Bromocriptine for the treatment of PPCM
A multicenter, randomized study

Results and Implication

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PPCM is defined as a cardiomyopathy that develops in the last month of pregnancy or within 6 months post-partum in absence of recognizable heart disease prior the last month of pregnancy.

The key diagnostic criteria is an LV systolic dysfunction with an EF <45% or FS <30%.

USA and Western Europa: 1: 1.400 to 1:3.500
Africa: 1: 100 to 1:1.000
Haiti: 1: 300

Variety in cardiac phenotypes in PPCM patients suggest different pathomechanisms initiating and driving the disease

ECG abnormalities

Inflammation

PPCM with transient borderline non-compaction phenotype

Dilatation with ventricular thrombus

Hilfiker-Kleiner et al. YBOOG 2013

Haghikia et al. BRC 2013
An estimated 16% of peripartum heart failure may be due to preexisting genetic cardiomyopathy unmasked by pregnancy stress.

Non-genetic modifications in PPCM: Reduced STAT3 protein is present in cardiac tissue of some PPCM patients.

Posttranscriptional and translational mechanisms are likely to reduce STAT3 in hearts from PPCM patients

Hyperosmolar stress is reducing STAT3 protein (Lornejad-Schafer, M et al. FEBS Lett 2005)

Also in cardiomyocytes

Delivery itself, in particular when associated with substantial bleeding, produces hypovolemic and therefore hyperosmolar conditions.

An ethnic tradition in Nigeria is to treat postpartum women with a high-salt diet, which is likely to generate hyperosmolarity. These women have the highest incidence of PPCM (1:100) (Fillmore, SJ et al. Circulation 1977)

Additional mechanisms may involve previous anthracycline treatment that decreases cardiomyocyte STAT3 (Hoch et al. Cell Stem Cell 2011). Previous chemotherapy is a risk factor for PPCM (Haghikia, A et al. BRIC 2014)

Mice with a cardiomyocyte-specific knockout of STAT3 (CKO) develop PPCM

Blocking prolactin release by Bromocriptine attenuates PPCM in CKO mice as well as in additional mouse models

Ricke-Hoch et al. CVR 2014
Different etiologies initiate PPCM and merge in a common pathway: Increased oxidative stress promotes the generation of an antiangiogenic 16 kDa prolactin fragment which together with additional anti-angiogenic factors, (sFlt-1) and reduced expression of pro-angiogenic factors (VEGF) induces and drives PPCM.

Genetic involvement: TTN, MYH7, SCN5A, PAI-1

Modified from Hilfiker-Kleiner D and Sliwa K. Nature Reviews in Cardiology 2014
First pilot trial shows lower mortality and better cardiac function in PPCM patients obtaining Bromocriptine on top of standard therapy for heart failure.

<table>
<thead>
<tr>
<th></th>
<th>PPCM Bromo Baseline*</th>
<th>PPCM Bromo 6 months*</th>
<th>PPCM Std Baseline*</th>
<th>PPCM Std 6 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF, %</td>
<td>28 ± 9</td>
<td>58 ± 11</td>
<td>28 ± 9</td>
<td>26 ± 11</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mitral ERO, cm²</td>
<td>0.45 ± 0.13</td>
<td>0.11 ± 0.03</td>
<td>0.44 ± 0.18</td>
<td>0.34 ± 0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>TDI E’ medial, m/sec</td>
<td>7.0 ± 1.3</td>
<td>12.4 ± 2.4</td>
<td>6.5 ± 1.1</td>
<td>7.3 ± 2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>TDI E’ lateral, m/sec</td>
<td>7.2 ± 1.1</td>
<td>12.4 ± 2.5</td>
<td>6.6 ± 1.0</td>
<td>7.3 ± 2.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Value = mean ± 1 SD

PPCM Bromocriptine, n=10: Mortality 10%
PPCM Standard therapy, n=10: Mortality 40%
CONCLUSION:
The first validated, population-based European estimate of PPCM incidence is 1 in 10 149 deliveries, which places Denmark between American and Japanese estimates. Clinical outcome in the cohort was similar to those reported in recent cohorts. Women with concomitant hypertensive disorder of pregnancy had a milder course of PPCM. Baseline LVEF predicted LVEF 10-14 months after diagnosis and cabergoline predicted complete recovery.
A randomized multicenter trial compares prolonged Bromocriptine treatment versus short-term treatment sufficient to stop lactation in addition to guideline-based heart failure therapy with regard to functional improvement and clinical outcome in patients with PPCM.

ClinicalTrials.gov, study number: NCT00998556
140 Patients were assessed for eligibility in 12 study centers

77 Were ineligible or declined to participate
   31 Had a LVEF > 35 %
   12 Did not give consent
   6 Were already on bromocriptin
   17 Had miscellaneous reasons

63 Underwent randomization

32 Were assigned to 1W Bromocriptine
   3 Withdrew consent
   1 Was lost to follow-up
   1 Did not undergo valid randomization
   1 Was not treated according to protocol §

31 Were assigned to 8W Bromocriptine

3 Withdrew consent
1 Was lost to follow-up
1 Did not undergo valid randomization
1 Was not treated according to protocol §

Baseline clinical characteristics were similar between 1W and 8W groups

26 Completed the study*

31 Completed the study#
The primary endpoint “delta LVEF“, as assessed by CMR from baseline to 6 months follow-up, was not different between the 1W and 8W Bromocriptine groups.
The 8 weeks Bromocriptine treatment was associated with higher number of patients displaying full recovery after 6 months follow-up compared to the 1 week treatment.

- LVEF $\geq 50\%$
- LVEF $35\% - 50\%$
- LVEF $<35\%$, premat.
- terminated the trial or had missing data

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>All Patients</th>
<th>1W Bromocriptine</th>
<th>8W Bromocriptine</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF $\geq 50%$</td>
<td>60%</td>
<td>50%</td>
<td>70%</td>
</tr>
<tr>
<td>LVEF $35% - 50%$</td>
<td>20%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>LVEF $&lt;35%$, premat.</td>
<td>5%</td>
<td>20%</td>
<td>5%</td>
</tr>
</tbody>
</table>
After 6 months no patient needed a HTX or LVAD or died, overall recovery rate was 92% and only 8% of patients remained in severe heart failure and after 12 months 98% had recovered.

The number 1 to 5 mark time course of the five patients who did not recover LVEF >35% after 6 months.
After ≥12 months patient number 1, 3 and 4 displayed a LVEF≥50% and patient 2 a LVEF=47%.
Only one patient, number 5, remained in severe heart failure with an LVEF=15%.
The treatment with Bromocriptine, 1W or 8W, was associated with a better outcome with regard to morbidity, mortality and complete functional recovery compared to most previously published studies.

Clinical Outcomes for Peripartum Cardiomyopathy in North America: Results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). McNamara DM et al. JACC 2015
Among 100 PPCM patients full recovery rate was 72%, mortality, HTX or LVAD rate was 6%

LVEF at presentation was 27%, at 6 months 50% fully recovered, mortality and HTX: 16%

Among 24 patients 45.8% recovered completely while mortality rate was 25%.

Left ventricular function improved in 42.9% of PPCM patients, mortality rate: 11.6%

Full recovery in 66.7% of patients with PPCM, mortality rate was 8.3%.

Sliwa et al. Lancet 2006
In earlier studies full recovery rate was around 30% and mortality rates were between 9% and 15%
Comparison of subgroups with baseline LVEF<30% between the present Bromocriptine study and the IPAC registry support a benefit of Bromocriptine treatment in severe PPCM.

Comparing only patients with baseline LVEF<30%
Bromocriptine for the treatment of peripartum cardiomyopathy: welcome on BOARD

Mattia Arrigo¹, Alice Blet², and Alexandre Mebazaa²,³*
While the bromocriptine trial suggests that 7 days low dose bromocriptine is sufficient for beneficial effects in PPCM, our own clinical experience suggests that critically ill patients may profit from prolonged additional of bromocriptine
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Genes affected: TTN, MYH7 and SCN5

**Titin (TTN):** 17 truncating variants also found in DCM

**β-myosin heavy chain (MYH7):** 3 missence variants associated with HCM

**sodium voltage-gated channel 5 (SCN5):** 7 missence variants associated with long-QT syndrome