ORIGINAL ARTICLE

Predictors of Mortality or Heart Transplantation in Peripartum Cardiomyopathy

MARGARITA A. PERADEJORDI†, LILIANA E. FAVALORO*, ALEJANDRO BERTOLOTTI, DANIEL ABSI, CARLOS VIGLIANO, RUBÉN LAGUENS, MIRTA DIEZ†††, ROBERTO R. FAVALORO†††

Received: 01/02/2012
Accepted: 11/22/2012
Address for reprints:
Dr. M. Peradejordi
Hospital Universitario Fundación Favaloro
Av. Belgrano 1746/1782
(C1093AAS) Buenos Aires,
Argentina
Fax number: (+5411) 4378-1247
e-mail: mperadejordi@ffavaloro.org / www.fundacionfavaloro.org

ABSTRACT

Background
Peripartum cardiomyopathy is an uncommon form of congestive heart failure with unpredictable outcome. Very little is known about its real incidence and prevalence, and its etiology is still unknown, although a number of contributing factors, including diverse risk factors, have been proposed.

Objective
The aim of this study was to analyze the predictors of mortality or need for heart transplantation.

Methods
Twenty three patients were retrospectively evaluated between 1992 and November 2011. Patients with decompensated heart failure were managed with hemodynamic monitoring. Median follow-up was 7.3 years (3.2-17.5). Univariate Cox regression analysis was performed and overall survival was calculated using the Kaplan-Meier method.

Results
Mean age was 28.7±8.8 years and 8 patients were multipara. Seventy three percent of patients were in functional class III-IV. Systolic blood pressure and diastolic blood pressure were 103±23 and 67±11 mm Hg, respectively, and heart rate was 92±19 bpm. All patients were in sinus rhythm. The cardiothoracic index was 0.56±0.07. End-diastolic and end-systolic left ventricular dimensions were 67.5±10.2 and 56.7±10.1 mm, respectively; left atrial dimension was 42.5±6 mm and left ventricular ejection fraction was 24.6%±10.8%. Mean pulmonary artery pressure was 25±9 mm Hg and pulmonary capillary wedge pressure 18.4±7.8 mm Hg; cardiac index was 2.6±0.6 L/min/m2. Seven patients died and 3 patients underwent heart transplantation. Univariate analysis revealed that functional class, cardiac index, systolic and diastolic blood pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, cardiac index and left atrial dimension were associated with mortality and heart transplantation. Survival at one, three and six years was 91%, 82% y 64%, respectively.

Conclusions
In-hospital mortality was 4.3% and need for heart transplantation or mortality during follow-up was 39%. Hemodynamic parameters at admission were the main predictors of mortality and heart transplantation.

Key words
Cardiomyopathies - Heart Failure - Pregnancy - Myocarditis - Heart Transplantation

Abbreviations
- EMB Endomyocardial biopsy
- FC Functional class
- LVDD Left ventricular diastolic dimension
- LVSD Left ventricular systolic dimension
- ECG Electrocardiogram
- LVEF Left ventricular ejection fraction
- CI Cardiac index
- CTI Cardiothoracic index
- DCM Dilated cardiomyopathy
- PPCM Peripartum cardiomyopathy
- NYHA New York Heart Association
- DBP Diastolic blood pressure
- MPAP Mean pulmonary artery pressure
- SBP Systolic blood pressure
- PCWP Pulmonary capillary wedge pressure
- HTx Heart transplantation

BACKGROUND
Peripartum cardiomyopathy (PPCM) is an uncommon cause of congestive heart failure, and due to its unpredictable outcome it is considered a distinct disease entity among cardiomyopathies. It is defined as an idiopathic cardiomyopathy presenting with heart failure towards the end of pregnancy or in the first months postpartum, without any other evident cause of heart failure. (1)

Very little is known about the incidence and prevalence of PPCM. According to different authors its estimated incidence in different geographic regions is between 1/300 to 1/1,000 in Africa and Haiti and between 1/250 to 1/4000 pregnancies in the USA. (1) The etiology of PPCM remains unclear although several mechanisms have been involved, including risk factors as age at pregnancy, multiparity, twin pregnancy, history of hypertension or preeclampsia, African people, selenium deficit and use of tocolytics.

Peripartum cardiomyopathy is considered a form of dilated cardiomyopathy (DCM) of relatively good prognosis. However, it has been associated with high maternal and fetal morbidity and mortality, ranging between 15% and 50% due to heart failure, arrhythmias and thromboembolic events. Heart transplantation (HTx) may be necessary in a few cases. (2-4)

The goal of the present study was to evaluate the clinical, hemodynamic and functional characteristics of patients with PPCM and to analyze the predictors of mortality or need for HTx.

METHODOLOGY

Twenty-three consecutive patients with PPCM, referred to our center between 1992 and November 2011, were retrospectively evaluated. All the patients were admitted with heart failure for evaluation of PPCM or the possibility of undergoing HTx.

Diagnostic approach
The diagnostic criteria recommended by Pearson - Rahimtoola and by the European Society of Cardiology to define PPCM was used. (1)

On admission electrocardiogram (ECG), chest X-ray and color Doppler echocardiography was evaluated in all the patients. Functional studies were not performed to patients with signs of severe heart failure. Patients with decompen-sated heart failure were managed with hemodynamic monitoring using a Swan-Ganz catheter until clinical stabilization was achieved. An endomyocardial biopsy (BEM) was performed in a group of patients in whom the diagnosis of myocarditis was defined following the Dallas criteria. (5)

Analyzed variables
The following variables were analyzed on admission: age and number of pregnancies, New York Heart Association (NYHA) functional class (FC), systolic blood pressure (SBP), heart rate (HR), presence of rales or third cardiac sound, cardiothoracic index (CTI) on chest x-ray, cardiac rhythm, presence of complete left bundle branch block, left ventricular diastolic and systolic dimensions (LVDD, LVSD), left atrial dimension and left ventricular ejection fraction (LVEF).

The evaluated hemodynamic parameters were: systolic pulmonary artery pressure (SPAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and cardiac index (CI).

Treatment
Standard therapy for acute heart failure was used: intravenous diuretics, vasodilators and inotropic agents in case of low cardiac output. Mechanical support devices were used in refractory cardiogenic shock as bridge to heart transplantation. All the patients received anticoagulant therapy with intravenous heparin to prevent thromboembolic events. Pelvic examination and inhibition of lactation was performed to all the patients with recent diagnosis.

Follow-up
All patients were followed-up until December 2011. Deaths and need for HTx were recorded. Follow-up included ambulatory clinical and echocardiographic control and telephone contact with the patients or the treating physicians. The primary endpoints were all-cause mortality and need for HTx.

Statistical analysis
Continuous variables were expressed as mean and standard deviation or median (25-75% interquartile range) and categorical variables as percentage. Normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test.

Differences between groups were analyzed with Student’s t test for continuous variables with normal distribution, Fisher’s test for categorical variables and Mann-Whitney test for numerical variables with non-Gaussian distribution.

The primary endpoints of all-cause mortality and HTx were represented by a Kaplan-Meier curve.

Univariate Cox regression analysis was performed and the hazard ratios and 95% confidence intervals were calculated for each variable and endpoint.

A two-tailed p value < 0.05 was considered statistically significant. The study protocol was approved by the Ethics and Research Committee of our institution. The patients signed an informed consent form to undergo EMB, ensuring the confidentiality of the information.

RESULTS

Characteristics of the population
From a total of 1365 patients transferred to our institution for evaluation of cardiomyopathy or pre-heart transplantation assessment, 520 had idiopathic DCM and diagnosis of PPCM was made in 23 (4.4%). All were Caucasian patients, with average age 28.7 ± 8 years, and 39% were primigravidae. The main symptom on admission was NYHA FC III-IV dyspnea in 73.9% of patients. Only two patients (8.7%) had an embolic event (embolic stroke). The baseline characteristics of the population are described in Table 1.

The patients were analyzed in two groups: those who survived (n = 13) and those who required heart transplantation or died (n = 10). Most of the patients in the last group were multipara and were hospitalized with hemodynamic instability, in FC II-IV, with systemic hypotension and presence of third heart sound. The CTI was higher and LVEF was lower. The hemodynamic parameters measured by right ventricular catheterization showed a reduced CI and...
There were no significant differences in symptoms presentation, HR, presence of arrhythmias, intraventricular conduction abnormalities or left ventricular dimensions.

Endomyocardial biopsy was performed in 17 patients (85%) with evidence of myocarditis in 5 (29.4%) and without significant differences between both groups (Figure 1).

Univariate analysis identified FC at admission, CTI and LVEF as predictors of mortality or need for HTx. Systolic blood pressure, DBP, CI, MPAP and PCWP were identified as prognostic markers (Table 2). The presence of myocarditis in EMB was not a predictor of adverse outcome.

Treatment
Medical treatment upon admission and during follow-up is shown in Figure 2. A high percentage of patients...
received angiotensin-converting enzyme inhibitors during puerperium. Use of beta blockers was low at the moment of admission. Only 45% of patients were receiving anticoagulant agents on admission. Nine patients required intravenous inotropic agents and 5 patients ventricular assist devices: intraaortic balloon pump in 4 patients and a Novacor® device in one due to refractory shock.

**Follow-up**
Median follow-up was of 7.3 years (3.2-17.5). In-hospital mortality was of 4.3%, in one patient due to refractory cardiogenic shock. Nine patients (39%) required HTx or died during the follow-up period. Three patients underwent orthotopic HTx during follow-up, one of which presented humoral rejection immediately after transplantation and died of graft vascular disease two years later. Of the 13 surviving patients, left ventricular systolic function recovery occurred in 7 cases (54%) with favorable clinical outcome. Survival rate at 1, 3 and 6 years was 91%, 82% and 64%, respectively (Figure 3).

**DISCUSSION**
Although the association between congestive heart failure and pregnancy has been reported since 1849, it was not until 1937 that Gouley et al. recognized PPCM as a distinctive clinical entity. (6-8)
The incidence and prevalence of PPCM is low. International publications have reported a significant variation depending on race and analyzed region; however, there is little information about its prevalence in our country. (9) From studies conducted in large cohorts in Africa we selected the ones by Silaw et al. and Desai et al. who reported mortality rates of 15% and 14%, respectively, but had no available information on the need for HTx. (10, 11) In a retrospective study conducted by Mielenzuk et al. in 171 patients with PPCM in the USA, 42% were Caucasian but

![Fig. 1. A. A 24-year old multipara patient admitted in cardiogenic shock and FC IV with LVEF < 25%. EMB one month after onset of symptoms shows lymphohistiocytic myocarditis and associated focal myocyte injury (hematoxylin-eosin stain 200×). The patient had a favorable outcome with LVEF recovery to > 50%. B. A 27-year old primipara patient admitted in cardiogenic shock and FC IV with LVEF < 25%. The patient evolved with progression of the disease. The EMB performed 14 months after onset of symptoms shows focal lymphocytic myocarditis (hematoxylin-eosin stain 200×). The patient underwent emergency HTx 14 months after onset of symptoms. C. A 34-year old multipara patient admitted in cardiogenic shock and FC IV with LVEF < 20%. The initial response to inotropic therapy was good. The EMB performed after 14 months after onset of symptoms shows focal lymphocytic myocarditis (hematoxylin-eosin stain 100×) and moderate to severe intermyocytic fibrosis with focal replacement fibrosis. The patient developed severe ventricular dysfunction and required multiple hospitalizations due to CHF. Seven years after the first episode she became pregnant again and presented aggravation of the disease and severe pulmonary hypertension. She refused to join the waiting list for HTx and died of decompensated HF. D. Image C with hematoxylin-eosin stain 200×.](image)

![Fig. 2. Pharmacological treatment. ACEI: Angiotensin-converting enzyme inhibitor. β: Beta blockers AMD: Amiodarone](image)

<table>
<thead>
<tr>
<th>Country</th>
<th>Univariate analysis (Cox)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at pregnancy</td>
<td>0.95 (0.88-1.02)</td>
<td>0.178</td>
<td></td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>1.35 (1.01-1.80)</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>First pregnancy</td>
<td>0.11 (0.01-0.91)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 pregnancies, n (%)</td>
<td>4.26 (1.15-15.75)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Functional class (NYHA)</td>
<td>3.60 (1.35-9.61)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>0.89 (0.82-0.97)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.06 (0.01-0.48)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.88 (0.82-0.95)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>0.89 (0.82-0.97)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>1.09 (1.01-1.18)</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>PCWP</td>
<td>1.10 (1.01-1.20)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.01 (0.98-1.04)</td>
<td>0.486</td>
<td></td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>0.44 (0.09-2.10)</td>
<td>0.305</td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>2.02 (0.57-7.18)</td>
<td>0.277</td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic index</td>
<td>1.14 (1.04-1.24)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>LVDD</td>
<td>1.01 (0.96-1.07)</td>
<td>0.588</td>
<td></td>
</tr>
<tr>
<td>LVSD</td>
<td>1.05 (0.99-1.11)</td>
<td>0.122</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>1.29 (1.12-1.50)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Myocarditis (EMB)</td>
<td>0.81 (0.61-4.04)</td>
<td>0.799</td>
<td></td>
</tr>
</tbody>
</table>

HR: Hazard ratio. CI: confidence interval. Other abbreviations as in Table 1.
The etiology of PPCM is uncertain, yet the presence of myocarditis in EMB is a common finding. Felker et al. have reported an incidence of myocarditis in EMB is a common finding with variable incidence. Felker et al. have reported an incidence of 62% (12) and Rizek et al. of 8.8%. In our series, the prevalence of myocarditis in EMB was 29%. These differences might be due to the criteria used to define myocarditis, the time interval between EMB and symptoms onset and to demographic and epidemiological variations.

As it happens with other cardiomyopathies, the genetic factor cannot be ruled out. An association with a family history of DCM has been recently found in PPCM cases. In a group of 90 families carrying DCM, the incidence of PPCM was 6% with a mutation in the gene encoding cardiac troponin C in a subgroup of patients. None of the patients had a family history of cardiomyopathy.

The role of inflammatory cytokines in the pathogenesis of PPCM has been widely analyzed, and elevated levels of TNF-α, IL-6 and Fas/APO-1 have been identified in patients with PPCM. (10, 21)

An abnormal response to the hemodynamic stress of pregnancy has been suggested as another etiopathogenic factor. During the second trimester of pregnancy, left ventricular end-diastolic volume and cardiac output may increase by 10% and 45%, respectively. Prolonged use of tocolytics and selenium deficit has also been postulated as an etiological hypothesis. In our group of patients, the diagnosis of heart failure was made in 22% of cases before delivery, in 35% during the first postpartum month and in 43% between the second and fifth postpartum months.

Conventional medical treatment for heart failure was used. The patients referred to our institution were admitted postpartum. At admission, 80% received angiotensin converting enzyme inhibitors, 10% beta blockers and 20% spironolactone, considering that 65% of the patients were admitted more than 15 years ago. Anticoagulation therapy should be considered in this condition, as pregnancy is a hypercoagulable state associated with an increase in coagulation factors II, VII, VIII and X and fibrinogen and increased platelet adhesion until 4 or 6 weeks postpartum. Thromboembolic events have been reported in 50% of cases. In our series, two patients presented stroke as first clinical event, only one of whom was receiving previous anticoagulation therapy. All the patients were treated with anticoagulants during the acute phase until ventricular function recovery.

Use of other therapeutic options to conventional treatment is currently under study. (22) The association of pentoxifylline, an inhibitor of proinflammatory cytokines, and intravenous immune globulin with immune modulatory properties, has been suggested. (23) In our experience, only one patient received intravenous immune globulin therapy with partial response to treatment and none of them received immunosuppressive therapy.

A 16-kD proapoptotic form of prolactin has been recognized as an etiopathogenic factor in PPCM. Therefore, drugs that inhibit prolactin secretion as bromocriptine may represent a novel therapy. (22, 24) Recently, a pilot study has demonstrated beneficial effects of standard care plus bromocriptine. (25) We do not have experience with chronic bromocriptine therapy.
treatment, as this agent was only used to inhibit lacta-
tion.

Heart transplantation is a therapeutic option to be
considered in the group of patients unresponsive to
standard care. In 1987, Aravot et al. published six cas-
es with 30% mortality due to infection and rejection.
(26) The outcome of HTx in these patients is favorable
and long-term survival is similar to that of women un-
dergoing HTx for idiopathic DCM, although the rate of
rejection within the first six months is greater. (27)
The use of ventricular assist devices as a bridge to
transplantation or to myocardial recovery is indicated
in patients with refractory cardiogenic shock. (28, 29)
In our series, 9 patients required inotropic support
due to cardiogenic shock and three underwent HTx:
two patients in emergent conditions with intraaor-
tic balloon pump and one patient in urgent inotropic
support. Only one patient died two years after HTx
of graft vascular disease. Two patients presented ven-
tricular function recovery and 4 died: two with left
ventricular assist devices in the waiting list for HTx
and two during follow-up.

Felker at al. reported that patients with PPCM
after the acute phase had a better long-term progno-
sis than those with other cardiomyopathies. (30, 31)
Mortality rate varies; Demakis and Veille reported
25% and 50% mortality, respectively, within the first
six months postpartum. (32) In our analysis, in-hos-
pital mortality was 4.3% (one patient in cardiogenic
shock, with ventricular assist device, in the waiting
list for HTx). During follow-up, the combined end-
point of HTx and mortality was 39% (3 patients
underwent HTx, one died while in the waiting list with
ventricular assist device, 5 died due to progression of
the disease, and 2 became pregnant again and were
not referred for HTx assessment). In the group of pa-
tients who survived, 7 improved LVEF > 45% and re-
duced LVDD by 15%. Several authors have analyzed
the different prognostic predictors; Carballo, Cole,
Ravikishore et al. have agreed in demonstrating that
the prognosis of this disease is related to cardiomegaly
reduction and ventricular function improvement. (33)

Recommendations about subsequent pregnancies
are still controversial. Patients without recovery of
ventricular function should not get pregnant due to
high risk of relapse (25% and 50%). (34) On this point,
there is also lack of agreement regarding patients
with recovery of ventricular function or those with
abnormal contractile reserve. (35, 36) Thus, dobutami-
ne stress echocardiography may be useful for assess-
ment of subclinical systolic dysfunction due to hemody-
namic stress during pregnancy. (40) Maternal and fetal
prognosis of women with PPCM and new pregnancies
is still unfavorable, even for those patients with recov-
ery of left ventricular function. (13, 38)

Study limitations
The small number of cases is the main limitation of
our study because of the low incidence and prevalence
of PPCM in our country to draw significant conclu-
sions. It should be pointed out that this group of pa-
tients had a median follow-up of 7.3 years with het-
erogeneous medical treatment. An analysis by time
periods was not possible due to the small number of
patients. We believe that the high mortality or need
for HTx is biased due to the characteristics of our in-
stitution, a high complexity center with heart trans-
plantation facilities. Currently, the European Society
of Cardiology is conducting an international registry
of patients with PPCM for a better understanding and
treatment of this disease. (39)

CONCLUSIONS
In our series, after a median follow-up of 7.3 years,
survival free of death or no need for HTx was 91%,
82% and 64% at 1, 3 and 6 years, respectively. In-hos-
pital mortality was 4.3% and late mortality or need
for HTx was 39%. Hemodynamic parameters were the
main predictors of survival.

Peripartum cardiomyopathy has a low prevalence
but a great impact on the affected population. The re-
sults of national and international registries and mul-
ticenter prospective studies will help to understand
the etiopathogenesis of the disease and to find novel
therapeutic options to improve its outcome.
y diastólica, la presión capilar y pulmonar media, el índice cardiorariocal y el diámetro auricular izquierdo se asociaron con mortalidad y trasplante cardíaco. La supervivencia a 1, 3 y 6 años fue del 91%, 82% y 64%, respectivamente.

Conclusiones
La mortalidad hospitalaria fue del 4,3% y el requerimiento de trasplante cardíaco o la muerte en el seguimiento fueron del 39%. Los parámetros hemodinámicos al ingreso fueron los principales predictores de mortalidad y de trasplante.

Palabras clave > Cardiomiyopatías - Insuficiencia cardiaca - Embarazo - Miocarditis - Trasplante cardíaco

Conflicts of interest
None declared.

REFERENCES
15. Hibbard JU, Lindeheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echo cardiogra-