Peripartum Cardiomyopathy
Subsequent pregnancy & Long-term outcome

Karen Sliwa, MD, PhD, DTM&H, FESC

Hatter Institute for Cardiovascular Research in Africa
Department of Medicine & Cardiology,
Faculty of Health Sciences,
University of Cape Town, South Africa
A lot is new - update on recent publications

Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM)

EuroObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM

Karen Sliwa1,2,*, Alexandre Mubaza3, Denise Hiflier-Kleiner4, Mark C. Petrie1,4, Aldo P. Maggioni5, Cecile Lerach6, Vera Regitz-Zagrosek4, Maria Schaafelberger8, Luigi Torazzi7, Peter van der Meer11, Julien W. Roos-Hesselink7, Petar Seferovic15, Karin van Spadeenck-Zwarte14, Annam Mbaekwem6, Michael Böhm13, Frederic Mouquet11, Berlert Pieske15, Roger Hall11, Piotr Ponikowski11, and Johann Bauersachs9

European Journal of Heart Failure (2017) 0, 0-0
doi:10.1002/ejhf.808

Outcome of subsequent pregnancies in 34 patients with a history of peripartum cardiomyopathy

Denise Hiflier-Kleiner1, Arash Haghi1, David Masuko2, Justus Nonhoff1, Dominik Held1, Elena Libhaber3, Mark C Petrie4, Niki L. Walker4, Edith Podevski1, Dominik Berliner1, Johann Bauersachs1 and Karen Sliwa2,9

Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study

Denise Hiflier-Kleiner1, Arash Haghi1,*, Dominik Berliner1, Jens Vogel-Clausen3, Johannes Schwab4, Annegret Franke4, Marzio Schwartzkopf5, Philipp Ehlermann1, Roman Pfister7, Guido Michels1, Ralf Westenfeld4, Verena Stang6, Ingrid Kindermann10, Uwe Kühl2, Christiane E. Angermann11, Axel Schlitt11, Dieter Fischer1, Edith Podevski1, Michael Böhm13, Karen Sliwa13, and Johann Bauersachs16

European Journal of Heart Failure (2017) 0, 1–9
doi:10.1093/eurhj/hix355

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

Karen Sliwa1,2,*, Mark C. Petrie1, Denise Hiflier-Kleiner4, Alexandre Mubaza3, Alice Jackson1, Mark R. Johnson9, Peter van der Meer1, Annam Mbaekwem6, and Johann Bauersachs1

European Journal of Heart Failure (2017) 18, 781–792
doi:10.1002/ejhf.1170
Overview

- **Definition and epidemiology**
- Bromocriptine in the management of PPCM
- Subsequent pregnancy and long-term outcome
What is Peripartum Cardiomyopathy?

- Idiopathic form of cardiomyopathy
- Presenting with heart failure towards the end of pregnancy, or in the months following delivery
- No other causes of heart failure are found
- A diagnosis of exclusion
- Left ventricular ejection fraction usually below 45%
PPCM (34%) and complications of RHD (25.3%) were the most important causes of heart failure and maternal death.

<table>
<thead>
<tr>
<th>Factors contributing to maternal death ((&lt;42 \text{ days post partum}))</th>
<th>Whole group</th>
<th>Peripartum cardiomyopathy</th>
<th>Rheumatic heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidable factors</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Patient delay in seeking help</td>
<td>49 (41.5)</td>
<td>16 (39.0)</td>
<td>16 (45.7)</td>
</tr>
<tr>
<td>Lack of expertise by medical staff managing case</td>
<td>35 (29.7)</td>
<td>16 (39.0)</td>
<td>12 (34.3)</td>
</tr>
<tr>
<td>Delay in referral to appropriate level of care</td>
<td>31 (26.3)</td>
<td>13 (31.7)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Delay in appropriate action</td>
<td>43 (36.4)</td>
<td>15 (36.6)</td>
<td>15 (42.9)</td>
</tr>
</tbody>
</table>
Management
Medical treatment of heart failure in peripartum women

**Non Pregnant (cardiomyopathy)**
According to standard heart failure guidelines

**Early Pregnancy**
Diuretics  
Hydralazine  
Beta Blocker

**Late Pregnancy**
Diuretics  
Hydralazine  
Beta Blocker

**Postpartum**
Diuretics  
ACE Inhibitor  
Beta Blocker

Effect on fetus
Clinical update

Peripartum cardiomyopathy: current management and future perspectives

Denise Hilfiker-Kleiner*, Arash Haghikia, Justus Nonhoff, and Johann Bauersachs

Department of Cardiology and Angiology, Medical School Hannover, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

Received 28 October 2014; revised 8 December 2014; accepted 8 January 2015
Bromocriptine in PPCM - clinical studies

An anti-angiogenic cleaved prolactin fragment is considered causal for peripartum cardiomyopathy (PPCM). Experimental and first clinical observations suggested beneficial effects of the prolactin release inhibitor bromocriptine in PPCM.

Sliwa K, Circulation 2010

PPCM Br: 28 to 56% versus PPCM Std: 28-36%, p=0.006
PPCM Bromo: 10 % Mortality
PPCM Standard Care: 40% Mortality

Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study

The treatment of PPCM, should consist of Bromocriptine, Oral heart failure therapies, Anticoagulation, vasoRelaxing agents, and Diuretics. Non-invasive ventilation should be added in patients with pulmonary congestion.
2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by: the International Society of Gender Medicine (IGM), the German Institute of Gender in Medicine (DGeSM), the European Society of Anaesthesiology (ESA), and the European Society of Gynecology (ESG)

Authors/Task Force Members: Yvonne Regitz-Zagrosek* (Chairperson) (Germany), Jolien W. Roos-Hesselink* (Co-Chairperson) (The Netherlands), Johann Bauersachs (Germany), Carina Blomström-Lundqvist (Sweden), Renata Cifkova (Czech Republic), Michele De Bonis (Italy), Bernard Jung (France), Mark Richard Johnson (UK), Ulrich Kintscher (Germany), Peter Kräne (Germany), Irene Marthe Lang (Austria), João Morais (Portugal), Petronella G. Pieper (The Netherlands), Patrizia Presbitero (Italy), Susanna Price (UK), Giuseppe M. C. Rosano (UK/Italy), Ute Seeland (Germany), Tommaso Simoncini2 (Italy), Lorna Swan (UK), Carole A. Warnes (USA)
Figure 6: Management of acute heart failure during/after pregnancy *(modified from Bauersachs et al.)*. Diuretics have to be used with caution due to potential reduction in placental blood flow. ACE-I = angiotensin-converting enzyme inhibitor; AHF = acute heart failure; ARB = angiotensin receptor blocker; ECG = electrocardiogram; HF = heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; MCS = mechanical circulatory support; MR = mineralocorticoid receptor; NIV = non-invasive ventilation; PDA = Peridural analgesia; PPCM = peripartum cardiomyopathy; RR = respiratory rate; SBP = systolic blood pressure.
Selected revised recommendations and selected new recommendations

Comment/comparison with 2011 version

2018

Strengthening mWHO classification of maternal risk.
It is recommended to perform risk assessment in all women with cardiac disease of any age and before conception, using the mWHO classification of maternal risk (IC).

Upgrade in class of recommendation: patients with severe MS should undergo intervention before pregnancy.

In 2011, GAGs were recommended during the second and third trimesters until the 36th week. VKAs are recommended in women needing a low-dose low-dose VKA, warfarin <5 mg/day, phenprocoumon <3 mg/day, or acenocoumarol <2 mg/day) (IC).

Sotalol deleted.
Flucloxacillin or propafenone are recommended for prevention of SVT in patients with WPW syndrome (IC).

Changed in high-risk patients from UFH to LMWH. Dosing based on body weight is introduced.
LMWH is the drug of choice for the prevention, and treatment of VTE in all pregnant patients (IB). It is recommended that the therapeutic dose of LMWH is based on body weight (IC).

Changes: dose adjustment of UFH or LMWH dose within 36 h now recommended.
In pregnant women on LMWH or UFH, it is recommended to perform weekly anti-Xa level monitoring or aPTT monitoring with dose adjustment (within 36 h) (IC).

Upgrade of recommendation: IIb to IIa.
Catheter ablation with electrophysiological systems should be considered in experienced centres in case of drug-refractory and poorly tolerated SVT (IIa).

Change from D-dimers to imaging as the first line of investigation, as D-dimers are unreliable in pregnancy.
If compressive ultrasound is negative, magnetic resonance venography should be considered to diagnose VTE (IIIC).

FDA categories A–X were used for all drugs in 2011.
Declaration-making based on former FDA categories is no longer recommended (IIIC).

Pro-pregnancy surgery is now deleted.
Now also information on Turner syndrome with aortic dissection corrected for BSA.

Prognosis is not recommended in patients with severe dilatation of the aorta (h柜台Germany, thoracic aortic disease such as Marfan syndrome >45 mm, bicuspid aortic valve >50 mm, >27 mm²/m² BSA, or Turner syndrome ASI >25 mm²/m² BSA (IIIC).

Selected new recommendations

Right heart catheterization is recommended to confirm the diagnosis of PAH. This can be performed during pregnancy but with very strict indications (IC).

LMWH in therapeutic dose is recommended in pregnant patients with chronic thrombo-embolic pulmonary hypertension (IC).

In patients with pulmonary embolism, thrombolytic therapy is recommended only in severe hypotension or shock (IC).
In women at high risk for thromboembolism, it is recommended to convert LMWH to UFH at least 36 h prior to delivery and stop the UFH infusion 4–6 h prior to anticipated delivery. aPTT should be normal before regional anaesthesia (IC).
In women low risk for thromboembolism on therapeutic LMWH, induction or caesarean section is recommended to be performed 24 h after the last dose of LMWH (IC).
In women considering pregnancy and requiring heart valve surgery, it is recommended to choose prostheses in consultation with a pregnancy heart team (IC).
It is recommended to manage pregnancy in women with mechanical heart valves in a centre with a pregnancy heart team (IC).
In treatment of valve regurgitation in patients, initiating treatment should be considered (IIb).
In patients with history of aortic dissection, caesarean delivery should be considered (IIb).
Beta-blocker therapy throughout pregnancy should be considered in women with Marfan syndrome and other heritable thoracic aortic diseases (IIa).
Induction of labour should be considered at 40 weeks gestation in all women with cardiac disease (IIa).
In patients with PCI/PVI, trombolysis treatment may be tried for prophylactic and enhance recovery (Ib)
Induction of labour should be considered in patients with vascular Ehlers–Danlos syndrome (IIb).
Breastfeeding is not recommended in mothers who take antiprerenal agents other than low-dose aspirin (from section 3, see section 12) (IIIC).

New concepts
Enforcing mWHO classification of maternal risk.
Introduction of the pregnancy heart team.
More attention for assisted reproductive therapy.
Discussion of the use of bortezomib in PPCM.
Introduction of specific levels of surveillance based on low-medium/high risk for arrhythmias with haemodynamic compromise at delivery.
New information on pharmacokinetics in pregnancy, more detailed information on pharmacodynamics in animal experiments on all drugs (Supplementary Data).
Perinatal caesarean section is discussed.
Advice on contraception and the termination of pregnancy in women with cardiac disease is now provided.

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by: the International Society of Gender Medicine (IGM), the German Institute of Gender in Medicine (DGGfM), the European Society of Anaesthesiology (ESA), and the European Society of Gynecology (ESG)

Authors/Task Force Members: Vera Regina Zignanelli (Chairperson) (Germany), Jochen W. M. Rosen-Huschke (Co-Chairperson) (The Netherlands), Johannes Bauer (Germany), Carina Bloorstra-Linck (Sweden), Renault Gilboa (Czech Republic), Michel De Borger (Italy), Bernard Lang (France), Marit Richard-Christiansen (NO), Ulrich Kiesewetter (Germany), Peter Knottnerus (Germany), Irene Martina Lang (Austria), Jose Moral (Portugal), Penelope G. Paparr (The Netherlands), Patricia Picozzi (Italy), Susana Prieto (UK), Giuseppe M. C. Ripamonti (UK/Italy), Ute Seidel (Germany), Tore F. Spronk (UK/Latvia), Bente Svendsen (UK), Coraly A. Winters (USA)
Overview

- Definition and epidemiology
- Bromocriptine in the management of PPCM
- Subsequent pregnancy and long-term outcome
Outcome of subsequent pregnancies in 34 patients with a history of peripartum cardiomyopathy

Denise Hilfiker-Kleiner, Arash Haghikia, David Masuko, Justus Nonhoff, David Masuko, Justus Nonhoff, Dominik Held, Elena Libhaber, Mark C Petrie, Niki L. Walker, Edith Podewski, Dominik Berliner, Johann Bauersachs and Karen Sliwa

Aims

- Subsequent pregnancies (SSPs) in patients with peripartum cardiomyopathy (PPCM) have a high risk of heart failure relapse.
- We report on outcome of SSPs in 34 PPCM patients in Germany, Scotland, and South Africa.
Results

- From the 34 PPCM patients with a SSP, pregnancy ended prematurely in 4 patients.

- Overall relapse rate (LVEF <50%, or death after at least 6 months’ follow-up) was 56%, with 12% (4/34) mortality.

- Relapse of PPCM after SSP was not associated with differences in para, twin pregnancy, gestational hypertension or smoking.

- Persistently reduced LVEF (<50%) before entering SSP was present in 47% of patients, while full recovery (LVEF ≥50%) was present in 53%. Persistently reduced LVEF before SSP was associated with a higher mortality (25% vs. 0%) and a lower rate of full recovery at follow-up.
Time-course of left ventricular ejection fraction (LVEF), before SSP, early after SSP delivery and at SSP follow-up (>6 months) treated with standard care and bromocriptine

(a) Time-course of individual LVEF in patients treated with STHF + bromocriptine (BR) immediately after delivery of SSP (n = 21).

(b) Time course of individual LVEF in patients treated with standard therapy of heart failure (STHF) alone after delivery of SSP (n=9); * patients who died after delivery and during follow up of SSP.
Conclusion

- Full recovery of LVEF before SSP was associated with lower mortality and better cardiac function at follow-up.
- Addition of bromocriptine to standard therapy for heart failure immediately after delivery was safe and seemed to be associated with a better outcome of SSP in African and Caucasian patients.
This position paper: summarizes current evidence for long-term outcome, risk stratification of further pregnancies and overall management. Based on the best available evidence, as well as the clinical experience of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy members, a consensus on pre- and postpartum management algorithms for women undergoing a subsequent pregnancy is presented.
Table 2. Studies of peripartum cardiomyopathy patients undergoing a subsequent pregnancy

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>No.</th>
<th>Pregnancies*</th>
<th>Post index pregnancy LV function</th>
<th>Persistent LVSD post subsequent pregnancy** n (%)</th>
<th>Maternal death</th>
<th>Number of deaths in unrecovered LV function (% of total deaths)</th>
<th>Miscarriage/fetal death n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutton</td>
<td>1991</td>
<td>4</td>
<td>4</td>
<td>4 (100)</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Witlin</td>
<td>1997</td>
<td>6</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>1 (17)</td>
<td>1 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Albanesi Filho</td>
<td>1999</td>
<td>12</td>
<td>16</td>
<td>6 (50)</td>
<td>6 (50)</td>
<td>NA</td>
<td>1 (8)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>de Souza</td>
<td>2001</td>
<td>7</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>7 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elkayam</td>
<td>2001</td>
<td>44</td>
<td>35</td>
<td>28 (64)</td>
<td>16 (36)</td>
<td>9 (20)</td>
<td>3 (7)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Avila</td>
<td>2002</td>
<td>18</td>
<td>19</td>
<td>7 (39)</td>
<td>11 (61)</td>
<td>4 (44)^</td>
<td>1 (6)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Sharieff</td>
<td>2003</td>
<td>9</td>
<td>NA</td>
<td>2 (22)</td>
<td>7 (78)</td>
<td>5 (56)</td>
<td>2 (22)</td>
<td>NA</td>
</tr>
<tr>
<td>Sliwa</td>
<td>2004</td>
<td>6</td>
<td>6</td>
<td>2 (33)</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>2 (33)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Chapa</td>
<td>2005</td>
<td>6</td>
<td>8</td>
<td>4 (67)</td>
<td>2 (33)</td>
<td>5 (83)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Fett</td>
<td>2006</td>
<td>15</td>
<td>16</td>
<td>1 (7)</td>
<td>14 (93)</td>
<td>7 (47)</td>
<td>1 (7)</td>
<td>NA</td>
</tr>
<tr>
<td>Mishra</td>
<td>2006</td>
<td>9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5 (56)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hilfiker-Kleiner</td>
<td>2007</td>
<td>12</td>
<td>12</td>
<td>12 (100)</td>
<td>0</td>
<td>6 (50)</td>
<td>3 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Habli</td>
<td>2008</td>
<td>37</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Modich</td>
<td>2009</td>
<td>NA</td>
<td>15</td>
<td>4 (27)</td>
<td>11 (73)</td>
<td>NA</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Chee</td>
<td>2009</td>
<td>2</td>
<td>1</td>
<td>2 (100)</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Fett</td>
<td>2010</td>
<td>56</td>
<td>61</td>
<td>29 (52)</td>
<td>27 (48)</td>
<td>9 (15)^^^</td>
<td>1 (2)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Mandal</td>
<td>2011</td>
<td>6</td>
<td>6</td>
<td>5 (83)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Hilfiker-Kleiner</td>
<td>2017</td>
<td>34</td>
<td>31</td>
<td>18 (53)</td>
<td>16 (47)</td>
<td>17 (53)^***</td>
<td>4 (12)</td>
<td>4 (100)</td>
</tr>
</tbody>
</table>

LV, left ventricular; LVSD, left ventricular systolic dysfunction; NA, not available.

*Number without therapeutic abortion; †At last follow-up; $n =$9 with follow-up data; §Denominator is number of pregnancies; #n =32 with follow-up data.;
*Fractional shortening 30% used as cut-off; bUnknown cut-off; cEjection fraction 50% used as cut-off; dEjection fraction 40% used as cut-off.; eEjection fraction 55% used as cut off; fEjection fraction 45% used as cut-off.
Figure 1: Management of women with PPCM and a subsequent pregnancy

**PPCM with partially or fully recovered LV function (EF>50%)**
- Substantial risk of relapse with subsequent pregnancy
- Risk of heart failure or death (<10%)
- Usually good fetal outcome

**PPCM with poorly recovered LV function (EF<50%)**
- High risk of relapse with subsequent pregnancy
- Risk of heart failure or death (>10%)
- Risk of premature delivery
- Risk of fetal death

**General Maternal Health Factors**
- Age < 18 or Age > 35
- Poor maternal education
- Low household income
- Long distance to appropriate care
- Late presentation (> 20 weeks)

**Specific management**
- Pregnancy can continue but some risks remain
  - monthly echocardiograms
  - NT-ProBNP monitoring pre- and postpartum
  - Bromocriptine: consider post partum
  - Admission to ICU if in decompensated heart failure

**General Management**
- Referral to experienced centre
- Careful counselling of risk
- Close monitoring by cardiac-obstetric-anaesthetic team
- Careful post partum care
- Contraception advice post partum
Adequate post diagnosis counselling, including future pregnancies and prognosis
- Counselling and education of families
- Prescription of formula milk provided if women is not breastfeeding
- Adequate dose of heart failure medication
- Contraceptive advice provided
- Referral to appropriate centre if unable to come back to expert centre
- Referred to social worker if unable to work/low income circumstances

Figure 2: Post-discharge check box for women diagnosed with peripartum cardiomyopathy.
Figure 3: Sketch illustrating different types of contraceptives.

**Contraception (Female)**
- **Intrauterine contraceptive device** (e.g. Mirena or copper IUCDs)
- Oral contraceptive (combined or progestin only pills)
- Depomedroxyprogesterone acetate (DMPA) injections
- Tubal ligation
- Diaphragm
- Contraceptive implants
- Contraceptive patch
- Hysteroscopic tubal occlusion (HTO)
- Vaginal ring
- Safe period

**Contraception (Male)**
- Condom
- Vasectomy
Overall Summary & Conclusions

- PPCM is a global disease.
- PPCM remains a difficult condition to both diagnose and treat.
- PPCM symptoms mimic typical symptoms of pregnancy/early postpartum period. High index of suspicion warranted.
- There is a need to dissect impact of biomolecular factors versus socio-demographic factors.
- Treatment with standard medication and bromocriptine is currently being investigated in larger trials and registries.
- Need to identify biomarkers for facilitating early diagnosis and predicting outcome.
- Long-term prognosis is not well established.
- More awareness for the disease is important!
Thank you!