Peripartum Cardiomyopathy

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Case

- Had an uncomplicated C-section at 33 weeks B/O preeclampsia.
- Patient readmitted to the hospital 3 days after D/C (6 days PP) for abdominal pain and had a surgical evacuation of abdominal wall hematoma.
- D/C home in “stable condition” although HR at 115-120 bpm (attributed to anemia) and ECG demonstrated deeply inverted T-waves.
Case

- 4 days post discharged (2 weeks PP) patient was found without vital signs at home and was pronounced dead.

- Autopsy showed enlarged heart with bi ventricular dilation with normal wall thickness and normal coronaries.
Traditional Definition

- Development of HF in the last month of pregnancy or within 5 months of delivery
- Absence of identifiable cause for HF
- Absence of recognizable heart disease prior to the last month of pregnancy
- Left ventricular systolic dysfunction demonstrated by echocardiography

Peripartum Cardiomyopathy
Updated Definition

- PPCM is an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found.

- It is a diagnosis of exclusion.
Table 1. Distribution of Cases, Birth Prevalence, and Case-Fatality by Race, Ethnicity, and Age

<table>
<thead>
<tr>
<th>Race and Ethnicity</th>
<th>Distribution of All Cases</th>
<th>Cases Per Live Birth</th>
<th>Prevalence, Cases Per 10,000 Live Births (95% CI)</th>
<th>No. of Deaths (Fatality Rate Per 100 Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>85 (100)</td>
<td>1/2,772</td>
<td>3.61 (2.88–4.46)</td>
<td>14 (16.5)</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>33 (38.9)</td>
<td>1/4,266</td>
<td>2.34 (1.61–3.29)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>50 (58.9)</td>
<td>1/1,087</td>
<td>9.20 (6.83–12.12)</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (1.1)</td>
<td>1/31,140</td>
<td>0.32 (0–1.79)*</td>
<td>0</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>1 (1.1)</td>
<td>1/5,954</td>
<td>1.68 (0.04–9.35)*</td>
<td>0</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 18</td>
<td>2 (2.3)</td>
<td>1/4,763</td>
<td>2.10 (0.25–7.58)*</td>
<td>0</td>
</tr>
<tr>
<td>18–24</td>
<td>23 (27.1)</td>
<td>1/3,563</td>
<td>2.81 (1.78–4.21)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>25–29</td>
<td>16 (18.8)</td>
<td>1/3,904</td>
<td>2.56 (1.46–4.16)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>30–34</td>
<td>17 (20.0)</td>
<td>1/3,188</td>
<td>3.14 (1.82–5.02)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>35–39</td>
<td>23 (27.1)</td>
<td>1/997</td>
<td>10.03 (6.36–15.04)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Older than 39</td>
<td>4 (4.7)</td>
<td>1/1,134</td>
<td>8.82 (2.40–22.56)</td>
<td>1 (25.0)</td>
</tr>
</tbody>
</table>

Cl, confidence interval. Data are n (%) unless otherwise specified.
* These estimates are unstable because of small numbers.

<table>
<thead>
<tr>
<th>Pregnancy-Related Complications</th>
<th>All (N=79)*</th>
<th>Survivors (n=71)</th>
<th>Decedents (n=8)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hypertension</td>
<td>10 (12.7)</td>
<td>9 (12.7)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>18 (22.8)</td>
<td>15 (21.1)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>11 (13.9)</td>
<td>9 (12.7)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>1 (1.3)</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>1 (1.3)</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Preeclampsia superimposed on chronic hypertension</td>
<td>10 (12.7)</td>
<td>8 (11.3)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>7 (8.9)</td>
<td>7 (9.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pregestational diabetes</td>
<td>5 (6.3)</td>
<td>5 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Multifetal gestation</td>
<td>7 (8.9)</td>
<td>5 (7.0)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Ejection fraction at time of diagnosis</td>
<td>0.28 (0.08-0.50)‡</td>
<td>0.30 (0.08-0.50)§</td>
<td>0.18 (0.10-0.20)¶</td>
</tr>
</tbody>
</table>

**Multifetal gestation** 9%
Peripartum Cardiomyopathy

Associated conditions in the US

- Maternal age > 30 yrs.
- Black.
- Twin pregnancies.
- History of HTN / Preeclampsia.
- Multiparity.
Preeclampsia and PPCM
An e-mail from a patient

“My OB was concerned with my high BP and swelling but his only thought was preeclampsia. He did tests to rule it out but didn't rule out issues with my heart or asked me if I had difficulty breathing while laying down”.

“When a patient is experiencing high BP and edema PPCM needs to come to their minds just as preeclampsia does. The doctors need to be more educated so they can educate their patients on signs and symptoms of PPCM”.
Cardiac Angiogenic Imbalance Leads to PPCM
Patten IS et al, Nature 2012

Sup Figure 8

Harvard teaching hospitals last 9 years
## PPCM or Preeclampsia?

### Left Ventricular Structure and Function in Preeclampsia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia</th>
<th>Normotensive pregnant</th>
<th>Normotensive non pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>40</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>LA Dimension (mm)</td>
<td>36±3</td>
<td>35±3</td>
<td>31±2</td>
</tr>
<tr>
<td>LVED Volume (ml)</td>
<td>115±17</td>
<td>103±12</td>
<td>103±20</td>
</tr>
<tr>
<td>LVES Volume (ml)</td>
<td>39±10</td>
<td>33±8</td>
<td>30±10</td>
</tr>
<tr>
<td>LVEF(%)</td>
<td>66±6</td>
<td>68±5</td>
<td>71±5</td>
</tr>
</tbody>
</table>

PPCM or Preeclampsia?

- Preeclampsia presenting with heart failure – Think PPCM.

- Order an echocardiogram to assess LV function and BNP.
Delayed diagnosis is common
(Goland, Elkayam, J cardiac Failure 2009)

- ≥ 1 week delay in diagnosis after onset of symptoms reported in 60% of 182 cases.
- Complications preceded the diagnosis of PPCM in 50% of pts.
- 32% of surviving patients without cardiac transplantation, had residual brain damage.
periartum Cardiomyopathy

Clinical Presentation

- CHF signs and symptoms.
- Arrhythmias (with or without CHF).
- Thromboembolism.
Outcome of PPCM in the US

182 Patients

- Recovery EF $\geq 50\%$ (at last f/u): 49%
- Persistent LV dysfxn (at last f/u): 41%
- Cardiac Transplantation: 6%
- Death: 7%

Goland et al. J cardiac Fail 2009;15:645
Outcome of PPCM in the US
Goland, Elkayam et al J Cardiac Failure 2009;15:645

182 Patients

Recovery
EF ≥ 50%
(at last f/u)
49%

Persistent
LV dysfxn
(at last f/u)
41%

Cardiac Transplantation
6%

Death
7%

IPAC Study
100 patients
LV recovery (>50%) 68%
Mortality 3%
LVAD 3%
Transplantation 1%
Baseline LVEF a strong predictor of LV Recovery in PPCM


Fig. 2. Failure to achieve left ventricular ejection fraction (LVEF) of 50% and 30% at ≥6 month in different groups according to baseline LVEF: group I: 10%−19%; group II: 20%−29%; and group III: 30%−45%.
PPCM
Breast feeding

- “On the basis of the postulated negative effect of prolactin sub fragment, breast feeding is not advised in women with PPCM” (Sliwa 2010, ESC working group on PPCM)
- Higher degree of recovery of LV function in women who breast fed (Safirstein 2011).
- Most HF medications categorized as compatible with breast feeding by AAP.
Relations Between LVEF and Major Complications

Goland, Elkayam. J Cardiac Failure 2009

In the IPAC study 4/5 pts with MAE had EF < 30%

LVEF ≤ 25% HR = 4.2, CI: 2.04-8.64.
Peripartum Cardiomyopathy
Therapeutic considerations during pregnancy

Safe Drugs:
- Digoxin
- Nitrates
- Hydralazine
- Heparin
- Diuretics
- Metoprolol tartrate

Unsafe Drugs:
- ACE-I
- Nitroprusside
- Amiodarone
- Warfarin
- No information
- Spironolactone
- Carvedilol
- Metoprolol succinate
Peripartum Cardiomyopathy
Therapeutic considerations post partum

- ACE-I, beta blockers, aldosterone receptor antagonists.
- Anti coagulation until LV improves.
- Temporary mechanical support (IABP, LVAD) may be useful as bridge to recovery.
- Wearable or defibrillator in high risk patients (LVEF < 30%).
Wearable defibrillator
LV Thrombus in PPCM
Meyer GP J Med Case Rep 2010;4:80

35 YO African woman. 4 weeks after C section. class IV. LVEF 9%.

Figure 1 Four-chamber view on initial echocardiogram demonstrates a large thrombus (arrow) attached to the lateral wall of the left ventricle (LV) at baseline (A), which has completely resolved after two months (B).
32 YO F diagnosed 10 d after C section, LVEF @ 20%. 1 mo later echo showed new LV apical mural thrombus 35x20 mm, coagulation studies negative. Started on warfarin. 1 week later thrombus became mobile (fig 1) and was removed by emergency surgery. 3 d later 3 new LV thrombi (fig 2) treated successfully with AC, D/C with EF 33%, 2 y later NYHA I, EF 63%

Mobil LV thrombus 6 weeks after C section, EF 20%

Fig 1. A long axis view of a perioperative transthoracic echocardiogram. Note the mobile mass at the apex (white arrow).

Fig 2. A short axis view of a postoperative transthoracic echocardiogram taken on postoperative day 3. Three mural thrombi were prominent (white arrows), which were neither present during intraoperative observation nor visible in an intraoperative transesophageal echocardiogram.

Shimamoto T. Circ J 2008;72:853
Embolus to the LCX artery

Fig. 1 An embolus is present in the left circumflex artery (large arrow) and the distal left anterior descending coronary.
18 YO G1 developed tachycardia and hypertension with severe hypoxemia (PO2 30%) and acidosis during C section which was not corrected with Inotropic support and 100% oxygen. LVEF 18%. ECMO was use successfully for 24 h, Pt. extubated on day 4 and was D/C home on day 12 with LVEDD of 42 from 52 mm and LVEF of 56%.

Severe hypoxemia and acidosis during C section, LVEDD 52 mm, EF 18%

Fig 1. Severe pulmonary edema was shown in the chest x-ray taken at admission.

1 month after D/C
LVEDD 42 mm, EF 56%

Fig 2. Chest x-ray taken during an outpatient visit (1 month after discharge).
PPCM

New Concepts in Pathophysiology and Management
The Oxidative Stress Hypothesis: Rational for the use of Bromocriptine for the treatment of PPCM

A Cathepsin D-Cleaved 16 kDa Form of Prolactin Mediates Postpartum Cardiomyopathy

Denise Hilfiker-Kleiner,¹,* Karol Kaminski,¹ Edith Podewski,¹ Tomasz Bonda,¹ Arnd Schaefer,¹ Karen Sliwa,³
Olaf Forster,³ Anja Quint,¹ Ulf Landmesser,¹ Carola Doerrjes,¹ Maren Luchtefeld,¹ Valeria Poli,⁴
Michael D. Schneider,⁶ Jean-Luc Balligand,⁶ Fanny Desjardins,⁶ Aftab Ansari,⁷ Ingrid Struman,⁸
Ngoc Q.N. Nguyen,⁸ Nils H. Zschemisch,¹ Gunnar Klein,¹ Gerd Heusch,⁹ Rainer Schulz,⁹
Andres Hilfiker,¹,² and Helmut Drexler¹

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*Correspondence: hilfiker.denise@mh-hannover.de
DOI 10.1016/j.cell.2006.12.036
Pregnancy, mostly because of the mitochondria-rich placenta, is a condition that favors oxidative stress.

STAT3 (Signal Transducers and Activators of Transcription 3) is involved in cardiac protection from oxidative stress, by up regulation of antioxygenative enzymes (manganese superoxide dismutase - MnSOD). Megoro, Circ 2001
In addition STAT3 plays an important roll in promoting myocardial angiogenesis. 
Hilfiker, Circ Res 2004

Female mice with cardiomyocyte-specific knockout of STAT3 developed PPCM. 
Hilfiker, Cell 2007
In the absence of STAT3, oxidative stress enhances the expression of cardiac cathepsin D (A protease) which cleaves the nursing hormone Prolactin to a 16 kDa form.

Corbacho, J Endocrinol 2002
Bromocriptine in the treatment of PPCM

- 16 kDa Prolactin causes apoptosis, capillary dissociation, vasoconstriction and impaired myocyte metabolism which lead to myocardial dysfunction.

- Treatment with bromocriptine, an inhibitor of prolactin, prevents the development of PPCM.
  Hilfiker, Cell 2007
Luck of STAT3 (Signal Transducers and Activators of Transcription) results in decreased Mn SOD

↑Superoxide production → Cardiac cathepsin D expression

Generates cleaved form of PROLACTIN (16 kDa)

Anti-angiogenic
Pro-apoptotic

Endothelial cell apoptosis, capillary dissociation, Vasoconstriction.

Impaired microcirculation and myocardial dysfunction
A Cathepsin D-Cleaved 16 kDa Prolactin Mediates PPCM
Hilfiker-kliner d et al Cell 2007;128:589
Survival in Relation to Number of Pregnancies

Hilfiker-kliner d et al Cell 2007;128:589
Effect of Bromocriptine for 3 month post delivery

Hilfiker-kleiner D et al Cell 2007;128:589

Cardiac dimensions and function in patients with subsequent pregnancies with (n=6) or without (n=6) BR treatment

<table>
<thead>
<tr>
<th></th>
<th>Peripartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UT group</td>
<td>BR group</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>6.2±0.6</td>
<td>5.5±0.5</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>4.8±5</td>
<td>4.2±0.7</td>
</tr>
<tr>
<td>EF (%)</td>
<td>45±7</td>
<td>40±14</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.4±0.5</td>
<td>1.8±0.9</td>
</tr>
</tbody>
</table>

Mortality: STD Tx 3/6, BR 0/6
Bromocriptine in The Treatment of PPCM

Sliwa K et al Circulation 2010;121:1465
Bromocriptine in The Treatment of PPCM

Sliwa K et al Circulation 2010;121:1465

![Bar chart showing comparison between PPCM-Std and PPCM-Br](chart.png)

- **Death**: PPCM-Std 40%, PPCM-Br 10%
- **NYHA FC III/IV**: PPCM-Std 50%, PPCM-Br 0%
- **EF <35%**: PPCM-Std 33%, PPCM-Br 0%
- **Combined endpoint**: PPCM-Std 80%, PPCM-Br 10%

*P = 0.006*
### Table 4. Comparison of NYHA Functional Class in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

<table>
<thead>
<tr>
<th>NYHA functional class</th>
<th>PPCM-Br at Baseline (n=10), n (%)</th>
<th>PPCM-Br at 6 mo (n=9), n (%)</th>
<th>PPCM-Std at Baseline (n=10), n (%)</th>
<th>PPCM-Std at 6 mo (n=6), n (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>9 (100)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 (50)</td>
<td>5 (50)</td>
<td>3 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>5 (50)</td>
<td>5 (50)</td>
<td>3 (50)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Comparing the change from baseline to 6 months in PPCM-Br and PPCM-Std patients.

Sliwa K et al. Circulation 2010;121:1465
Bromocriptine in The Treatment of PPCM - A Proof of Concept?
Elkayam U, Goland S, Circulation 2010;121:1463

- Small study.
- Very high mortality rate in controls.
- No LV recovery in any of the controls.
- Data may not be applicable to non-African patients.
- Safety? (Seizures, stroke, AMI)
German cohort of patients with PPCM
Haghikia a et al 2012

Figure 3

<table>
<thead>
<tr>
<th></th>
<th>IMP</th>
<th>NIMP</th>
<th>LVAD</th>
<th>HTX</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR-Therapy, n=50</td>
<td>46</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>No BR-Therapy, n=24</td>
<td>16</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

N=50
N=24

IMP – Improved
NIMP - Not improved
Summary

- PPCM may be associated with an imbalance between enhanced oxidative stress and blunted induction of antioxidant enzymes, leading to detrimental conversion of prolactin to its anti-angiogenic derivative 16 kDa.

- Inhibition of prolactin release with bromocriptin may be effective in some patients.
Summary

The efficacy and safety of bromocriptine for the treatment of PPCM needs to be evaluated in a prospective study before it can become standard therapy.