Peripartum cardiomyopathy and heart failure in the young

Anders Barasa

UNIVERSITY OF GOTHENBURG

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Anders.barasa@gu.se

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"Elimu haina mwisho" - proverb
Education has no end

ABSTRACT

Aim: The overall aim of this thesis was to determine comorbidity, incidence and mortality in heart failure (HF) in young adults and particularly in peripartum cardiomyopathy (PPCM). More specific objectives in PPCM patients were to describe the role of concomitant preeclampsia, prognostic factors of symptomatic and left ventricular recovery. Finally we also wanted to assess left ventricular and arterial compliance in PPCM patients.

Methods: In paper I we linked mortality data from the Cause-specific Death Register and discharge diagnoses from the Inpatient Register. In paper II we further linked these two registries with the Medical Birth Register. In paper III we reviewed a clinical cohort with PPCM and compared prognostic factors associated with early and late symptomatic recovery. In paper IV consecutive PPCM patients were compared with healthy controls with respect to left ventricular contractile reserve, diastolic function and arterial stiffness.

Results: Paper I: From 1987 to 2006, there were 443 995 HF hospitalisations among adults 18–84 years in Sweden. Of these, 3.0% occurred in people aged 18–54 years. An almost 50% increase among people aged 18–44 years was seen in contrast to people ≥45years where incidence peaked in the mid-1990s. Case fatality decreased for all age groups, but only up until 2001. Paper II: Countrywide 272 PPCM cases and 1341 controls were identified. Mean incidence was 1 in 9191 deliveries. PPCM cases had higher BMI (OR) 1.05, were more likely to be of non-OECD country origin OR 1.61, have multifetal births OR 2.26 and have a higher prevalence of preeclampsia OR 13.02. From 1987-2006, 8.1% of cases and 0.4% of controls had died. Preeclampsia was inversely associated with mortality. Paper III: 24 cases of PPCM were identified. Mean (SD) LVEF at diagnosis was 34.7% (10.7). All patients received β-blockers and ACE-I/ARB. Review was performed at 4.8 (2.8) years. Late/non-recovery vs. early recovery was associated with larger LV size at diagnosis, *P*=0.02. Preeclamptic PPCM cases (58.3%), recovered earlier, *P*=0.001. Paper IV: 22 PPCM cases and 15 controls, underwent review 3 years after diagnosis, including 2-D echo and arterial stiffness assessment at rest and immediately post-exercise. Blood pressure was higher among cases (122/76) than controls (111/67), *P*=0.01. NT-proBNP was elevated in all cases. Increased LV and arterial stiffness was seen in cases compared with controls.

Conclusions: We showed that the incidence of HF among adults <55 years increased while mortality decreased between 1987 and 2006. PPCM incidence during the period was 1 in 9200 deliveries, which is lower than most other studies. Mortality at the end of the study period was >20 higher in cases than controls. Preeclampsia was strongly associated with PPCM, but inversely associated with mortality. Likewise paper III and IV revealed that large LV size and the absence of concomitant preeclampsia was linked to worse prognosis. LV and arterial compliance remain reduced 2.7 years after diagnosis. Longer follow-up of PPCM patients should be pursued with specific attention to diastolic function and reduced arterial compliance. Hence the notion of complete PPCM recovery, may need revision.

Key words: Heart failure, Young adults, Epidemiology, Cardiomyopathy, Peripartum, Pregnancy, Preeclampsia, Prognosis, Incidence, Echocardiography, Vascular age

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LIST OF PAPERS

This thesis is based on the following papers.

I Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M, Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden.
Eur Heart J. 2014 Jan;35(1):25-32.

II Barasa A, Rosengren A, Zverkova Sandström T, Ladfors L, Schaufelberger M. Peripartum cardiomyopathy and pregnancy-associated heart failure: incidence and long-term mortality in Sweden 1987-2010.
Submitted

III Barasa A, Goloskokova V, Ladfors L, Patel H, Schaufelberger M. Symptomatic recovery in a clinical cohort with peripartum cardiomyopathy.
Submitted

IV Barasa A, Schaufelberger M, Nyberg G, Basic C, Johansson M. Increased arterial stiffness and persisting altered left ventricular structure and function in peripartum cardiomyopathy.
Manuscript

CONTENTS

ABREVIATIONS

ACHD	Adult congenital heart disease (grown-up congenital heart disease - GUCH)
AIx	Augmentation index
BMI	Body mass index
BP	Blood pressure
CDR	Cause-Specific Death Register
ESC	European Society of Cardiology
HF	Heart failure
HR	Heart rate
HTN	Hypertension
ICU	Intensive care unit
IHD	Ischemic heart disease
IPR	Inpatient Register
LA	Left atrium
LV	Left ventricular
LVDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic diameter
MBR	Medical Birth Register
OECD	Organization for Economic Cooperation and Development
OR	Odds ratio
PPCM	Peripartum cardiomyopathy
PWV	Pulse wave velocity
SD	Standard deviation

INTRODUCTION

Heart failure

Heart failure (HF) is a syndrome and not per se a diagnosis. HF has no singular pathological process or etiology. HF is - in keeping with the current ESC guidelines for the diagnosis and treatment of acute and chronic HF 2012 - for clinical purposes defined as: *"a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles and displaced apex beat) resulting from abnormality in cardiac structure and function".*[1] HF can be difficult to diagnose as many of the symptoms are non-discriminating and of low diagnostic value, but with the aid of echocardiography and natriuretic peptides levels, the diagnosis can still be verified despite a vague or mild presentation. HF is numerically a disease of the elderly with a dramatic increase in incidence from the age of 70. Therefore, Sweden which has a relatively old population, also has a disproportionately high disease burden - despite declining age-adjusted prevalence - amounting to 144 000 persons who have been hospitalised for and living with HF in 2007.[2] HF is associated with frequent readmissions, and accounts for the highest share of cardiac admissions incurring more healthcare expenditure than any other cardiovascular diagnosis.[3] Despite improved outcomes in the management of coronary heart disease and HF,[4] the disease in the elderly still carries a 50% five-year mortality, parallel to that of many cancers.[5, 6] While studies indicate that HF incidence and mortality in Sweden, Scotland and Australia have been decreasing since the early 1990s,[7-9] worldwide HF prevalence is still on the rise as middle and lower income countries have entered the era non-communicable diseases.[1]

Heart failure in young adults

HF among the young is uncommon, but may exert greater impact on active and income-generating individuals with several dependents.[1] Most HF data are based on older adults, and accordingly, little is known about the aetiology, incidence and trends in HF among younger patients.[10, 11] While ischemic heart disease and hypertension are predominant causes of HF among older patients, the aetiological make-up of HF in young adults, according to trial data, is more heterogeneous.[12, 13] Causes of HF among the young include adult congenital heart disease (ACHD), idiopathic cardiomyopathies, myocarditis or alcohol- or drug-related myocardial lesions.[14, 15] Even more disruptive than HF in young age, is possibly HF during pregnancy, albeit a rare occurrence, it constitutes the most common cause of cardiovascular disease in pregnant women.[16] HF during pregnancy poses particular dangers as symptoms may mimic those of physiological pregnancy.[17]

PPCM – an introduction

The primary focus of this thesis – peripartum cardiomyopathy, constitutes a subset of HF in the peripartum period. PPCM is defined as pregnancy-associated cardiomyopathy characterised by unexplained new-onset systolic - LVEF <45% - HF during the last months of pregnancy or in the months following delivery where no other cause of pre-existing HF is found.[18]

The epidemiology of PPCM is largely unknown and the incidence in Asia and Europe is uncertain.[17] Previous studies have shown varying incidence rates from approximately 1:1000 in South Africa,[19] to 1:2000 to 1:9700 in various sub-populations in USA,[20-23] and 1:20 000 in Japan.[24] Published European clinical data are scarce,[17,25,26] but largely in agreement with existing US studies[27, 28] where high maternal age, multifetal pregnancy, diabetes and African descent are known to be associated with PPCM.[26, 28-31]

Putative risk factors are advanced maternal age, high parity, multifetal pregnancy, sub-Saharan African heritage and preeclampsia[22, 24, 32] and more recently anaemia and substance abuse.[33]

Preeclampsia deserves separate attention as it very frequently coexists with PPCM, but little is known about its influence on the clinical course and symptomatic recovery in PPCM.[34, 35] Preeclampsia is known to increase therapy resistant hypertension and arterial stiffness postpartum.[36, 37]

The underlying causes of PPCM have not been fully elucidated, but a number of hypotheses including inflammatory processes and genetic predisposition[18] have been proposed. Increasing evidence now points towards endothelial dysfunction, uncontrolled oxidative stress and impaired angiogenesis as main drivers in the pathogenesis.[38, 39, 40]

Endothelial dysfunction affects vessel stiffness and is known to affect myocardial systolic and diastolic function and performance,[41] including coronary perfusion and cardiovascular hemodynamics.[38] Endothelial dysfunction is also associated with adverse outcome in HF,[41] and it has been shown that increased arterial stiffness is an added independent marker of future cardiovascular adverse outcome.[42, 43] It also correlates well with global diastolic dysfunction and reduced LV compliance though their exact causal relationship remains unclear.[44]

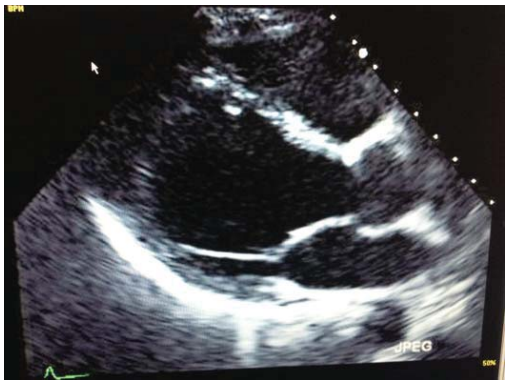
No data on prognosis for PPCM beyond seven years have been reported.[27] Survival is known to vary geographically.[24, 33, 45, 46] Thus 7-year mortality in one study was reported to be 24% among African American women.[47] Identifying independent predictors of mortality has been difficult, as the number of reported fatalities remains low. In outcome studies, African-American ethnicity, left ventricular end-diastolic diameter and low LVEF <25–30% at presentation all have been associated with reduced left ventricular recovery or death.[21, 46, 47]

Prognosis in terms of LV recovery has mostly been examined with respect to left ventricular ejection fraction (LVEF) and LV dimensions, but other parameters of LV function such as contractile reserve, longitudinal contractility, and global diastolic function are poorly examined in this population.[26, 46, 48, 49] Also little is known about the long term effects of PPCM on cardiovascular ageing.

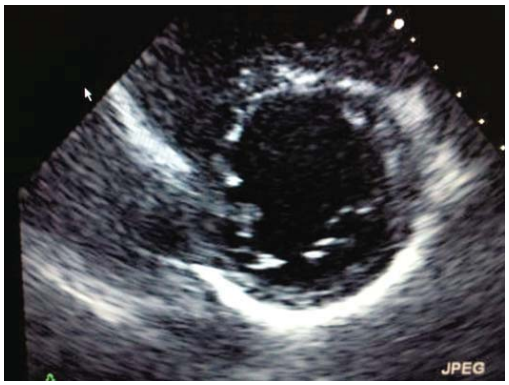
PPCM is managed according to the current guidelines for HF,[18] but there are no tailored evidence based guidelines for the medical management of PPCM neither at presentation, nor during recovery.[16]

Echocardiography

Transthoracic echocardiography examination (TTE) is the preferred imaging modality to assess cardiac function. It relies on ultrasonography and is the golden standard for functional non-invasive cardiac evaluation. Several methodologies including, M-mode, 2-D (Figure 1), Doppler, Tissue Doppler and 2-D strain imaging are available. These modalities allow for the measurement of the timing and rate of myocardial contractility, determination of cardiac volumes in the different phases of the cardiac cycle, assessment of the hemodynamics of cardiac valves, the assessment of myocardial stiffness and velocity, and quantification of myocardial thickening and incursion. In HF both systolic and diastolic dysfunction can readily be assessed through TTE provided adequate echogenicity is achieved. TTE is crucial in the assessment of LV function in HF and PPCM as subnormal LVEF and diastolic dysfunction are signs of persistent left ventricular dysfunction calls for continued treatment optimization. Further, LVEF <36% should prompt targeted pharmacological treatment.[1] LV global contractility is defined by pressure rise during the early LV contraction phase, dP/dt.[50]



A.



B.

Figure 1. Transthoracic echocardiographic images of the heart. A: parasternal long-axis view. B: Parasternal short-axis view.

Arterial stiffness

Arterial stiffness or vascular ageing also implies impaired endothelial function and is a condition of deficient vessel compliance. Compliance describes volume change per incremental pressure change ($C = \Delta V/\Delta P$). Arterial stiffness has increasingly been investigated as a sentinel marker of cardiovascular disease and is known to be an added independent marker of future adverse outcomes.[42, 43] It is also known to affect myocardial systolic and diastolic function[41], coronary circulation and cardiovascular hemodynamics.[38] Endothelial dysfunction is associated with adverse prognosis in HF,[41] and increased arterial stiffness is an added independent marker of future cardiovascular adverse outcome.[42, 43] It also correlates well with global diastolic dysfunction and reduced LV compliance though their exact causal relationship remains unclear.[44] Arterial stiffness it is largely assessed through by pulse wave (PWV) velocity and augmentation index (AIx) measurements.

PWV is a known index of compliance in the large collagenous conduit vessels in contrast to the muscular resistance vessels of the peripheral vasculature. Increased PWV at the aortic level is correlated with arterial ageing and predicts cardiovascular adverse events beyond traditional risk factors.[51]

AIx measures arterial stiffness and is an index of peripheral vascular tone and resistance at the arteriolar level and thus of endothelial function.[52] It is calculated as the difference between the direct and reflected systolic peak pressures, divided by the pulse pressure, mmHg (PP); $(P_{reflected}-P_{direct})/PP \times 100$). Arteriograph©, a device used to determined arterial stiffness, has been validated against SphygmoCor© - an older device - and invasive recordings. Both Arteriograph© and SphygmoCor© were independently strongly correlated with invasive recordings.[53,54]

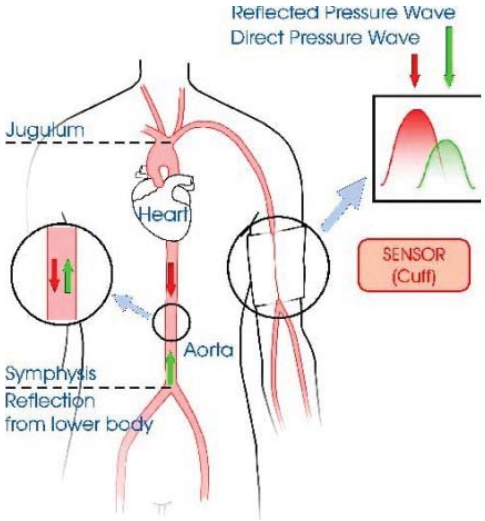


Figure 2. The principle of the Arteriograph©. A pressure sensor in the blood pressure cuff records the pressure fluctuations at 35 mmHg above systolic pressure. The time between the two peaks, the red ejection peak and the green reflected peak corresponds to twice the aortic distance. The surrogate measure is the distance between the symphysis and the jugular notch. The brachial augmentation index is calculated from the difference in height between the two peaks.[53]

AIMS

The overall aim of this thesis was to gain more knowledge about HF in young adults and particularly PPCM through epidemiological and clinical data collection and targeted cardiovascular examination.

Specific objectives

- Through linking the national Inpatient (IPR) and Cause-Specific Death (CDR) registries we aimed to investigate age-specific national trends in HF in approximately 440,000 hospital discharges over a period of 20 years concerning:
  - incidence
  - comorbidity
  - one-year case fatality

- Through linking population-based data from the Swedish national Medical Birth Register (MBR), the IPR, and the CDR to identify a PPCM cohort and primarily determine the following:
  - incidence of PPCM in Sweden
  - patient characteristics
  - mortality between 1987 and 2010.

- In a Swedish clinical cohort of PPCM patients to identify or describe:
  - basic patient characteristics
  - the hallmarks of PPCM with and without coexisting preeclampsia
  - prognostic clinical markers of poor symptomatic recovery
  - pharmacological management in these patients.

- In PPCM cases, compared with age- matched healthy controls who had undergone clinical and echocardiographic review, to assess:
  - arterial stiffness
  - LV structure and function
  - LV contractile reserve through functional tests at rest and during exercise

METHODS

Study populations and design

In paper I we retrospectively looked at all adults younger than 55 years who developed HF in a period from 1987-2006. Patients were identified through linking data from the IPR and CDR using the unique national personal identity number. Paper II was a retrospective case-control study where we linked data from the two registers mentioned above, with the MBR to identify a subpopulation of young adults with HF, but specifically women with pregnancy-associated HF or PPCM between 1987 and 2010. The age- and year of delivery-matched controls were sampled from the MBR. Between 1987 and 1996, the International Classification of Diseases Ninth Revision (ICD-9) was in use, and thereafter, ICD-10. In paper III and IV we clinically identified a cohort of women with PPCM in two western Swedish counties (*Halland and Västra Götaland*) between 2005 and 2013 and did journal, clinical and echocardiographic reviews.

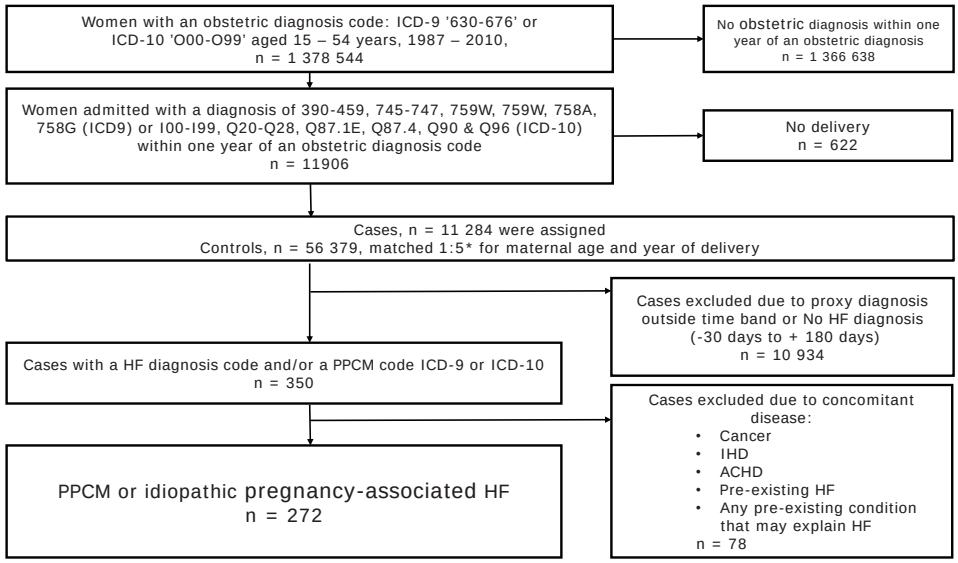
Young adults with HF – I

We included all patients aged 18 to 54 years from 1987 to 2006 who had a first-ever HF diagnosis code in any position. Secondary HF diagnoses were included because a large percentage of younger patients with HF have other primary aetiological diagnoses e.g. myocarditis or hypertension.

PPCM and pregnancy-associated HF in Sweden – II

From 1987–2010, 1 378 544 mothers aged 15–54 years were registered with an obstetric diagnosis of 630–676 (ICD-9) or O00–O99 (ICD-10), of which 11 284 cases received any concurrent diagnosis of the circulatory system: 390–459, 745–747, 758A, 758G, 759W (ICD-9) or I00–I99, Q20–Q28, Q87.1E, Q87.4, Q90 & Q96 (ICD-10), within a year of any obstetric diagnosis and delivery. Each case was then randomly assigned 5 controls from the MBR matched for maternal age and year of delivery, for a total of 56 379 controls. Of the 11 284 cases, 350 had a diagnosis code within the pre-specified time range to delivery of −30 days up to +180 days. Because our own clinical experience had indicated that a substantial number of women with new-onset HF towards the end of pregnancy and in the months following delivery, do not receive a PPCM code (674W (ICD-9) or O903 (ICD-10)), but a diagnosis of heart failure or cardiomyopathy; we used the following as proxy codes, i.e., cardiomyopathy 425 (ICD-9), I42, I43 (ICD-10) and/or HF 428A, 428B, 428X (ICD-9) and I50 (ICD-10) within 30 days before delivery up to 180 days post-partum. To avoid inclusion of other underlying aetiologies, we used the following exclusion codes: any diagnosis of cancer 140–208 (ICD-9), C00–C97 (ICD-10); adult congenital heart disease (ACHD) 745–747 (ICD-9), Q20–Q28, Q87, Q89 (ICD-10); ischemic heart disease (IHD) 410–414 (ICD-9), I20–I25 (ICD-10), or pre-existing HF. Because the diagnosis codes used did not have 100% accuracy, and because an HF diagnosis did not guarantee idiopathic HF, manual review of the MBR and IPR of these 350 entries was performed to validate the diagnosis. In this way, another 78 cases were excluded

owing to: the PPCM or HF diagnosis being ambiguous (a 674W code with no other indication of HF), previously unidentified pre-existing HF, IHD, ACHD or cancer, valvular disease, arrhythmia, pulmonary embolism, septicaemia, and a case of sickle cell-induced anaemia (Figure 3).



*Only 16 cases had less than 5 matched controls

Figure 3. Flow-chart, inclusion of PPCM cases.

PPCM in western Sweden – III & IV

The study population comprised PPCM cases from five hospitals in western Sweden (*Sahlgrenska University Hospital, Södra Älvborgs Sjukhus, Halmstad Sjukhus, Norra Älvsborg Länssjukhus, and Kärnsjukhuset Skövde*) with a catchment area constituting 20% of all Swedish deliveries. All departments of cardiology/internal medicine in the region were contacted to identify women with a PPCM or any idiopathic pregnancy-associated HF diagnosis from 2004 – 2013. Patient records were followed from presentation to the date of the final review (October 13th 2013).

Consecutive patients were identified in a two-prong process:

1) For hospitals outside Gothenburg where the authors had no access to the medical records, the chief physicians from all departments of cardiology/medicine were contacted who then identified cardiologists within their respective departments known to have a special interest in pregnancy-associated HF, who could then aid in the transfer of medical records of PPCM cases to the authors. Because PPCM is rare in Sweden, these cases were easily identified. Through this procedure, a total of 6 cases were identified, 4 of which fulfilled the inclusion criteria.

2) Within Gothenburg - which comprises one tertiary referral hospital, the Sahlgrenska University Hospital - the authors had direct access to the electronic records. ICD-codes and journals were reviewed for any women aged 15 – 54 years who were discharged from the hospital between January 2004 and October 2013 with an ICD-10 diagnosis code of PPCM, HF or cardiomyopathy (O90.3, I50, I42 and I43). Women lacking a concurrent obstetric ICD-codes were excluded as non-pregnant. By these criteria another 31 cases were identified. Six of these were excluded because they were lost to follow-up, most having moved out of the region. Another 5 did not meet the PPCM criteria, leaving 20 cases in Gothenburg for inclusion.

For the echocardiographic and arterial assessment review, 17 healthy controls were identified, recruited through local advertisement. Inclusion criteria for the controls were:

1) At least one past pregnancy and delivery with emphasis on the absence of any complication including mild gestational hypertension or diabetes.

2) Freedom of any past or present cardiovascular disease.

3) Freedom of any current health issue requiring medical supervision, medication or which would interfere with the data collection.

Upon investigation, two controls were excluded – one because of LV wall motion abnormalities, and a second case due to bicuspid aortic valve disease, both findings potentially affecting LV loading conditions and arterial compliance.

The registries

Sweden has universal healthcare providing low-cost hospital care to all Swedish permanent residents. As the vast majority of Swedish residents are managed within the public healthcare system, data keeping becomes equally manageable. Therefore when hospitals are obliged to report data to national registers, coverage tends to be high. It is this high coverage, accuracy and the long time span within which these registers have been available, that has allowed for the high data quality used in this thesis, and which has ultimately allowed for an unusual complete dataset.[55-57] The registers used cover deaths, hospitalisations and births.

The Cause-Specific Death Register

The CDR includes death certificates and autopsy reports for all Swedish residents dating back to 1961. The international version of the ICD-10 is currently employed. The CDR was validated in one report from 1995 which showed an accuracy of 87% for ischemic heart disease, but generally stated that the more sudden the death and the younger the person, the higher the validity. The latest report from the National Board of Health and Welfare states that 3% of diagnoses are given a faulty code, but only 0.3% of ICD-10 codes remain incorrect by the time they are entered into the CDR. It also states that whereas autopsy was performed in 50% of decedents in the 1970s, that number has shrunk to 20% today.[58]

The Inpatient Register

The Inpatient Register (IPR) collects all diagnosis codes on discharge for any patient in the entire country. Since 1987 reporting discharge diagnoses for all hospitalisations to the nationwide IPR has been mandatory. The data are person-based and include primary and secondary discharge diagnoses of any given hospitalised patient [56]. From 1987 to 1996, a primary discharge diagnosis was lacking in less than 1% of all admissions. The diagnosis of HF in the Swedish Inpatient register has been validated showing 96% accuracy for primary diagnoses in internal medicine or cardiac wards, and 86% and 91% for secondary diagnoses in internal medicine and cardiac wards, respectively.[59] From 1987–1996, a primary discharge diagnosis in the IPR was lacking in less than 1% of all internal medicine and cardiac ward admissions. The diagnosis of HF in the IPR has been validated for the period 1976-2001, showing 95% accuracy for primary diagnoses and 91% accuracy for secondary diagnoses in cardiac wards.[56, 59] Unpublished data from a study in metropolitan Gothenburg showed that a cardiomyopathy diagnosis could be validated in nearly 90% of the cases. No change in diagnostic accuracy was seen over time.

The Medical Birth Register

Since 1973, 97.0–99.4% of deliveries have been reported to the Medical Birth Register (MBR) which includes information from the first antenatal visit up to the last perinatal care.[57, 60] The most extensive validation of the MBR from 2002 and the latest report from the MBR, *Pregnancies, Deliveries and New born Infants* from 2012, both written in liaison with the National Board of Health (*Socialstyrelsen*), found missing MBR registrations in 1.0% (1973–1998) and 0.6% (2010) of cases respectively. The MBR prior to 1998 did not distinguish between singleton and multiple births, but ICD codes from IPR allowed us to assess this information. An increasing number of deliveries among mothers born outside the Nordic countries was seen: 3% in 1973 and 21.5% in 2010. Further an unknown number of these deliveries took place prior to registering with the Swedish authorities and likely went unreported.[56, 60]

Definitions and procedures

Paper I

First admission was defined as any hospital admission with no previous admission for HF in the past seven years. This was done to ensure the probability of being admitted for the first time was similar for any given time period. We defined the employed diagnosis codes as follows:

Table 1. ICD-codes used to define HF, cardiomyopathy, IHD, valvulopathy and ACHD respectively

ICD code	ICD-9 (1987 – 1996)	ICD-10 (1997 – 2006)
Cardiomyopathy	425	I42, I43
HF	428A, 428B and 428X	I50
IHD	410-414	I20–I25
Valvulopathy	391, 394-398, 421, 424	I05-I09, I33-I39
ACHD	745-747	Q20–Q28, Q87, Q89

Paper II

Data for the controls were extracted from the MBR and IPR. Mean parity was defined as the number of deliveries including the index delivery. Assisted pregnancies were defined from data from the MBR as: in-vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) or high-dose hormonal therapy. Caesarean section included both acute and elective procedures as defined in the MBR. Preeclampsia was defined by IPR data, and codes 642 (ICD-9) and O11–O15 (ICD-10). Comorbidity diagnosis codes were collected from the IPR for both cases and controls. Diabetes was defined by codes 250 (ICD-9) and E08–E13 (ICD-10) and I10 – I15 (ICD-10), and thyroid disease as codes 240–246 (ICD-9) and E03–E07 (ICD-10). Nationality was defined as the mother's country of birth and an Organisation for Economic Co-operation and Development (OECD) country as member states at the beginning of the study period. Neonate characteristics adhered to the standard definition of small for gestational age (SGA), referring to a birth weight <2 standard deviations smaller than the average and large for gestational age as >2 standard deviations larger than the average.[61]

Paper III

Maternal age was determined at the time of delivery. Body mass index (BMI kg/m^2) was measured at first antenatal visit (9–12 weeks of gestation). Normotensive was any BP <140/90 mmHg. Parity was the number of deliveries per woman including the index pregnancy delivery. Assisted pregnancy included the following fertility enhancing methods: in-vitro fertilization (IVF), intra-cytoplasmic seminal injection (ICSI) and assisted hormonal therapy. All non-elective caesarean sections (CS) were classified as acute. Gestational diabetes was classified as the development of diabetes in any pregnant woman with no known pre-existing diabetes. Preeclampsia was defined as proteinuria and new onset hypertension after 20 weeks of gestation. Clinically significant postpartum hemorrhage was defined as estimated blood loss of >500 ml within 24 hours of delivery.[62] Small for gestational age (SGA) was defined as a birth weight of less than the 10^{th} percentile for gestational age assuming 3500 g as the mean birth weight at 40 weeks of gestation in Sweden during the period.[60] Preterm birth was delivery before 37 weeks of gestation. Substance abuse was defined as any mention of clinically relevant illegal drug use in the medical records. Self-reported alcohol consumption was recorded at the first antenatal visit, and at 30 weeks gestation. Left ventricular mass was indexed to patient height.[63]

Paper IV

The commercially available sonography machine (Philips E33 Andover, MA, USA) was used and images stored digitally. Images were recorded by an experienced echo-technician or cardiologist at the department of physiology at Sahlgrenska university hospital. Images were acquired at rest and during stress in accordance with current guidelines.[64] Reporting was performed by two independent readers, blinded to clinical data and patient identification. Standard 2-D measurements of LV size and mass, LVEF (Teicholz) and Simpson's method (mode of discs) were performed in adherence to current guidelines.[64] Contractile cardiac reserve was defined as ΔLVEF and Δ-cardiac output and was calculated from images acquired at rest and during submaximal stress. Early (E), and atrial (A) trans-mitral inflow velocities were measured. In apical

4-chamber view we registered, tissue Doppler atrioventricular (AV) plane long-axis velocity, at the lateral and septal border of the LV, and at the RV free wall. Systolic velocity, (s') and early diastolic velocity, (e') were measured. E/e'-ratio, an index of LV end-diastolic filling pressure was calculated using the mean value of lateral and septal recordings. Further tissue Doppler derived isovolumic contraction (ICT) and relaxation times (IRT), ejection time (ET) were measured at the level of the septal AV-plane. LV myocardial performance index, (MPI) is an index of both systolic and diastolic dysfunction and is calculated as MPI = (ICT+IRT)/ET).[65] Global longitudinal strain (GLS) based on echo speckle tracking was measured in apical views (Table 2).

Table 2. Cardinal echocardiographic parameters

Cardinal echo parameters	Explanation
LVEDD	Left ventricular end-diastolic diameter
LVESD	Left ventricular end-systolic diameter
LVEF	Left ventricular ejection fraction
LA	Left atrium
E/A-ratio	Trans-mitral inflow maximal velocity during early (E) and atrial (A) diastolic phases
s'	Tissue Doppler derived atrioventricular (AV) plane long-axis velocity – in systole
e'	Tissue Doppler derived atrioventricular (AV) plane long-axis velocity – in diastole
E/e'-ratio	LV filling pressure (indirect pulmonary capillary wedge pressure)
Cardiac contractile reserve	ΔCardiac output at rest and during stress
Myocardial performance index	Myocardial effectivity (ejection time vs. isovolumetric systo-diastolic times)^2
Global longitudinal strain	Summation of left ventricular longitudinal deformation using Q-lab's cardiac motion.

For arterial stiffness assessment, PWV measurements were recorded with the patient in the supine position. No sleeping or talking was allowed during measurements. Arteriograph©, a non-invasive device which only requires an upper arm cuff and the distance from the jugular notch to the pubic protuberance (an approximation of the length of the descending aorta) was used. Based on sphygmomanometric measurements, it uses an algorithm to calculate PWV, AIx and dP/dt relying on the premise that the oscillatory pulse waves are reflected, crucially at the iliac artery junction, or as the aorta branches out. The time elapsed between the direct pressure wave (P_1), and the reflected pressure wave (P_2) reach the brachial cuff, allows for determination of PWV (m/s), AIx, aortic (%), AIx, brachial (%) and (dP/dt) (mmHg/s). AIx, brachial was calculated directly from the pulse pressure wave at the cuff level, whereas AIx, aortic was estimated from an empirically derived regression algorithm which estimates indirect central aortic pressures changes. Both AIx, aortic and AIx, bra-

chial were normalized to 80 beats per minute (bpm). Arteriograph© has been validated against SphygmoCor© and invasive recordings. Both Arteriograph© and SphygmoCor© were independently strongly correlated with invasive recordings (Table 3).[53, 54]

Table 3. Parameters of arterial stiffness

Parameters of arterial stiffness	Explanation
Arterial compliance	Volume change due to incremental pressure change ($C = \Delta V/\Delta P$) (ml/mm Hg).
PWV, Pulse wave velocity	Speed with which the oscillatory pulse propagates from the LV out the aorta and adjacent vessels (m/s).
AIX, Augmentation index	ΔP – between direct and reflected systolic peak pressures, divided by the pulse pressure, (PP); $(P_{reflected}-P_{direct})/PP \times 100$) (a ratio).
dP/dt max	LV maximal pressure rise measured at the brachial cuff level in early systole.

Statistical methods

While paper I and II are epidemiological studies that warrant parametric tests, paper III and IV are clinical low population studies, where non-parametric tests are appropriate. In paper II and IV case-control study designs were chosen.

Paper I

Annual HF incidence rates per 100,000 person-years and 95% confidence intervals (CIs) were calculated using the method of direct standardisation, using the median year 1996 as a standard. Descriptive statistics were applied to summarise the comorbidity prevalence within the identified HF population. In addition, we used joinpoint regression for estimation of the annual percentage change and to find the specific years when significant changes in the trends occurred (Joinpoint Regression Program, version 3.3.1. April 2008; Statistical Research and Applications Branch, National Cancer Institute). We fitted the data in a log-linear model and set the number of possible joinpoints between 0 and 3. For each estimate of mean annual percentage change, 95% confidence intervals were calculated. Further, one-year, age- and sex-specific case fatality rates were calculated up to one year after admission in patients aged 18 to 34, 35 to 44, 45 to 54 and 55 to 84 years over the periods 1987-1991, 1992-1996, 1997-2001 and 2002-2006. To estimate changes in one-year case fatality, hazard ratios for each time period of hospitalisation were calculated by means of Cox regression with the period of 1987-1991 as reference, and adjusted for age, sex, diabetes, ischemic heart disease, cardiomyopathy and adult congenital heart disease and/or valve disease. Kaplan–Meier survival curves were applied to illustrate three-year case fatality.

Paper II

All data were analysed using SAS 9.3. To assess differences in baseline characteristics between cases and controls, the χ^2 test was used for dichotomous variables, and the t-test for continuous variables. Odds ratios were obtained using bivariate logistic regression. Multivariate logistic regression was used to estimate independent factors of importance with respect to differences between cases and a) matched controls, and b) all controls. Significance was assumed at $P<0.05$.

Paper III

Statistical analysis was performed using MedCalc for Windows, version 12.7.5 (MedCalc Software, Ostend, Belgium) and IBM© SPSS© version 21. Non-parametric tests, Mann-Whitney U analysis for independent data and Wilcoxon's test for paired data were used. Fisher's exact test was used to assess mean differences for categorical data or when data did not meet the criteria of other non-parametric tests. Data are presented as mean (SD). A two-sided $P<0.05$ was considered significant.

Paper IV

Data are described as mean (SD). Time to investigation was defined from the time of delivery to the date of cardiovascular examination. All continuous data between cases and controls during follow-up were compared using Mann-Whitney *U* tests with no assumption of distribution (exact test). For comparison of categorical variables between groups, Fisher's exact test was used. Two-sided $P<0.05$ was considered significant. All analyses were performed with IBM© SPSS© Statistics version 21 (IBM Corp, Somers, NY).

Ethical considerations

All four papers were approved by the local ethical committee of Gothenburg University, for papers III and IV with informed written consent from all participants.

RESULTS

Incidence

Table 4 illustrates the divergent trends in HF hospitalisation between younger and older patients. Whereas hospitalisation in the 55-84 year age group peaked in 1992 to 1996 at 854 per 100,000 decreasing to 603 per 100,000 in 2002 to 2006, HF hospitalisation among persons <45 years increased throughout the entire observation period. Trends among persons aged 45-54 years were similar to those aged 55 to 84 years with a less marked decrease after 1996. A joinpoint analysis confirmed the continuous increase throughout the period for the 18-34 year age group, and from 1999-2006 for the age group 35-44 years. Further in adults >45 years a rising then falling pattern was seen 1994 signifying the marked breaking point for a decline in heart failure rates.

Table 4. Incidence of first hospital admissions for heart failure per 100 000 person years in Sweden 1987 to 2006 by age, sex, and period. HR, hazard ratio

Age group		1987-1991	1992-1996	1997-2001	2002-2006
18 -34	n	266	312	319	387
Per 100 000		2.5	2.8	2.9	3.7
HR (95% CI)		**1.00**	**1.15**	**1.19**	**1.5**
35-44	n	706	875	814	981
Per 100 000		10.2	13.6	12.7	14.6
HR (95% CI)		**1.00**	**1.33**	**1.25**	**1.43**
45 -54	n	2 456	3 830	3 806	3 415
Per 100 000		46.2	59.6	55.6	53.6
HR (95% CI)		**1.00**	**1.29**	**1.20**	**1.16**
55 -84	n	105 741	125 138	102 067	92 882
Per 100 000		719	854	688	603
HR (95% CI)		**1.00**	**1.19**	**0.96**	**0.84**

From 1987 - 1991 to 2002- 006, the mean incidence of HF with cardiomyopathy more than doubled in all age groups (HRs 2.0 to 3.0). In patients <55 years this was not at the expense of other diagnoses as the incidence of HF from other causes not related to IHD or cardiomyopathy also increased.

In pregnancy-associated HF an increasing trend was also seen. The cumulative incidence of PPCM for the period was 1 in 9 191 deliveries, increasing from 1 in 26 226 deliveries from 1987-1991 to 1 in 4521 deliveries for 2007-2010. The proportion of PPCM cases of non-OECD origin increased from 18% in 1987–1991 to 31% in 2007-2010 which suggests a positive trend, *P*=0.03 (Figure 4).

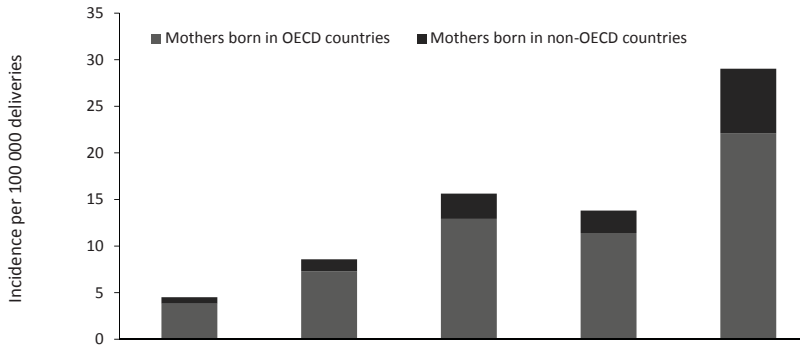


Figure 4. PPCM incidence/100 000 deliveries in Sweden, 1987–2010. Total incidence, and mothers of OECD vs. non-OECD country of origin

Mortality

In paper I, one-year case fatality at the beginning of the study period was high in all age groups, with about one in four dead at ages 18-54 years and 39% >55 years. From 1987-1991 to 2002-2006 a marked adjusted one-year relative case fatality reduction of 60-62% at 18-44 years was observed, and correspondingly 56% and 38% at 45-54 and 55-84 years respectively. Figure 5 demonstrates the survival benefit was sustained up to three years, but that no further significant improvement in case fatality occurred in the <55 year age group after 2001.

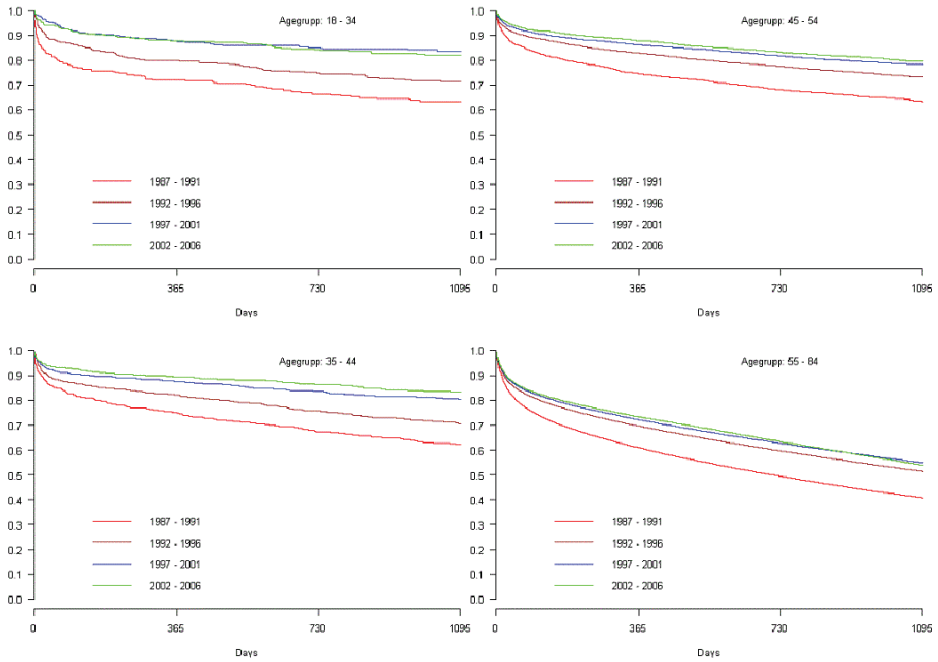


Figure 5. Kaplan-Meier survival curves. One-year case fatality after first HF hospitalisation in patients aged 18 – 84 in four different time periods as indicated.

In paper II we exclusively looked at mortality among women with pregnancy-associated HF. The mean follow-up was 16.4 years with 22 (8.1%) cases, and 5 (0.4%) controls dying during the follow-up period, OR 23.5 (95% CI 8.8–62.6). In cases, 73% of deaths occurred within the first 3 years of diagnosis. In comparison, none of the controls died within 3 years of delivery (Figure 6). Mortality among unmatched controls was similar to matched controls, with 347 decedents (0.6%) by the end of the study period.

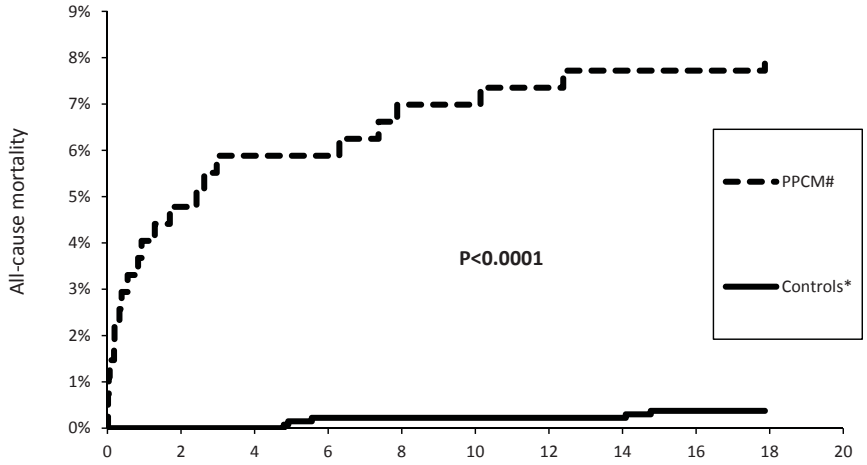


Figure 6. All-cause mortality among cases vs. controls.

The characteristics of PPCM fatalities versus PPCM survivors did not differ significantly as the limited number of deaths in the PPCM group (n=22) did not provide sufficient statistical power to assess independent factors related to a fatal outcome. Autopsy was performed in 7 cases (31.8%). HF was stated as an underlying cause of death in 11 (50%) patients, 7 of whom had concomitant cardiomyopathy. Other cardiovascular disease related deaths included stroke with cerebral herniation, acute pulmonary embolism, and two cases of diabetes. The primary non-cardiovascular causes were: lung cancer, breast cancer, non-Hodgkin's lymphoma, substance abuse (n=3), and one death of unknown cause. Among the 11 HF case fatalities, the mean/median time to death was 1.9/0.6 years compared with 5.7/3.0 years among the 11 non-HF related deaths (NS). Only 5 matched controls died, but mean time to death among fatalities in the unmatched control group (n=33) was 11.7 years.

Among PPCM survivors and fatalities statistical differences could not be assessed because of the low number of observations, but age and BMIwere numerically similar. Diabetes was 6 times more common in fatal cases, however, confidence intervals were wide (OR 6.4, 95% CI 1.5-27.7). Mean number of in-hospital days for fatalities was 16.0 compared with 7.4 for survivors.

Mortality in paper III was confined to one case at 10 months postpartum. The 4.8-year mortality in the study remained at one death in 24 cases (4.1%).

Comorbidities and clinical characteristics

In the first paper it was seen that the overall burden of comorbidity in a young Swedish HF population was substantial. Of patients aged <45 years, 21% had IHD with 15% having acute myocardial infarction (MI). Fourteen per cent had diabetes, 4% a prior stroke and 8% any cancer. For patients aged 45 to 54 years, IHD, MI and diabetes, stroke and cancer was found in 39%, 27% and 20%, 5% and 9% respectively. Concomitant cardiomyopathy was registered in 20% of those aged <45 years and in 13% of those aged 45-54 years. Cardiomyopathy increased from 15% to 25% and from 9% to 15% over the four periods in the <45 and 45 to 54 age groups respectively. Concomitant valve disease and ACHD among patients younger than 45 years remained stable throughout the study. About 5% had no other diagnosis than HF (data not shown).

Figure 7 shows the mutually exclusive categories of comorbidities by age over the entire study period. The proportion of IHD-related HF hospitalisation increased substantially with age, whereas cardiomyopathies decreased. The proportion of patients diagnosed with ACHD was 12.0% among the youngest age group and 0.3% among the oldest. The proportion with valve disease and ACHD did not change materially over time in any age group. The prevalence of the combined common aetiologies of IHD, diabetes and hypertension below the age of 55 years was stable throughout the study period in patients <55, but not in older patients (increase 54% to 66%), chiefly as a result of a decrease in other causes. Cardiomyopathy increased across all age groups. A closer look at the large and heterogeneous group of patients labelled 'other' revealed no qualitative differences between the first and the last periods, the most common diagnoses being malignancy, perimyocarditis and infectious diseases.

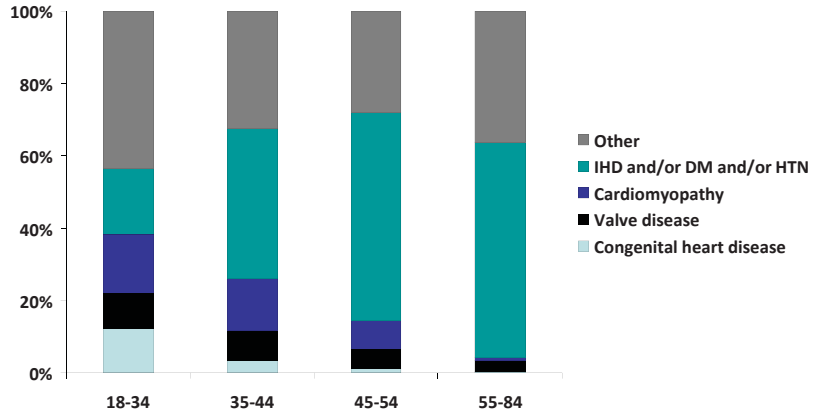


Figure 7. Comorbid prevalence (%) of mutually exclusive diagnoses among HF patients of different ages.

In paper II, exclusively looking at comorbidities in women with PPCM, a multivariable analysis approach taking relevant potential causal factors into consideration, was employed. Patients with PPCM, compared with matched controls, had higher BMI (multiple-adjusted odds ratio (OR) 1.05 per unit, 95% confidence interval (CI) 1.02-

1.08), were more likely to be born in a non-OECD country (OR 1.61, 95% CI 1.07-2.43), have twins or triplets (OR 2.26, 95% CI 1.20-4.23). Diabetes and assisted pregnancy were not independently associated with PPCM. Comparison with all controls demonstrated an independent association between age and PPCM (OR: 1.50 per 10 years, 95% CI 1.17-1.91). The estimate for BMI, multiple births, and country of birth increased slightly (Table 5).

Table 5. Multivariable analyses comparing PPCM cases and controls matched for age and year of delivery to PPCM cases and all controls

	Cases vs matched controls (204 cases, 1121 controls)			Cases vs all controls (204 cases, 43,654 controls)		
	Adjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Variable						
Age, per 10 years	0.94	(0.71–1.24)	0.68	1.50	(1.17–1.91)	0.001
BMI, per unit	1.05	(1.02–1.08)	0.001	1.07	(1.04–1.10)	<0.001
Born outside OECD country	1.61	(1.07–2.43)	0.02	2.00	(1.43–2.80)	<0.001
Multiple birth, yes/no	2.26	(1.20–4.23)	0.01	2.69	(1.70–4.26)	<0.001
Diabetes*	1.93	(0.34–10.89)	0.45	2.21	(0.78–6.28)	0.14
Assisted pregnancy, yes/no	1.58	(0.81–3.11)	0.18	1.65	(0.98–2.80)	0.06

OR, odds ratio; CI, confidence interval; *Pre-existing and gestational disease included.

The time of diagnosis clustered around the time of delivery with 29.4% of cases diagnosed in the last month of pregnancy and 82.3% within a month prior to or immediately postpartum (Figure 8).

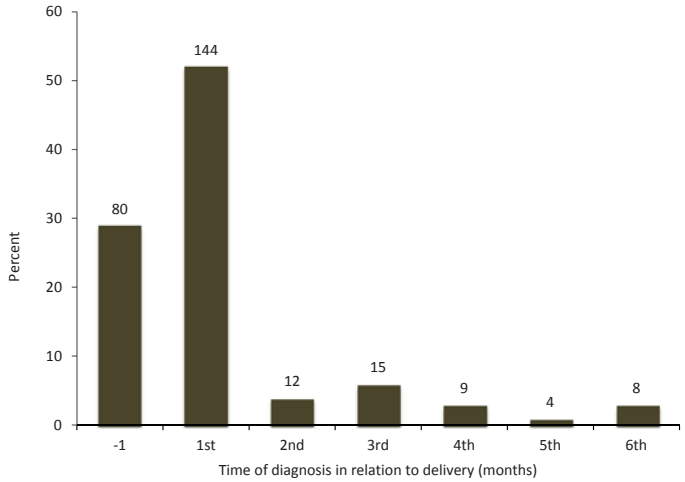


Figure 8. Time of diagnosis in relation to delivery. Months before/after delivery, n=272.

In paper III more detailed data was obtainable due to having access to the complete medical records including laboratory results and serial echocardiography.

The mean patient age among PPCM patients was 34.2 (5.0) years. Eighteen women (75%) were >30 years old at delivery. Postpartum presentation of PPCM occurred in 20 (83%) patients; of these 20 patients, it occurred within the first week in 11 (55%).

The average BMI at the first antenatal visit was 24.6 (3.8); six patients (25%) were obese. Seven patients (36.4%) consumed alcoholic beverages regularly at the time of conception. Comorbidities at conception included four patients with past or present depression, two with asthma, two with recurring migraine, and two with adult congenital heart disease not associated with HF (one patient with a restrictive ventricular septal defect with prior embolic stroke to the retinal artery and one with a known atrial septal defect with transient ischaemic attack). Eight patients (36.4%) had fertility problems, three of whom became pregnant after in vitro fertilization and one of whom became pregnant after hormone treatment. The mean/median gestational age at delivery was 35.2 (5.1)/37 weeks. Postpartum haemorrhage occurred in 39.1% of the patients. Ten patients were transferred to the intensive care unit (ICU) at the time of hospital admission. Five of these 10 patients had pulmonary oedema and received respiratory support. The NT-proBNP level was available in 17 patients (mean, 6636 ng/L) and was elevated in all, but decreased to a mean of 570 ng/L at 1 to 3 months postpartum (Figure 9).

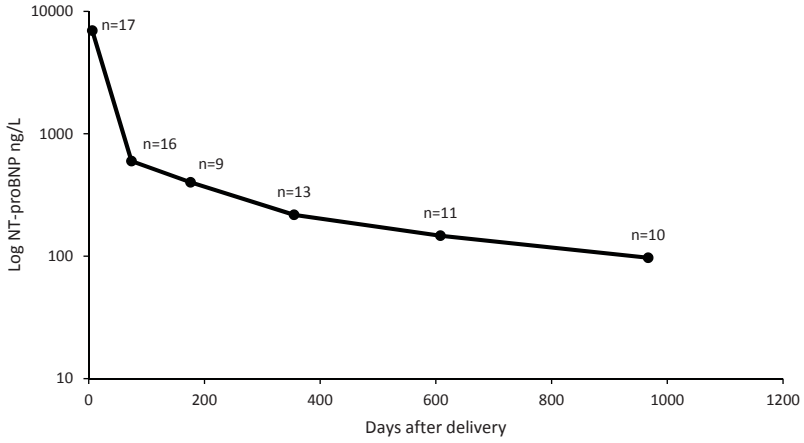


Figure 9. Serial natriuretic peptide levels at diagnosis and postpartum in all patients.

Five twin deliveries were recorded. Fifteen neonates were premature, including four of the twin sets. Sixteen mothers had underwent acute CS necessitated by preeclampsia or HF. The CS rates among preeclamptic and non-preeclamptic patients were 85% and 56%, respectively. Only one delivery was documented as spontaneous and unaided. Nine neonates (31.0%) were <2500 g, but only 3 (11.1%) were SGA. No stillbirths were recorded, and all infants were alive at the time of the review.

In paper IV a substantial overlap was seen. Here a total of 37 subjects, 22 cases and 15 controls were included. Mean follow-up after diagnosis was 3.0 (2.2), (range 0.46–7.0) years in cases. Maternal age did not differ between cases and controls. BMI trended to be higher among cases, 26.9 vs 24.0, P=0.11. Although 12 of 22 cases were still on HF medication, both systolic and diastolic blood pressure was significantly higher among cases, 122/76 mmHg (range 107/50-139/91) vs 111/67 (range 98/54-140/84) among controls. Serum creatinine in cases was higher than among controls, but within normal range, 65 vs 58 μmol/L. Of the 22 cases, 81% were in NYHA-I. NT-proBNP was elevated in 27.3% of the cases.

Pharmacological management

In paper III all patients received β-blockers for a mean duration of 20.9 months. Twelve received metoprolol, eight received bisoprolol, and four received carvedilol. Metoprolol was the preferred β-blocker in breastfeeding mothers because was is regarded as safest. Metoprolol was discontinued in four patients because of side effects, the most common being lethargy, bradycardia, dizziness, hypotension, nightmares, and mood swings. Two of these patients were subsequently started on bisoprolol, and one was started on carvedilol. Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACE-I/ARBs) were initiated in all patients, but only during the postpartum period (mean duration, 32 months). Ramipril was used in 12 patients (50%), enalapril in 4, and candesartan in 8. Seven patients were switched to candesartan because of side effects of ACE-I; two because of angioedema and five because of a dry cough or other respiratory symptoms. Fifteen patients received intravenous loop diuretics, and 16 received oral furosemide. Ten patients (43.5%) were commenced and maintained on a mineralocorticoid receptor antagonist (MRA) (exclusively spironolactone), while the 14 remaining experienced hypotension and dizziness why MRA was not initiated. Six patients received an oral anticoagulant: four because of an LVEF of <25%, and two because of postpartum thromboembolism (Table 6).

Table 6. Pharmacological management of peripartum cardiomyopathy

Agent	n (%)	Median introduction after diagnosis, weeks (range)	Mean duration, weeks
ACE-Is/ARBs	24/24 (100.0)	0.1 (0.1–10.1)	138.8
β-blockers	24/24 (100.0)	0.1 (0.0–14.7)	91.1
MRAs	10/23 (43.5)	0.9 (0.4–19.9)	40.2[§*]
Oral loop diuretics	16/24 (66.7)	5.1 (-2.7–14.3)	22.3
Coumarins (warfarin)	6/24 (33.3)	8.0 (2.0–21.6)	36.8

Seven patients stopped breastfeeding before 2 weeks postpartum; six of these received the dopamine agonist bromocriptine administered according to the protocol described by Sliwa et al.[66] Only four patients continued breastfeeding beyond 2 months. Worsening HF was seen in one patient when her HF medication was discontinued by her primary care physician, but she recovered upon reinstatement of the medication. Treatment titration and tapering was primarily governed by the patients' symptoms, LVEF, and natriuretic peptide levels. Treatment was never discontinued earlier than 1 year after normalization of the LVEF and achievement of NYHA class I. At the time of the review, seven patients were still on medication, and two of these had residual dyspnoea. Among the remaining 16 surviving patients, β-blockers and ACE-Is were discontinued without any cases of worsening HF after a mean duration of 1.8 and 2.7 years, respectively.

PPCM & Preeclampsia - paper II, III & IV

Preeclampsia was associated with PPCM evidenced in papers II, III and IV. In paper II the OR for preeclampsia was 13.02, (95% CI 8.41-20.15), which decreased to OR 9.56, (95% CI 7.08-12.91) if compared to all controls as opposed to matched controls only. One percent of cases with concomitant preeclampsia died, compared with 12.2% of cases with PPCM only, OR 13.8 (*P*=0.001).

In paper III 14 (58.3%) developed preeclampsia at a mean of 30.8 (5.3) weeks of gestation. All 24 patients were normotensive at the first antenatal visit. Patients with preeclampsia had lower parity and more frequent headaches, eye symptoms and nausea; in contrast, dyspnoea was the cardinal symptom among women with PPCM only. Patients with preeclampsia (this group included all patients who developed pulmonary oedema) also had higher ICU admission rates. Preeclamptic women also had higher LVEFs both at presentation (*P*=0.02) and at the time of the review (*P*<0.001). All patients with preeclampsia had an LVEF of ≥50% at 12 months and 11 of the 14 patients with preeclampsia were in the early recovery group. In contrast, only 4 of the 10 patients without preeclampsia were in the early recovery group (*P*=0.04).

In paper IV preeclampsia was prevalent with 14 patients (63.6%) out of 22 patients with PPCM. Patients with concomitant preeclampsia did not differ from non-preeclamptic cases in regards to mean-follow up, age or BMI; but on average the natriuretic peptide level at the time of review was below the clinical threshold for HF compared with non-preeclamptic cases at 67 vs 277 ng/L respectively, *P*=0.02.[1] Systolic and diastolic LV dimensions were significantly smaller in cases with concomitant preeclampsia, *P*=0.02. LVEF was higher in cases with concomitant preeclampsia (58.9%) vs cases with PPCM only (51.7%), but only borderline significant, *P*=0.07.

Left ventricular function

In paper III we assessed LV function in relation to symptomatic recovery. Early symptomatic recovery (NYHA I in ≤1 year) was seen in 13 patients. Of the remaining 11 patients, 7 had reached NYHA I by the time of the review. The mean time to NYHA I among the patients in the arbitrarily defined early recovery group and among the survivors in the late/non-recovery group was 4.8 and 30.2 months, respectively (Figure 10). One case of sudden death occurred 10 months postpartum in a stable patient that had clinically improved but had persistent LV dysfunction (LVEF of 40%).

The mean time to normalization of NT-proBNP (<125 ng/L) was 8.2 and 16.4 months in the early and late/non-recovery groups, respectively. Only one patient had an elevated natriuretic peptide level at 3 years postpartum. The presence of preeclampsia tended to be positively associated with early recovery (*P*=0.08).

LV recovery was assessed by serial TTE (see also Figure 11). The time to last TTE was not significantly different between the two groups (*P*=0.39). The mean ΔLVEF from presentation to review was 21.2% and 21.3% in the early and late/non-recovery groups, respectively. In the early recovery group, 10 (92%) patients had an LVEF of ≥50% by 3 to 6 months postpartum as opposed to only 7 (64%) patients in the late/

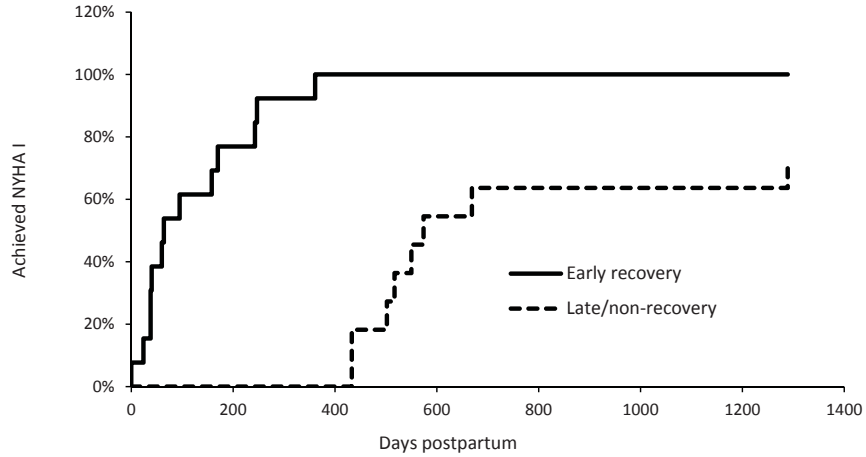


Figure 10. Symptomatic recovery. Proportion of patients with NYHA I at ≤1 year (early recovery) vs >1 year (late/non-recovery).

non-recovery group. The LV end-diastolic diameter at presentation was positively associated with late/non-recovery (P=0.02). Conversely, patients in the late/non-recovery group had higher end-systolic diameters at the time of the review (P=0.02). The LV mass index decreased in all patients individually, but the difference between the early and late/non-recovery groups was not statistically significant.

In paper IV measurements of resting echocardiography revealed important differences between cases and controls as described. At rest cases had structurally larger hearts with higher systolic and diastolic LV volumes and LV mass index (LVMI). LVEF<50% was more prevalent among cases (6 out of 22 cases vs 0 out of 15 controls, P=0.05). E wave peak velocity was lower in cases, and so were both septal systolic and early diastolic longitudinal tissue Doppler AV plane velocities, s' septal (7.5 vs 8.6 cm/s, P=0.01) and e' septal (9.2 vs 11.5, P=0.004). MPI differed in controls vs cases, (controls, 0.37 vs 0.53, P<0.001). Resting echo vs stress echocardiography, did not reveal significant difference between cases and controls neither during stress, nor in terms of Δ-cardiac output which increasing from 4.1 to 7.5L in cases, and 3.7 to 7.6 L/min in controls respectively, P=0.51 mean HR during stress 125 (99–144) bpm.

Arterial stiffness

In paper IV arterial stiffness was compared between PPCM patients and controls. HR at rest was similar in controls and cases, but the increase was more pronounced in cases vs controls (Δ19 vs Δ12 bpm respectively). Arterial compliance was reduced in cases as both PWV, aortic and brachial AIx trended to be higher at rest and were significantly higher post-stress: PWV 8.9 vs 7.6 m/s, P=0.006; AIx, aortic 15.8 vs 4.9%, P<0.001 and AIx brachial, -24.8 vs -65.0, P<0.001. However, we did not see any significant difference, neither between ΔPWV nor ΔAIx between cases and controls.

DISCUSSION

Main findings

Among young patients with HF, we observed an increase in hospitalisation which was divergent from the continuing decrease after 1992 -1996 seen among patients older than 54 years of age. The incidence of concomitant cardiomyopathy more than doubled during this period in all age groups. Mortality in young patients was reduced by more than half, but with no further decrease after 2001.

Among women with PPCM we used the unique approach of combining several national registries, to identify a cohort of 272 patients with PPCM or pregnancy-associated HF over a period of 24 years, further emphasising the rarity of this condition in a Western population. Compared with age-matched controls, cases more often had preeclampsia, twins or triplets, were obese, or were born outside an OECD country. Just over 8% of cases died during follow-up, with two thirds of fatalities occurring within 3 years. Preeclampsia was strongly linked to PPCM but inversely associated with mortality.

In a clinical cohort of 24 women with PPCM, 5-year prognosis was favourable even though half required ICU admission and only one-third were asymptomatic 3 months after delivery. LV dilatation at presentation was the best predictor of recovery later than one year. Women with concomitant preeclampsia had a more acute presentation, but experienced faster LV and symptomatic recovery.

Systolic and diastolic function, and arterial stiffness in 22 PPCM patients three years after diagnosis, revealed clinically significant pathological markers when compared with 15 healthy controls. Patients, whether recovered or not, had higher blood pressures than healthy controls and markers of arterial stiffness were elevated in patients evidenced by increased PWV and AIx.

HF and PPCM incidence

HF incidence, according to data from Sweden, Netherlands and Scotland has levelled off and eventually declined.[7, 9, 67, 68] This is also the case in the USA.[69] Because HF is predominantly a disorder of the elderly, there is a lack of data on trends in younger people. Decreasing mortality and increasing readmission rates influence hospitalisation rates, but in our data 97.8% of admissions were unique individuals. For the same reason mortality reduction cannot explain the increasing hospitalisation rates. Because the national discharge registry only reached full coverage from 1987, it was not possible to exclude all readmissions within the seven years prior to 1987. However, the expected effect on our dataset would be an overestimation, not an underestimation of the incidence in the first seven years. Epidemiologic studies of HF in patients <45 years of age are scarce. The Framingham cohort comprised patients aged 28 to 62 years, but none of the analyses from that cohort identified enough cases to appropriately address trends in HF in this age group. In a sub-study of the CARDIA cohort, a 20-year follow-up prospective analysis of 5 115 patients 18 - 30 years revealed new

onset HF in a mere 27 subjects.[15] Hypertension, diabetes and IHD are major targets for reduction of HF. In the CARDIA study hypertension was a major aetiological risk factor in the development of early HF. [15] In our HF population diabetes and IHD were common and increased with age, but not over time. The rising prevalence of hypertension in HF patients may influence the incidence of HF, but as the validity of this diagnosis is poor [56], this conjecture remains speculative. The introduction of reimbursement by diagnosis related groups systems in 1992 may explain some of the increase in HF seen in our data between the first two periods, but does not explain the continued and accelerating increase in hospitalisation for patients <45 years seen after 1996.

The incidence of PPCM in paper II was lower than studies from South Africa[19] and lower than most US register data,[20, 22, 28] but higher than data from Japan.[24] The incidence increased continuously throughout the study period, but changing from ICD-9 to ICD-10 may have influenced data. Heightened awareness, improved diagnostic testing and case recognition over the years may have increased the number of observed cases, but it is unlikely that pregnant women with overt HF would be more likely to be managed out-patient in the early parts of the study period, especially as the admission threshold has continued to increase since 1980.[70] Therefore, increasing maternal age, rising obesity, and an increasing number of non-OECD born women among PPCM cases in Sweden, may have played a role.[60]

Prognosis in HF and PPCM

In Swedish patients with HF, one-year case fatality was substantially reduced in all age groups from 1987 to 2006. There is a dearth of mortality data among persons <55 years of age. Rochester population-based data show stable one-year mortality ranging from 23% in 1981 to 28% in 1991 (mean age 74 years).[71] Another survey from the same population (1979 – 2000) reported a 52% survival improvement among men in their 60s, but only 28% among men in their 80s, a finding congruent with the more pronounced case fatality reduction observed among younger subjects in our population.[72]

Our HF data did not show any further improvement in fatality after 2001. We know neurohormonal blockade has improved survival in patients with systolic HF.[73-75] The largest relative reduction in case fatality occurred from 1987-1991 to 1997-2001, i.e. prior to the publication of the landmark trials validating beta-blocking agents in HF treatment, suggesting either that beta-blocker treatment had not been fully implemented,[74, 75] or did not impact fatality in this population.

In women with pregnancy-associated HF in Sweden, deaths among cases were >20-fold that of controls. Almost 3/4 of deaths among cases occurred within 3 years from diagnosis, whereas the deaths among the controls occurred evenly across the follow-up period (Figure 6). Though mortality was somewhat lower than in case series from the USA, it was higher than in three large similar register studies from California totalling 341 cases.[20, 22, 28]

Notable geographical differences in PPCM incidence and mortality exist. Like in these data, Japanese, German and American PPCM data show lower incidence, lower

mortality, and higher prevalence of concomitant preeclampsia[24, 26, 28] when compared with data from Haiti, Turkey and India where higher incidence, mortality and a less pronounced increase in the prevalence of concurrent preeclampsia is seen.[45, 76, 77] South African studies often exclude women with preeclampsia which precludes direct comparison, but both the incidence,[19] and especially the mortality is higher than the mentioned studies from North America and Germany. Hence, Blauwet and colleagues found a 6-month mortality of 13% compared to just over 3% in our Swedish countrywide cohort presented in paper II.[46] Suri and colleagues likewise found high maternal mortality, 28%, at 3 months postpartum all dying of congestive HF.[78] In contrast our data from paper III, comprising the clinical cohort of 24 women studied, only one death occurred at ten months after diagnosis equivalent to a 5-year mortality of 4.2%. In the same paper prognosis after a PPCM diagnosis was good with more than half of the patients achieving NYHA I in less than a year. All patients in the early recovery group and 83.3% of those in the late/non-recovery group had recovered by the end of the 4.8-year review. In the early recovery group, 50% of the patients achieved NYHA I in 100 days as opposed to 700 days in the late/non-recovery group. This overall prognosis is markedly better than that reported in South African[47] and most American studies,[32] but is consistent with a recent German cohort.[26]

Factors associated with PPCM

PPCM has consistently been linked to high maternal age.[28] In our cohort from all of Sweden as presented in paper II, >50% of the patients were ≥30 years. The corresponding figure for all delivering mothers in Sweden is 28%.[60] Contrary to what was reported by Gunderson and colleagues,[28] PPCM in our study was not associated with increased early infant mortality, but SGA neonates were more prevalent among cases than controls (OR 4.9, 95% CI 2.8–8.7).

As reported in paper II, diabetes and obesity were more prevalent in cases, but in these data prevalence was lower. Diabetes, defined at discharge, was not independently associated with PPCM if adjusted for BMI which is congruent with data from a German PPCM cohort.[26] Although obesity is a known risk factor for the development of symptomatic HF in the general population, it has not been proven to be independently linked to the development of cardiomyopathy.[79] In our population, obesity was more prevalent among cases, and because we used weight at first visit (gestational week 9–12), it is unlikely that water retention would explain the observed difference in BMI between cases and controls.

Mothers born outside OECD member countries were over-represented among cases. We could not determine from these data whether this was confounded by socioeconomic status or genetic factors which both are known to be linked to PPCM,[47] but the parameter remained significant in a multivariable analysis. Data from the Swedish Board of Health indicate that among delivering mothers, 47% of African and 27% of Asian nationals residing in Sweden had not received any education beyond secondary school as opposed to only 8% among Swedish born residents.[60] A study from the relatively wealthy Martinique with a mixed population of African heritage showed much lower incidence of PPCM than in Haitian or South African cohorts - therefore socioeconomic factors may play a bigger role than previously assumed.[80] Swedish registry

data further show that after 1990, the number of births from mothers born outside the Nordic countries has increased with a notable presence of Somali and Iraqi nationals. Our data confirm an increasing proportion of immigrants of non-OECD country origin among mothers with PPCM which also coincides with an increased number of immigrants from these countries. Thus the percentage of delivering mothers born of African and Asian descent in the study period, increased from 0.5 to 4.2% and 1.7 to 10.0% respectively.[60]

Among the 24 patients that were reviewed in detail, the mean age at delivery in this study was high (34.2 years). The mean gestational age at delivery was around 35 weeks, chiefly explained by the high CS rates associated with congestive HF and preeclampsia. High rates of CS performed due to preeclampsia and acute HF have consistently been found in women with PPCM[17] and reached 72.7% in the present cohort; this rate is 4-fold that of the background population (18%).[60] The register data from the whole county showed that women with PPCM have higher BMIs,[28] but this was not confirmed in this small cohort. Like in the data for the entire country, twin pregnancies, were more prevalent in this cohort than in the general Swedish population[60] of delivering mothers.[26, 28] Nine patients (37.5%) experienced postpartum haemorrhage; this rate is >7-fold higher than the rate in the Swedish population (5%).[82] As seen in other cohorts from both Germany and the US,[27, 29] neonates of mothers with PPCM were more likely to be preterm (43.5% vs 4.0%), be SGA (14.8% vs 4.5%), or have low birth weight (<2500 g) (29.6% vs 6.5%) than neonates of mothers in the background population.[61] Low birth weight is predictably related to preterm delivery and associated with increased mortality and morbidity.[81, 82] A US study found that infants born to PPCM patients had poorer health outcomes and higher mortality 8.2/1000 and 1.7/1000 births respectively.[28] Studies from other parts of the world however, reveal much higher infant mortality rates.[78]

PPCM and concomitant preeclampsia

Three percent of Swedish pregnancies are associated with preeclampsia,[83] but preeclampsia is much more common in the presence of PPCM. In an excerpt of three studies of patients with PPCM (n=778), 29%-68% had concomitant preeclampsia.[26,32,84] In paper II describing a cohort of the entire country, more than 35% had preeclampsia with a multiple-adjusted OR of 13.2. PPCM and preeclampsia share many risk factors including low socioeconomic status, high maternal age, multifetal pregnancies, and African-American race. They also share pre-existing conditions that confer higher risk including chronic hypertension, diabetes, obesity, and connective tissue diseases.[34] The strong association between preeclampsia and PPCM has led to diverging views on whether HF in the presence of preeclampsia constitutes frank PPCM or a different disease entity. However, in the majority of pregnant women, preeclampsia does not cause reduced LVEF.[85] On the contrary, when compared with healthy pregnant controls, they exhibit increased fractional shortening, cardiac output, and stroke volume indices.[86] Likewise, the recent findings in a meta-analysis specifically addressing preeclampsia and PPCM, support the concept of a shared pathogenesis,[35] further corroborated by Patten et al who suggest anti-angiogenic properties common to both conditions.[40]

In paper III, more than half of the patients in the clinical cohort of 24 patients had concomitant preeclampsia. Patients with preeclampsia had higher rates of pulmonary oedema and more frequent need for intravenous diuretics, and higher ICU admission rates than patients with PPCM only. Although the prevalence of preeclampsia is higher among African-Americans and sub-Saharan Africans, studies from South Africa have excluded these patients, and while many studies have examined the prevalence of preeclampsia in patients with PPCM, Bello et al. contend that the relative prognosis in patients with concomitant preeclampsia is unknown.[35] Nevertheless, a few studies suggest the occurrence of more rapid recovery in patients with concomitant preeclampsia.[21, 27] Among this evidence is the data from paper II which shows that concomitant preeclampsia was associated with lower mortality. In paper III, we noted a shorter time to symptomatic recovery and a higher LVEF, both at presentation and at the last 2D-echo examination in patients with concomitant preeclampsia compared to patients with PPCM only. The difference in the clinical course, LV performance, and prognosis between women with concomitant preeclampsia and women with PPCM only, may indicate that they are different disease entities; however, the prevailing notion is that these two groups of patients have a shared pathogenesis in which preeclampsia may potentiate PPCM.[17]

In paper IV concomitant preeclampsia was confirmed in almost 2/3 of cases. Cockerill et al suggested using the Arteriograph© in early pregnancy could serve a practical application in gestational hypertensive disorders. They found a tendency towards higher PWV at 16 weeks of gestation in women with poor obstetric outcome, compared with those with normal outcome, whereas peripheral or central blood pressures did not differ.[87] Our results would support further research into the use of early arterial stiffness assessment in pregnancy in order better to detect and care for cases of preeclampsia. Also, capillary rarefaction has been shown to precede preeclampsia,[88] and structural micro- and macro-vascular changes dominate in women a decade after preeclampsia,[89] suggesting that PPCM is related to structural changes rather than endothelial dysfunction. Our results corroborate the conclusion arrived at by Hausvater et al in their meta-analysis of studies investigating the association of arterial stiffness and preeclampsia which also saw increased arterial stiffness in women with preeclampsia compared with normal pregnancies.[37] However, one would expect PPCM cases with coexisting preeclampsia would have less compliant arteries than those with PPCM only, but our findings suggest similar arterial compliance in these two groups, and in the case of PWV measurements, at trend towards the opposite.

LV function and structure in PPCM

In paper III the cut-off for symptomatic recovery was NYHA I at one year postpartum. Early LV recovery was defined as LVEF of ≥50% in ≤1 year. This was seen in 13 patients, and late recovery in another 6 women in less than two years. One recovered later than two years postpartum and three still had persistent LV dysfunction and at the end of the study period. There may, however, still be a chance of the last three recovering. A Haitian study found that LV recovery continued beyond 5 years.[56] Only LV dilatation at presentation was significantly associated with subsequent late/non-recovery, which is congruent with previous findings.[23, 46, 90]

Figure 11 shows the rapid postpartum normalization of LVEF and left atrium size. Although even healthy women experience significant haemodynamic changes during pregnancy, these changes usually reverse within 2 to 4 weeks of delivery (4–6 weeks in women with preeclampsia).[16] However, one study showed that the LV mass index in healthy pregnant women was still elevated at 8 weeks postpartum.[91] The LV mass index in a Framingham cohort of healthy non-pregnant women was 47 (7) g/m^2.[92] All patients in the clinical cohort had LV mass indices well above that figure more than 2 years postpartum. As noted, early symptomatic recovery correlated well with LV function and NT-proBNP levels at 1 year. The natriuretic peptide level at presentation was, however, a poor marker of subsequent outcomes, but correlated well with the severity at presentation (e.g., pulmonary oedema and need of mechanical ventilation). A recent study did not find NT-proBNP elevated in healthy pregnant women at 48 hours postpartum.[93] In contrast, all women in this cohort had elevated natriuretic peptide levels, further strengthening the evidence regarding NT-proBNP as a valuable diagnostic marker of disease in women with suspected pregnancy-associated HF toward the end of pregnancy.

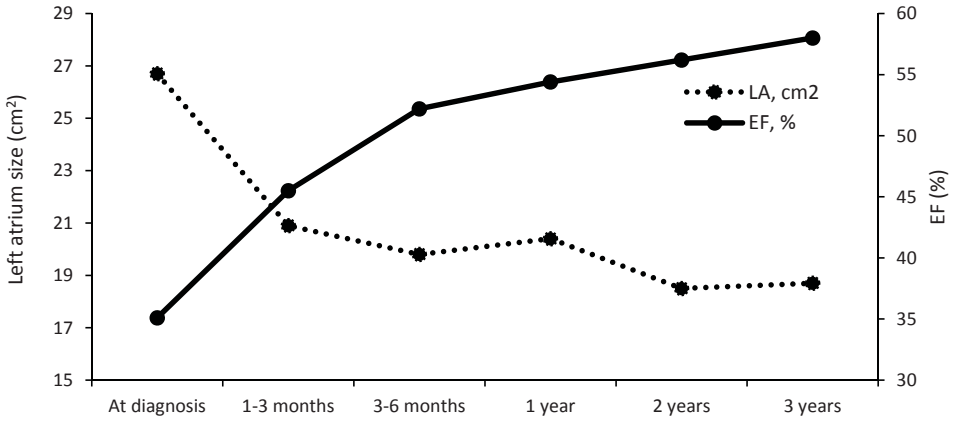


Figure 11. LVEF and left atrial size at diagnosis and postpartum in all patients.

In paper IV review three years after diagnosis revealed similar LVEF in patients vs controls, however, comprehensive echocardiographic evaluation revealed important alterations in both LV structure and function in patients. LV systolic and diastolic diameter and LV mass was still increased. Patients had impaired LV longitudinal function with reduced septal velocities in both systole and diastole, a pattern often seen in hypertensive disease.[94] That the septum was more affected than the lateral wall might be due to geometrical factors, as the curvature of the septum is less pronounced than that of other LV segments and the wall stress of the septum is higher making the septum more affected by high LV afterload.[95] The decrease in e' among cases reflects slower ventricular diastolic relaxation, a sign of reduced diastolic function, but as the mitral E wave was decreased, the E/e'-ratio remained unchanged indicating similar

LV filling pressures among cases and controls. RV e' was reduced indicating affected RV function, has been found in hypertension[96] GLS has been found to be lower in improved DCM patients who have undergone reverse remodelling, even when LVEF is normal.[97] In the current study the difference in GLS between cases and controls did not reach statistical significance.

The time sequence of contraction and relaxation was disturbed with cases having increased MPI compared with controls. Reduced long-axis function and increased MPI are both known to be negative prognostic signs.[98, 99] These findings are both parts of the pathophysiology of diastolic dysfunction.[100] We did not see any difference in contractile reserve in cases vs controls. To our knowledge no studies have examined contractile reserve using bicycle exercise stress test in PPCM. At least two dobutamine stress echo studies exist in which contractile reserve at initial presentation did not predict LV recovery at 4.7 to 6 months' follow-up.[101, 102] In paper IV post exercise BP was higher in cases, and we know LVEF is afterload dependant. Cases also had lower HR during physical exercise, but the HR between cases on and off β-blocker treatment was similar, rather indicating the difference in HR may have been attributable to chronotropic incompetence secondary to LV dysfunction.[103] Interestingly supposedly recovered patients where medication had been discontinued seemed, to some extent, to have under gone reverse remodelling with near normal cardiac macro-anatomic structure, but still had significant reduced cardiac function with residual impaired LV and arterial compliance which is a novel finding in this population.

Vascular and cardiac changes in PPCM

Only paper IV dealt specifically with vascular changes in PPPM. We know that sympathetic stimulation through various mechanisms increases arterial stiffness.[104,105] Physical exercise involves increased sympathetic activation, which persists after exercise. Yet nitric oxide and prostaglandin mediated AIx decreases[106] occur in the arm and leg during, and up to 15 minutes after exercise in healthy subjects.[107, 108] Post-exercise sympathetic nerve activity is more pronounced in HF patients, but the peripheral resistance can be reduced to that of normal controls with exercise induced preconditioning.[109] AIx has also been shown to be inversely correlated with heart rate, i.e. each 10 bpm increase is associated with 4% decrease in AIx.[106] In the present data HR at rest and post-stress did not differ significantly. Hence ΔAIx from rest to post-stress, in both PPCM cases and controls, did not differ significantly, indicating that the vasodilatory response was not substantially different between the two groups. Both PWV and AIx were higher in the PPCM group post-exercise suggesting structural arterial change caused this difference as confirmed in a recent study.[110] There is an inverse relationship between diastolic function and arterial stiffness in healthy men and women,[111] which suggests that structural changes extend through the entire arterial system. Further supporting this, is the fact that PWV, mainly determined by aortic stiffness, and not endothelial vasodilatory action was significantly higher in PPCM patients at rest.

Patients perceived to be recovered with normalized LVEF and low levels of symptoms where medication had been tapered off and discontinued completely, remarkably showed reduced longitudinal septal velocities at par with the medicated cases almost five years after diagnosis. Thus AIx and PWV post exercise were similar in cases on

and off medication which indicate residual reduced arterial on exertion in supposedly recovered cases. No studies have examined arterial stiffness in PPCM, but studies on dilated cardiomyopathy indicate an inverse relation between arterial compliance and LV stiffness, remodelling and myocardial fibrosis.[112]

Pharmacological management in PPCM

Paper III allowed us the unique opportunity to monitor the pharmacological management of PPCM in a clinical cohort with almost 5 years follow-up. Pillarisetti et al. reported that 82% and 85% of PPCM patients received β-blockers and ACE-Is/ARBs, respectively.[113] Haghikia et al. also found that standard treatment with β-blockers, ACE-Is/ARBs, and bromocriptine was associated with better outcomes in a German cohort.[26] All patients in the present population received β-blockers and ACE-Is/ARBs for a mean duration of 20 and 30 months with complete termination of the treatment in 16 patients at 1.7 and 2.7 years, respectively. MRAs were initiated in less than half of the patients, mainly because of symptomatic hypotension. Previous findings related to the duration of HF medication are conflicting. One study reported no deterioration in the LVEF after discontinuation of medication,[29] whereas Goland et al, pharmacological treatment notwithstanding, recommend annual follow-up with TTE despite complete LV recovery.[21] In paper III, only one woman experienced decreased LVEF after a primary care physician discontinued her medication. However, in the entire cohort, HF medication was successfully discontinued less than 2 years postpartum in two-thirds of the patients without any adverse events at the time of the review.

Strengths and limitations

The completeness of the data in paper I and II, and the detailed information in paper III and IV present the greatest strengths in the thesis. Paper I, which characterised HF in young patients in all of Sweden, had several advantages such as an unselected and large population comprising data from the entire nation, and near-complete follow-up in a 20-year period.

The first population based data in a PPCM cohort, a case-control design with age-matched controls and a 24 year near-complete follow-up. Unlike the IPR and CDR, the MBR contains unique data, including important biological variables.

In paper III we provided a detailed account of clinical data from early pregnancy including natriuretic peptide levels and serial 2D-echo recordings. It also provided valuable information about the pharmacological management of PPCM up to more than 2½ years postpartum.

Paper IV retrieved data from the same cohort. This case-control study had several strengths such as detailed echocardiographic data including the first data on diastolic function and arterial compliance in women with PPCM.

There were, however also limitations, of which methodological restraints were most important. In paper I we used discharge diagnosis codes which posed a risk of underestimation.[114] Further, hospital admission rates and not true incidence were employed.

It is reasonable to believe that young patients with new onset HF undergo comprehensive assessment, including echocardiography in a cardiac ward where the validity of the HF diagnosis is higher than stated by Ingelsson et al in their study of elderly men.[59] Additionally the lack of further mortality reduction over the last period would not indicate a spurious inflation in incidence because of inclusion of milder cases. Coding practices may certainly have influenced the data, but if so most likely at all ages.

Diagnosing practices for cardiomyopathy changed in the mid-1990s.[115] Accordingly, the group classified as other, could have harboured undiagnosed cases of cardiomyopathy from earlier periods. Unpublished data from an on-going validation study by our group, showed that a diagnosis of DCM from 1989 to 2009 could be confirmed in 86% of cases (n = 219), importantly with no change in diagnostic accuracy over time. A systematic and variable underreporting of hypertension, a major cause of HF, was probably present, but this is unlikely to have influenced hospitalisation rates differentially in different age groups. The stagnating mortality reduction observed does not support a falsely inflated incidence rate in the young. Thus, potential drifts in diagnoses and classifications are unlikely to explain the opposing trends in HF incidence in younger and older patients.

The lack of important biological variables, increasingly used over the period, such as measurement of natriuretic peptides, or ejection fraction was an important deficiency. The absence of such objective measurements obviously detracts from the comparability of HF rates over time. Heart failure is, however, largely a clinical diagnosis, and though we contend that the lack of biological variables is unlikely to explain the diverging changes in HF incidence over time in the different age groups, we acknowledge that their addition would have added value to the study.

In paper II the lack of echocardiography data was arguably more problematic as confirming the PPCM diagnosis only using ICD-9 and -10 coding proved difficult. This inherent weakness intrinsic to many registers, was particular important here as LVEF <45% is part of the definition of PPCM. Of the 272 cases, only just over a quarter of cases (n=71) had a PPCM code, but of these only 14 had the ambiguous ICD-9 code, 674W additionally coding for uterine involution and hepato-renal syndrome. These cases were not included unless other data supporting HF in the registers were found. The remaining 201 cases were identified by linking the index pregnancy to the first occurring HF diagnosis and meticulously excluding all patients with pre-existing conditions including ACHD, IHD, cancers, and pre-existing HF. IPR data has only been validated up to 2001, however our own unpublished data do not indicate any decreasing validity of the register towards the end of the study period.

PPCM patients were almost invariably assessed at departments of internal medicine or cardiology where the validity of the HF diagnosis code is known to be high in the elderly, and possibly more so among the young and pregnant.[59] In our view the risk of underestimating the true incidence of PPCM appears more likely, as the data from paper III indicate that cases who present with mild or transient symptoms, often experience speedy recovery and diagnosis may be missed as symptoms resolve fully without them seeking care.

Finally, as shown in paper II, when compared with large US register studies based on private healthcare delivery and systems that are subject to selection, IPR and MBR comprise >3 million unselected delivery diagnoses – which was virtually all deliveries in an entire country in a 24-year period - irrespective of medical coverage or socioeconomic status.[20, 22, 27, 28]

In paper III we only evaluated PPCM retrospectively, which deprived us the chance to perform interventions and increased the risk of selection bias as mild cases may have gone unnoticed. Missing data from the medical records represented another weakness, jeopardizing the validity of most notably the symptoms, the mode and duration of pharmacological treatment, and data related to smoking and drug abuse.

Paper III and IV had two weaknesses in common: small sample sizes and disparate examination times. The former limited the statistical power, which may have led to an underestimation of the clinical significance of important parameters. The average time of the review postpartum varied greatly, as did the collection times of blood tests, clinical data, and echocardiographic measurements, complicating the comparisons. Thus patients with an early follow-up tended to be on medication whereas patients who were reviewed at a later stage had often recovered and were off medication. This was also the case in paper IV where most cases were examined within 2012 -2013, but investigations were carried out at disparate times after diagnosis which compromised the uniformity of the group, but also allowed for ample comparison between early medicated vs late recovered cases. Thus the patients who were still on medication at follow-up, were on average reviewed 2.9 years sooner after diagnosis than those off medication (Table 7).

Table 7. Characteristics of PPCM cases, on and off medication - and healthy controls

	Cases on medication n=12	**Cases off medication n=10**	**All cases n = 22**	**Controls n = 15**	**P***
Mean FU, years after diagnosis,	1.7 (1.45)	4.6 (1.8)	3.0 (2.2)	6.3 (3.8)[§]	0.004
Diagnosis, days after delivery	16.3 (27.3)	5.3 (7.7)	11.3 (21.1)	NA	NA
Maternal age, years	35.1 (4.8)	39.9 (4.3)	37.3 (5.1)	38.1 (3.0)	0.67
BMI, kg/m^2	28.7 (5.3)	24.8 (3.5)	26.9 (4.9)	24.0 (4.3)	0.11
Breastfed ≤1 week, n (%)	9 (75)	6 (60)	15 (68)	NA	NA
Breastfeeding, weeks	5.0 (9.0)	9.9 (15.8)	7.2 (12.5)	NA	NA
NYHA class I, n (%)	10 (84.3)	8 (80)	18 (81)	15 (100)	0.13
NYHA class II-IV, n (%)	2 (16.7)	2 (20)	4 (19)	0	0.13
QRS-width, ms	88 (10)	86 (7)	87 (9.0)‡	81.3 (6.6)	0.05

All values are mean (SD) unless otherwise stated; FU, follow-up; BMI, Body mass index; *P for controls vs. all cases; [§]years after last delivery; †no data available - normal range given; ‡ missing n=2.

The lack of an exercise induced difference in ΔLVEF between cases and controls in paper IV could be due to few participants, or the fact that LVEF is a parameter dependent of both pre- and afterload.[116] More likely, however, images at rest were acquired with the patient supine, whereas the exercise data were collected with the patient in an inclined position and tachypnoic, compromising image quality. In such instances the less physiological dobutamine stress-echo, may have been a preferable choice.

CONCLUSIONS

General conclusion

HF among young adults appears to be on the rise. PPCM in particular is poorly described on the European continent. These data suggest that increasing incidence of both PPCM and other cardiomyopathies are taking place. Whether this is due to true demographic changes including rising obesity and increased levels of immigration from countries with higher incidences; or can indeed be ascribed to methodological reasons like improved case ascertainment, could not be conclusively discerned. Mortality in young patients with HF decreased drastically up to the turn of the millennium.

PPCM is rare in Europe and constitutes a unique entity among the cardiomyopathies as long-term prognosis in PPCM appears to be better than in all other types of idiopathic cardiomyopathies. Prognosis in these Swedish data is comparable to data from Germany and USA, but more favourable than data from outside the West. Even though long-term mortality in PPCM was low, PPCM was still associated with more than 20-fold increased risk of death compared with controls, with most deaths occurring within 3 years of diagnosis.

Clinically PPCM often presents dramatically. However, early diagnosis and timely management may improve prognosis. Medication was successfully initiated and tapered in 2/3 of PPCM patients with no known adverse effects after almost five years.

As seen in most cohorts, and even in this population, preeclampsia was strongly linked to PPCM, but it was inversely associated with late recovery and mortality in concomitant PPCM.

Echocardiographic assessment revealed that LV size, but not LVEF predicted symptomatic recovery in PPCM at 1 year. The NT-proBNP level at presentation was a good marker of disease and was elevated in all patients, but bore no correlation with long-term recovery.

Reduced compliance of the left ventricle and the arterial vasculature in PPCM patients was present up to almost five years after diagnosis irrespective of whether the patients were clinically recovered or still under medication.

Specific conclusion

- Our findings indicate HF admissions in young adults continue to increase despite decreasing HF hospitalisation in older adults since the mid-90s.
- Mortality rates in HF in the young have more than halved since the 80s, but with a stagnating trend.
- Cardiomyopathy diagnoses at least doubled in all age groups between 1987 and 2006.

- PPCM is relatively rare in Sweden (approximately 1 in 9200), but the incidence appears to be on the rise.
- Data from the entire country show that obesity, multi-fetal pregnancies, non-OECD country origin are associated with PPCM.
- Mortality (mean follow-up 16.4 years) in PPCM patients is more than 20 times that of healthy controls.
- More than two-thirds of PPCM deaths occur within 3 years after diagnosis.
- Concomitant preeclampsia in PPCM appears to be linked to a better outcomes.
- We only identified LV size at presentation as predictor for one-year outcome in PPCM.
- NT-proBNP was elevated in all patients with PPCM but was not related to long-term prognosis, but rather to high blood pressure, preeclampsia and the severity of symptoms at presentation.
- Residual increased blood pressure, pulse wave velocity and augmentation index was shown in cases off medication up to almost five years after diagnosis.
- Despite normalized cardiac structures and LVEF, arterial stiffness persists years after the diagnosis of PPCM.

FUTURE PERSPECTIVES

HF is increasingly being recognized in young age as more physicians are cognizant of the economic burden on the healthcare systems and the financial and emotional strain it can put on the families in question. The declining case fatality reduction with lack of further improvement after 2001 is a cause for concern and despite the recent progress with the addition of the angiotensin-neprilysin agents (the so-called ARNEs),[117] new ways other than renin-angiotensin system inhibition should be sought after.

PPCM, a condition which at early presentation mimics physiological pregnancy, requires early detection. To achieve this, tools for identifying sentinel signs of endothelial and vessel disease may be of value. Large prospective studies are needed to confirm these findings. Of particular utility would be to confirm if weight control in early pregnancy and closer monitoring of preeclamptic mothers at diagnosis would be cost-beneficial in avoiding the development of PPCM. Also future studies should focus on to what extent genetic or environmental factors account for the excess incidence and mortality in women of sub-Saharan African descent.

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SAMMANFATTNING PÅ SVENSKA

Hjärtsvikt (HF) drabbar tusentals svenskar varje år, men den samlade förekomsten av nydiagnosticerade fall har minskat sedan mitten på 90-talet. Huruvida detta också gäller unga med hjärtsvikt har inte fastställts. Inte heller vet man mycket om dödligheten och karaktären av hjärtsvikt hos unga. Vi ville klarlägga detta genom studier av Patientregistret och Dödsorsaksregistret av alla hjärtsviktinläggningar bland unga vuxna yngre än 55 år i Sverige mellan 1987-2006.

Peripartum kardiomyopati (PPCM) är hjärtsvikt under slutet av graviditeten eller under barnsängstiden utan känd orsak. Ämnet har studerats vid en del säten framförallt i USA, Sydafrika och Haiti, men senare också i Tyskland, men aldrig i Sverige. Vid genomgång av alla graviditetsrelaterade hjärtsviktsfall i Sverige från 1987–2010 syftade vi till att identifiera: omfattningen och dödligheten av PPCM i hela Sverige och vilka patientkarakteristika som är förknippade med tillståndet. Vi hade ytterligare förmånen att kunna genomföra klinisk uppföljning och journalgenomgång på 24 kvinnor med PPCM och ytterligare utföra hjärtultraljudsundersökningar i vila och under arbete samt bestämma artärstyvhet hos 22 kvinnor med PPCM diagnos och jämföra dessa med 15 friska mödrar.

Första delarbetet visade att HF hos unga vuxna fortsätter att öka trots minskande HF inläggningar hos äldre sedan mitten av 90-talet. Dödligheten i HF hos unga har mer än halverats sedan slutet på 80-talet, men med en stagnerande trend. Kardiomyopatidiagnosen ställdes minst dubbelt så ofta i slutet av undersökningsperioden (1987-2006) som i början.

I andra delarbetet där vi hittade 272 kvinnor med PPCM i hela Sverige såg vi att tillståndet är relativt ovanligt (1 på 9200 födslar) i Sverige, men förekomsten verkar vara på uppgång (1 på 4500 födslar i slutet av perioden). Data från hela landet visar också att fetma, tvilling/trillinggraviditeter och att vara född i ett icke-OECD-land alla är förknippade med ökad förekomst av PPCM. Dödligheten bland PPCM-patienter var mer än 20 gånger så hög som hos friska kontroller, och mer än två tredjedelar av dessa dödsfall inträffade inom 3 år efter diagnos. Samtidig preeklampsi hos dessa kvinnor verkade vara kopplad till en bättre prognos.

Hos 24 kvinnor med ultraljudsverifierad PPCM identifierades endast vänsterkammarstorlek som prediktor för gynnsamt utfall vid ett års uppföljning. Nivåerna av natriuretiska peptider som indikerar kraftig tänjning i hjärtkamrarna var förhöjda i samtliga patienter med PPCM, men var inte relaterade till långtidsprognosen, utan snarare till högt blodtryck och svåra symtom vid insjuknadet.

I sista delarbetet, där vi fokuserade på hjärtultraljudsfynd och icke-invasiva artärstyvhetsmätningar hos 22 PPCM-fall, sågs förhöjt blodtryck och ökad pulsvågshastighet i artärerna hos patienterna jämfört med friska kontroller, i upp till nästan fem år efter diagnos, oavsett om patienterna hade trappats ur medicinering och därmed friskförklarats eller inte. Således kvarstår artärstyvhet hos kvinnor med PPCM lång tid efter diagnos trots normaliserade hjärtstrukturer och normalisering av vissa mått på vänsterkammares pumpförmåga.

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