ORIGINAL RESEARCH ARTICLE

Prevalence of heart failure and other risk factors among first-degree relatives of women with peripartum cardiomyopathy

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ABSTRACT

Objectives Peripartum cardiomyopathy (PPCM) is a rare disease carrying a risk of death and chronic heart failure.It is unknown if women with PPCM have a family history of heart failure. We investigated the prevalence of heart failure and hypertension in first-degree relatives to women with PPCM.

Methods A cohort of 61 women with PPCM was identified through the nationwide Danish registers from 2005 to 2014, and each individual diagnosis of PPCM was validated through review of patient records. We excluded 13 women due to lack of data on relatives. In a case–control design, the 48 remaining women were matched (on age, year of childbirth, parity and number of siblings) to 477 birth-giving Danish women without heart failure. We obtained information on first-degree relatives (parents and siblings) through the National Danish Registers.

Results The cohort of 48 women with PPCM had a mean age of 31 years (SD 6). The prevalence of heart failure in any first-degree relative was higher in women with PPCM, compared with controls (23% vs 10%, p=0.011). A first-degree relative with any cardiovascular diagnosis was not more frequent in women with PPCM versus controls (77% vs 70%, p=0.280), but for siblings only, any cardiovascular diagnosis was more frequent in siblings to women with PPCM (29% vs 16%, p=0.026).

Conclusion Having a first-degree relative with heart failure was significantly more frequent in a cohort of validated PPCM cases than in controls, supporting the notion of shared aetiology between PPCM and other forms of heart failure.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a rare but severe disease, with a reported incidence rate ranging from 1/968 to 1/4000 women giving birth in the USA.[1 2] In Denmark, a recent study demonstrated an incidence of approximately 1/10000 deliveries.[3] The disease is characterised by left ventricular systolic dysfunction accompanied by clinical heart failure and occurs towards the end of pregnancy or in the months following delivery in previously healthy women.[4] The outcome of PPCM ranges from complete recovery to end-stage heart failure.[5 6]

The causes of PPCM are unknown, but multiple hypotheses exist, including genetics. One of the main hypotheses of the present work was that there would be a high familial clustering of cardiovascular disease in women with PPCM and a particular high prevalence of heart failure in their first-degree relatives. Previous studies have suggested a phenotypic resemblance to dilated cardiomyopathy,[7 8] and a few studies of selected PPCM cases and families have also suggested a genetic link between dilated cardiomyopathy and PPCM.[9 10] Furthermore, a study reported that mutations in the gene TTN, which encodes the protein titin, were present equally frequent in patients with idiopathic dilated cardiomyopathy and PPCM.[11] Recently, this mutation in the TTN gene was also found to be more common in women with pre-eclampsia, supporting the link between pre-eclampsia and cardiomyopathy.[12]

Several other hypotheses have focused on endocrine factors that peak during the end of pregnancy and the first months postpartum, such as prolactin or soluble Fms-like tyrosine kinase-1 (sFlt-1).[13–15] The antiangiogenic, placenta-derived protein sFlt-1 regulates vascular homeostasis and endothelial function during pregnancy by binding free vascular endothelial growth factor (VEGF). In tissues, local secretion of VEGF usually opposes this to maintain angiogenesis, but a rodent model has shown how pregnant individuals with mutations in certain cardiac genes may exhibit impaired VEGF secretion and subsequently develop heart failure in response to sFlt-1 exposure.[14] It has further been found that sFlt-1 levels are elevated in women with PPCM compared with matched postpartum controls.[14]

The genetic links to PPCM appear to regard more than the TTN mutations and a single nucleotide polymorphism (SNP) variant located near the parathyroid hormone-like hormone (PTHLH) gene was reported to be associated with PPCM.[16] The PTHLH mobilises calcium for breast milk secretion and modulates cardiac myocytes.[16 17] The identified SNP is always inherited together with another SNP (ie, the two SNPs are in complete linkage disequilibrium) that has been shown to be associated with osteoporosis.[18] Osteoporosis has previously been linked to heart failure, but whether calcium metabolism is significantly and clinically important for the pathophysiology of PPCM is unknown.[19]

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Only few studies have reported on the family history of cases of PPCM, and previous published literature is based on very few cases[20] or self-reported information on family history.[7] To our knowledge, no previous study has investigated the prevalence of all-cause heart failure in first-degree relatives of women with PPCM. We therefore aimed to investigate the association of PPCM with heart failure and other cardiovascular comorbidities in first-degree relatives, using a cohort of women with a validated diagnosis of PPCM in Denmark in 2005–2014. We also investigated if osteoporosis (as a measure of impaired calcium metabolism) was more frequent in first-degree relatives of PPCM cases than in controls, given the prior study suggesting a link between PPCM and PTHLH.

METHODS

Study design

The study was a matched case–control study, where women with PPCM were matched to birth-giving Danish women on age, year of childbirth, parity and number of siblings.

Data

Denmark has a public healthcare system, and to keep track of the public health status and expenses, all health data are registered continuously and kept in several registers. These registers can be cross-linked through a unique personal civil registration number, assigned to all Danish citizens at birth or when immigrating to Denmark.

We used four nationwide registers: the Civil Registration Register, the Danish Fertility Register, the Danish Register on Medicinal Product Statistics and the National Danish Patient Register. The Civil Registration Register holds information on date of birth and sex. The Danish Fertility Register contains information on first-degree relatives of children born since 1954 and also contains information on adoptions. This information was used to investigate the prevalence of heart failure and other risk factors in first-degree relatives of the PPCM cohort. The Danish Register on Medicinal Product Statistics was used to obtain information regarding claimed prescriptions of antihypertensive medication and medication for osteoporosis (see online supplementary table 1 for codes). The register contains the date of claim, type of drug (listed according to the Anatomical Therapeutic Chemical [ATC] classification) and is complete from 1995 and onwards.[21] The National Danish Patient Register encodes all information on hospitalisations and outpatient visits, discharge dates and diagnoses according to the International Classification of Disease (ICD) coding system. From 1994 and onwards, the ICD-10 coding system has been used, before that it was ICD-8 codes (ICD-9 was never used in Denmark). The register has been complete since 1977.[22] Through this register, we obtained information on diagnosis of heart failure (including cardiomyopathy), ischaemic heart disease for first-degree relatives and deliveries in controls, and we included both inpatient and outpatient diagnoses (see online supplementary table 1, for a list of codes and diseases).

Hypertension in first-degree relatives was included as two different variables. The first was according to the ICD-10 diagnosis code, but this definition might only include patients with severe hypertension managed in outpatient hospital clinics. Furthermore, since uncomplicated hypertension is mostly managed in primary care in Denmark, we also included hypertension defined by the use of antihypertensive drugs, according to previous literature.[23] Further osteoporosis was defined as the use of medication for osteoporosis, listed by ATC codes presented in online supplementary table 1.

Hypertensive disorders of pregnancy were defined as the presence of chronic and gestational hypertension and pre-eclampsia/eclampsia.

Cases

The diagnosis of PPCM in the main cohort of 61 patients was validated for each case. In brief, within the period of 2005–2014, women with the ICD-10 diagnosis code DO903 were identified through the Danish National Patient register; additionally, birth-giving women with one of the following ICD-10 codes DI42, DI43, DI50 or DO754 within the period of 9 months prior to the date of delivery or 12 months following date of delivery were identified. For patients who fulfilled the above described criteria, patient files (from 17 different hospitals) for the period of 1 January 2005–31 December 2014 were carefully reviewed, and only patients who fulfilled the criteria specified by the European Observational Research Program (EORP) PPCM registry were included.[3 24]

Controls

Controls were selected among all Danish birth-giving women during the study period. The controls were identified through the National Danish Patient Register by ICD-10 codes for deliveries (see online supplementary table 1).

First-degree relatives

First-degree relatives were defined as parents and siblings to the case/control, and they were identified through the Danish Fertility register. Siblings were defined as siblings if they shared the same mother of the case/control.

The diagnosis of heart failure (and other diseases) in first-degree relatives was included from the entire study period (2005–2014). As a sensitivity analysis, we stratified the diagnosis of heart failure by ischaemic aetiology, defined as an additional diagnosis of ischaemic heart disease prior to or within a year following the diagnosis of heart failure. Heart failure among the first-degree relatives was obtained at any time within the study period.

Statistical analysis

The cohort of women with PPCM was matched with birth-giving women, randomly selected from the entire Danish population. Cases were matched on the following four criteria: age, year of childbirth, parity and number of siblings. We used the g-match macro in SAS based on the greedy matching principle.[25] The match ratio was up to 10 controls for every case. Due to rules about dissemination of data on individuals, numbers are presented as <3 (NA) if the number of cases were less than 3.

Difference between cases and controls was tested using Cochran-Mantel-Haenszels statistics for dichotomous variables (Fisher's exact test with groups of less than five events). Conditional logistic regression models were used to derive the odds ratio (OR) estimates (with 95% CIs) of having a first-degree relative with disease for PPCM women, compared with controls.

All statistical analyses were performed using SAS V.9.4.

Ethics

Studies that use anonymised register-based data in Denmark do not require approval by the ethics committee. This study was approved by the Danish data protection agency.

Table 1 Baseline characteristics of women with peripartum cardiomyopathy

	n=48
Age, mean (SD)	31 (6)
BMI, mean (SD)	27 (6)
Gestational age at delivery, days, mean (SD)	265 (23)
Duration from delivery to diagnosis, days, mean (SD)	22 (41)
Left ventricle ejection fraction (%) at diagnosis, mean (SD)	27 (10)
Parity, N (%)	
1	26 (54)
2	14 (29)
3 or more	8 (17)
Twin pregnancy, N (%)	4 (8)
Postpartum bleeding, N (%)	8 (17)
Caesarean delivery, N (%)	33 (69)
Pre-eclampsia, N (%)	21 (44)
HELLP, N (%)	3 (6)
Any hypertensive disorders of pregnancy, N (%)	27 (56)
Labetalol during pregnancy, N (%)	16 (33)
Methyldopa during pregnancy, N (%)	8 (17)
Smoking during pregnancy, N (%)	11 (23)
Comorbidities, N (%)*	18 (38)
Mechanical circulatory support, N (%)†	5 (10)

*Asthma, thyroid disorders, chronic hypertension, depression, epilepsy, rheumatoid arthritis, ADAMTS13 deficiency, antiphospholipid syndrome, Crohn's disease and factor V Leiden mutation.
†HeartMate II left ventricular assist device, Levitronix left ventricular assist device, Impella left ventricular assist device, extracorporeal membrane oxygenation and all the mechanical support were implemented postpartum as a part of the heart failure treatment.
BMI, body mass index; HELLP haemolysis elevated liver enzymes and low platelet count.

RESULTS

The entire cohort consisted of 61 women with a validated diagnosis of PPCM in the period of 2005 through 2014. In total, 13 women were excluded due to the lack of registration of first-degree relatives, leaving a cohort of 48 women for the case–control analysis. There were six immigrants in the original cohort, and all of them were among the 13 women that were excluded; thus, the cohort consisted only of women with Caucasian background.

The mean age for women with PPCM was 31 years (SD 6), and most women were diagnosed in association to the delivery of their first child. More than 50% of the women had a Caesarean delivery and 44% had pre-eclampsia during their pregnancy (see table 1 for baseline characteristics).

Matched analysis and diseases among first-degree relatives

The cohort of 48 women with PPCM was successfully matched to 477 controls (three cases had only nine eligible controls).

A first-degree relative (including the mother, father and siblings) with a diagnosis of heart failure was significantly more prevalent among women with PPCM compared with the controls (23% vs 10%, p=0.011) (table 2). Stratified by type of relative, only a paternal heart failure diagnosis was significantly higher in PPCM cases versus controls (p=0.025) (see online supplementary table 2). The OR for having a first-degree relative with various cardiovascular disorders versus controls are given in figure 1.

The mean age at diagnosis was 63 years (SD 13) for paternal heart failure and 66 years (SD 12) for maternal heart failure in parents of the cases. Mean age at diagnosis was 61 years (SD 14) for paternal heart failure, and 64 years (SD 10) for maternal heart failure in parents of the controls. For sensitivity purposes, we stratified heart failure by coexistent ischaemic heart disease, which revealed that 64% of unspecified heart failure among the first-degree relatives of PPCM women also had a diagnosis of ischaemic heart disease, but ischaemic heart failure alone was not significantly more frequent in relatives to PPCM women than in relatives of controls (p=0.056) (table 2). Any diagnosis of cardiovascular disease in first-degree relatives was not different in cases versus controls (77% vs 70%, p=0.280), although more siblings to PPCM cases than controls had prevalent cardiovascular disease (29% vs 16%, p=0.026).

Table 2 Analysis of first-degree relatives to PPCM cases and controls

	Cases n=48	Controls n=477	P value for difference
Pooled analysis with any first-degree relative, n (%)			
Heart failure	11 (23)	50 (10)	0.011
Heart failure and ischaemic heart disease	7 (15)	33 (7)	0.056
Ischaemic heart disease but without heart failure	13 (27)	108 (23)	0.486
Heart failure but without ischaemic heart disease	4 (8)	17 (4)	0.115
Ischaemic heart disease	19 (40)	136 (29)	0.109
Antihypertensive medication	35 (73)	303 (64)	0.196
Hypertension diagnosis	24 (50)	176 (37)	0.075
Any cardiovascular diagnosis	37 (77)	332 (70)	0.280
Peripheral vascular disease	6 (13)	28 (6)	0.075
Cerebrovascular disease	4 (8)	41 (12)	0.951
Atrial fibrillation	8 (17)	60 (13)	0.422
Diabetes mellitus	7 (15)	77 (16)	0.779
Renal disease	4 (8)	50 (8)	0.641
Osteoporosis	3 (6)	66 (14)	0.139

PPCM, peripartum cardiomyopathy.

The diagnosis of heart failure (and other diseases) in first-degree relatives was included during the entire study period, and for first-degree relatives to women with PPCM, 36% had their diagnosis of heart failure within the same year the woman was diagnosed with PPCM or later. This was a bit higher for controls where 50% of first-degree relatives had the diagnosis of heart failure the same year or later after the control gave birth. For the majority of PPCM cases, their first-degree relatives was diagnosed before the woman had the diagnosis of PPCM. When we only included first-degree relatives diagnosed with heart failure before the case was diagnosed with PPCM, the analysis yielded similar results, as 13% of PPCM cases had a first-degree relative with heart failure versus 5% in controls, p for difference 0.052.

Women with PPCM had a significantly higher prevalence of at least one sibling with a diagnosis of hypertension compared with controls (p=0.023) (see online supplementary table 2). No difference was detected between cases and controls, with regard to parental hypertension or in the pooled analysis. For hypertension, defined by the use of antihypertensive medication, analysis did not yield significance in any of the groups or the pooled analysis (see online supplementary table 2 and table 2).

No women in the cohort had a first-degree relative with PPCM. As an explorative analysis, we investigated the burden of hypertensive disorders of pregnancy in PPCM cases with and without a family history of any cardiovascular disease, and no significant difference was detected (see online supplementary

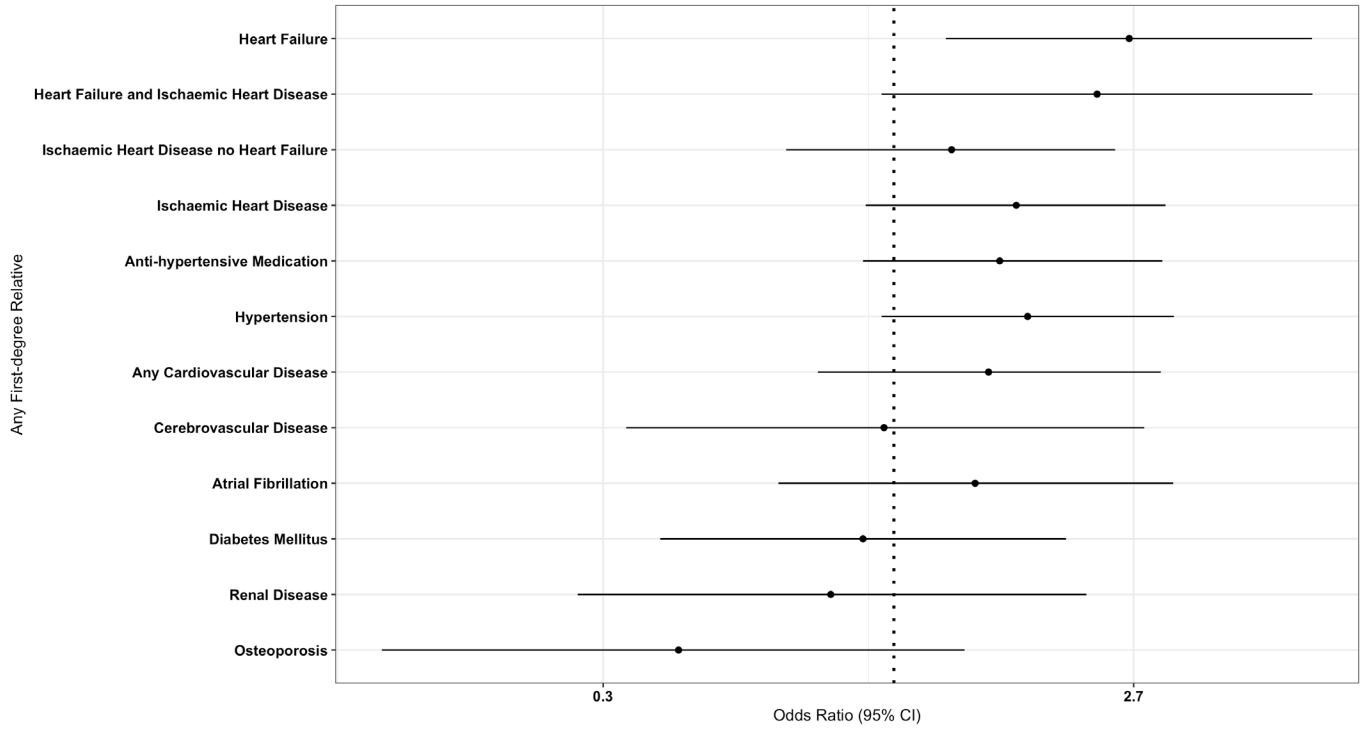

Figure 1 Representation of the odds ratios of having a first-degree relative with disease, for women with PPCM compared to controls. The vertical dotted line represents an odds ratio of 1. PPCM; Peripartum cardiomyopathy.

table 3). We also investigated if there was a difference in the prevalence of cardiovascular disease in first-degree relatives to women with PPCM stratified by hypertensive disorders of pregnancy, no difference was found (online supplementary table 4).

The prevalence of first-degree relatives with osteoporosis was not significantly different between cases and controls (see online supplementary table 2 and table 2).

DISCUSSION

In this cohort of women with a validated diagnosis of PPCM, we found that significantly more cases had a first-degree relative with heart failure, compared with matched controls. Siblings with hypertension and any cardiovascular diagnosis were more frequent among women with PPCM, compared with controls.

Previous studies have demonstrated a possible relationship of PPCM with a family history of dilated cardiomyopathy.[7 9 11] Somewhat surprisingly, in our study, 64% of first-degree relatives with heart failure had concomitant ischaemic heart disease. Based on the registers, however, we cannot conclude if some of these patients suffered from dilated cardiomyopathy. An explanation of these novel findings could be that patients who present with heart failure are more likely to undergo investigations for ischaemic heart disease, or that some patients may be genetically predisposed to heart failure, and thus have a more vulnerable myocardium which, as a consequence of additional cardiac stressors/strain (in relation to, for example, pregnancy or ischaemic heart disease), may lead to overt heart failure. This suspected genetic predisposition could possibly be linked to sFlt-1, as both pre-eclampsia and PPCM share the pathophysiological mechanism of sFlt-1-mediated endothelial dysfunction,[15] and it can be speculated that a hereditary susceptibility to endothelial dysfunction exists and predisposes to a generally increased cardiovascular risk. Furthermore, in our study cohort, the prevalence of pre-eclampsia was high (44%), supporting an existing relation between PPCM and pre-eclampsia.[26]

The mean age at diagnosis of heart failure in parents was about 10–15 years lower in our cohort (both for cases and controls) than in the general population (78 years of age). This could be explained by the study start (2005); thus, many of the parents had not reached 78 years yet. The young age of the parents may also explain why the prevalence of maternal heart failure did not reach significance, as onset of heart failure in women usually occurs later in life.

Moreover, we observed that siblings of women with PPCM were more likely to suffer from hypertension and have a cardiovascular diagnosis; this has not previously been reported. Also, maternal ischaemic heart disease was significantly more frequent in women with PPCM compared with controls, p=0.027. The previous literature report how women with pre-eclampsia have higher risk of developing ischaemic heart disease, hypertension and idiopathic cardiomyopathy later in life.[27 28] This supports the hypothesis that women with PPCM may be predisposed for vascular disease, in line with our findings of a high prevalence of ischaemic heart failure in first-degree relatives, although results were insignificant, p=0.056. However, many other cardiovascular comorbidities such as atrial fibrillation, diabetes mellitus, renal disease and cerebrovascular disease did not yield significance in any of the analyses, which contradicts the hypothesis of a predisposed cardiovascular burden but could also be explained by lack of power in our cohort. Previous work has also suggested that Takotsubo cardiomyopathy may occur after for instance C-section,[29] but unfortunately our work could not contribute to further insights into this matter.

Recent genome-wide association studies have found a SNP to be significantly associated with PPCM, and this SNP is located very close to the gene that codes for PTHLH. The product

of PTHLH, the parathyroid related protein, is involved in calcium transfer in the placenta and uterus, where it regulates blood flow,[30] and is also involved in the regulation of cardiac myocytes[16 17] Thus, we hypothesised that osteoporosis might be more frequent in the families of women with PPCM, but we did not observe this. The lack of significance may be explained by the fact that the parents of birth-giving women were still in the lower age ranges with respect to osteoporosis, as median age of diagnosis for osteoporosis is about 70 years.

Strengths and limitations

This study is based on a cohort with a carefully validated diagnosis of PPCM and is a relatively large cohort, given the rarity of the disease. To our knowledge, this study is the first reporting on family history of heart failure and hypertension in PPCM, and only a few studies have investigated the family history of cardiomyopathy in these women. We chose to include the diagnosis of unspecified heart failure, as it is widely used and the validity of the dilated cardiomyopathy diagnosis in our registers is unknown. As previously described, the diagnosis of PPCM, in this study, was validated thoroughly by chart review according to the criteria set by EORP PPCM register, which adds strength to this study. The main limitation of this study was the small size of the cohort, which precludes further stratification and subgroup analyses and may be associated with a risk of type I errors. The study consisted only of women with Caucasian background, which limits the comparison with some other studies and cohorts of PPCM, as prevalence differs according to ethnicity, which may reflect a difference in genetic risk factors and/or socioeconomic status.

Furthermore, the study lacked clinical data (such as left ventricular ejection fraction) for first-degree relatives. Thus, distinguishing between heart failure with preserved versus reduced ejection fraction was not possible.

CONCLUSIONS

This study suggests that women with PPCM are more likely to have a first-degree family member with heart failure than matched controls. Our findings suggest a genetic predisposition for heart failure in PPCM women and support the hypothesis of shared aetiology between these diseases.

Key messages

What is already known on this subject?

- Previous studies have suggested a shared genetic link between dilated cardiomyopathy and peripartum cardiomyopathy (PPCM). To our knowledge, no previous study has investigated the prevalence of all-cause heart failure in first-degree relatives to women with PPCM.

What might this study add?

- This study shows a higher prevalence of all-cause heart failure in first-degree relatives to women with PPCM and a higher prevalence of hypertension in siblings to women with PPCM compared with controls.

How might this impact on clinical practice?

- The results of this study suggest a shared aetiology between PPCM and other forms of heart failure; thus, a family history of all-cause heart failure could potentially be a risk factor for PPCM.

Contributors Study concept and design: MNC, CA, LK and JGS. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: MNC. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: MNC and CA. Administrative, technical or material support: CT-P, LK and ASE. Study supervision: CA, LK and ASE.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Danish data protection agency (reference number GEH-2014–015 and I-Suite number 02733, and I-suite number 04729).

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