolism, and is, at least in some women, one of the key biological drivers of PPCM.[7] There is also a significant genetic overlap with dilated cardiomyopathy (DCM), with ~15% of PPCM patients carrying pathogenic variants in DCM-associated genes, mainly in *TTN*.[8]

The striking finding that hypertensive disorders of pregnancy occur concomitantly in 40% of women with PPCM (~15% with hypertension and 25% with preeclampsia), provides plausible evidence of shared pathophysiological mechanisms.[9] It is certainly possible that LV systolic impairment in the peripartum occurs along an overlapping spectrum, with intrinsic heart muscle disease, enriched for inherited cardiomyopathy pathogenic genetic variants, at one end, and a predominantly vascular phenotype, characterised by hypertension, endothelial and diastolic dysfunction at the other.[10]

In this issue of the Journal, Jackson, Bauersachs and colleagues present clinical outcomes of participants in the European Society of Cardiology (ESC) EURObservational Research Programme (EORP) PPCM Registry, and explore geographical variation in clinical outcomes. The registry enrolled women from 51 countries across the globe over six years, from 2012 to 2018, with outcomes at 6 months previously reported.[11] The investigators are to be congratulated for extending the follow-up period of this invaluable registry and now reporting on outcomes at 1 year. In this manuscript they present data on the rates of mortality, thromboembolism, stroke, re-hospitalization, recovery and echocardiographic measures of remodelling among women who completed follow-up at 1 year, representing 71% of the original cohort (535 women).

The first key take-home point relates to the overall rates of adverse outcomes and clinical recovery. A number of studies have previously explored these, with variable lengths of follow-up and breadth of included outcomes. These have been recently summarized in a meta-analysis including 62 studies involving 4,282 patients reporting outcomes of PPCM >1 year.[12] In this study, the mean LVEF was 28% and 47% at diagnosis and last follow-up respectively. It included observational and interventional studies, mostly from the United States (n = 27), with a minority of studies from Turkey (n = 6), China (n = 3), France (n = 2), Germany (n = 3), and other countries (n = 19). The mean follow-up was 4.5 years. During this time, nearly half of the patients achieved myocardial recovery (47%). Left ventricular assist device implantation and heart transplantation were required in 7%, and 11% of patients respectively. Over the follow-up time 9% of patients died. Despite the shorter follow-up in the present paper, Jackson, Bauersachs et al's results corroborate the mortality figure with a reported rate of 8.4%. On the other hand, there is a remarkable difference in the rate of recovery, which is 66.1% in the ESC EORP PPCM Registry - nearly 20% higher despite the shorter mean follow-up. There are many possible explanations for this. First, it might relate to a degree of selection bias as it was not possible to follow up all women included in the original registry, with marked geographical

differences in the rate of loss to follow-up (e.g. 20% in Europe and 47% in the Middle East). Second, it might have occurred due to inclusion of individuals from a broader number of countries compared to previous studies. This is supported by the fact women in Asia-Pacific had the greatest recovery rate, as high as 77.5%. Finally, it might be driven by the impressive adherence to guideline-directed therapy in the participating centres: 78% of women in the registry were treated with an ACE inhibitor or ARB and 80% with a beta blocker. In addition to mortality and recovery data, Jackson, Bauersachs *et al*'s study provides contemporary data on outcomes that have not been previously extensively explored. In this cohort, 15% of women were re-admitted to hospital at least once within the first year; and 3.5% were hospitalized more than once. In women with follow-up at 1 year, the proportions with thromboembolism and stroke were 6.3% and 2.5%, respectively.

The second take-home message relates to the marked geographical variation in clinical outcomes. Mortality across the studied regions varied from as low as 4.9% in Europe to 18.9% in the Middle East. Similarly, LV recovery was high among women in Europe (66.5%), Africa (72.8%) and Asia Pacific (77.5%) but comparatively low in the Middle east (32.7%). The trend of worse outcomes for women in the Middle East is mirrored across the different outcome categories and in the echocardiographic data, with women in the Middle East only achieving a mean increase in LVEF over follow-up of 13.5% [±13.1]; nearly half of that achieved in Asia-Pacific (23.6% [±11.0]). This picture occurs in the context of comparable guideline-directed medical therapy, except for a lower use of mineralocorticoid antagonists (MRA) than in Europe and Africa, lower percentage of patients on at least ≥50% guideline-recommended dose of beta-blocker use, and the lowest mean ramipril-equivalent dose. These geographical differences may be caused by a difference in underlying risk profiles (e.g. rates of multiparity, maternal age, baseline comorbidities and rates of concomitant hypertensive disorders of pregnancy); environment-specific risk factors (e.g. selenium and other nutritional deficiencies[13]), different access to healthcare, medications and follow-up, and perhaps ancestry-specific genomic predisposition to disease or pharmacogenetic response to therapies. In depth understanding of the reasons behind this geographic variability must remain a key priority if we are to achieve health equity for these young patients and their families.

Jackson, Bauersachs and colleagues' work highlights the importance of international collaborations in the field of rarer cardiac conditions and the value of large-scale registries. In the last few years, landmark studies have ushered in the new era of quadruple therapy in heart failure with reduced LV ejection fraction. There is therefore already the need to reassess the

rates of morbidity, mortality and recovery in PPCM on contemporaneous optimal medical therapy, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and angiotensin receptor-neprilysin inhibitor. Recovery in LV function and size occurs in around 40% of individuals with DCM.[14] It has been established that withdrawal of heart failure medications in patients that recovered from previous dilated cardiomyopathy leads to high relapse rates (~40%), and therefore treatment should continue indefinitely.[15] The very high rates of LV systolic improvement at 1 year in women with PPCM, ~66% across the cohort and even higher in some geographies, raise pressing questions for future work. It can be argued that PPCM is a distinct subgroup of cardiomyopathy or alternatively, that PPCM is an umbrella term for LV dysfunction of different aetiologies, some of which are time-limited and unlikely to occur outside pregnancy. It follows that if not all cases of peripartum LV dysfunction are caused by intrinsic and permanent heart muscle disease, at least some of these women will have achieved myocardial "cure" rather than remission on heart failure therapy. This is a particularly important point, as with the exception of beta-blockers, heart failure medications would be contraindicated during subsequent pregnancies. Therefore, improved risk stratification strategies and the role of long-term heart failure therapy need to be assessed in PPCM-specific studies. To achieve continued progress and reduce inequity, at the pace and scale that is required, the bonds and collaborations within the international PPCM community must not only be renewed but strengthened.

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