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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Circulation 2010, 121:1465-1473: originally published online March 22, 2010
doi: 10.1161/CIRCULATIONAHA.109.901496
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy

A Proof-of-Concept Pilot Study

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Background—Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease that occurs in previously healthy women. We identified prolactin, mainly its 16-kDa angiostatic and proapoptotic form, as a key factor in PPCM pathophysiology. Previous reports suggest that bromocriptine may have beneficial effects in women with acute onset of PPCM.

Methods and Results—A prospective, single-center, randomized, open-label, proof-of-concept pilot study of women with newly diagnosed PPCM receiving standard care (PPCM-Std; n=10) versus standard care plus bromocriptine for 8 weeks (PPCM-Br, n=10) was conducted. Because mothers receiving bromocriptine could not breast-feed, the 6-month outcome of their children (n=21) was studied as a secondary end point. Blinded clinical, hemodynamic, and echocardiographic assessments were performed at baseline and 6 months after diagnosis. Cardiac magnetic resonance imaging was performed 4 to 6 weeks after diagnosis in PPCM-Br patients. There were no significant differences in baseline characteristics, including serum 16-kDa prolactin levels and cathepsin D activity, between the 2 study groups. PPCM-Br patients displayed greater recovery of left ventricular ejection fraction (27% to 58%; $P=0.012$) compared with PPCM-Std patients (27% to 36%) at 6 months. One patient in the PPCM-Br group died compared with 4 patients in the PPCM-Std group. Significantly fewer PPCM-Br patients (n=1, 10%) experienced the composite end point of poor outcome defined as death, New York Heart Association functional class III/IV, or left ventricular ejection fraction <35% at 6 months compared with the PPCM-Std patients (n=8, 80%; $P=0.006$). Cardiac magnetic resonance imaging revealed no intracavitary thrombi. Infants of mothers in both groups showed normal growth and survival.

Conclusions—In this trial, the addition of bromocriptine to standard heart failure therapy appeared to improve left ventricular ejection fraction and a composite clinical outcome in women with acute severe PPCM, although the number of patients studied was small and the results cannot be considered definitive. Larger-scale multicenter and blinded studies are in progress to test this strategy more robustly. (***Circulation.*** **2010;121:1465-1473.)**

Key Words: cardiomyopathy ■ heart failure ■ hormones ■ parturition ■ pregnancy

Peripartum cardiomyopathy (PPCM) is characterized by new onset of heart failure between 1 month before and 5 months after delivery in previously healthy women.[1] The clinical presentation and management of PPCM and its outcome have been reviewed recently.[1,2] Only 23% to 54% of patients show recovery of cardiac function within 6 months.[3–6] Investigation of a large cohort of PPCM patients demonstrated that this condition is associated with a proinflammatory response, as evidenced by elevated plasma levels of tumor necrosis factor-α, Fas-Apo-1, interleukin-6, and C-reactive protein (CRP).[5,7,8]

Editorial see p 1463
Clinical Perspective on p 1473

We recently reported that enhanced oxidative stress in a mouse model for PPCM (mice with a cardiac-specific deletion for signal transducer and activator of transcription-3) triggers the activation of cathepsin D, a ubiquitous lysosomal

Received August 13, 2009; accepted January 11, 2010.

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This study is a proof-of-concept study and was initiated before the new Declaration of Helsinki 2008 was published. Therefore, it has not been registered as a clinical trial on a publicly accessible Web site.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.109.901496**

Table 1. Baseline Characteristics, Treatment, and 6-Month Results for 20 PPCM Patients

Patient	Group	Age, y	Parity, n	Symptom Onset Postpartum, d	Carvedilol Dose, mg BID	Enalapril Dose, mg/d	Furosemide Dose, mg/d	Aldactone Dose, mg/d
1	PPCM-Std	23	2	25	6.25	10	80	25
4	PPCM-Std	21	2	18	12.5	10	80	25
5	PPCM-Std	22	1	20	6.25	5	80	25
9	PPCM-Std	46	3	21	12.5	10	120	50
10	PPCM-Std	24	2	26	25	10	80	25
12	PPCM-Std	21	1	26	6.25	5	80	0
13	PPCM-Std	24	1	22	25	10	80	25
16	PPCM-Std	44	6	28	12.5	5	80	0
17	PPCM-Std	18	1	12	6.25	5	80	0
20	PPCM-Std	38	3	7	12.5	10	80	25
2	PPCM-Br	22	2	8	6.25	5	80	25
3	PPCM-Br	38	3	14	6.25	5	80	12.5
6	PPCM-Br	24	1	26	12.5	5	80	25
7	PPCM-Br	22	2	7	6.25	5	80	25
8	PPCM-Br	18	2	24	6.25	5	80	25
11	PPCM-Br	24	2	7	6.25	10	120	25
14	PPCM-Br	23	1	4	25	5	80	50
15	PPCM-Br	28	1	30	25	5	80	25
18	PPCM-Br	22	1	2	6.25	5	80	25
19	PPCM-Br	18	1	3	12.5	5	120	0

LVEDD indicates LV end-diastolic diameter; CHF, congestive heart failure; and NR, not reported.

enzyme that subsequently cleaves serum prolactin into its antiangiogenic and proapoptotic 16-kDa form.[9] This is associated with endothelial inflammation, impaired cardiomyocyte metabolism, and reduced myocardial contraction, suggesting that oxidative stress, inflammation, and prolactin may be interconnected and responsible for initiating PPCM.

Similarly, we found evidence for increased oxidative stress, enhanced cathepsin D activity, and increased prolactin cleavage in patients with acute PPCM.[9] More recently, we documented a close correlation between N-terminal brain natriuretic peptide (NT-proBNP; a marker of ventricular wall stress and heart failure), prolactin, and markers of oxidative stress (oxidized low-density lipoprotein) and inflammation (interferon-γ), further supporting the detrimental role of the oxidative stress–prolactin axis.[10]

Importantly, blockade of prolactin with the dopamine-2D agonist bromocriptine prevented the onset of PPCM in mice and in 6 women at high risk of this condition as a result of documented PPCM in a previous pregnancy.[9] Several case reports have also described seemingly beneficial effects from the addition of bromocriptine to standard heart failure therapy in patients with acute PPCM.[9,11,12] Although these preliminary results suggesting beneficial effects of bromocriptine treatment in patients with acute PPCM appear promising, concerns have been raised about the risk of thrombotic complications, including cerebral vascular incident and myocardial infarction, related to bromocriptine therapy[13–16] and the consequences for the children of these patients because the mothers are unable to breast-feed.[17]

The present work summarizes data from the first randomized study to assess the efficacy of bromocriptine on recovery of left ventricular (LV) function, symptom status, and other clinical measures in patients presenting within the first month postpartum with new-onset symptomatic PPCM and an LV ejection fraction (LVEF) <35%. The progress of the newborn children over the 6-month follow-up period was also studied. All open-label efficacy assessments were made by independent blinded investigators.

Methods

Study Design and Patient Recruitment

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa, and complies with the Declaration of Helsinki. All patients and control subjects gave written informed consent before study entry. Twenty consenting consecutive patients diagnosed with PPCM and fulfilling the inclusion criteria were enrolled in the study. All patients were included and randomized with a computer-generated randomization list within 24 hours of diagnosis.

The study was conducted at the Chris Hani Baragwanath Hospital. Patients were referred from local clinics, secondary hospitals, and the Department of Obstetrics at the Chris Hani Baragwanath Hospital. History of preexisting cardiac symptoms and signs, occurrence of preeclampsia, and mode of delivery were obtained from the patient and confirmed by examination of the obstetric card carried by each patient. Symptoms and signs were recorded during first presentation at the cardiac unit at the Chris Hani Baragwanath Hospital (baseline) and after a follow-up period of 6 months. Clinical assessment, echocardiography, and blood analysis were performed at baseline and at 6 months. Cardiac magnetic resonance imaging (MRI) was obtained 4 to 6 weeks after diagnosis in patients receiving bromocriptine.

Inclusion criteria were symptoms of congestive heart failure that developed in the last month of pregnancy or during the first month postpartum, no other identifiable cause for heart failure, and LVEF

Table 1. Continued

Prolactin at Baseline, μg/L	Prolactin at 6 mo, μg/L	NYHA Class at Baseline	NYHA Class at 6 mo	LVEDD at Baseline, mm	LVEDD at 6 mo, mm	LVEF at Baseline, %	LVEF at 6 mo, %	Prespecified End Point of Poor Outcome
54	60	III	III	46	43	33	40	Yes
11	NR	II	NR	61	NR	28	NR	Yes (died 1 mo after baseline of sudden death)
9	NR	IV	NR	65	NR	18	NR	Yes (died 1 mo after baseline of CHF)
16	16	IV	III	62	60	24	22	Yes
50	48	II	II	60	62	19	24	Yes
50	9	II	I	59	52	34	50	No
5	NR	II	NR	62	NR	34	NR	Yes (died 3 mo after baseline of CHF)
233	7	III	III	57	43	32	44	Yes
52	NR	IV	NR	59	NR	14	NR	Yes (died on index admission)
30	8	II	II	60	74	32	37	No
135	8	IV	I	33	44	34	58	No
122	6	II	I	65	59	29	37	No
22	7	II	I	68	65	30	62	No
56	7	II	I	54	51	27	72	No
4	6	II	I	56	48	30	56	No
91	25	III	I	63	51	30	58	No
55	8	IV	I	55	47	33	60	No
18	13	II	I	49	34	32	75	No
NR	NR	III	NR	55	NR	18	NR	Yes (died on index admission)
5	12	III	I	54	56	8	48	No

<35% by transthoracic echocardiography. Exclusion criteria were systolic blood pressure >160 or <95 mm Hg or diastolic >105 mm Hg; clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers such as sepsis, autoimmune disease, or HIV positivity; significant liver disease (defined as liver transaminase levels >2 times the upper limit of normal); history of peptic ulcer disease; history of psychiatric disorders; impaired renal function (defined as urea and/or creatinine >1.5 times the upper limit of normal); and any clinical condition that, according to the investigators, precluded inclusion in the study such as ischemic heart disease or malignancy.

All patients received treatment with the diuretic furosemide and the angiotensin-converting enzyme (ACE) inhibitor enalapril. Patients with an LVEF <25% or LV thrombus received anticoagulation therapy with warfarin for 6 months. Carvedilol was added after resolution of overt heart failure. Enalapril and carvedilol doses were titrated upward as tolerated during the first 4 weeks after diagnosis and then remained unchanged throughout the remainder of the 6-month study period. Furosemide dose was decreased as indicated according to clinical assessment during the 6-month study period. The 10 patients randomized to standard therapy (PPCM-Std group) were treated as outlined above. The 10 patients randomized to standard therapy plus bromocriptine (PPCM-Br) received bromocriptine 2.5 twice daily for 2 weeks followed by 2.5 mg daily for 6 weeks in addition to standard heart failure therapy. After the initial screening and baseline visits, monthly outpatient visits were scheduled for clinical assessment and evaluation of medication compliance.

Echocardiography, Cardiac MRI, Assessment of New York Heart Association Functional Class, and Noninvasive Blood Pressure Measurements

Patients were diagnosed by specialist physicians and cardiologists working at the Chris Hani Baragwanath Hospital. Patients were included in this trial within 24 hours after diagnosis once the diagnosis was confirmed by a cardiologist (K.S.), who repeated the echocardiography. Two-dimensional and targeted M-mode echocardiography with Doppler color-flow mapping was performed with either a Hewlett Packard Sonos 5500 (Royal Philips Electronics, Amsterdam, the Netherlands) or a VIVID i (General Electric Company, Fairfield, Conn) echocardiography machine. Systolic and diastolic LV dimensions were measured according to the American Society of Echocardiography guidelines.[18] Measurements of LV dimensions and function were determined by use of the average of ≥3 cycles. Mitral effective regurgitant orifice area and Doppler parameters of diastolic function were measured according to American Society of Echocardiography guidelines.[19,20] Echocardiography was recorded on video or a compact disk and stored within the Soweto Cardiovascular Research Unit Division for further reference, audit purposes, and repeat blinded analysis by a single operator.

Cardiac MRI was performed 4 to 6 weeks after diagnosis in patients receiving bromocriptine to detect possible mural thrombi. Studies were performed with a 1.5-T MRI scanner (General Electric, Milwaukee, Wis) with a cardiac-dedicated phased-array coil. The cardiac MRI studies were ECG triggered by standard software. Studies consisted of steady-state free precession and spin echo. Short-axis, transverse, and coronal views were obtained. Steady-state free-precession sequences were performed to assess regional wall motion abnormalities and LVEF. Slice thickness was 8 mm with no gap, 256×256 matrix, 400-mm field of view, and 1.6×1.6×8-mm voxel size. The total time required for the investigation was 30 to 45 minutes. Gadolinium enhancement was not studied. Ventricular parameters were assessed in a standard manner by 1 observer using commercially available software (CAAS MRV, Pie Medial Imaging, Maastricht, the Netherlands). The cardiac MRI studies were assessed by 2 independent experienced observers who determined the presence or absence of intracavitary thrombi.

New York Heart Association (NYHA) functional class of each patient at baseline and follow-up visits was evaluated by a physician who was provided clinical data but was blinded to treatment allocation and was unaware of the results of the laboratory tests. Heart rate and systolic and diastolic blood pressures were measured noninvasively with a Critikon Dinamap Vital Signs Monitor 1846

and calculated as mean values from 5 readings. Measurements were made after a 30-minute resting period in patients in the sitting position with 2-minute intervals between successive measurements.

Research-Specific Blood Tests

Blood (8 mL) was withdrawn from an antecubital vein, collected in prechilled tubes containing EDTA acid or clot activator, and mixed rapidly. Plasma or serum was separated by centrifugation at 2500 rpm for 7 minutes within 10 minutes of collection. Aliquots were stored at −80°C for possible future analysis. High-sensitivity CRP (hsCRP) was measured as described previously.[5,7,8] In addition, prolactin, NT-proBNP, full blood count, liver function, and creatinine were measured. Serum levels of 16-kDa prolactin were measured by immunoprecipitation followed by Western blotting. Cathepsin D activity was assayed with the Sensolyte 520 Cathepsin D Assay Kit (MoBiTec) as previously described.[9]

Analysis of Outcome

The prespecified combined end point of poor outcome was defined as death, NYHA functional class III/IV, or LVEF <35% at 6 months as previously described.[8]

Assessment of Children

Standard growth monitoring charts issued by the South African Department of Health and maintained by primary physicians were obtained for the newborn children of mothers included in this study. These charts listed the weight of each child at birth and at regular intervals to 6 months and beyond. Weights were plotted on World Health Organization weight-for-age Child Growth Standard charts for girls and boys.[21,22]

Statistical Analysis

Data were analyzed with the SAS version 9.1 statistical program (SAS Institute Inc, Cary, NC). Results are expressed as mean±SD or median (range). Comparison between groups at baseline and within groups (baseline to 6 months) of class variables was analyzed by χ^2 test or the Fisher exact test when adequate. NT-proBNP data were log transformed. To assess differences between the 2 treatment groups, we analyzed mean changes (baseline to 6 months) in all continuous variables with a t test or an exact Wilcoxon 2-sample test when distribution was not normal. For within-group comparisons, a paired t test or a sign test when distribution was not normal was performed. Significance was assumed at a 2-sided value of $P<0.05$.

Results

Baseline Characteristics and Treatment

Ninety-three patients with suspected PPCM were screened to recruit 20 consecutive patients with confirmed PPCM who were HIV negative and presented within 1 month postpartum. As depicted in Tables 1 and 2, the baseline characteristics of patients in the PPCM-Br and PPCM-Std groups were similar in terms of age, parity, NYHA functional class, systolic and diastolic blood pressures, heart rate, LV end-diastolic and end-systolic dimensions, and LVEF. Median prolactin and median NT-proBNP levels were comparable, whereas serum levels of 16-kDa prolactin and cathepsin D activity were elevated to a similar degree in all patients (Figure 1).

Treatment with standard heart failure medications was similar between the PPCM-Br and PPCM-Std groups (Table 1). Median dose of enalapril in the PPCM-Br group was 5 mg/d (range, 5 to 10 mg/d) and in the PPCM-Std group was 10 mg/d (range, 5 to 10 mg/d). Median dose of carvedilol in the PPCM-Br group was 6.25 mg twice daily (range, 6.25 to 25 mg) and in the PPCM-Std group was 12.5 mg twice daily (range, 6.25 to 25 mg). Median dose of furosemide at 6 months was 80 mg/d (range, 80 to 120 mg). All patients, including those with normalized LV systolic function, continued on medical therapy with ACE inhibitor and carvedilol during the 6-month study period. Cardiac transplantation or implantation of a LV assist device is not performed in state hospital patients in the Gauteng province of South Africa.

Table 2. Baseline Characteristics of PPCM-Br Versus PPCM-Std Patients

	PPCM-Br (n=10)*	PPCM-Std (n=10)*	P
Clinical parameters			
Age, y	24±6	28±10	0.60
Parity, n (range)	1.5 (1–3)	2 (1–6)	0.52
Systolic blood pressure, mm Hg	116±23	110±19	0.50
Diastolic blood pressure, mm Hg	70±16	76±18	0.45
Heart rate, bpm	102±13	108±15	0.34
NYHA functional class, n (%)			1.00
II	5 (50)	5 (50)	
III/IV	5 (50)	5 (50)	
Echocardiographic parameters			
LVEDD, mm	55±10	59±5	0.25
LVESD, mm	46±9	52±6	0.16
LVEF, %	27.2±8.1	26.9±7.6	0.87
Mitral regurgitation (grade)	2.1±0.6	1.9±0.6	0.70
Mitral ERO, cm^2	0.45±0.13	0.44±0.18	0.90
Laboratory parameters			
Hemoglobin, g/dL	13.0±2.2	11.8±1.9	0.22
Creatinine, μmol/L†	71 (6–109)	66 (5–96)	0.43
hsCRP, mg/L†	7.8 (1.1–58.0)	6.0 (4.0–115.3)	0.86
Prolactin, μg/L†	49.9 (3.8–135.0)	30.0 (5.1–233.0)	0.87
Log NT-proBNP	8.54±1.14	8.45±1.24	0.88

LVEDD indicates LV end-diastolic diameter; LVESD, LV end-systolic diameter; and ERO, effective regurgitant orifice.
*Values are mean±SD unless otherwise specified.
†Values are median (range).

Hemodynamic and Echocardiographic Parameters

Changes in systolic and diastolic blood pressures and heart rate from baseline to 6 months were not significantly different between the 2 treatment groups. In contrast, recovery of LVEF between baseline and 6 months was greater in the PPCM-Br group (31%) than in the PPCM-Std group (9%; $P=0.012$; Table 3 and Figure 2). Furthermore, the degree of mitral regurgitation significantly improved in the PPCM-Br group compared with the PPCM-Std group ($P=0.013$), as did several parameters of diastolic function (Table 3). No significant differences were observed in LV end-diastolic and end-systolic dimension change from baseline to 6 months between the 2 groups (Table 3).

NYHA Functional Class

All 9 surviving patients in the PPCM-Br group recovered to NYHA functional class I at 6 months. In contrast, all patients

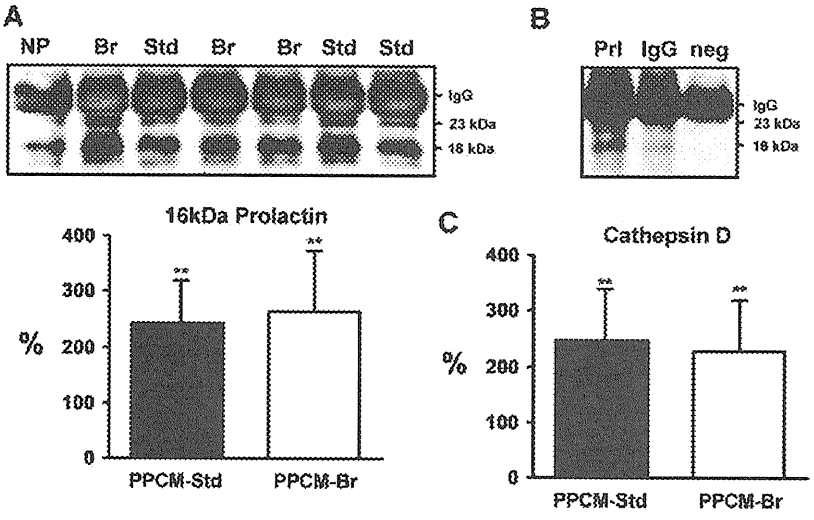

Figure 1. Analysis of prolactin subforms and cathepsin D activity in baseline serum probes from PPCM patients. A, Representative Western blot showing 16-kDa prolactin immunoprecipitated from serum probes of PPCM patients and from serum of a nulliparous (NP) control. Bar graph depicts 16-kDa prolactin serum levels in PPCM-Std (Std; n=7) and PPCM-Br (Br; n=8) vs the mean value of NP (n=3), which was set at 100% (**$P<0.01$ vs NP). B, The specificity of the immunoprecipitation (IP) was confirmed with anti-prolactin antibodies (Prl), nonspecific immunoglobulin G (IgG), and no antibody (neg) in a PPCM serum probe, followed by detection of 16-kDa prolactin by Western blot. C, Bar graph depicting cathepsin D activity in serum probes from PPCM patients (PPCM-Std, n=8; PPCM-Br, n=9) at baseline and in NP (n=7). Mean value of NP was set at 100% (**$P<0.01$ vs NP).

from the PPCM-Std group who survived 6 months were in NYHA functional class II (3 patients) or III (3 patients) (Tables 1 and 4).

Survival

The single patient who died in the PPCM-Br group presented in severe heart failure and survived only 7 days. All 9 remaining patients in the PPCM-Br group survived 6 months. Four patients in the PPCM-Std group died during the 6-month follow-up period: 1 died of heart failure during the index admission, 2 died of heart failure 4 to 12 weeks after diagnosis, and 1 experienced sudden cardiac death 1 month after baseline assessment.

Laboratory Parameters

There was a difference in change of log NT-proBNP levels from baseline to 6 months of borderline statistical significance in the PPCM-Br patients compared with the PPCM-Std patients ($P=0.05$), whereas the reductions in prolactin and hsCRP levels at 6 months were similar between the 2 groups (Table 5).

Table 3. Comparison of Hemodynamic and Echocardiographic Parameters in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

	PPCM-Br Baseline (n=10)*	PPCM-Br 6 Months (n=9)*	PPCM-Std Baseline (n=10)*	PPCM-Std 6 Months (n=6)*	P†
Clinical parameters					
Systolic blood pressure, mm Hg	116±23	118±13	110±19	115±9	0.78
Diastolic blood pressure, mm Hg	70±16	74±9	76±18	73±6	0.77
Heart rate, bpm	102±13	64±7	108±15	79±15	0.22
Echocardiographic parameters					
LVEDD, mm	55±10	51±9	59±5	56±12	0.50
LVESD, mm	46±9	34±10	52±6	45±11	0.18
LVEF, %	27±8	58±11	27±8	36±11	0.0007
Mitral regurgitation (grade)	2.1±0.6	0.22±0.44	1.9±0.6	1.5±1.0	0.0042
Mitral ERO, cm^2	0.45±0.13	0.11±0.03	0.44±0.18	0.34±0.18	0.02
Left atrial diameter, cm	3.54±0.25	3.36±0.53	3.83±0.62	3.93±0.83	0.25
Mitral E velocity, cm/s	86±19	66±24	89±23	85±24	0.53
Mitral A velocity, cm/s	32±7	48±19	33±6	45±12	0.80
Mitral E velocity/A velocity ratio	2.82±0.76	1.63±1.13	2.73±0.68	1.94±0.67	0.82
Deceleration time, ms	118±26	197±59	136±30	168±36	0.08
Mitral medial annular (E') TDI velocity, cm/s	7.0±1.3	12.4±2.4	6.5±1.1	7.3±2.5	0.014
E/E' (medial annular velocity)	12.5±3.0	5.4±2.5	14.0±4.6	12.4±4.6	0.08
Mitral lateral annular (E') TDI velocity, cm/s	7.2±1.1	12.4±2.5	6.6±0.97	7.3±2.5	0.007
E/E' (lateral annular velocity)	12.0±2.0	5.4±2.5	13.8±4.2	12.1±3.9	0.051

Abbreviations as in Table 2, plus TDI indicates tissue Doppler imaging.
*Values are mean±SD.
†Comparing the change from baseline to 6 months in PPCM-Br and PPCM-Std patients.

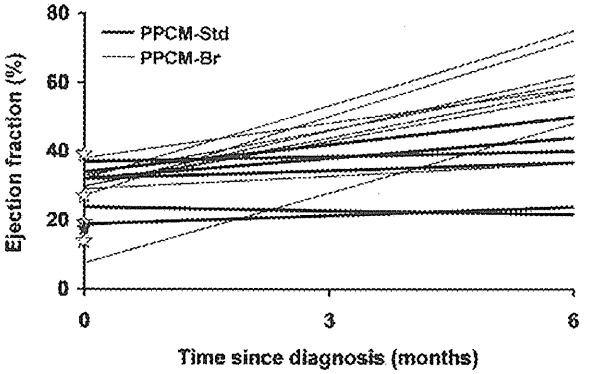

Figure 2. Change in LVEF from baseline to 6 months among survivors. Stars represent baseline LVEF for patients who died during the study period.

Combined Measure of Poor Outcome

The combined measure of poor outcome that included LVEF <35% (surviving PPCM-Br, 0 of 9 [0%] versus surviving PPCM-Std, 2 of 6 [33%]), NYHA functional class III/IV at 6 months (surviving PPCM-Br, 0 of 0 [0%] versus surviving PPCM-Std, 3 of 6 [50%]), or death within 6 months (PPCM-Br, 1 of 10 [10%] versus PPCM-Std, 4 of 10 [40%]) revealed that the PPCM-Br patients had better outcome than the PPCM-Std patients (P=0.006; Figure 3).

Thrombi and Thromboembolism

No adverse effects, including thromboembolism, were reported in either group. Cardiac MRI was performed at 4 to 6 weeks after diagnosis in 8 of the 10 patients in the PPCM-Br group to assess for thrombus formation. MRI results were not available for 1 patient who died before becoming stable enough for the MRI, and the images acquired for a second patient were not of sufficient quality for reliable assessment. None of the remaining patients had intracavitary thrombi (Figure 4).

Infant Growth Curves and Survival

All 21 children of the PPCM-Br and PPCM-Std patients showed normal growth curves when plotted on the World Health Organization standard weight-for-age growth charts (Figure 5A and B). Although the survival of all 21 children through the 6-month follow-up period was verified, weight-for-age data at 6 months were available for only 13 children.

Table 4. Comparison of NYHA Functional Class in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

	PPCM-Br at Baseline (n=10), n (%)	PPCM-Br at 6 mo (n=9), n (%)	PPCM-Std at Baseline (n=10), n (%)	PPCM-Std at 6 mo (n=6), n (%)	P*
NYHA functional class					0.008
I	0	9 (100)	0	0	
II	5 (50)		5 (50)	3 (50)	
III/IV	5 (50)		5 (50)	3 (50)	

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

The mothers of 5 children died during the course of the study and family members could not provide the children's growth charts, and the growth charts of the 3 other children with missing data were incomplete because of challenges in the delivery of quality care in the primary healthcare system in South Africa. However, all children had weight data up to the age of 3 months, and there were no significant differences in growth curves between the children of the PPCM-Br patients and those of the PPCM-Std patients.

Discussion

This prospective, single-center, randomized, open-label pilot study with blinded efficacy assessments showed that the addition of bromocriptine to standard heart failure therapy in women with PPCM appeared to result in significantly greater improvements in NYHA functional class, LV systolic and diastolic function, and degree of functional mitral regurgitation than seen with standard therapy alone. Bromocriptine seemed to be well tolerated, and no thrombotic complications were observed. Moreover, although bromocriptine stopped lactation and breast-feeding in the PPCM patients, the growth and survival of those infants were normal. However, our study was very small, and these findings are in no way definitive. On the other hand, these findings are encouraging and suggest that a larger study should be considered.

This proof-of-concept pilot study was performed in a group of homogeneous patients in terms of ethnic background, age, time point of diagnosis, and baseline characteristics. Unfortunately, blinding of the study was not possible because the PPCM-Std group continued to nurse their infants while the PPCM-Br group could not breast-feed because of bromocriptine-induced cessation of lactation. However, investigators were blinded for data analysis. We believe that the homogeneous patient cohort, well-balanced baseline characteristics, and blinded assessment of outcomes to some extent compensate for the small size of our study and its open-label design.

The design of the present study was chosen on the basis of our hypothesis that a cleaved form of the hormone prolactin initiates and drives PPCM and that early pharmacological blockade of prolactin with bromocriptine may improve the condition of patients with acute onset of PPCM before irreversible damage caused by cell death, fibrosis, and remodeling. Increased serum levels of 16-kDa prolactin and augmented cathepsin D activity at baseline in PPCM patients included in the present study support this hypothesis. The rationale for the dose and length of bromocriptine therapy was based on previous observations in animal models and a previous pilot study,[11] as well as several case reports in patients with PPCM.[12,23,24] We believe that some of the apparently beneficial effects of bromocriptine result from eliminating the detrimental 16-kDa prolactin form, the harmful effects of which on the heart and the vasculature have been described experimentally.[11,24] In addition, both forms of prolactin promote inflammation,[24] a reaction that seems to be associated with PPCM in this African cohort, because most patients displayed increased serum levels of the inflammatory marker hsCRP.[5]

Table 5. Comparison of Laboratory Parameters in PPCM-Br and PPCM-Std Patients at Baseline and 6 Months

	PPCM-Br at Baseline (n=10)	PPCM-Br at 6 mo (n=9)	PPCM-Std at Baseline (n=10)	PPCM-Std at 6 mo (n=6)	P†
Hemoglobin, g/dL†	13.0±2.2	12.7±1.5	11.8±1.9	13.0±1.4	0.58
Creatinine, μmol/L‡	71 (6–109)	78 (52–113)	66 (5–96)	62 (41–73)	0.86
hsCRP, mg/L‡	7.8 (1.1–58.0)	4.7 (1.0–10)	6.0 (4.0–115.3)	1.8 (1.1–15.1)	0.18
Prolactin, μg/L‡	49.9 (3.8–135.0)	8.0 (5.9–25.0)	30.0 (5.1–233.0)	12.5 (7.4–60.0)	0.72
Log NT-proBNP†	8.54±1.14	5.62±0.80	8.45±1.24	6.64±0.60	0.056

*Comparing the change from baseline to 6 months in PPCM-Br and PPCM-Std patients.
†Values are mean±1SD.
‡Values are median (range).

Apart from its prolactin blocking role, bromocriptine may exert additional "off-target effects" in PPCM patients. For example, effects of bromocriptine on hemodynamic parameters in patients with heart failure were described 30 years ago[25] before treatment with ACE inhibitors and β-blockers was routine. Positive effects of bromocriptine on blood pressure, vascular resistance, and plasma norepinephrine levels have been described.[25] Moreover, bromocriptine has been shown to increase stroke volume index and to decrease LV filling pressure.[25,26] Whether these potential beneficial effects of bromocriptine on hemodynamic parameters play a role in contemporary patients with heart failure who are treated with ACE inhibitors and β-blockers remains to be elucidated.

Bromocriptine may also affect metabolic parameters. We observed that PPCM patients display increased oxidized low-density lipoprotein serum levels compared with healthy postpartum women,[9] suggesting impaired antioxidative defense mechanisms and potential metabolic perturbations. In turn, Wexler and McMurtry [27] reported that, experimentally, bromocriptine treatment reduced triglyceride, free fatty acid, total cholesterol, and glucose levels in isoproterenol-induced heart failure. Whether such parameters play a role in the pathophysiology of PPCM is currently under investigation in experimental models.

In addition, bromocriptine has been shown to inhibit oxidative stress–induced cell death in neuronal cells by dopamine D2 receptor–dependent transactivation of c-Src/endothelial growth factor receptor and downstream PI3K-Akt signaling, which results in upregulation of antiapoptotic Bcl-2.[28] Preliminary data show that bromocriptine treatment increases Akt activation and upregulates Bcl-2 expression in the heart of postpartum mice (D.H.-K., unpublished data, 2010), suggesting that bromocriptine may indeed have direct cardioprotective effects. Taken together, these data show that off-target effects of bromocriptine on metabolism, oxidative stress, and cytoprotection may act in concert with its prolactin-lowering capacity and may help to explain the positive effects of prolonged treatment with bromocriptine beyond an effective prolactin blockade.

We found that the overall mortality rate in the PPCM-Std group was high. Other studies have demonstrated a lower PPCM mortality rate (averaging ≈15%), including our own series of 100 patients[1,5,8] and the prospective long-term study by Fett et al.[4] One explanation for the differences in mortality rate between the present study and our other series of 100 patients might be the inclusion criteria. In the present study, patients were enrolled very early (within 24 hours after diagnosis). This timely enrollment was not possible for the previous cohort of 100 patients. As a consequence, some patients in that study died between diagnosis and enrollment. In addition, our previous study included patients diagnosed

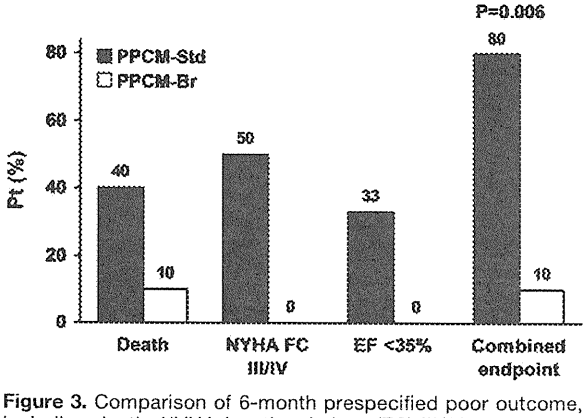

Figure 3. Comparison of 6-month prespecified poor outcome, including death, NYHA functional class (FC) III/IV, and LVEF <35% among survivors, and the combined end point including all 3 of these end points for PPCM-Br vs PPCM-Std patients (Pt).

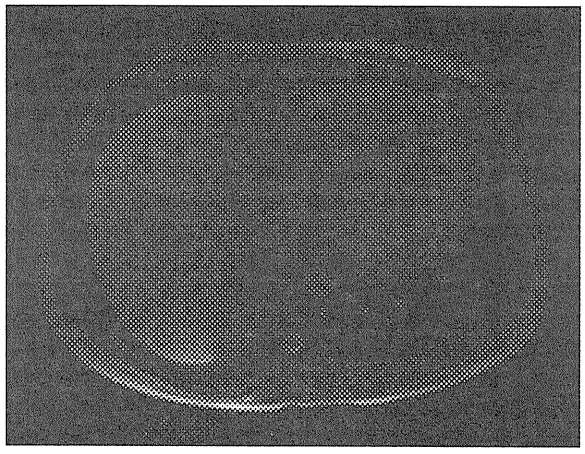

Figure 4. Cardiac MRI (transverse view, steady-state free-precession sequence) in a young African woman 2 months after delivery demonstrates marked dilation of both ventricles and the right atrium. LVEF is 8%.

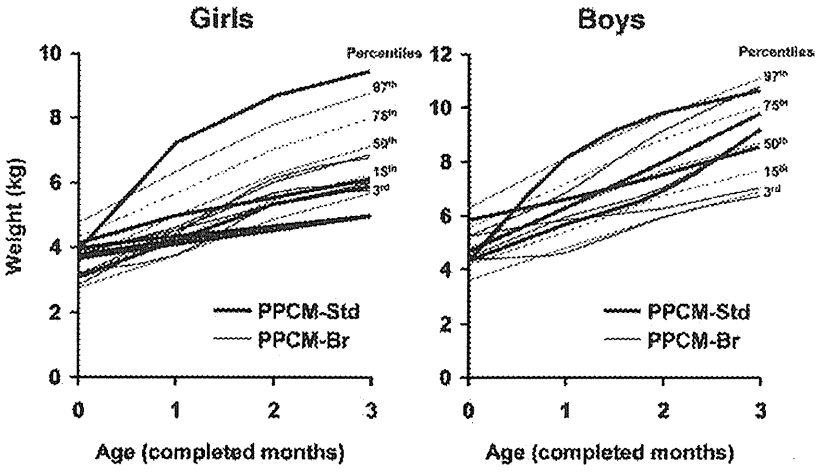

Figure 5. Growth and survival of children of PPCM study mothers from birth to 3 months plotted on World Health Organization growth charts.

between 4 weeks and 5 months postpartum. The development of symptoms >4 weeks postpartum may be a manifestation of milder forms of this disease.

In this study, the cause of death in the PPCM-Std group was either heart failure or sudden cardiac death, with all deaths occurring within 3 months of randomization. In contrast, the 1 patient who died in the PPCM-Br group was admitted with severe heart failure and died 7 days after diagnosis while still in the intensive care unit.

The safety of bromocriptine treatment during pregnancy has already been assessed by a survey of 1400 pregnant women who took bromocriptine primarily in the first few weeks of pregnancy and found no increased rates of abortion or congenital malformations.[29] In the postpartum phase, bromocriptine has been used worldwide since 1980 to suppress lactation. However, concerns have been raised about a potential risk for cerebral and cardiovascular complications, as emphasized in some case reports describing stroke,[13] seizure,[15] coronary artery thrombosis,[15] and coronary artery vasospasm.[14] Although these data were observational, bromocriptine was withdrawn from the market in the United States in 1994 for use as an agent to block lactation.

It is known that the postpartum period is associated with an increased risk of thrombosis and myocardial infarction, probably because of changes in coagulation that may have evolved as a protection from bleeding caused by miscarriage and childbirth.[30] We observed no adverse effects in any of the 9 surviving patients in the PPCM-Br group. However, the number of patients studied was small, and because of poor cardiac function, all patients in the present study received subcutaneous low-molecular-weight heparin during their index admission. Therefore, although the data suggesting that bromocriptine has a prothrombotic effect are not robust, we cannot rule out such an effect.

There has been some concern that PPCM patients in developing countries treated with bromocriptine will no longer be able to breast-feed, which may increase the risk for malnutrition and infection in their infants.[17] The survival rate of infants of the PPCM-Br patients was not affected, and no serious illnesses were reported, although the number of children we studied was very small. Normal weight gain from birth to 3 months was observed in all infants and continued to be normal during the 6-month follow-up period in those for whom data were available. Although this was a small study with only short-term follow-up, our results suggest no disadvantage to the infant of a PPCM patient who could not breast-feed because of bromocriptine treatment. However, we are aware that larger studies in Soweto and other developing areas in the world are needed to support this statement.

Conclusions

In this trial, the addition of bromocriptine to standard heart failure therapy appeared to improve LVEF and a composite clinical outcome in women, although the number of patients studied was small and the results cannot be considered definitive. Larger-scale multicenter and blinded studies are in progress to test this strategy more robustly.

Acknowledgments

We would like to thank the clinicians at CH Baragwanath Hospital for referring the patients to us and Dr Peter Zartner for his valuable input in measuring outcome in the children. The excellent work of Bridget Phooko is acknowledged.

Sources of Funding

Laboratory investigations have been funded through the Medical Research Council of South Africa and the University of the Witwatersrand. Experimental work has been supported by the Leducq Foundation.

Disclosures

None.

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CLINICAL PERSPECTIVE

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease that occurs in previously healthy women. We identified prolactin, mainly its 16-kDa angiostatic and proapoptotic form, as a key factor in PPCM pathophysiology. Blockade of prolactin with the dopamine-2D agonist bromocriptine had previously been shown to prevent the onset of PPCM in mice and in women at high risk of this condition because of documented PPCM in a previous pregnancy. We recruited 20 women with onset of severe acute PPCM during the first month postpartum within 24 hours of diagnosis and randomized them into 2 groups: standard care (PPCM-Std; n=10) or standard care plus bromocriptine for 8 weeks (PPCM-Br, n=10). PPCM-Br patients displayed greater recovery of left ventricular ejection fraction compared with PPCM-Std patients at 6 months. Four PPCM-Std patients died; only 1 PPCM-Br patient did not survive. Significantly fewer PPCM-Br patients met the composite end point of poor outcome defined as death, New York Heart Association functional class III/IV, or left ventricular ejection fraction <35% at 6 months. Because the PPCM-Br mothers could not breast-feed, the outcome of their children was assessed. Infants of mothers in both groups showed normal growth and survival at 6 months. Our findings suggest that the addition of bromocriptine to standard heart failure therapy appears to improve left ventricular ejection fraction, functional class, and survival in women with severe acute PPCM with no obvious detriment to their children.

Correction

In the article, "Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy: A Proof-of-Concept Pilot Study" by Sliwa et al, which appeared in the April 6, 2010 issue of the journal (Circulation. 2010;121:1465–1473), there was a misspelling of one author's name. Ingrid Struhman should be spelled Ingrid Struman.

The online version of the article has been corrected. The authors regret the error.

DOI: 10.1161/CIR.0b013e3181e3a433

(*Circulation*. 2010;121:e425.)

***Circulation* is available at http://circ.ahajournals.org**

Peripartum Cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) Workshop Recommendations and Review

Gail D. Pearson; Jean-Claude Veille; Shahbudin Rahimtoola; et al.

JAMA. 2000;283(9):1183-1188 (doi:10.1001/jama.283.9.1183)

http://jama.ama-assn.org/cgi/content/full/283/9/1183

Peripartum Cardiomyopathy

National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) Workshop Recommendations and Review

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Objective Peripartum cardiomyopathy (PPCM) is a rare life-threatening cardiomyopathy of unknown cause that occurs in the peripartum period in previously healthy women. In April 1997, the National Heart, Lung, and Blood Institute (NHLBI) and the Office of Rare Diseases of the National Institutes of Health (NIH) convened a Workshop on Peripartum Cardiomyopathy to foster a systematic review of information and to develop recommendations for research and education.

Participants Fourteen workshop participants were selected by NHLBI staff and represented cardiovascular medicine, obstetrics, immunology, and pathology. A representative subgroup of 8 participants and NHLBI staff formed the writing group for this article and updated the literature on which the conclusions were based. The workshop was an open meeting, consistent with NIH policy.

Evidence Data presented at the workshop were augmented by a MEDLINE search for English-language articles published from 1966 to July 1999, using the terms *peripartum cardiomyopathy*, *cardiomyopathy*, and *pregnancy*. Articles on the epidemiology, pathogenesis, pathophysiology, diagnosis, treatment, and prognosis of PPCM were included.

Recommendation Process After discussion of data presented, workshop participants agreed on a standardized definition of PPCM, a general clinical approach, and the need for a registry to provide an infrastructure for future research.

Conclusions Peripartum cardiomyopathy is a rare lethal disease about which little is known. Diagnosis is confined to a narrow period and requires echocardiographic evidence of left ventricular systolic dysfunction. Symptomatic patients should receive standard therapy for heart failure, managed by a multidisciplinary team. If subsequent pregnancies occur, they should be managed in collaboration with a high-risk perinatal center. Systematic data collection is required to answer important questions about incidence, treatment, and prognosis.

JAMA. 2000;283:1183-1188 www.jama.com

HEART FAILURE IN THE PUERPERIUM has been recognized since the 18th century, but cardiomyopathy was not identified as its cause until an article by Gouley et al was published in 1937.[1] Peripartum cardiomyopathy (PPCM) is now considered to be a cardiomyopathy of unknown cause that occurs in the peripartum period in women without preexisting heart disease.[2,3] Peripartum cardiomyopathy is relatively rare, but can be devastating, with reported mortality rates between 18% and 56%.[3-5] Survivors may not recover completely and may require heart transplantation. Even if left ventricular function does return to normal, exercise tolerance may remain abnormal and the long-term sequelae, including risks of future pregnancies, are not known.

In April 1997, the National Heart, Lung, and Blood Institute (NHLBI) and the Office of Rare Diseases of the National Institutes of Health (NIH) convened a Workshop on Peripartum Cardiomyopathy to foster a multidisciplinary review. Experts in cardiovascular medicine, ob-

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This article is one of a series sponsored by the American Heart Association.

stetrics, immunology, and pathology met to discuss the available information and make recommendations (a list of participants appears at the end of this article). The objectives for the Workshop on PPCM, modeled on a previous NHLBI Workshop on Idiopathic Dilated Cardiomyopathy,[6] were to (1) summarize existing information on PPCM, specifically its definition, epidemiology, cause, clinical characteristics, treatment, and prognosis; (2) review diagnostic criteria and discuss means of differentiating early symptoms of heart failure from normal physiological changes associated with pregnancy, such as tachypnea and fatigue during the third trimester of pregnancy; (3) develop recommendations for future research on PPCM; and (4) discuss educational measures to increase awareness of PPCM and thus facilitate prompt diagnosis. A representative subgroup of 8 participants and NHLBI staff formed the writing group for this article and updated the literature on which the conclusions were based. The workshop was an open meeting consistent with NIH policy.

PPCM: LITERATURE REVIEW

Data presented at the workshop were augmented with a MEDLINE literature search (English language) for the years 1966 to July 1999 that included the terms *peripartum cardiomyopathy*, *cardiomyopathy*, and *pregnancy*. The literature search was updated following the workshop to provide the most timely references. The bibliographies of articles identified in this fashion were searched for additional references, and the search was further supplemented with articles recommended by workshop participants. This review, which workshop participants felt to be important because of the reported rarity of the condition, the consensus that the condition may be more prevalent than reported, and because of new data concerning cause, includes the majority of articles identified through these processes covering epidemiology, pathogenesis, pathophysiology, diagnosis, treatment, and prognosis of PPCM.

Table 1. Definition of Peripartum Cardiomyopathy

Classic
Development of cardiac failure in the last month of pregnancy or within 5 months of delivery
Absence of an identifiable cause for the cardiac failure
Absence of recognizable heart disease prior to the last month of pregnancy
Additional
Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria, such as depressed shortening fraction or ejection fraction

Definition

Peripartum cardiomyopathy is defined on the basis of 4 criteria, adapted from work by Demakis et al[3,7] and summarized in TABLE 1. The importance of adhering to the interval from 1 month before delivery to 5 months postpartum was emphasized to exclude preexisting causes of cardiomyopathy that may be exacerbated by pregnancy rather than arising as a result of pregnancy. For example, heart failure occurring earlier in pregnancy may be caused by previously unsuspected dilated cardiomyopathy unmasked by the hemodynamic or hormonal stress of pregnancy. Peripartum cardiomyopathy is defined as occuring only in those patients with no prior history of recognizable heart disease and can be diagnosed only in the absence of another explanation for the cardiomyopathy.

Incidence and Risk Factors

The incidence of PPCM is not known because population-based estimates are not available, and the diagnosis of this rare disease is not always straightforward. Incidence rates reported in individual studies are based on the experience at a particular institution and may reflect referral bias as well as individual practice patterns. Although the reported incidence rates range from 1 per 1485[8] to 1 per 15 000,[9] the currently accepted estimate of incidence is approximately 1 per 3000 to 1 per 4000 live births, which would translate to between 1000 and 1300 women affected each year in the United States.[10]

Risk factors for PPCM classically identified in the literature include multiparity, advanced maternal age, multifetal pregnancy, preeclampsia and gestational hypertension, and African American race.[3] It is unclear whether race represents an independent risk factor or whether it is the interaction of race with hypertension that increases the risk of PPCM. Until risk factors can be delineated confidently, it is difficult to develop recommendations for screening high-risk populations.

Etiology

Workshop participants concurred that PPCM is a distinct entity, rather than a clinically silent underlying cardiomyopathy unmasked by the hemodynamic stresses of pregnancy, because the reported incidence is higher than the incidence of idiopathic cardiomyopathy,[6] and because the high frequency of myocarditis would not be expected in a population presenting with decompensation of preexisting heart disease due to hemodynamic stress. However, reliable data comparing the incidence of cardiomyopathy in pregnant women compared with age-matched nonpregnant women are not available. A number of possible causes have been proposed for PPCM, including myocarditis, abnormal immune response to pregnancy, maladaptive response to the hemodynamic stresses of pregnancy, stress-activated cytokines, and prolonged tocolysis. In addition, there have been a few reports of familial PPCM,[11-13] raising the possibility that some cases of PPCM are actually familial dilated cardiomyopathy unmasked by pregnancy. The key hypotheses are presented below.

Myocarditis. There is more evidence for myocarditis as a cause of PPCM than for other purported etiologies. Melvin and colleagues[14] first reported myocarditis by endomyocardial biopsy in 3 consecutive patients with PPCM. The incidence of myocarditis in subsequent authors' series has varied. The variability is likely due to the inclusion of patients outside the accepted time frame of PPCM, the inherent difficulties in establishing the diagnosis of myocarditis by endomyo-

cardial biopsy,[15,16] the variability in the inclusion of patients with borderline myocarditis with those with histologic myocarditis as defined by the Dallas histologic criteria, the potential geographic variability of patient populations affected, and the variable interval between presentation and the performance of the endomyocardial biopsy. The highest incidence of myocarditis in PPCM (76%) was reported by Midei and colleagues.[17] This group performed endomyocardial biopsies on patients with symptoms of congestive heart failure at the time of presentation and included patients with histologic borderline myocarditis as well as those with active myocarditis.

The absent or muted immune response during pregnancy may allow for unchecked viral replication and thus a greater likelihood of myocarditis in the setting of a viral infection. Studies in pregnant mice demonstrate enhanced susceptibility to viral myocarditis due to coxsackieviruses and echoviruses.[18,19] In the near future, electron micrography combined with molecular biological techniques should permit not only identification of viral particles in myocardium, but also the putative viruses implicated. The presumption is that if viral genetic products are evident, the postviral immune response of the patient may have been inappropriately directed against otherwise cryptic cardiac tissue proteins, leading to ventricular dysfunction.

Abnormal Immune Response to Pregnancy. Several reports have documented the occurrence of chimerism of the hematopoietic lineage cells from the fetus to the mother during pregnancy.[20-23] It is postulated that fetal cells may escape into the maternal circulation and remain there without being rejected, due to weak immunogenicity of the paternal haplotype of the chimeric cells, or to the naturally occurring immunosuppressive state of the mother, or both. If chimeric hematopoietic cells take up residence in cardiac tissue during the immunosuppressed pregnant state and, following postpartum recovery of immune competence, are recognized as nonself by the maternal immune system, a pathologic autoimmune response may be triggered. Prior exposure to paternal major histocompatibility complex antigens expressed by spermatozoa or previous immunization from prior pregnancies may play a role in inducing local tissue inflammatory response. Cytokines and similar signaling molecules are then released, leading to nonspecific bystander myocytotoxicity and myocarditis. The evidence (TABLE 2) that PPCM is associated with high titers of autoantibodies against select cardiac tissue proteins (eg, adenine nucleotide translocator, branched chain α-keto acid dehydrogenase) supports abnormal immunologic activity as a possible cause of PPCM.[24]

Response to Hemodynamic Stresses of Pregnancy. During pregnancy, blood volume (preload) and cardiac output increase and afterload decreases. An echocardiographic assessment of cardiac hemodynamics in normal pregnancies performed by Geva et al[25] demonstrated a 10% increase in left ventricular end-diastolic volume, a 45% increase in cardiac output, and a 26% to 28% decrease in end-systolic wall stress, a sensitive measure of myocardial afterload. In addition, the left ventricle remodels in response to the hemodynamics of pregnancy, resulting in transient hypertrophy. The research by Geva et al[25] and other studies[26] have shown a reversible decrease in left ventricular systolic function in the second and third trimesters that persisted into the early postpartum period, but returned to baseline shortly thereafter. It is possible that PPCM may be due, in part, to an exaggeration of this decrease in systolic function, although there are no data in women supporting this hypothesis.[27]

Other Etiologic Factors. Other causes for PPCM that merit further study have been suggested and include the following: (1) prolonged tocolysis*,[28]; (2) stress-activated proinflammatory cytokines such as tumor necrosis factor α or interleukin 1 that have been implicated in the pathophysiology of idiopathic dilated cardiomyopathy[29]; (3) abnormalities of relaxin, primarily an ovarian hormone produced during pregnancy, recently found in cardiac atria, shown to have positive inotropic and chronotropic properties[30] and potentially involved in excessive relaxation of the cardiac skeleton; and (4) deficiency of selenium,[31] which may make the heart more susceptible to injury from viral infection, hypertension, or hypocalcemia.

DIAGNOSIS AND MANAGEMENT OF PPCM

The diagnosis of PPCM rests on the echocardiographic identification of new left ventricular systolic dysfunction during a limited period surrounding par-

Table 2. Serum Levels of Antibodies to Cardiac Muscle Proteins in Patients With Peripartum Cardiomyopathy (CM) and Idiopathic Dilated Cardiomyopathy*

Patient Group	Antibody Titer Levels†		
	<1:20	1:20-1:160	>1:160
	ANT		
Idiopathic CM	16/56 (28)	29/56 (52)	11/56 (20)
Peripartum CM	1/10 (10)	1/10 (10)	8/10 (80)
	BCKD		
Idiopathic CM	30/56 (53)	21/56 (38)	5/56 (9)
Peripartum CM	0/10 (0)	2/10 (20)	8/10 (80)
	Myosin		
Idiopathic CM	18/56 (32)	27/56 (48)	11/56 (20)
Peripartum CM	1/10 (10)	1/10 (10)	8/10 (80)

*A. Ansari, MD, unpublished data, 1997.
†Reciprocal of the highest dilation of serum samples showing reactivity arbitrarily divided into those with low (<1:20), medium (1:20-1:160), and high (>1:160) titers. ANT indicates adenine nucleotide translocator; BCKD, branched chain α-keto acid dehydrogenase. Data presented as No./Total (%) of patients in each group.

turition. This presents a challenge because many women in the last month of a normal pregnancy experience dyspnea, fatigue, and pedal edema, symptoms identical to early congestive heart failure. Peripartum cardiomyopathy may, therefore, go unrecognized, leading to underestimation of incidence. Symptoms and signs that might raise the suspicion of heart failure include paroxysmal nocturnal dyspnea, chest pain, cough, neck vein distention, new murmurs consistent with atrioventricular valve regurgitation, and pulmonary crackles. There are no specific criteria for differentiating subtle symptoms of heart failure from normal late pregnancy, so it is important that a high index of suspicion be maintained to identify the rare case of PPCM.

The diagnosis of PPCM requires excluding other causes of cardiomyopathy and is confirmed by standard echocardiographic assessment of left ventricular systolic dysfunction, including depressed fractional shortening and ejection fraction. Strong consideration should be given to screening family members of PPCM patients because PPCM may be the forme fruste of a genetic predisposition to cardiomyopathy.

In the absence of systematic studies comparing therapeutic approaches in PPCM, standard heart failure therapy (diuretics, vasodilators, and digoxin[32] as needed) should be initiated. Careful attention must be paid to fetal safety and to excretion of drug or drug metabolites during breastfeeding after delivery. Collaboration among medical specialists, including obstetricians, cardiologists, perinatologists, and neonatologists, is essential. The discussion that follows should be considered a general guide, rather than a specific algorithm.

Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy because of teratogenicity, but should be considered a mainstay of treatment for PPCM after delivery. Safe alternatives during pregnancy include hydralazine and nitrates. Calcium channel blockers can be used during pregnancy to control blood pressure (and decrease uterine contractility), but most have negative inotropic properties that may make them unacceptable for use in this situation. Amlodipine, a dihydropyridine calcium channel blocker, has been shown to improve survival in nonischemic cardiomyopathy patients[33] and may have a role in management of PPCM. Plasma levels of interleukin 6, a proinflammatory cytokine, were reduced among amlodipine recipients in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial,[34] providing an additional potential rationale for its use in PPCM.

Second-generation β-adrenoreceptor antagonists have beneficial effects in selected patients with dilated cardiomyopathy. Studies of β-adrenoreceptor antagonists in patients with congestive heart failure have demonstrated safety and modest clinical benefit, but conflicting results regarding survival.[35] Vasodilating β-blockers such as carvedilol also reduce afterload through α_1 adrenergic blockade. Data from the US Carvedilol Heart Failure Program suggest a potential clinical benefit, including mortality reduction, in dilated cardiomyopathy.[36] These drugs are not contraindicated in pregnancy, but as with other agents, there are no data evaluating their use in PPCM. A reasonable approach would be to use β-adrenoreceptor antagonists in the postpartum period in patients who continue to have symptoms and echocardiographic evidence of left ventricular compromise despite more than 2 weeks of standard heart failure management.

With mild left ventricular dysfunction, therapy can be initiated in the outpatient setting. Patients with severe heart failure may require hospitalization and more aggressive support, including intravenous inotropic agents, oxygen, and invasive monitoring. Patients with significantly depressed left ventricular function (ejection fraction ≤35%) may benefit from anticoagulation therapy (heparin before delivery, warfarin afterward) to prevent thrombosis and emboli. Arrhythmias should be treated according to standard protocols. Immunosuppressive therapy may be considered in patients with myocarditis documented by endomyocardial biopsy who fail to improve spontaneously within 2 weeks of initiation of standard heart failure therapy. The Myocarditis Treatment Trial failed to demonstrate an overall advantage for immunosuppressive therapy, but did not evaluate its merits in women with PPCM.[37] A more recent retrospective study suggested that women with PPCM treated with intravenous immune globulin had a greater improvement in ejection fraction during early follow-up than patients treated conventionally.[38] Women who fail maximal medical management may be candidates for cardiac transplantation. One study of 10 PPCM patients who underwent heart transplantation reported survival comparable to age-matched women undergoing heart transplantation for other indications, but noted a marginally higher rate ($P = .05$) of biopsy-proven early rejection, necessitating increased cytolytic therapy.[39]

Salt and water restriction are important in patient management, particularly in women with symptoms and signs of heart failure. Once heart failure symptoms have been controlled, modest exercise may improve symptoms as well as peripheral muscular and arterial tone. The need for early delivery and the mode of delivery should be assessed through collaboration with cardiologists and anesthesiologists. There is little systematic evidence that infants born to women with PPCM are adversely affected, although one study did report a premature delivery rate of 21% in 14 women.[40]

PROGNOSIS FOR WOMEN WITH PPCM

The prognosis for women with PPCM appears to depend on the normalization of left ventricular size and function within 6 months after delivery. In one study, approximately half of 27 women studied had persistent left ventricular dysfunction. In this group, the cardiac mortality rate was 85% over 5 years, compared with the group in whom cardiac size returned to nor-

mal, who experienced no reported cardiac mortality in the same time interval.[3] A more recent study corroborates these results: 50% (7/14) of patients had dramatic improvement soon after delivery, but 6 of the 7 remaining patients died.[41] Survivors were found to have a higher mean ejection fraction (23% vs 11%) and smaller mean left ventricular cavity size (5.8 vs 6.9 cm) at diagnosis.

Currently, there is no consensus regarding recommendations for future pregnancy after PPCM. Patients whose left ventricular size or function does not return to normal should be counseled strongly to avoid subsequent pregnancy[3] and treated accordingly, including adopting a heart-healthy diet and lifestyle. Patients whose cardiomyopathy apparently resolves completely are a more difficult group to counsel. In the long-term follow-up study reported by Demakis et al,[3] 8 of 14 patients whose heart size returned to normal after the first episode of PPCM had subsequent pregnancies. Of the 8 patients, 2 developed PPCM with subsequent pregnancies. Sutton and colleagues[41] reported normal subsequent pregnancies and normal left ventricular function (by echocardiography) in 4 women whose heart size returned to normal after PPCM in a prior pregnancy. Because PPCM has been associated with multiparity in some studies, the risk of irreversible cardiac damage may increase with each subsequent pregnancy. In addition, even though the left ventricular size and function return to normal, there is evidence that contractile reserve is impaired,[42] and recurrence of PPCM despite rapid return of heart size and function to normal in the prior affected pregnancy has been reported.[43] Therefore, subsequent pregnancies, if they cannot be avoided, should be managed in collaboration with a high-risk perinatal center.

SUMMARY AND RECOMMENDATIONS

Peripartum cardiomyopathy is a rare disease of unknown cause that strikes women in the childbearing years, may recur, and is associated with a high mortality rate. Hypotheses about the cause center on interactions of peripartum physiology with infectious, inflammatory, genetic, hormonal, or metabolic factors. Diagnosis of PPCM is challenging and requires vigilance. Once PPCM is identified based on the workshop criteria, the primary goal of therapy is to alleviate symptoms of congestive heart failure. If left ventricular size returns to normal after pregnancy, the short-term prognosis is likely to be favorable, although long-term sequelae, particularly with repeat pregnancy, still are not known. Failure of heart size to return to normal is associated with excess morbidity and mortality.

Based on the information presented at the workshop and on the identified gaps in knowledge, participants made the following clinical and research recommendations:

- Adherence to the criteria in Table 1, especially the timing and the necessity for echocardiographic demonstration of left ventricular systolic dysfunction, is important in making the diagnosis of PPCM.
- Once the diagnosis is made, close collaboration between specialists in obstetrics, perinatology, and cardiology is essential. If the diagnosis is made before birth, the team should include anesthesiology and neonatology as well, and transfer to a high-risk perinatal center should be considered.
- For affected patients, family history may be revealing and should be elicited.
- Therapy should be initiated using standard heart failure protocols. Angiotensin-converting enzyme inhibitors should be avoided prenatally, but are a mainstay of therapy otherwise.
- Immunosuppressive therapy can be considered if an endomyocardial biopsy indicates myocarditis, and if there is no improvement after 2 weeks of standard heart failure therapy.
- Subsequent pregnancies remain controversial, but at the very least should be managed in a high-risk perinatal center if they cannot be avoided.

Workshop participants also made recommendations about the need for additional research and dissemination of information:

- An international registry should be established to capture prospectively all women with PPCM to facilitate the following: (1) development of better incidence and prevalence estimates, (2) determination of risk factors and prognostic variables, (3) ascertainment of cardiovascular risks for subsequent pregnancies, (4) establishment of a centralized serum and tissue bank to help facilitate identification of the cause of PPCM, and (5) evaluation of therapeutic interventions.
- A review of current knowledge about PPCM should be prepared for publication. This article fulfills that recommendation.
- Because PPCM is an under-recognized obstetrical problem, an educational brochure should be prepared for broad dissemination to individuals involved in the care of women of childbearing age.

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European Journal of Heart Failure (2010) **12**, 767–778
doi:10.1093/eurjhf/hfq120

POSITION STATEMENT

Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy

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Received 8 June 2010; accepted 9 June 2010

Peripartum cardiomyopathy (PPCM) is a cause of pregnancy-associated heart failure. It typically develops during the last month of, and up to 6 months after, pregnancy in women without known cardiovascular disease. The present position statement offers a state-of-the-art summary of what is known about risk factors for potential pathophysiological mechanisms, clinical presentation of, and diagnosis and management of PPCM. A high index of suspicion is required for the diagnosis, as shortness of breath and ankle swelling are common in the peripartum period. Peripartum cardiomyopathy is a distinct form of cardiomyopathy, associated with a high morbidity and mortality, but also with the possibility of full recovery. Oxidative stress and the generation of a cardiotoxic subfragment of prolactin may play key roles in the pathophysiology of PPCM. In this regard, pharmacological blockade of prolactin offers the possibility of a disease-specific therapy.

Keywords Peripartum cardiomyopathy • Definition

Introduction

Heart failure (HF) in the puerperium was recognized as early as the nineteenth century.[1] Peripartum cardiomyopathy (PPCM) is not caused by aggravation of an underlying idiopathic dilated cardiomyopathy (IDCM) by pregnancy-mediated volume overload. Haemodynamic stresses reach their peak just before delivery and volume load is greatly reduced after delivery, which is when

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PPCM often presents. Instead, it is now widely accepted that PPCM is distinct from other types of HF,[2] although the cardiac phenotype of PPCM resembles that of a DCM. The clinical course, however, is highly variable and rapid progression to end-stage HF may occur, often within a few days.[3] On the other hand, spontaneous and complete recovery of ventricular function may also occur. Both features are unusual in other forms of cardiomyopathy.[4,5]

Definition and epidemiology

Peripartum cardiomyopathy has been variably defined (*Table 1*).[2,6,7] The definition of the Workshop held by the National Heart Lung and Blood Institute and the Office of Rare Diseases (2000) states that it must develop during the last month of pregnancy or within 5 months of delivery. We believe that this time frame along with echocardiographic cut-offs are arbitrary and may lead to under-diagnosis of PPCM. We propose the following simplified definition:

'Peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with HF secondary to left ventricular (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. The LV may not be dilated but the ejection fraction (EF) is nearly always reduced below 45%'.

Incidence

Very little is known about the incidence of PPCM (*Table 2*).[5,8–12] Most studies have been conducted in the USA, South Africa, or Haiti with few from the rest of the world, including Europe. The studies that have been performed were mostly single-centre case series. From the available literature, the incidence of PPCM appears to be around 1 in 2500–4000 in the USA, 1 in 1000 in South Africa, and 1 in 300 in Haiti (*Table 2*). Prospective, population-based, well-conducted, epidemiological studies are required.

Pathophysiology

The precise mechanisms that lead to PPCM remain ill-defined, but a number of contributing factors have received attention. These include general risk factors for cardiovascular disease (such as hypertension, diabetes, and smoking) and pregnancy-related factors (such as age, number of pregnancies, number of children born, use of medication facilitating birth, and malnutrition).[13]

Prolactin, 16 kDa prolactin, and cathepsin D

Recent data suggest involvement of a cascade involving oxidative stress, the prolactin-cleaving protease cathepsin D, and the nursing-hormone prolactin, in the pathophysiology of PPCM. Oxidative stress appears to be a trigger that activates cathepsin D in cardiomyocytes and cathepsin D, subsequently, cleaves prolactin into an angiostatic and pro-apoptotic subfragment.[3] Patients with acute PPCM have increased serum levels of oxidized low-density lipoprotein, indicative of enhanced systemic oxidative stress, as well as increased serum levels of activated cathepsin D, total prolactin, and the cleaved, angiostatic, 16 kDa prolactin fragment.[3]

In a mouse model, the 16 kDa prolactin fragment has potentially detrimental cardiovascular actions that could play a pathophysiological role in PPCM. It inhibits endothelial cell proliferation and migration, induces endothelial cell apoptosis and disrupts already formed capillary structures.[3] This form of prolactin also promotes vasoconstriction[3] and impairs cardiomyocyte function.[3] Consistent with the idea that 16 kDa prolactin-mediated apoptosis may contribute to the pathogenesis of PPCM, pro-apoptotic serum markers (e.g. soluble death receptor sFas/Apo-1) are increased in PPCM patients and are predictive of impaired functional status and mortality.[13,14]

In this regard, an efficient antioxidant defence mechanism in the maternal heart, late in pregnancy and the post-partum period, seem crucial as markers of cellular oxidation rise during pregnancy, culminating in the last trimester (as part of normal pregnancy-related physiology).[15] Experimental data in a mouse model of PPCM (i.e. mice with a cardiomyocyte-restricted deletion of the signal transducer and activator of transcription-3, STAT3) suggest that defective antioxidant defence mechanisms may be responsible for the development of PPCM.[3]

Furthermore, a key functional role of an activated oxidative stress–cathepsin D–16 kDa prolactin cascade in PPCM is strongly supported by the observation that suppression of the production of prolactin by the dopamine D_2 receptor agonist, bromocriptine, prevented the onset of PPCM in the mouse model of PPCM.[3]

Preliminary reports of the possible clinical effects of bromocriptine in patients with acute PPCM are discussed below.[16–18]

Other putative pathophysiological mechanisms

Inflammation

In addition to oxidative stress, inflammation may play a role in the pathophysiology of PPCM. Serum markers of inflammation [including the soluble death receptor sFas/Apo-1, C-reactive protein, interferon gamma (IFN-γ), and IL-6] are elevated in patients with PPCM.[3,13,14,19] This mechanism is underscored by the apparent clinical benefit of the anti-inflammatory agent pentoxifylline in a non-randomized trial in 58 patients with PPCM.[20] Furthermore, that failure to improve is clinically associated with persistently elevated IFN-γ suggests that inflammatory status is important in the prognosis of patients with PPCM.[19]

Viruses

Viral infection of the heart is another possible cause of peripartum inflammation, although clinical data are far from conclusive. Although some reports have implicated cardiotropic enteroviruses in PPCM,[21,22] others have not found a higher frequency of viral infections in patients with PPCM than in those with IDCM.[23] Human immunodeficiency virus infection does not seem to be implicated in PPCM.[24]

Autoimmune system

In addition, autoimmune responses may play a role in the pathophysiology of PPCM. For example, serum derived from PPCM patients affects *in vitro* maturation of dendritic cells differently than serum from healthy post-partum women.[25] High titres of auto-antibodies against selected cardiac tissue proteins have