Peripartum cardiomyopathy: clinical pictures and prognosis
Cardiomyopathie du péripartum: aspects cliniques et pronostiques

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Résumé

Introduction : La cardiomyopathie du péripartum (CMPP) est une entité rare et méconnue d'insuffisance cardiaque survenant le dernier mois de la grossesse ou les cinq premiers mois du postpartum en l'absence d'étiologie connue. Le but de notre travail était de décrire les aspects cliniques et pronostiques de la CMPP et de dégager les facteurs prédictifs de rémission du ventricule gauche au cours de cette affection.
Methods : Nous avons mené une étude rétrospective de 20 cas de CMPP hospitalisés dans le département de cardiologie Adulte de l'hôpital la Rabta entre 2009-2016. Toutes les patientes ont été explorées par une échographie cardiaque à l'admission et après un suivi de 6 mois et de 1 ans. Une analyse multivariéé a été menée afin de dégager les facteurs prédictifs de rémission de la fonction ventriculaire gauche au cours de cette affection.
Résultats. L'âge moyen de nos patients était de 32 ans±2, 12 patients étaient multipares, une prééclampsie était notée dans 9 cas. Le diagnostic of CMPP était déclaré essentiellement en post partum. Le maitre symptôme était la dyspnée stade III. Un traitement médical de l'insuffisance cardiaque était prescrit à toutes les patientes. Nous avons déploré deux cas de décès. Au cours du suivi, la fonction ventriculaire gauche s'est améliorée dans 50%des cas avec une rémission complète dans 7 cas (38.8%). Les facteurs prédictifs de rémission en analyse multi variée étaient: un diagnostic en postpartum de CMPP, une fraction d'éjection<30%, un diamètre télediastolique du ventricule gauche <6 cm.
Conclusion :La CMPP est une étiologie rare de cardiomyopathie dilatée. L'étiopathologie reste mal élucidée. Le diagnostic repose sur l'échocardiographie cardiaque, l'évolution est imprévisible.

Mots-clés
Cardiomyopathie du péripartum, échocardiographie, pronostic

Summary

Introduction : Peripartum cardiomyopathy (PPCM) is a rare and unrecognized entity of HF occurring during the last month of pregnancy or the first five months of the postpartum in the absence of a known etiology.
Aims of the study was to describe clinical pictures and prognosis of PPCM and to identify the predictive factors of left ventricular (LV) recovery in this disease.
Methods : We retrospectively reviewed the records of 20 patients hospitalized in our department between 2009-2016 for the diagnosis of PPCM. All subjects had an echocardiogram to assess left ventricular ejection fraction (LVEF) at admission and at 6 and 12 months post-partum. We performed a multivariable analysis un order to determinate predictive factors of recovery left ventricular function during PPCM.
Résults : The mean age was 32±2years, 12 patients were multiparous, 9 patients had presented severe preeclampsia. Diagnosis of PPCM was discovered essentially in post-partum within Symptomatology was characterized by a dyspnea stage III. All patients received medical treatment of HF. We reported 2 cases of deaths. During follow up, 50% of patients had a complete improved in left ventricular ejection fraction (LVEF). It was a complete recovery in 7 cases (38.8%). Factors associated with a higher likelihood of recovery in multivariate analysis were: postpartum diagnosis of PPCM, LVEF>30%, LV diastolic dimension <6 cm
Conclusion : PPCM is a rare case of dilated cardiomyopathy .it's etiopathology is remains poorly elucidated. Echocardiography appears to be extremely valuable in diagnosing PPCM. Its evolution is unpredictable.

Keywords
peripartum cardiomyopathy, echocardiography, prognosis

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INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a rare type of heart failure(HF) of unknown cause occurring late in pregnancy or in the postpartum.Although the disease is relatively uncommon it's incidence is increasing, and it can be associated with important morbidity and mortality; Unfortunately, PPCM is a disease process whose underlying etiology were poorly understood. It's natural history and outcome were unpredictable.

PURPOSE

To describe clinical and prognostic pictures of PPCM and to identify the predictive factors of left ventricular (LV) function recovery.

METHODS

We retrospectively reviewed the records of 20 patients hospitalized in our department of cardiology in Rabta hospital between 2006-2016.
Inclusion critera were women with signs of HF appeared in the last month of pregnancy and up to five months postpartum, with absence of identifiable causes of heart failure before the last month of pregnancy and with left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria such as ejection fraction (less than 45%) and a left ventricular end diastolic dimension of more than 2.7 cm/m2 of body surface area.
Exclusion critera were patients with a history of prior cardiomyopathy attributable to other causes or structural heart disease were excluded.
All delivery records and follow-up encounters were reviewed for clinical and demographic information especially maternal and fetus characteristics.
Symptoms, physical examination, electrocardiogram finding at admission were collected for all patients.
All subjects had echocardiography, we collected anatomic and functional parameters of LV,right ventricule function, the pulmonary blood pressure and eventual mitral regurgitation, and we assess left ventricular ejection fraction (LVEF) at the time of admission which was considered the Baseline LVEF.Each patients was followed up over time to assess LVEF at 6months and 12 months.
A left ventricular global longitudinal strain (GLS) us a parameter evaluating LVEF was calculated only for 10 patients who had a good echogenicity at time of diagnosis of PPCM but this parameter was not used for a follow up of left ventricular function.
Time to recovery was noted for patients who had improvement in LV function. The date of the last echocardiogram was used to measure the period during which no improvement in LVEF was observed.

Definition of improvement.
-An LV EF>50% was considered complete recovery.
. If LV EF remained <30% patients was considered no improvement
- If the follow-up LV EF was between 35% and 50%, the improvement was considered partial.

Statistical analysis
Quantitative variables are expressed as means ± standard deviations. Comparisons between groups were carried out using student's *t*-test or the chi2 test in depends of the type of variable. Multivariable analysis was performed, using logistic regression model incorporating in order to determinate predictor factors of recovery of LV and for each factors, Odd ratio (OR) was calculated; statistical significance was considered present when $p<0.05$ in the multivariate analysis.

RÉSULTS

Maternal and fetal characteristics
A total of 20 patients were enrolled, the mean age was 32 ±2years (22-44); 12 patients were multiparous, 8 women had multifetal pregnancies. Caesarean section was performed in 10 patients, 9 patients had presented severe preeclampsia. Diagnosis of PPCM was discovered in ante partum in 5 cases with a gestational age ranging from 35 to 38 weeks of amenorrhea, and in post-partum in 15 cases. The mean time to diagnosis PPCM was 15 weeks after delivery. Symptomatology was characterized by a dyspnea stage III and IV in respectively 12 and 8 women, orthopnea in 8 cases, signs of pulmonary oedema in 10 patients, right signs of heart failure in 6 patients and cardiogenic shock in 2 cases. Electrocardiogram showed a tachycardia in 20 cases, ventricular arrhythmia in 9 cases, atrial fibrillation in 7 cases, left bundle block in in 5 cases, four women had left ventricular hypertrophy. Echocardiographic findings at admission to hospital revealed dilatation of the left ventricule (LV) with a mean ejection fraction (EF) of 26 % (11%-40%)(figure 1).

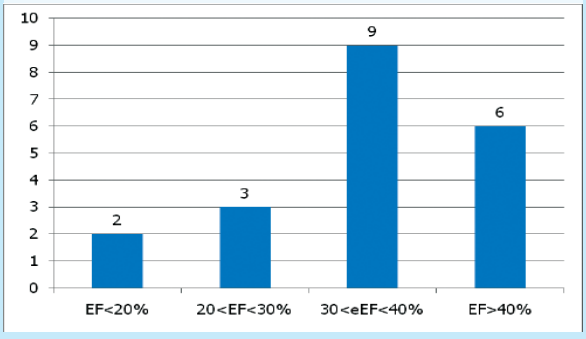

Figure 1: Distribution of patients according baseline LVEF at admission

A right ventricular dysfunction was noted in 6 cases, a functional mitral regurgitation in 9 cases. Pulmonary hypertension was observed in 5 cases, no patient had left ventricular thrombus. Left ventricular global longitudinal strain (GLS) was calculated for 10 patients with a had good echogenicity, it was altered in all cases with a mean value of -11,26±1.8 %

Treatment and prognosis

All patients received intravenous diuretics in case of acute heart failure then oral doses. Converting enzyme inhibitors were prescribed only in 15 cases because of hypotension.12 women were put on beta blockers and mineralocortid. The minimum duration of treatment was about 6 months for 9 patients and over a year for the others patients. Inotropics drugs, and circulatory support were necessary in 2 cases.

We reported 2 cases of death, so that hospital mortality rate was about 1%.The.mean time between death and diagnosis of PPCM was respectively 2 days and 1 months. Half of patients had not improved LVEF after a mean follow up of 26±3months, whereas 9 patients (50%) had a complete improved of LVEF. It was a complete recovery in 7 cases (38.8%) and a partial recovery in 2 cases (11.2%) within a delay of 6 months in 6cases and 24 months in 3 cases. Baseline characteristics of survival patients with and without improvement in ejection fraction were shown in (table1).

Table 1: Characteristic of survival patients .

	total (n=18)	improved (n=9)	Nonimproved (n=9)	p value
age(years)	30+- 6.5	30 +-7	30+- 6.2	0.7
Préclampsia (%)	44%	55	33	0.4
Multiparty (%)	55.5%	44	66.6	0.09
Postpartum diagnosis(%)	75%	88	55.5	0.04
Cesarean section (%)	55.5 %	66.6	44.4	0.08
LVEF >30%	77.5%	88%	66.6%	0.04
LVEDD <6.0cm	66.5%	88.8%	44.5%	

LVEF: left ventricular ejection fraction
LVEDD:leftventricule end diastolic diametre

A number of factors have been associated with a higher likelihood of LV recovery in multivariable analysis: postpartum diagnosis of PPCM, LVEF>30%, left ventricular end- diastolic diameter(LVEDD) <6 cm (table 2).

A subsequent pregnancy was notated in 5 women who had a totally recovered LVEF, a reccurence of cardiomyopathy was observed in 3 women and imposing an interruption of pregnancy ; but in the other cases, the evolution was favorable without relapse of PPCM.

Tableau 2: Multivariable study : Predictors factors of LV EF function recovery

	OR	95% confidence interval	p value
postpartum diagnoses	2	1.2; 6	0.01
LVEF>30%	3	2;7	0.02
LVEDD <6.0cm	0.45	0.2-0.6	0.04

LVEF: left ventricular ejection fraction
LVEDD:left ventricule end - diastolic diametre

DISCUSSION

The major findings of our study are as follows. 1) Strong associations have been shown between PPCM and multiparity, multifetal pregnancy and preeclampsia, 2) The majority of patients were diagnosed after delivery (75%),3) The present study underlines the low mortality rate (1%) in these women, 4) A substantial proportion of patients with PPCM recover LV function (50%); a complete recovery occurred in 38.2% of patients and partial in 11.2 %, 5) Our follow-up duration was long enough to note delayed complete recovery of EF beyond 6 months in the majority of the patients.

PPCM is defined as a non-familial form of peripartum heart failure, characterized as an idiopathic cardiomyopathy presenting with heart failure secondary to left-ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found as proposed by the working group on PPCM of the heart failure association of the european society of cardiology**(1).**

The ejection fraction is nearly always reduced below 45%. (**1**). PCCM is considered an independent disease, whose diagnosis relies on its relation to pregnancy and the exclusion of other cardiomyopathies.The etiology of PPCM is still unknown, and many potentials causes have been proposed but not proven **(2)**.Strong associations have been shown between PPCM and older maternal age (3), history of hypertension (**3),** multiple pregnancies(4), and multiparity **(3)**. Major of these factors associated to PPCM were reported in our study.

Most patients with PPCM present with typical signs and symptoms of heart failure, including dyspnea and orthopnea (**5**); similar symptomatology was noted in our patients. Electrocardiogram usually shows sinus tachycardia with nonspecific ST-T wave changes. Hypertrophy can be found as well as, conduction abnormalities including left bundle brunch block (**6**). These same anomalies were reported in our study.

Echocardiography shows variable degrees of LV dilatation, with moderate to severe depression of systolic function.Right ventricular and biatrial dilatation as well as moderate to severe mitral and tricuspid regurgitation are commonly seen, with increased

pulmonary pressures and mild pulmonary regurgitation, As well as moderate to severe mitral commonly seen, to with increased pulmonary pressures (7). Cardiac magnetic resonance imaging (MRI) has been used in a limited number of patients for the assessment of cardiac function and the detection of mural thrombi or myocardial fibrosis (8). Although MRI is probably safe during pregnancy intravenous gadolinium crosses the placenta, and the 2007American College of Radiology document on safe MRI practices recommends that it be avoided during pregnancy and used only if absolutely essential(9). In our study the use of MRI was not necessary since diagnosis of PPCM was confirmed by echocardiography.

Treatment included: Diuretic agents, intravenous and oral vasodilators, intravenous inotropes, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, spironolactone, and digoxin (10). In general, the treatment of HF in patients with PPCM should follow recent guideline recommendations (1), except during pregnancy, when drug therapy may need to be altered because of potential detrimental effects on the fetus especially ACE Inhibitors and spiranolactone. In fact the use of ACE Inhibitorsis contra indicated during pregnancy because of toxic effects, mostly on the developing fetal kidneys. Other potential side effects include oligohydramnios, prematurity, bony malformation, limb contractures, patent ductus arteriosus, pulmonary hypoplasia, respiratory distress syndrome, hypotension(11).There is no report of a teratogenic effect of spiranolactone in humans, but there is concern regarding the antiandrogenic effect of the drug in humans andfeminization reported in male rat fetuses (12).

Experimental drug therapy was tested in some studies (1.13,14); the effect of pentoxifylline, a xanthine agent known to inhibit the production of tumor necrosis factor and prevent apoptosis, was investigated by sliwa et al. (1) in 30 south African patients with PPCM. the results of the study demonstrated a significant improvement in a combined endpoints including death, failure to improve LVEF; Despite these positive results, no further studies have been conducted, and this therapy has not been widely used.

bozkurtet al. (13) added Intravenous immune globulin to conventional therapy in patients with PPCM and reported a significantly greater improvement in LVEF compared with control patients who received conventional therapy alone. Although the results seemed encouraging, averysmall number of patients and the lack of a blindly randomized, well-matched control group limited the study.

Sliwa et al. (14) attempted the use of bromocriptine. 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. In our study no experimental treatment was used.

PPCM can be associated with important and lasting complications, including severe heart failure, cardiogenic shock, arrhythmias, thromboembolic complications (15); we reported us a complication 2 cases of cardiogenic shocks. The mortality rate during PPCM is about 25% and alf of the deaths occur early in the first three postpartum months (16). In our study we notated 2 cases of deaths this was explained by the few number of cardiogenic shocks. The.mean time between death and diagnosis PPCM was respectively 2 days and 1 month For surviving patients, The evolution is often favorable with a recovery of left ventricular function from 20% to 60% of patients (17). Recent publications have reported recovery of LV function (LVEF >50%) at 6 months in 45% to 78% of patients, with a mean of 54% (18,19).mostly occurring within 2 to 6 months. After diagnosis later recovery, however, is possible and occurs in some patients. Our result was similar to those reported in these studies with a rate of recovery of 50%.

A number of factors have been shown to be associated with a higher likelihood of recovery, including LV diastolic dimension (5.5 to 6.0 cm), systolic function (LVEF> 30%)

At the time of diagnosis (19), lack of troponin elevation (20), a lower level of plasma BNP

(21), absence of LV thrombus (18), breast-feeding (19), diagnosis after the delivery (19), and non-African American ethnicity (15). PPCM with LVFE> 30%, diastolic diameter (LV EDD)<6cm and those diagnosed in the postpartum period appear to be the most likely to recover in our study.

Studies (22) demonstrates that in women who have had PPCM, subsequent pregnancies may be associated with deleterious fetal and maternal outcomes such as premature delivery and maternal cardiac dysfunction, including symptomatic heart failure and even death.

The risk of relapses of PPM was about 21% if the systolic function has returned to normal normally and 44% if a LV dysfunction persists (23).

Peripartum cardiomyopathy patients should be informed about contraceptive options since cardiac dysfunction re-emerges frequently in the peri- and postpartum phase often with worse outcome especially when LVEF structure and function did not completely recover (24). The use of an intrauterine device is recommended for PPCM patients since hormona contraceptives may interact with heart failure medication (1).

Study limitations

0ur study is a hospital based retrospective analysis subject to biais. The limited number of patients present another limitation; so that our result may not reflect the real course of PPCM in general population, national

multicentre epidemiological data are needed to confirm these finding.

CONCLUSION

PPCM is a rare, life-threatening disease.It's etiopathologyis remains poorly elucidated. Echocardiography appears to be extremely valuable in diagnosing PPCM formulating prognosis of recovery.

The course of this disease still remains a mystery and can be delayed.The treatment is until now symptomatic waiting a better understanding of the pathophysiology of this syndrome.

Conflicts of interest
No conflict of interest

REFERENCES

1. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A. 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. Eur J Heart Fail.2010;12:767–778.
2. Ntusi N, Mayosi BM. Etiology and risk factors of peripartum cardiomyopathy a systematic review. Int J Cardiol 2009;131:168 –79
3. Elkayam U, Akhter, MW, Singh H et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. Circulation.2005;11:2050
4. RussellRb, PetriniJr, Damus K, MattisonDr, Schwarz Rh. The Changing Epidemiology Of Multiple Births In The United States.ObstetGynecol.2003;101:129 –35
5. Lang RM, Lampert MB, Poppas A, Hameed A, Elkayam U. Peripartal cardiomyopathy. In: Elkayam U, Gleicher N, editors.Cardiac Problems in Pregnancy. 3rd edition New York, NY: Wiley-Liss, 1998:87–100.
6. Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: anomnious diagnosis. Am J ObstetGynecol.1997;176:182– 8
7. Chapa JB, Heiberger HB, Weinert L, DeCara J, Lang R, HibbardJU. Prognostic value of echocardiography in peripartum cardiomyopathy. ObstetGynecol. 2005; 105:1303– 8.
8. 8- Kawano H, Tsuneto A, Koide Y.Magnetic resonance imaging in a patient with peripartum cardiomyopathy. Intern Med. 2008;47:97–102.
9. Kanal E, Barkovich AJ, Bell C et al. ACR guidance document for safe MR practices: 2007. AJR Am J Roentgenol.2007;188:1447–74
10. 10-. Lindenfeld J, Albert NM, Boehmer JP. Executive summary: HFSA 2010 comprehensive heart failure practice guideline. J CardFail.2010;16:475–539.
11. Shotan A, Widerhorn J, Hurst A, Elkayam U. Risks of angiotensin converting enzyme inhibition during pregnancy: experimental andclinical evidence, potential mechanisms and recommendations foruse. Am J Med. 1994;96:451– 6.
12. Briggs GG, Freeman RK, Yatte SJ. Drugs in Pregnancy and Lactation. 8th edition Philadelphia, PA: Wolters Kluwer, 2008.
13. Bozkurt B, Villaneuva FS, Holubkov R.Intravenous immune globulin in the therapy of peripartum cardiomyopathy. J Am CollCardiol.1999;34:177– 80.
14. Sliwa K, Blauwet L, Tibazarwa K. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof concept pilot study. Circulation 2010;121:1465–73.
15. Goland S, Modi K, Bitar F.Clinical profile and predictors of complications in peripartum cardiomyopathy. J Card Fail.2009;15:645–50.
16. Bhakta P, Biswas BK, Banerjee B. Peripartum cardiomyopathy: review of the literature. Yonsei Med J 2007;48:731-47.
17. Chee KH. Favourable outcome after peripartum cardiomyopathy: aten-year study on peripartum cardiomyopathy in a university hospital.Singapore Med J.2013;54:28–31.
18. Amos A, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. Am Heart J 2006;152:509 –13.
19. Safirstein JG, Ro AS, Grandhi S, Wang L, Fett JD, Staniloae C. Predictors of left ventricular recovery in a cohort of peripartum cardiomyopathy patients recruited via the internet. Int J Cardiol.2010;154 :27-31
20. Hu CL, Li YB, Zang JM. Troponin T measurement can predict persistent left ventricular dysfunction in peripartum cardiomyopathy.Heart.2007;93:488 –90.
21. Forster O, Hilfiker-Kleiner D, Ansari AA.Reversal ofIFN-gamma, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. Eur J Heart Fail.2008;10:861– 8.
22. Elkayam U, Tummala PP, Rao K. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med. 2001;334:1567–71
23. Uri Elkayam, M.D, Padmini, Tummala, M.D, Kalpana Rao M. Maternal and Fetal Outcomes of Subsequent Pregnancies in Women with Peripartum Cardiomyopathy. N Engl J Med. 2001; 344:1567-1571
24. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa Kb et al. A cathepsin D-cleaved 16 k Daform of prolactin mediates postpartum cardiomyopathy. Cell.2007;128:589–600