**Title:** Peripartum Cardiomyopathy: A Rare and Little Understood Disease that Needs a Global Effort to Find a Cause and Cure.

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**Abstract:**

In this review we present our current understanding of peripartum cardiomyopathy (PPCM) based on reports of the incidence, diagnosis and current treatment options. We summarise opinions on whether PPCM is triggered by vascular and/or hormonal causes and we examine the influence of the comorbidity, preeclampsia. Two reviews published in 2021 strongly support the hypothesis that PPCM may be familial. Using large cohorts of PPCM patients, they summarised the available genomic DNA sequence data that are expressed in human cardiomyocytes. While PPCM is considered a disease predominately of the left ventricle, there are data to suggest that some cases also involve RV failure. Finally, we conclude that there is sufficient evidence to warrant an RNAseq investigation and that this would be most informative if performed at the cardiomyocytes level rather than analysing genomic DNA from the peripheral circulation. Given the rarity of PPCM, the combined resources of four international human heart tissue biobanks have assembled 30 ventricular tissue samples from PPCM patients, and we are actively seeking to enlarge this patient base by collaborating with human heart tissue banks who would like to join us.

**What is Peripartum Cardiomyopathy (PPCM)?**

Literally translated, PPCM means: *Peri*- (around the time of), *Partum* means birth or delivery, *Cardio* refers to the heart, *myo*- means muscle, and *pathy* which is Greek for something wrong with. Therefore, it is a disease that affects the heart muscle that occurs either late in pregnancy, or more commonly within 6 months following delivery. However, it is quite common for the onset of heart failure to present more than 6 months following birth. PPCM is a life-threatening disease and despite it being the largest contributor to pregnancy-related cardiomyopathies, the cause remains unknown i.e. idiopathic.

**Incidence, Risk Factors**

The NIH website for rare diseases provides the following information: (<https://beta.rarediseases.info.nih.gov/diseases/220/peripartum-cardiomyopathy>) The global estimated number of people with PPCM is between 800-1000 and 5,000,000, and in the USA the estimated number of women with PPCM is between 30,000 and 200,000. The risk factors for PPCM include: obesity, hypertension, diabetes, a person history of heart disease, malnutrition, smoking, alcoholism, Afro-American descent, multiple pregnancies, childbirth of the age of 30, and premature delivery medications.

In a recent review, Honiberg et al. (2019) reported that while the incidence is low, it differs markedly worldwide. In China it is about 1:350 live births (Fett et al. 2005), in the USA (Kolte et al. 2014) and in South Africa (Desai et al. 1995) it is about 1-2:1,000 live births, and in Japan it is about 1:20,000 live births (Kamiya et al. 2011). In Australia, the incidence is estimated to be the same as in the USA. In the USA there are marked differences in its incidence, depending on the age of the mother. In 2004, mothers with PPCM aged between 15-19, 20-29 and 30-39 have incidences of 0.5-1:1000 births, compared to 40-54 year-old mothers where the incidence is about 1:270 live births. A follow-up study seven years later found the incidence in those younger than 40 years old increased to about 4.5:1000 live births. The increase may be due in part to improved diagnosis, but also because older maternal age is a risk factor. Other major risk factors for the increased incidence of PPCM include pre-eclampsia, hypertensive disorders, and women with multiple gestations that result in a 9-22% increased prevalence compared to the general population worldwide (Silwa et al. 2017).

**Diagnosis**: PPCM is often a fatal disease with patients rapidly developing an enlarged and weakened contractile heart with a reduced left ventricular ejection fraction (LVEF) of <45% in the absence of other identifiable causes. It is observed in the third trimester or most commonly within five-six months postpartum. PPCM is not a precisely defined entity (Honiberg et al. 2019). The disease not only affects the mother, but it also affects her baby, as well as her immediate and/or extended family who will be needed to care for the baby in the months while the mother is extremely unwell. While most patients respond to conventional medication (see below), some may require mechanical circulatory assistance such as a left ventricular assist device (or LVAD) while others may proceed to orthotopic heart transplantation (Rassmussen et al. 2012). The NIH website (above) lists the following symptoms: Tachycardia, chest pain, excessive fatique, tiredness during activity, shortness of breath, swelling of feet and ankles, and increased urination.

**Is PPCM a Variant of Dilated Cardiomyopathy?** Like Idiopathic Dilated Cardiomyopathy (IDCM), PPCM is a diagnosis of exclusion. Even when the LVEF is <45%, the left ventricle may not be dilated (van Spaendonck-Zwarts et al. 2014) There is mounting evidence that PPCM is a familial disease that mainly impacts cardiomyocytes and, in several respects, it resembles familial dilated cardiomyopathy (FDCM) (Ware et al. (2016).

**Treatment**, **Medications**

30-50% of PPCM patients fully recover, but 4% will proceed to require insertion of a left and/or right ventricular assist device (LVAD) as a “bridge” to heart transplantation (Hu et al. 2013), and 9% will die following transplantation. Medications include loop diuretics, beta blockers, nitrates, digoxin, and others (Angiotensin Converting Enzyme inhibitors, angiotensin blockers) that broadly reduce fluid accumulation. However, some of these medications are incompatible with pregnancy and lactation (Davis et al. 2020). Individual prognosis is worst for patients with the lowest LVEF or severe diastolic dysfunction. Up to 25% of patients with PPCM rapidly develop heart failure and will require orthotopic heart transplantation. Patients at St Vincent’s Hospital Heart & Lung Transplant Unit in Sydney who received donors hearts following circulatory death (DCD) remain at NYHA class I with essentially normal biventricular function (Chew et al. 2019).

For non-medically trained readers, Hassanabad et al. (2020) provide a lucid account of the dramatic case of a 35-year-old PPCM patient from when she arrived at a hospital with severe bi-ventricular heart failure (LVEF <10%), how her medical history was assessed, how she was differentially diagnosed, investigated and managed as she goes through multiple interventions including temporary left ventricular assist support, as well as other complications.

**American Women of African Descent**

A recent retrospective review of 220 PPCM patients clearly demonstrated that American women of African descent are significantly worse off than non-African American PPCM patients (Irizarry et al. 2017). In this study, African American women typically presented at a younger age with less than 40% of the population over the age of 30 compared to the 70% of non-African patients in the >30 years bracket. While the diagnosis was made in 90% of both cohorts during the post-partum period, ethnicity resulted in a surprisingly divergent trend from the initial diagnosis. In the non-African cohort, close to half of the diagnoses were made within the first week post-partum, with the numbers dropping off exponentially thereafter. However, in the African American cohort, only about 20% of the diagnoses were made in the first week, and the number of initial diagnoses steadily increased towards the 5-month mark. In the latter group, almost half of those that initially presented with an LVEF<30% were twice as likely to worsen compared to their non-African counterparts. Furthermore, those that recovered, took nearly twice as long despite comparable treatment regimens (Irizarry et al. 2017). The underlying cause of the disparity in disease onset and outcomes between ethnicities remains unknown. A more recent report by Getz et al. (2021) showed that socioeconomic status also contributes to the outcomes of African American PPCM patients.

Nabbaale et al. (2020) studied 236 PPCM cases in black Ugandan women and reported clinical data (echocardiology, NYHA class III/IV, LVEF ≤55%)that weresimilar to Irizarry et al. (2017) except the Ugandan cohort reported had no maternal or foetal mortality.

In a cohort of 97 women with PPCM, patients carrying mutations for the TT isoform of the GNB3 gene, had a lower LVEF, and the differences increased with time (Sheppard et al. 2016).

**Plasma Markers PPCM Suggest Vascular and/or Hormonal Cause**

An early report based on a mouse model suggested that PPCM may be a disease triggered by placental and pituitary hormones (Hilfiker-Kleiner et al. 2008). They showed that although signal transducer and activator of transcription 3 (STAT3) is not expressed in cardiomyocytes, it is never-the-less involved in a complex set of molecular interactions that involve increased production of cathepsin D, an enzyme secreted by cardiomyocytes. This enzyme cleaves the maternal pituitary-derived nursing hormone prolactin (PRL) producing a 16 kD fragment that induces apoptosis in cardiomyocytes (Hilfiker-Kleiner et al. 2007). A mouse knock-out of the *STAT3* gene developed a phenotype that included vascular “drop out” in late pregnancy. Importantly, administration of the drug Bromocriptine inhibited the secretion of prolactin, which in turn reversed peripartum cardiomyopathy in the mouse (Table 1). The 16 kD prolactin peptide also triggers endothelial cell apoptosis and secretion of miRNA146a into the circulation, producing dysfunction and apoptosis. Thus, miRNA16a is considered to be a circulating biomarker for PPCM (Halkein et al. 2013).

Circulating Fms-like tyrosine kinase (sFlt) is derived from the placenta and is elevated in preeclampsia, a pregnancy associated complication characterised by hypertension and proteinuria occurring after 20 weeks of gestation in previously normotensive women. sFlt is toxic to the heart and is therefore a potential cause of PPCM (Belo et al. 2015). It also inhibits Vascular Endothelial Growth Factor (VEGF) and leads to dysfunction and endothelial cell apoptosis.



Table 1. Plasma biomarkers that distinguish between Peripartum Cardiomyopathy, Preeclampsia and Normal Pregnancy.

**Focus on the Cardiomyocytes as the Main Genetic Cause of PPCM**

Goli et al. (2021) performed Next Generation Sequencing (NGS) using 67 genes on a cohort of 469 women (41% of African descent) who were retrospectively identified from multiple centres with PPCM. They reported that 10.4% of these women carried truncating mutations in the giant *TTN* gene, but they also identified over-representation of truncated variants in Filamin C (*FLNC)*, desmoplakin (DSP) and BAG cochaperone 3 (BAG3) which had not previously been associated with PPCM. From a cDNA study of 469 PPCM patients, 10.4% were found to carry truncating mutations in the titin gene (TTN) that encodes a sarcomeric protein, the largest known protein to man. Its N terminus is located in the Z disc of the cardiomyocyte sarcomere and runs un-interrupted through the I band and half the A band where its C-terminus binds to the C-terminus of another titin molecule from the other half of the sarcomere, a distance of over 1 µm (dos Remedios 2017). All of the *TTN* mutations are truncations and their loss-of-function are associated with the A band of the most important mutations lie in the A band portion of the molecule.

Figure 1 summarises the above discussion of the factors and highlights in red the role played by gene mutations in cardiomyocytes, which is the main thrust of the remainder of this review.

Figure 1: A simplified summary of the factors that contribute to peripartum cardiomyopathy. The text in the white boxes identify risk factors that contribute to the PPCM phenotype and are discussed in more detail in the text below. The green boxes represent the outcomes of the PPCM disease. The central theme of this review is a focus on the potential genes that may cause PPCM (red box), discussed in more detail in Table 2.

**Cardiomyocyte Gene Mutations That Contribute to PPCM**

The detailed focus of this review centres on next-generation sequencing of genomic DNA (blood samples) from a large cohort of 469 PPCM women identified with LVEF ≤ 45% towards the end of pregnancy in the months following delivery, where no other cause was identified. Goli et al. (2021) sequenced 67 genes previously associated with familial Dilated Cardiomyopathy (FDCM). Of the 70 truncating gene variants, 70% were in the *TTN* gene, but they also reported truncations in DSP, FLNC, BAG3, MYH6 , MHC7 and one in VCL. Truncations and missense mutations in these patients were compared to a reference population. Twenty-one genes were associated with cardiomyocytes that contribute to the genetic predisposition of PPCM patients (Spracklen et al. 2021). Another recent study identified 70 mutations in 12 genes associated with PPCM (Goli et al. 2021). Some of this information is built on research by Ware et al. (2016) who constructed sequencing libraries of 43 genes and identified 26 truncating variants in 8 genes that were associated with Dilated Cardiomyopathy. The available published data are summarised In Table 2. However, Ware et al. caution that although the data are suggestive, the value of genomic data in determining the prognosis for PPCM patients requires further studies.

Table 2: Mutated genes in reported in cardiomyocytes of Peripartum Cardiomyopathy patients

**Right Ventricular Failure in PPCM?** Almost without exception, the publications on PPCM refer to it as left ventricular failure, and although these papers do not specifically exclude right ventricular (RV) failure, the implication is clear. A search of PubMed revealed at least one report on RV failure. Haghikia et al. (2015) used cardiac magnetic resonance (CMR) to image the right ventricle in 34 patients with acute PPCM. They were diagnosed using CMR imaging days after delivery, and again within 3 days of developing acute heart failure. Mean LVEF was <35% in 2/3rds of the patients. 35% of the patients also had a reduced RV ejection fraction (RVEF) function (<40%). Moreover, patients with reduced RV function had enhanced LV dilatation. LV was dilated in 91% and RV was dilated in 24% of the patients. 59% of all patients completely recovered. Haghikia et al. pointed out that although echocardiography provides a very good estimate of LV size and function, CMR can more accurately quantify both LV and RV structure and function. They also used Late Gadolinium Enhanced MR to assess myocardial oedema and scar tissue. All the patients in this cohort were of German or European extraction, but similar RV similar involvement was reported using echocardiography in the tricuspid annual plane showing RV involvement in 54% of Nigerian patients. They concluded that CMR can identify a broader phenotype than simply LV dysfunction. They noted that the inclusion of a control group of healthy early postpartum patients would have been ideal. Another potential weakness is the failure of their report to provide pair-wise cardiac functions (LVEF, RVEF) for each of the 34 patients. Unlike FDCM where heart failure develops over a protracted period thereby allowing LV to result in secondary RV failure, failure in PPCM patients is acute.

**A Protocol for Collecting Samples from an Explanted Heart**

Although PPCM was first discovered in the 1800s, our understanding of the underlying etiology of PPCM remains elusive. We propose that a combined proteomic-transcriptomic approach to examine as large as possible cohort of PPCM patients is required. However, acquiring a large cohort of PPCM tissue samples has been a challenge, due in part to the rarity of the disease. The pooling of existing PPCM samples from our four heart banks will yield about 30 PPCM patient LV samples, sufficient to establish sample variance and to estimate the number of patients required. Further International collaboration will be needed to substantially increase these numbers. Identifying new sources of PPCM samples will only be useful if the quality of the sample collection and preservation is comparable.

Here is what we do.

We prepare for collecting a transplanted heart well in advance, so when we get a call from the transplant coordinator, usually at 1 am in the morning, we spring into action. Briefly, while the patient is prepared to receive a healthy donor heart, we confirm there is the patient’s consent and collect the relevant clinical data. Once the patient is connected to the perfusion machine that oxygenates the blood and returns it to the patient, the failing heart is ready to be removed (usually 40-60 minutes after the chest is opened). The failing heart is quickly removed so we can immediately begin isolating small (~1 gm) samples. We start by removing a ~1 cm wide strip from the LV anterior free wall which is cut it into 1 cm sections from base to apex and immediately snap-frozen in liquid nitrogen. This processing of LV strips is repeated until we have collected 25-30 cryovials (1.8 ml), each labelled with a printed label to identify the sample number, heart chamber, and a unique de-identified patient code. We then collect about 10 more cryovials of tissue from the RV, at least 10 from the interventricular septum, several vials from the papillary muscles, and finally 3-5 vials from each the left and right atria. With a two-person team it is possible for one of us to dissect the major coronary arteries (L main, LAD, circumflex, and R coronary) which are easily identified on the surface of the heart. When 40 minutes has passed after crossclamp time, collection ceases. The remainder of the heart is placed into formalin to be collected by Anatomical Pathology so a report can be prepared. We have collected heart samples from about 400 heart transplant patients. We have also collected 110 donor hearts (aged from 3 months through 65 years) that were not able to be tissue-type matched to patients waiting for a donor heart. The donor hearts come from patient’s that were declared to have suffered “brain death”, usually as a result of massive cerebral artery haemorrhage, but whose heart continued to beat. These hearts were removed from coordinator-certified donor patients. The donor hearts were perfused with sterile ice-cold cardioplegic solution that arrested contraction, packed in ice, and transported to St Vincent’s Hospital, often by private jet from around Australia. The donor hearts were processed as described above except that the entire heart was used, usually resulting in >100 vials per heart. Most of the hearts from healthy babies and children arose from swimming pool-drownings (dos Remedios et al. 2017).

In a report of the long-term outcomes for 1,938 PPCM transplant patients and 28 age-match controls, Bouabdallaoui et al. (2018) concluded that the outcomes “were favourable”, and this is supported by the experience at the St Vincent’s Hospital Heart & Lung Transplant Unit. Unfortunately, the Bouabdallaoui group did not collect tissue from these failing explanted hearts. More recently Rasmusson et al. (2018) reported that of 42,406 transplantations, 9,419 were women and 485 of these had PPCM (Rasmusson et al. 2012). These patients had a higher list status and were younger, but graft survival was lower than comparable other women. In the USA, 1,258 women received LVADs either as a bridge to recovery or to transplantation, and this is another source of ventricular tissue that may have been snap-frozen and stored. If even a small fraction of these were snap-frozen, they would be valuable for research.

We therefore need to look for existing (and future) sources of PPCM transplanted hearts. The registry of the International Society for Heart and Lung Transplantation (Taylor et al. 2007) reported that about 5,000 heart transplantation procedures are performed annually.

Another potential source of tissue is formalin-fixed paraffin-embedded (FFPE) tissue. While this is not the ideal source for RNA sequencing because formalin fixation degrades RNA and crosslinks it to its ligands, the 10x Genomics FFPE Visium slides employ clever chemistry to retrieve and immobilize mRNA and visually connect it the cells of origin. The current technology has a spatial resolution of 55 µm but in 2022 they will release Visium slides with a resolution of about 5 µm, sufficient to examine the individual nuclei of human cardiomyocytes. In the context of PPCM, this is noteworthy because it opens a previously untapped source of tissue in FFPE archived blocks in hospital pathology departments. Details of sample preparation and a demonstration protocol can be viewed here: <https://support.10xgenomics.com/spatial-gene-expression-ffpe/sample-prep>

**RNAseq Collaboration**

Collectively, we have agreed to contribute LV and RV tissue samples to undertake RNAseq analysis from PPCM patients and compared them to tissue-type matched healthy female donor hearts provided by the Sydney Heart Bank (Li, Lal, and dos Remedios, 2019), Ken Campbell’s tissue bank at the University of Kentucky (McDonald et al. 2020) and Zolt Arany at the University of Pennsylvania (Arany et al. 2016). Collectively we have about 30 snap-frozen samples from failing PPCM transplant patients, sufficient to establish the sample variance for the genes list in Table 2. We will continue our global search for PPCM heart samples (they are readily transported internationally in nitrogen vapour dewars that maintain -180°C for a week). Our aim is to achieve a tissue cohort of up to 100 hearts to achieve single cell RNAseq using the 10xVisium slide system. Tissue samples of 10-50 mg are sufficient to achieve this kind of RNAseq.

**Mass Spectrometry and PPCM**

If RNAseq has a failing, it is because it usually begins with a few milligrams of tissue and yields data based on the aggregated RNA content of *all* the cells in the sample, including cardiomyocytes, endothelial cells fibroblasts and other resident or transient cells in the sample. In other words, it is not cardiomyocyte specific. Mass spectrometry (MS) provides information about the proteins and has similar limitations. Shot-gun MS requires trypsin digestion of the heart proteins, but since so many of the proteins listed in Table 2 involve truncation mutations, and several involve post-translation modification this makes it impossible to detect if some of these proteins might be truncated by mutations. Accordingly, our collaborator Professor Ying Ge will combine her expertise in cutting-edge high-resolution top-down MS-based, proteomics and metabolomics and functional studies to quantify intact proteins including their post-translational modifications of most proteins (Tucholski et al. 2020) to samples from PPCM patients.

**Track Record of Collaboration**

When the senior author began collecting tissue samples from heart transplant patients’ hearts in 1989 with encouragement of the late Dr Victor Chang, we realised that alone we could not expect to understand the molecular nature of human heart failure without the help and expertise of the many colleagues and friends. By sharing failing and non-failing human heart tissue with a considerable number of these researchers, we have made some interesting discoveries and some real progress. So far, we have published about 160 papers (see Supplementary data) only one of which (Bollen et al. 2017) specifically addressed the role of titin question PPCM.

**Is There a “Cure” for PPCM and Other Inherited Cardiomyopathies?**

In most instances, the precursor of a “cure” requires an understanding of the molecular basis of the disease. In the case of Hypertrophic Cardiomyopathy (HCM), it was the understanding that depletion of myosin cross-bridges in the “super relaxed state” (McNamara et al. 2015) led to the realization that the drug mavacamten stabilises the super relaxed state (Anderson et al. 2018) and restores the heart to normal activity.

In the case of PPCM, Bollen et al. (2017) were searching for a mechanism that could explain why DCM patients progressively deteriorated without recovery, compared to PPCM patients that either recovered or rapidly deteriorated. They compared six cases of DCM, four with Ischemic Heart Disease and four with PPCM with 16 age- and sex-matched healthy donor hearts and found that only in the PPCMs was length-dependent activation significantly impaired, which they attributed to reduced protein kinase A (PKA) activity.

Then more recently, Fomin et al. (2021) from a large group of German laboratories (including Wolfgang Linke) and from the Karolinska laboratory, produced human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). They compared wild-type controls to CMs with either a patient-derived A-band-*TTNtv* truncation mutant (*TTNtv*) or a CRISPR-Cas9-generated M-band *TTNtv*. The amount of truncated TTNtv protein increased in proportional to the inhibition of proteasomal activity. However, in the engineered hiPSC-CMs the depressed contractility due to the TTNtv *could be* *reversed* *by correcting the mutation using CRISPR-Cas9* which eliminated the truncated TTN and raised the level of wild-type protein, thus restoring function. This exciting paper is more promising than anything reported so far.

**Open Invitation**

The authors of this review issue an open invitation to clinical research groups to collaborate with us to we can collaborate by assembling a large cohort of Peripartum Cardiomyopathy to better understanding of why the hearts decline and fail.

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