Long-term follow-up in peripartum cardiomyopathy patients with contemporary treatment: low mortality, high cardiac recovery, but significant cardiovascular co-morbidities

Valeska Moulig†1, Tobias Jonathan Pfeffer†1, Melanie Ricke-Hoch1, Stella Schlothauer1, Tobias Koenig1, Johannes Schwab2, Dominik Berliner1, Roman Pfister3, Guido Michels3, Arash Haghikia4, Christine S. Falk5, David Duncker1, Christian Veltmann1, Denise Hilfiker-Kleiner1*‡, and Johann Bauersachs1*‡

1Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; 2Department of Cardiology, Paracelsus Medical University, General Hospital Nuremberg, Nuremberg, Germany; 3Department of Cardiology, Pulmonology, and Vascular Medicine, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; 4Department of Cardiology, Charité Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany; and 5Institute of Transplant Immunology, Hannover Medical School, Hannover, Germany

Aims
Peripartum cardiomyopathy (PPCM) establishes late in pregnancy or in the first postpartum months. Many patients recover well within the first year, but long-term outcome studies on morbidity and mortality are rare. Here, we present 5-year follow-up data of a German PPCM cohort.

Methods and results
Five-year follow-up data were available for 66 PPCM patients (mean age 34 ± 5 years) with a mean left ventricular ejection fraction (LVEF) of 26 ± 9% at diagnosis. Ninety-eight percent initially received standard heart failure therapy (beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists), and 86% were additionally treated with dopamine D2 receptor agonists (mainly bromocriptine) and anticoagulation. After 1 year, mean LVEF had improved to 50 ± 11% (n = 48) and further increased to 54 ± 7% at 5-year follow-up with 72% of patients having achieved full cardiac recovery (LVEF >50%). At 5-year follow-up, only three patients (5%) displayed no recovery, of whom one had died. However, 20% had arterial hypertension and 17% arrhythmias, including paroxysmal supraventricular tachycardia, ventricular tachycardia, or ventricular fibrillation. Moreover, 70% were still on at least one heart failure drug. Subsequent pregnancy occurred in 16 patients with two abortions and 14 uneventful pregnancies. Mean LVEF was 55 ± 7% at 5-year follow-up in these patients.

Conclusion
Our PPCM collective treated with standard therapy for heart failure, dopamine D2 receptor agonists, and anticoagulation displays a high and stable long-term recovery rate with low mortality at 5-year follow-up. However, long-term use of cardiovascular medication, persisting or de novo hypertension and arrhythmias were frequent.

Keywords
Peripartum cardiomyopathy • Co-morbidities • Medication • Heart failure • Subsequent pregnancy

*Corresponding authors. Denise Hilfiker-Kleiner, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany. Email: hilfiker.denise@mh-hannover.de
Johann Bauersachs, Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. Email: bauersachs.johann@mh-hannover.de
†The first and second authors have contributed equally.
‡The two last authors have contributed equally.
Introduction

Peripartum cardiomyopathy (PPCM) is a rare life-threatening heart disease with onset in the last months of pregnancy, during delivery, or in the first months postpartum in previously heart-healthy women.

Over the past decade research on PPCM has advanced our knowledge on the acute clinical picture of the disease and expanded our insight into the pathophysiological mechanisms. However, many aspects of the disease still require further investigation. In particular, data regarding the long-term clinical course of PPCM months or years after diagnosis are sparse with regionally different results. For example, a study from an African collective reported a high recovery rate of left ventricular ejection fraction (LVEF) after 2 years but still a high mortality of 20%. Another prospective study of PPCM patients in Haiti reported a complete recovery rate of 28%, and a mortality rate of 15%. In contrast, the prospective Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, performed in the US, showed a mortality of only 4% in 91 PPCM patients. Moreover, subsequent pregnancies (SSP) in PPCM patients pose additional risks on mother and fetus. While patients with persistently reduced LVEF are considered to be at high risk during a SSP, data are limited to counsel patients with recovered cardiac function. So far, there are also no data on PPCM-associated co-morbidities later in life as has been reported for patients with pregnancy-associated hypertensive disorders. These patients face a higher long-term risk for hypertension and other cardiovascular diseases.

Here, we analyse 5-year follow-up data of 66 PPCM patients from our prospective German PPCM registry with regard to mortality, co-morbidities, SSP, and therapy. Based on the pathophysiological concept of a microvascular injury and impaired angiogenic factors as major underlying mechanisms of this disease, we additionally explored the long-term levels of vascular endothelial growth factor (VEGF) as compared to healthy controls. To our knowledge, this is the largest prospective cohort study with a confirmed PPCM diagnosis, detailed data on drug and device therapies and echocardiography over a 5-year observation period. The results of the study provide important insight into the long-term prognosis of PPCM under contemporary management in specialized PPCM centres in Germany.

Methods

Data collection

This study was approved by the local ethics committee of Hannover Medical School, Hannover, Germany (7970_BO_K_2018). The study complies with the Declaration of Helsinki and all patients and controls gave written informed consent, but not all patients agreed to blood sampling for research analyses at follow-up.

Inclusion criterion was a diagnosis of PPCM as defined by the Study Group on PPCM from the Heart Failure Association of the European Society of Cardiology (ESC), i.e. an LVEF ≤45% assessed by echocardiography and the absence of pre-existing cardiac disease. Each diagnosis was confirmed and, in doubt, further medical reports were requested from the patient, her general practitioner, or the referring hospital.

All patients who were diagnosed or referred with PPCM between February 2006 and August 2013 at Hannover Medical School were included. Additionally, patients from the bromocriptine trial, which were diagnosed at University Hospital Cologne and Paracelsus Medical University Nuremberg during that period, were enrolled. Patients were referred from general practitioners, cardiologists, or other hospitals at the time of diagnosis, or later for consultation. We defined 2006 as the earliest possible time of inclusion, because it seemed impossible to get access to sufficient data from older patient records in order to assure the diagnosis. Onset of symptoms and clinical signs of heart failure at initial presentation, LVEF (calculated with the biplane Simpson’s method), laboratory assessments, drug treatment, adverse events and SSP were recorded. Follow-up data were obtained after 6 months, 1 and 5 years after diagnosis. In 59% of cases, follow-up was conducted in one of the three university hospitals (Hannover, Cologne, and Nuremberg), in 30% by the local cardiologist, and in 11% data were collected via telephone interview. A very few data sets are not totally complete in this registry as index PPCM was in 93% diagnosed in community hospitals or in an outpatient clinic from where patients were referred.

Analysis of outcome

Patients were classified to display full cardiac recovery with LVEF ≥50%, partial recovery (LVEF 35–49%) and no recovery [death, left ventricular assist device (LVAD), heart transplantation (HTX), or LVEF ≤35%]. Additionally, we evaluated how many patients received a wearable cardioverter-defibrillator (WCD), an implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT).

Biomarker measurements

Blood samples were collected at a mean follow-up time point of 47 ± 21 months after diagnosis in S-Monovette tubes containing ethylenediaminetetraacetic acid. Plasma was separated by centrifugation at 1500 rpm for 10 min. Aliquots were stored at –80°C for future analysis. Plasma concentrations were determined using Bio-Plex Pro Assays (Human Cancer Biomarker Panel 2 18-plex 171AC600M, Bio-Rad, Hercules, CA, USA) according to the manufacturer’s instructions. A total of 41 PPCM long-term follow-up samples were measured and compared with 11 samples from postpartum and age-matched healthy women working as control group.

Statistical analysis

Data were analysed using GraphPad Prism version 7.03 for Windows (GraphPad Software, La Jolla CA, USA). Continuous data are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) and categorical data as frequencies (%). Normal distribution was assessed using D’Agostino–Pearson omnibus normality test. A two-tailed paired Student’s t-test was performed to compare the mean values of each time-point, with P-values <0.05 being considered significant.

Results

Overall, 74 patients met the inclusion criteria. Six patients were lost to follow-up, one patient did not give her informed consent, and
one patient had died. A total of 66 patients completed the 5-year follow-up (mean 63 ± 11 months) (Figure 1). Among those, clinical examinations were available for 59 patients and seven patients were interviewed via telephone. They were doing well, but did not attend any further cardioligic examination.

**Characterization of the study population**

Baseline and follow-up characteristics of all women included in this study are shown in Tables 1 and 2. Mean age at diagnosis was 34 ± 5 years, 95% were of Caucasian and 5% of African ancestry. Twenty-two percent of women suffered from hypertensive disorders during pregnancy; 62% had caesarean section as mode of delivery. 19% had a twin pregnancy, and N-terminal pro-brain natriuretic peptide levels were markedly elevated. At diagnosis, 96% of the patients presented with heart failure New York Heart Association functional class III or IV.

**Change in left ventricular ejection fraction**

At diagnosis, LVEF was reduced to 26 ± 9% (n = 67), increased to 48 ± 11% (n = 48; P < 0.0001) at 6-month follow-up (mean follow-up time: 5 ± 2 months) and further increased to 50 ± 11% (n = 48; P = 0.001) at 1-year follow-up (mean follow-up time: 13 ± 3 months) (Figure 2A and 2B).

At 6-month follow-up, full left ventricular recovery was present in 48%, partial recovery in 36%, and no recovery in 16%. Two patients with terminal heart failure needed an LVAD and no patient had died.

At 1-year follow-up (n = 50), full cardiac recovery was present in 60%, partial recovery in 28%, and no recovery in 12%.

At 5-year follow-up (n = 60), the rate of patients with full cardiac recovery had further increased to 72% whereas the rate of patients with partial (23%) or no recovery (5%) had slightly decreased (Figure 2C). Mean LVEF had further improved to 54 ± 7% (n = 58), though without reaching statistical significance (P = 0.0561). Two of the three patients without cardiac recovery needed an LVAD, of whom one died during follow-up.

**Pharmacological therapy**

At diagnosis, 98% of patients received standard heart failure therapy including beta-blocker (BB) and/or angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) and/or mineralocorticoid receptor antagonists (MRA) by their treating physician according to ESC guidelines10 (Table 3).

At 6-month follow-up, 80% (36 of 45 patients) and at 1-year follow-up, 75% (30 of 40 patients) received combined therapy including BB, ACE inhibitors/ARB and MRA. At 5-year follow-up, 30% were without heart failure medication while 70% (46 of 66 patients) were on at least one drug (64% BB, 59% ACE inhibitors/ARB, and 24% MRA). Notably, at 5-year follow-up, 50% of patients received their medication for other indications than heart failure such as arterial hypertension or cardiac arrhythmias.

**Prolactin blocking therapy with dopamine D2 receptor agonists and change in left ventricular ejection fraction**

In addition to standard heart failure therapy, 86% of patients received the prolactin release blocker bromocriptine or carbergoline, both are dopamine D2 receptor agonists, in combination with at least prophylactic anticoagulation according to the BOARD protocol (Bromocriptine, Oral heart failure drugs, Anticoagulation, Relaxants and Diuretics)11 at initial diagnosis. Another two patients who did not improve during standard heart failure therapy received bromocriptine after a delay of 4–7 months (Table 3): one patient did not further improve and showed a stable LVEF between 42%

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**Table 1 Baseline characteristics (n = 67)**

| Characteristic                              | Value         |
|--------------------------------------------|---------------|
| Age, years                                 | 34 ± 5        |
| Parity                                     | 1.7 ± 1       |
| LVEF, %                                    | 26 ± 9        |
| LVEDD, mm, n                               | 59 ± 7, 47/67 |
| Ancestry (ethnicity)                       |               |
| Caucasian                                  | 95%           |
| African                                    | 5%            |
| Time of diagnosis in relation to delivery  |               |
| Last month of pregnancy                    | 0 (0%)        |
| At delivery (± 5 days)                     | 32 (48%)      |
| 1 month after delivery                     | 17 (25%)      |
| 2–3 months after delivery                  | 9 (13.5%)     |
| >3 months                                  | 9 (13.5%)     |
| Caesarean section                          | 41 (62%)      |
| Twin pregnancy                             | 13 (19%)      |
| Gestational diabetes                       | 5 (8%)        |
| NT-proBNP at diagnosis, ng/L (median, IQR), n | 3220 (2036–9195), 45/67 |
| Elevated troponin                          | 27/42 (64%)   |
| Haemoglobin, mg/dL, n                      | 11.8 ± 1.8, 51/67 |
| NYHA functional class (I, II, III, IV)     | 1 (2%), 2 (3%), 30 (45%), 34 (51%) |
| Mechanical ventilation                     | 8 (12%)       |
| Catecholamines                              | 6 (9%)        |
| Levosimendan                                | 2 (3%)        |
| CPR at initial diagnosis                    | 2 (3%)        |
| Sinus rhythm                                | 62 (92.5%)    |
| Complete left bundle branch block           | 8 (12%)       |
| Systolic blood pressure, mmHg, n           | 115 ± 21, 36/67 |
| Diastolic blood pressure, mmHg, n          | 76 ± 13, 34/67 |
| Heart rate, bpm, n                         | 82 ± 20, 26/67 |

Data are presented as mean ± standard deviation, or n (%), unless otherwise stated.

CPR, cardiopulmonary resuscitation; IQR, interquartile range; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
Long-term follow-up in PPCM patients

197 patients with suspected PPCM at MHH and participants in the bromocriptine study from Hospital Nuremberg and Cologne were screened.

123 patients were excluded because
- initial diagnosis was before 2006 or after 8/2013
- PPCM diagnosis was not confirmed

74 patients matched inclusion criteria
- 59 patients had clinical examination including echocardiography
- 7 patients were interviewed via telephone
- 1 patient died after 3 years

67 patients were included in the main analysis
- 59 patients had clinical examination including echocardiography
- 7 patients were interviewed via telephone
- 1 patient did not give her informed consent

6 patients were lost to follow-up

Figure 1 Flowchart illustrating the selection process of peripartum cardiomyopathy (PPCM) patients eligible for long-term evaluation. MHH, Hannover Medical School.

Table 2 Characteristics at 5-year follow-up (n = 66)

| Characteristic                  | Value         |
|--------------------------------|---------------|
| Age, years                     | 39 ± 5        |
| LVEF, %                        | 54 ± 7        |
| LVEDD, mm, n                   | 51 ± 5, 46/66 |
| Haemoglobin, mg/dL, n          | 13.4 ± 1, 36/66 |
| NYHA functional class (I, II, III, IV) | 47 (71%), 15 (23%), 4 (6%), 0 (0%) |
| Sinus rhythm                   | 66 (100%)     |
| Systolic blood pressure, mmHg, n | 118 ± 14, 47/66 |
| Diastolic blood pressure, mmHg, n | 72 ± 9, 47/66 |
| Heart rate, bpm, n             | 68 ± 11, 54/66 |

Data are presented as mean ± standard deviation, or n (%), unless otherwise stated.
LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

and 47% during follow-up. The other patient improved from an LVEF of 17% after 7 months to an LVEF of 43% after 12 months and to an LVEF of 60% at 5-year follow-up.

Wearable and implantable cardioverter-defibrillators

Nine patients received WCD at diagnosis due to markedly reduced LVEF (<35%). Two patients received appropriate and successful WCD shocks due to ventricular fibrillation within 2 months after initial diagnosis. In these patients, LVEF was 20% and 30%, respectively.

Three patients received an ICD 11, 12 and 21 months after diagnosis and five patients needed a CRT with cardioverter-defibrillator (CRT-D) 2, 7, 8, 17 and 54 months after diagnosis. The last patient initially improved to an LVEF of around 40% before deteriorating again. This explains why CRT-D was implanted belatedly. Six devices were implanted for primary prevention and two for secondary prevention. One patient implanted with a CRT-D developed lead fracture of the right ventricular lead 8 months after implantation. Due to LVEF improvement to 47% and a concomitantly narrow QRS complex, the CRT-D system was explanted. One additional patient received several inappropriate shocks for atrioventricular nodal reentry tachycardia (AVNRT). After AVNRT ablation, she had no further ICD shocks.

Mechanical circulatory support and overall outcome

Two patients suffered from severe dyspnoea at the end of pregnancy requiring urgent caesarean section. Because of refractory cardiogenic shock, they received extracorporeal membrane oxygenation in veno–arterial configuration for initial haemodynamic stabilization. Both patients needed an LVAD 2 and 9 weeks after PPCM diagnosis. One of them died 3 years later due to LVAD thrombosis and consecutive stroke. The other patient also suffered a stroke 4 years after initial diagnosis. In total, mortality rate was 2% in our cohort.
Figure 2 Time course of left ventricular function. (A) Changes in left ventricular ejection fraction (LVEF) from baseline (BL) to 5-year follow-up in 41 peripartum cardiomyopathy patients with complete echocardiographic follow-up at all time points. Remarkably, LVEF further improves even after 1 year. Two patients had received a left ventricular assist device (LVAD) at 6-month follow-up and one of them died 3 years later. (B) Scatter blot showing echocardiographic data from all peripartum cardiomyopathy patients included in this study. (C) Proportion of patients with full cardiac recovery constantly increases. At 5-year follow-up, 72% had recovered completely and 23% partially. No recovery was observed in 5% (two patients needed LVAD, of whom one patient had died and one patient showed sustained impairment of LVEF \( \leq 35\% \)). *\( P < 0.05 \), and ***\( P < 0.001 \).

Subsequent pregnancy

Sixteen patients had a SSP: 14 women had uneventful full-term pregnancies, one woman wished to terminate pregnancy in week 8 and one woman had one spontaneous abortion 15 months after index PPCM and a tubal pregnancy 9 months later.

Fourteen patients (88%) had fully recovered before the SSP. Mean LVEF of all 16 patients before or in early pregnancy (maximum week 7 of pregnancy) was 55 ± 10%. LVEF did not change significantly after SSP (52 ± 12%; \( P = 0.2574 \)) (Figure 3). One patient had slightly reduced LVEF of 45% before SSP and remained stable during pregnancy and postpartum (LVEF 45% at 5-year follow-up). The other patient had entered pregnancy with reduced LVEF of 25% 1 year after index PPCM, but had a spontaneous abortion. After her second (tubal) pregnancy, LVEF was 20% and she was listed for HTX. Thereafter, she did not become pregnant again and her compliance regarding heart failure medication increased. At 5-year follow-up, LVEF had improved to 49% (Figure 3).

Almost all women with SSP were treated with bromocriptine postpartum (87%, 13 of 15), and were advised to stop breastfeeding.

Co-morbidities

Co-morbidities of PPCM patients are listed in Table 4. At 5-year follow-up, 20% (13 of 66 patients) suffered from arterial hypertension. Of those, four had been diagnosed with arterial hypertension before pregnancy and nine had developed hypertension after PPCM. Additionally, 3% (2 of 66 patients) were diagnosed with carotid artery dissection. There were a total of 13 arrhythmias in 11 patients (17%) and almost half of the patients developed arrhythmias after PPCM diagnosis (Table 4). Nine percent of the patients had thrombotic events during and after PPCM diagnosis. Furthermore, 38% had a pathologic condition of the thyroid gland with need for treatment.

Impairment in serum factors persists over several years in PPCM patients

We analysed VEGF-A and VEGF-D in a subgroup of 41 PPCM patients at a mean follow-up time of 47 ± 21 months and compared them to 11 healthy postpartum matched control subjects. In the long term we observed persistently reduced levels of VEGF-A...
Table 3 Drug treatment at diagnosis and in the long term

| Drug treatment                  | At diagnosis (n = 66) | After 6 months (n = 45) | After 12 months (n = 40) | After 5 years (n = 66) |
|---------------------------------|-----------------------|-------------------------|--------------------------|------------------------|
| BB                              | 64 (97%)              | 45 (100%)               | 40 (100%)                | 42 (64%)               |
| ACEi/ARB                        | 62 (94%)              | 43 (96%)                | 87 (95%)                 | 39 (59%)               |
| MRA                             | 55 (83%)              | 38 (84%)                | 29 (73%)                 | 16 (24%)               |
| Diuretics                       | 58 (88%)              | 22 (49%)                | 20 (50%)                 | 14 (22%)               |
| Ivabradine                      | 4 (6%)                | 1 (1.5%)                | 1 (1.5%)                 | 3 (5%)                 |
| Digitalis                       | 4 (6%)                | 1 (1.5%)                | 0                        | 0                      |
| BB, ACEi/ARB and MRA            | 50 (76%)              | 36 (80%)                | 30 (75%)                 | 14 (21%)               |
| BB + ACEi/ARB or BB + MRA       | 15 (23%)              | 9 (20%)                 | 8 (20%)                  | 23 (35%)               |
| BB or ACEi/ARB or MRA           | 0                     | 0                       | 2 (5%)                   | 9 (14%)                |
| No heart failure therapy        | 1 (2%)                | 0                       | 0                        | 20 (30%)               |
| Bromocriptine                   | 55 (83%)              | 2                       | 0                        | 0                      |
| Cabergoline                     | 3 (5%)                | 0                       | 0                        | 0                      |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist.

aData on heart failure treatment at initial diagnosis of one patient is missing.

bOne patient received both cabergoline and bromocriptine.

Table 4 Comorbidities at index pregnancy, before and afterwards

| Comorbidities                        | Before diagnosis of PPCM | At diagnosis of PPCM | During long-term follow-up | Total |
|--------------------------------------|--------------------------|----------------------|----------------------------|-------|
| Cardiac arrhythmias                  |                          |                      |                            |       |
| SVT                                  | 1                        | 2                    | 3 (5%)                     |       |
| AVNRT                                | 1                        | 1                    | 2 (3%)                     |       |
| NSVT                                 | 5                        | 5 (8%)               |                            |       |
| Ventricular fibrillation             | 1                        | 2                    | 3 (5%)                     |       |
| Arterial hypertension                | 4                        | 9 (20%)              | 13 (20%)                   |       |
| Hypertensive disorders of pregnancy |                          |                      |                            |       |
| Gestational hypertension             | 2                        | 2 (3%)               |                            |       |
| Preeclampsia                         | 9                        | 9 (13%)              |                            |       |
| HELLP syndrome                       | 4                        | 4 (6%)               |                            |       |
| Carotid artery dissection            | 2                        | 2 (3%)               |                            |       |
| Thrombosis/thromboembolism           | 6                        | 6 (9%)               |                            |       |
| Pathologic condition of thyroid gland on medication | 13 | 4 | 5 | 22 (33%) |
| Hypothyroidism                       | 1                        | 2                    | 3 (5%)                     |       |
| Hyperthyroidism                      |                          |                      |                            |       |

AVNRT, atrioventricular nodal reentry tachycardia; HELLP, haemolysis, elevated liver enzymes, and low platelet count; NSVT, non-sustained ventricular tachycardia; PPCM, peripartum cardiomyopathy; SVT, supraventricular tachycardia.

aBefore or during pregnancy.
bLast month of pregnancy to 1 month after first diagnosis.
cThere were 13 cardiac arrhythmias in 11 patients.

d and VEGF-D in PPCM patients despite recovery of left ventricular function (online supplementary figure S1). None of the other endothelial growth factors (e.g. VEGF-C) displayed significantly altered concentrations in serum of PPCM patients compared to controls.

Discussion

Our prospective 5-year follow-up study shows a high and stable long-term recovery rate in most PPCM patients. To our knowledge this is the largest prospective observational study of PPCM patients with confirmed diagnosis, assessment of LVEF, pharmacological therapy, cardioverter-defibrillator devices and mechanical circulatory support (MCS) up to 5 years after index PPCM in all individual patients. Almost all patients were initially treated with dopamine D2 receptor agonists. Mortality and poor outcomes were very low despite severe heart failure at diagnosis. Thus, our data support the current guidelines recommending standard heart failure medication combined with dopamine D2 receptor agonists, and appropriate cardiac device therapy when indicated. Further studies and large

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Immediately after SSP, 5 years afterwards and at 5-year follow-up in patients with peripartum cardiomyopathy. Fourteen of 16 patients entered SSP with recovered left ventricular ejection fraction (LVEF). One patient with slightly reduced LVEF remained stable, one patient with heavily reduced LVEF was listed for heart transplantation after two pregnancies but recovered significantly to 5-year follow-up. Thirteen of 15 patients received bromocriptine after delivery. At 5-year follow-up, LVEF stayed stable in all patients. (n = 14). In two patients we did not have LVEF measurements, but the patients reported of wellbeing during telephone interview.

Besides drug therapy the low mortality in our cohort was related to treatment with cardioverter-defibrillator devices and MCS. PPCM patients seem to be at high risk of ventricular arrhythmias. A possible mechanism for mortality in PPCM patients is sudden arrhythmic death. Our results emphasize the high risk for life-threatening arrhythmias in PPCM patients, thus we think WCD is useful to prevent sudden cardiac death. Consideration of WCD in patients with acute PPCM is also recommended by the ESC Study Group on PPCM. The low mortality in our cohort is in good agreement with the study of Amos and colleagues from the US: they observed no early mortality in 55 PPCM patients, but 10% needed HTX and two patients needed LVAD as bridge to HTX. IPAC study describes a mortality rate of 4% after 1 year despite therapy with LVAD and HTX in 5% of the patients. However, none of the studies reports the detailed course of heart failure medication over time, or WCD, ICD or CRT-D treatment. Thus, accurate comparison between the different treatment regimes and their relation to patients’ outcome in the different cohorts is not possible.

Mortality and poor outcomes may depend also on the proportion of patients with African descent as it is generally assumed that African women have inherently a worse outcome. However, there is no controlled study evaluating the response to treatment in patients with African as compared to Caucasian ancestry. Often no data are provided regarding adherence to therapy during follow-up, up-titration of heart failure medication, or implantation of ICD or CRT-D when indicated. In our cohort we had three patients with African ancestry. Two of them recovered completely and the other one recovered partly at 5-year follow-up.

Interestingly, first results of the ongoing international EORP PPCM registry show early mortality in non-ESC countries of only 1.4% (including 45% Africans and 5% Caucasians) and mortality in ESC countries of 3.4% (including 65% Caucasians and 5% Africans) after 1 month. On the other hand, women with African descent in the US have a shorter life expectancy, and maternal in-hospital-mortality is three times higher than in white women. To which proportion these differences are treatment-related, associated with low socio-economic status, reduced access to high-quality health care in due time, or potential genetic differences, has not been systematically assessed. Future studies and large registries are required to address these important questions. Nevertheless, given the worse outcomes in many patients with African ancestry, we should particularly take care of these high-risk patients and ascertain that they receive optimal treatment.

Whether patients after PPCM may become pregnant again is highly debated, but an important matter of care in most of these patients. In our current study, 16 patients had a SSP; however, we did not observe relapses with deterioration of left ventricular function neither in patients with recovered LVEF nor in the single patient who had only partially recovered before SSP. This finding is in contrast to most other reports, which showed deterioration or death in SSP also in patients with recovered LVEF. We cannot completely explain these differences and can only conclude that a recovered LVEF > 50% before SSP, close monitoring during pregnancy, and dopamine D2 receptor agonist therapy after delivery...
system. This hypothesis is further supported by the fact that the hypothesis that PPCM is a systemic disease of the vascular system. VEGF-R ligands. These data suggest ongoing subclinical pathophys- may point towards a novel pathomechanism involving the balance of ands for VEGF receptor (R) with cardiovascular co-morbidities and points to a higher susceptibility also in the long term. In this regard, our finding that despite full cardiac recovery in the majority of our patients, the circulating pro-angiogenic factors VEGF-A and D, both ligands for VEGF receptor (R) 1 and R2, respectively, are reduced even in the long term is startling. The lower concentrations of VEGF-A and -D at long-term follow-up in PPCM patients argue for reduced VEGF-R1 and R2 signalling in endothelial cells, which may point towards a novel pathomechanism involving the balance of VEGF-R ligands. These data suggest ongoing subclinical pathophysiological processes at the endothelial signalling level and support the hypothesis that PPCM is a systemic disease of the vascular system. This hypothesis is further supported by the fact that two patients in our cohort had arterial dissection, a rather rare disease. However, as we do not have information on circulating levels of VEGF-A and D before pregnancy and PPCM, it is unclear whether VEGF blood levels were already lower prior to pregnancy or are the consequence of PPCM leading to long-term vascular impairment and higher risk for cardiovascular disease. Here, large prospective registries would be needed to address this important question.

Arterial hypertension and cardiac arrhythmias may also explain the high rate of patients on heart failure medication after at least 5 years, which may contribute to the good outcome. Our observations extend the results of the recently published study from Denmark. These authors reported a high recovery rate but still subtle diastolic dysfunction and reduced maximal exercise capacity in PPCM patients compared to patients with preeclampsia. However, follow-up examination was performed in only 28 patients (less than half of the original cohort) and time of follow-up varied substantially between 25 and 156 months. Interestingly, also a large proportion (44%) of the Danish patients took antihypertensive/heart failure medication despite good recovery. However, detailed information was missing regarding pharmacological therapy, especially in patients without recovery.

Limitations

Some data are incomplete as many patients were initially treated in other hospitals, or follow-up visit was done in an ambulatory setting. Echocardiographic data were obtained from different echo labs. Although our study is the largest registry with almost complete detailed follow-up data, the study size is limited due to the rarity of disease. Six patients were lost to follow-up despite huge efforts, which may impact the overall mortality and outcome.

Conclusion

Three highly experienced centres observed a complete and sustained cardiac recovery in the majority of PPCM patients treated with standard heart failure medication and dopamine D2 receptor agonists, and further improvement of LVEF even beyond the first year. Therefore, a prolonged intensified treatment with heart failure medication is advocated, and the decision to implant devices such as ICD and CRT-D should be postponed at least 6–12 months. MCS and WCD seem to be helpful and should be considered in patients with severely reduced LVEF. A close monitoring during follow-up is recommended, as the risk for other cardiovascular diseases seems to be elevated. In patients with full cardiac recovery, a SSP may not be excluded in all cases.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Impairment of plasma biomarkers in PPCM patients during long-term course (47 ± 21 months).

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References

1. Sliva K, Petrie MC, Hilfiker-Kleiner D, Mebazaa A, Jackson A, Johnson MR, van der Meer P, Mbaikwem A, Bauersachs J. Long-term prognosis, subsequent pregnancy, contraception and overall management of peripartum cardiomyopathy: practical guidance paper from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Eur J Heart Fail 2018;20:951–962.

2. Sliva K, Forster O, Tibazarwa K, Libhaber E, Becker A, Yip A, Hilfiker-Kleiner D. Long-term outcome of peripartum cardiomyopathy in a population with high seropositivity for human immunodeficiency virus. Int J Cardiol 2011;147:202–208.

3. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005;80:1602–1606.

4. McNamara DM, Elkayam U, Alhareeri R, Damp J, Hiscic E, Ewald G, Modi K, Alexix JD, Ramani GV, Semigam MJ, Haytie J, Markham DW, Marek J, Gorkancan J, Wu WC, Lin Y, Halder I, Ptsarcik J, Cooper LT, Fett JD. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC study (Investigations of Pregnancy-Associated Cardiomyopathy). J Am Coll Cardiol 2015;66:905–914.

5. Elkayam U. Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy. J Am Coll Cardiol 2014;64:1629–1636.

6. Williams D. Long-term complications of preeclampsia. Semin Nephrol 2011;31:111–122.

7. Duncker D, Haghikia A, König T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mebazaa A, Hamdan R, Jackson AM, Forster O, Tibazarwa K, Libhaber E, Petrie MC, Bauersachs J. Poor outcomes in poor patients? Lancet 2012;379:2671–2679.

8. Regitz-Zagrosek V, Schaufelberger M, Bauersachs J, del Monte F, Hilfiker-Kleiner D, Karumanchi SA, Tudorache I, Bauersachs J, Mukherjee M, Khankin EV, Burke SD, Thiam A, Guenancia C, Zansonré P. Maternal and fetal prognosis of subsequent pregnancies in patients with peripartum cardiomyopathy: a multicentre randomized study. Int J Gynecol Obstet 2016;138:152–157.

9. Aragno M, Blaja B, Mebazaa A, Lund L, Bauersachs J, Schaufelberger M, Regitz-Zagrosek V, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, Schaufelberger M, 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