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Clinical Management and Long-Term Follow-Up of Patients with Peripartum Cardiomyopathy: A Prospective Registry Study

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Abstract

Introduction: Peripartum cardiomyopathy (PPCM) is a rare pathology in Western countries but is common in Africa. Its progression is highly variable, left ventricular function improves in almost one-third to one-half of patients. In sub-Saharan Africa, there are few prospective cohort studies. We aimed to describe the long-term evolutionary aspects of this pathology in a sub-Saharan African country, so we developed a PPCM registry; here, we present the first results after 2 years of follow-up. **Methodology:** This work was performed at the cardiology clinic of the Aristide Le Dantec Teaching Hospital of Dakar from January 01, 2017, to January 01, 2021, for a total duration of 4 years. This was an observational, longitudinal prospective study including patients admitted for peripartum cardiomyopathy. **Results:** During our study, 5372 patients were admitted to the cardiology clinic. Considering the inclusion criteria, 79 patients were consecutively recruited. The mean age was 30.5 ± 6.7 years, ranging from 18 to 42 years. Half of the patients came from rural areas (56.3%), and 78.2% of patients had a low socioeconomic status. Multiparity and twin pregnancies were noted in 72.8% and 20% of the patients, respectively. A total of 91% of patients had advanced NYHA stage 4 heart failure, and 3 patients had cardiogenic shock. Left ventricular dilatation was found in 52 patients, and severe left ventricular systolic dysfunction was found in 50 patients (90.9%). During hospitalization, 19 patients (34.5%) had complications. The evolution in the hospital was favourable in 45 patients (81.8%). The global mortality rate was 7.3% at 2 years. In multivariate analysis, fewer patients with a dilated left ventricle, a severe alteration of the LVEF

and an advanced age progressed towards remission. **Conclusion:** The long-term evolution of PPCM is very variable. Despite a good rate of remission, progression to end-stage heart failure and death is not negligible in cases of advanced maternal age and severe left ventricular impairment.

Keywords

Peripartum Cardiomyopathy, Pregnancy Cardiovascular Disease, Senegal

1. Introduction

Peripartum cardiomyopathy (PPCM) involves left ventricular systolic dysfunction (an LVEF less than 45%) [1] without an identifiable aetiology that occurs at the end of pregnancy or during the months following delivery and is responsible for a clinical state of heart failure. PPCM is a diagnosis of exclusion.

The incidence of PPCM is variable according to ethnicity and is higher in patients of African descent; PPCM is rare in Europe [2] [3].

In addition to the vital prognosis (low mortality rate of 1% - 2%) [4], the functional prognosis remains reserved due to the risk of persistent heart failure. The risk of recurrence during subsequent pregnancies is not negligible, sometimes making a subsequent pregnancy inadvisable.

The rapidity of evolution and the severity of this pathology require good knowledge of the diagnostic and therapeutic means that are usable in current practice. Internationally, many unknowns remain, particularly in sub-Saharan African countries, where long-term follow-up is lacking. This study contributes to the description of clinical presentations across different regions, worldwide mortality and morbidity.

This pathology has been the subject of some studies in Senegal; however, these studies were often retrospective, with small sample sizes and without long-term follow-up. To identify the evolutionary aspect of this condition, we decided to create a register to follow up PPCM patients; here, we present the first results after 2 years of follow-up. The main objective was to describe the long-term evolutionary aspects of this pathology in Senegal.

2. Methodology

This work was conducted in the cardiology clinic of the Aristide Le Dantec Teaching Hospital of Dakar from January 01, 2017, to January 01, 2021, for a total duration of 4 years. This study was approved by the ethics committee of the Cheikh Anta Diop University of Dakar.

This was an observational, longitudinal, prospective study including female patients admitted to the cardiology clinic of Aristide Le Dantec Hospital for peripartum cardiomyopathy. We consecutively recruited all patients admitted to the cardiology department of Aristide Le Dantec Hospital.

All patients with a diagnosis of PPCM according to the definition criteria of the European Society of Cardiology working group on PPCM who were hospitalized or followed-up in the department were included [1]. Patients who had a past history of PPCM and presented with new cardiac decompensation after a novel pregnancy were included.

We did not include patients with an echocardiographic aspect that did not correspond to the diagnosis, patients with another significant cardiopathy or any other cause of heart failure, and patients who refused to participate in the study.

We analysed the following epidemiological data: age, geographical origin of the patients, marital status, parity, twin pregnancy, preeclampsia or gestational hypertension and economic profile (which was subjectively assessed according to the profession, income, or assets of the patient or her family).

Clinical data included a family history of peripartum cardiomyopathy and a personal history of peripartum cardiomyopathy, preeclamsia and gestational hypertension. Functional and physical signs and paraclinical data included trans-thoracic echocardiography, including heart chamber diameters, kinetics, and left ventricular systolic function, the existence of thrombus or spontaneous intracavity contrast, and associated valve regurgitations.

Progression was assessed based on complications, with the occurrence of heart failure, thromboembolic events, the persistence of left ventricular dysfunction, cardiovascular collapse (defined as a new systolic blood pressure (SBP) < 65 mm Hg), cardiogenic shock and/or death as the main criteria. Cardiogenic shock was defined as an SBP < 90 mm Hg for >30 min or the provision of supportive interventions to maintain an SBP > 90 mm Hg and evidence of end-organ damage (cold extremities, oliguria, elevated serum creatinine).

Symptomatic and adjuvant treatments were also studied. We followed up the patients after hospitalization to assess their clinical status, and follow-up ultrasound was performed every 3 months.

We assessed the recovery rate and considered three classes: recovery (defined as an LVEF ≥ 50%); partial recovery (defined as an LVEF of 36% - 49%); and no recovery (defined as an LVEF ≤ 35%).

For the evolutionary data, we isolated two groups of patients:

• Group 1: patients who experienced remission within 12 months of treatment (defined as NYHA stage 1 and an LVEF ≥ 50%

• Group 2: patients without remission after 12 months of treatment (persisting LVEF < 50% and cardiac symptoms)

All collected data were entered into SPHINX software, and the analysis was performed by SPSS software version 21 and by Microsoft Excel.

Qualitative variables are described as percentages, and quantitative variables are described as means and standard deviations.

The different frequencies were compared using the chi-square test and Student's t test for quantitative variables following a normal distribution. Nonparametric tests were used where appropriate. A p value < 0.05 was considered sta-

tistically significant.

To identify the independent predictors of poor prognosis, we first performed binary logistic regression to identify significant variables. Univariate predictors were initially obtained, and if p was < 0.1, they were included in the multivariate analysis. Baseline EF was tested as a continuous variable to determine whether it predicted recovery or mortality. All values are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A p value < 0.05 and a 95% CI not containing 1 were considered statistically significant. Kaplan–Meier curves for improvement in the EF and mortality were constructed for the entire population.

3. Results

3.1. Clinical Characteristics of the Included Patients

The mean age was 30.3 ± 7.4 years, ranging from 18 to 46 years.

More than half of the patients (39%) were older than 30 years, as shown in Table 1.

Table 1. Clinical characteristics of the included patients.

Clinical characteristics	Number (N = 79)	Percentage
Age < 30 years	48	60.7
>30 years	31	39.3
Geographic origin		
Urban	38	48.7
Rural	41	56.3
Socioeconomic status		
low	65	82.3
median	11	13.9
high	3	3.8
Parity		
Primiparous	51	64.6
Multiparous	28	35.4
Twin pregnancy	13	16.5
Gestational hypertension or preeclampsia	24	30.4
Past history of PPCM	08	10.1
Episode of multiple heart failure	18	22.8
NYHA stage		
Stage III	14	18
Stage IV	65	82
Cardiovascular collapse	5	6.3
Heart failure	79	100
Moderate anaemia (8 - 10 g)	12	15.1
Cardiomegaly shown on chest X-ray	26/55	47.8
Left ventricular hypertrophy (ECG)	31	39.2

PPCM: peripartum cardiomyopathy; NYHA: New York Heart Association; ECG: electrocardiogram.

3.2. Doppler Echocardiography

Dilatation of the left ventricle was observed in 75 patients (94.9%). The mean left ventricular end-diastolic (LVED) diameter was 60 ± 4.3 mm, ranging from 46 to 77 mm. Left atrial dilatation was found in 52 patients. Left ventricular systolic dysfunction was found in all patients with a mean systolic ejection fraction of 29% ± 7.39%, calculated in Simpson biplane.

Nineteen (19) patients (24.1%) had moderate left ventricular systolic function impairment, and severe systolic function impairment was found in 60 patients (75.9%).

Five (6) patients (7.6%) had left ventricular thrombus. Spontaneous contrast was noted in 19 patients (24.1%). One case of moderate pericardial effusion was found in our study.

Functional mitral regurgitation was noticed in 23 patients (29.1%) and was associated with tricuspid regurgitation in 18 patients (22.8%). In our study, eight patients had a history of PPCM.

3.3. Treatment

A low-sodium diet was provided for all patients. The majority of the women were treated with optimal therapy for heart failure (beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers). Diuretics were used in all patients. ACE inhibitors and aldosterone receptor antagonists (spironolactone) were prescribed for 78 patients, and digitalis was prescribed for 4 patients during the acute phase. Sixty-three (73) patients (92.4% of the study population) had a beta-blocker in their discharge prescription. All patients had received anti-vitamin K (AVK) anticoagulant treatment. Bromocriptine was prescribed for 11 patients, and women on bromocriptine received prophylactic anticoagulation to prevent thrombus. Bromocriptine was stopped after 12 days of treatment in one patient who presented a thromboembolic complication of pulmonary embolism.

None of the patients had received immunosuppressive treatment, eplérenone or interventional treatment.

Adjuvant treatment consisted of contraception, which was effective in 61 patients (77%); 10 patients received iron supplementation, and 7 patients received nonspecific antibiotic therapy.

3.4. Evolution

The average length of hospitalization was 8 ± 5.02 days, ranging from 4 to 33 days. In-hospital progression was favourable in 70 patients (88.6%). During hospitalization, 19 patients (34.5%) had complications. The in-hospital mortality rate was 2.5%. Table 2 summarizes the complications that we observed in our series.

At six (6) months, follow-up echocardiography showed complete remission in 19% of patients (8/41).

Table 2. Complications observed in the population.

Complications	Number	Percentage (%)
Cardiogenic shock	3	3.7
Refractory heart failure	3	3.7
Thrombi and ventricular spontaneous echo contrast	12	15.1
Pulmonary embolism	1	1,8
Hospital mortality	2	2.5

At nine (9) months, two (2) patients had cardiac decompensation. Follow-up echocardiography showed complete remission in 15/48 patients (31.25%), partial remission (an LVEF > 45%) of systolic function in 10/48 patients (20.8%) and no remission in 23/48 patients (48%).

At twelve (12) months, one patient had died (one-year mortality rate of 5%). Twenty-seven (27) patients recovered normal left ventricular systolic function. The recovery rate at one year was 37%. At two years (24 months), we observed complete remission in 40 patients (50.6%); one patient died, and one patient had heart failure. A low LVEF persisted in 29 (36.7%) patients. Six patients were lost to follow-up. The overall mortality rate at 2 years was 5%. In the 8 patients with a history of PPCM who had a new pregnancy, the LVEF was normalized at 12 months, except in one patient. In **Figure 1**, we show the progression of LVEF recovery over time.

3.5. Prognostic Factors for Remission

A comparative analysis of the two groups with remission (Group 1) and without restoration of systolic function (Group 2) was performed.

Multivariate analysis showed that three independent criteria were strongly associated with non-recovery: ventricular dilatation, severe LVEF impairment and advanced age (**Table 3**).

4. Discussion

The major findings of our study are that during long-term follow-up, a substantial proportion of patients with PPCM recovered LV function (50.6%). Our follow-up duration was long enough to note delayed complete EF recovery beyond 6 months in the majority of cases. Our study showed a low mortality rate (5%) compared to a previous study in sub-Saharan Africa.

In the absence of a population-based multicentre study, the prevalence of PPCM is unknown in Africa, where only hospital data are available. In the United States, the incidence increased from 1/4000 pregnancies in 1993 to 1/2229 pregnancies in 2002 [5] [6].

Despite the lack of population-based data, the highest frequency of PPCM is reported in Africa, with proportions of 1 per 1000 births in South Africa and 1 per 3800 births in Burkina Faso [7] [8]. Finally, although PPCM remains a global pathology, the predominance of patients with black origins is undeniable and mostly represents an exposure factor for this pathology [9].

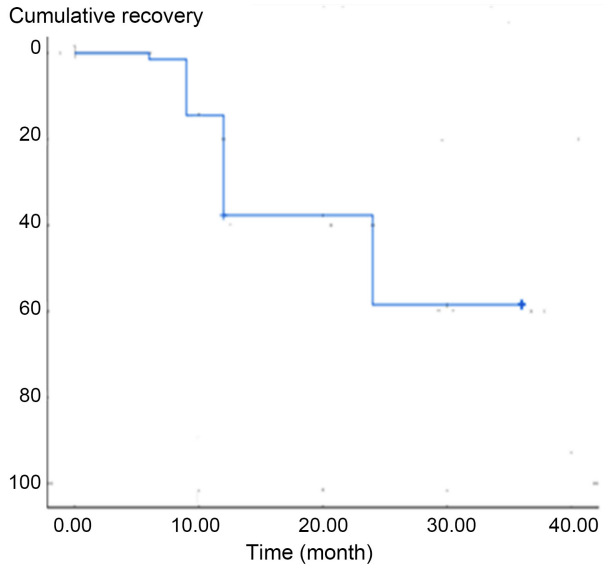

Figure 1. LVEF recovery curve as a function of time.

Table 3. Poor prognostic factors in bivariate and multivariate analyses.

Parameters	Patients in remission	Patients without remission	Bivariate analysis (p value)	Multivariate Analysis (p value)	Odd Ratio
Age	29.4 ± 8	32 ± 7	0.02*	0.031	1.14 [95% IC 1.01 - 1.29]
Twin pregnancy	14.8%	18.2%	0.181		
Parity	59.3%	59.1%	0.39		
Gestational hypertension	27.3%	25.9%	0.915		
NYHA stage III/IV	86.4%	88.9%	0.562		
Left heart failure	86.4%	92.6%	0.401		
LVED diameter ≥ 55 mm	44	35	0.0007*	0.011	1.16 [95% IC 1.03 - 1.31]
Baseline LVEF %	26.29 ± 8.8	35.8 ± 8.7	0.0001*	0.011	0.86 [95% IC 0.46 - 0.90]

NYHA: New York Heart Association, LVED: Left ventricular end-diastolic.

Furthermore, we noticed an increase in the rate of hospitalization for this pathology over the years in Senegal. The incidence found in our study was higher than that observed in previous studies carried out in Dakar, as it increased from 8.5 cases per year in 2001 [10] to 25.5 cases per year in 2019. This could probably be explained by improved diagnostic techniques and better access to care in Senegal.

Concerning the aetiological factors, PPCM occurs in relatively young multiparous women of low socioeconomic status, as found in our study and in the literature [11] [12]. Multiparity has also been reported as a factor by many authors [13]. In a large cohort registry on PPCM, under the auspices of the ESC

EURObservational Research Programme (EORP), African women were the youngest compared to other women with PPCM around the world [14].

Twin pregnancy is considered an aetiological factor of peripartum cardiomyopathy in Africa. In fact, 8% to 13% of patients with PPCM have a twin pregnancy [8]. We found that 16.5% of patients had a twin pregnancy.

NYHA stage IV was found in 82% of our population, and on echocardiography, left ventricular dilatation was noticed in 94.5% of patients. These data highlight the delay in the time from symptom onset to diagnosis. Furthermore, all women in the registry had severe heart failure at the time of presentation, suggesting that the condition is not diagnosed during the initial phase, perhaps because symptoms and signs such as dyspnoea, fatigue, and oedema are attributed to pregnancy or the postpregnancy state rather than heart failure. Prompt diagnosis should be a priority to allow timely initiation of heart failure therapies [14].

Regarding the therapeutic aspect, ACE inhibitors and beta-blockers were introduced for all our patients after the haemodynamic condition was stabilized. These drugs have shown beneficial effects on the mortality of heart failure patients regardless of the stage of progression [11].

Bromocriptine was prescribed in 11 patients (13.9%). Although bromocriptine is not often prescribed, its efficacy has been demonstrated in a princeps study by Sliwa [11], but further large-scale clinical trials are still needed to confirm its efficacy and safety.

The progression of PPCM is highly variable; progression to end-stage heart failure is not certain because left ventricular function improves in approximately one-third to one-half of patients during the first six months after delivery [15]. Recent data confirm that LVEF recovery often occurs but is delayed for up to six months to 1 year in the majority of patients [15] [16] [17].

During follow-up, we observed complete remission in 40 patients (50.6%). This rate improved significantly with the intensification of triple therapy of heart failure, increasing from 42.9% in 2001 [10] to 50.6% in our series. This could be explained by the progress in management, essentially earlier diagnosis, better optimization of ACE inhibitors and B-blocker treatment, and better follow-up due to the instauration of this registry.

In our study, the degree of restoration of left ventricular systolic function was better in patients receiving bromocriptine. The value of this parameter increased from 28.45% to 53.6% in patients receiving bromocriptine, while the LVEF increased from 28.45% to 42.1% in those receiving standard treatment alone ($p = 0.007$). Sliwa *et al.* found a significant improvement in LVEF at 6 months in patients receiving bromocriptine (LVEF increased from 27% to 58%; $p = 0.012$) [11]. This further confirms the benefit of bromocriptine in the treatment of PPCM.

Hilfiker-Kleiner *et al.* found an improvement in the left ventricular ejection fraction (LVEF) at 6 months by comparing a short and long course of bromocriptine ($n = 63$) [18]. This trial was informative regarding the favourable results

and relative safety of bromocriptine in PPCM patients, but due to the lack of a bromocriptine-free control group, the efficacy conundrum has not been fully resolved [18]. This treatment was used in 15% of patients in the ESC PPCM study [14]. Based on current evidence, the use of bromocriptine in patients with PPCM was recently given a Class II Level B recommendation in the 2018 European Guidelines on Cardiovascular Disease in Pregnancy.

Prognosis and Lethality

The prognosis of PPCM is unpredictable. Some patients die despite receiving treatment, while others progress favourably, and we observed complete recovery in most patients after 12 to 24 months. In our series, two patients died during hospitalization, with a lethality rate of 2.5%.

The lethality rate in PPCM patients is variable, varying from 0% to 28% according to the literature. We reported a mortality rate of 5% at two years. In the ESC global registry on PPCM, the six-month mortality rate was 6% [14]. The lower frequency of death reported in our registry compared with other previous studies on PPCM could reflect the effect of a prospective registry (it is possible that we provided higher quality in-patient management medical therapy and follow-up than prior retrospective studies, for example, the intensification of heart failure therapy according to the guidelines), but similar death rates have been reported in the literature.

Some authors have studied the elements of poor prognosis in PPCM patients [2] [9]. In this study, multivariate analysis showed that three independent criteria were strongly associated with nonrecovery: ventricular dilatation, severe LVEF impairment and advanced age. Factors suggested to be predictive of recovery in prior studies include the baseline ejection fraction and LV end-diastolic diameter [4] [19] [20]. Similar to our cohort, a report of 176 South African patients with PPCM who were followed up for only 6 months concluded that older age and a lower LV end-systolic diameter were predictive factors of PPCM.

This study presented certain limitations in addition to the small sample size, in particular, the number of patients receiving bromocriptine, which was due to the necessity to respect the criteria for prescribing bromocriptine, diagnostic wandering or the long delays in consulting our patients, which often led to a late diagnosis beyond 1 month. Additionally, during follow-up, we did not have enough data to make a comparative analysis after 1 month and at 3 months of treatment.

Despite these limitations, this is one of the first studies to present a long-term follow-up of PPCM patients in sub-Saharan Africa.

5. Conclusion

Peripartum cardiomyopathy (PPCM) is common in Africa. The prognosis is relatively improved because management has improved with the intensification of heart failure treatment. Bromocriptine should be considered in the acute phase

in patients with severe impairment.

Late recovery (>6 months) was noted in a substantial number of patients after long-term follow-up.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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