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Use of Bromocriptine in the Management of Peripartum Cardiomyopathy: A Systematic Review and Meta-analysis

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Abstract

Background: Peripartum cardiomyopathy (PPCM) is the onset of heart failure during the last month of pregnancy or the first 5 months postpartum in a previously healthy woman. Roles of prolactin metabolites, possibly cardiotoxic in humans, in the pathogenesis of this disease has been verified. In some studies, medical treatment with Bromocriptine (a dopamine agonist able to inhibit prolactin) associated with standard therapy has shown beneficial effects including improvement of left ventricular ejection fraction in patients with PPCM. However, no previous systematic review has proven its place in the optimal management of these patients.

Methods: We performed a literature review to identify randomized and, nonrandomized clinical studies that reported the use of bromocriptine in the management of PPCM in addition to standard heart failure regimen compared to standard heart failure regimen alone. A total of 9 databases containing articles from January 1, 2000 to July 31, 2017 were analyzed, including MEDLINE, Embase, Cochrane, DARE and Scopus.

Results: We identified and screened 410 potentially eligible publications through the databases. Based on our inclusion and exclusion criteria, From the 410 potential publications through the databases, 4 studies for a total of 263 patients were included in this analysis: two randomized control trials and two prospective studies that investigated the effect of bromocriptine in the management of acute PPCM. Compared with the control (standard therapy for heart failure alone), bromocriptine when combined with standard therapy improved the left ventricle ejection fraction by 11.37% (MD 11.37, 95% confidence interval [CI]: 9.55-13.19 p=0.001) after 6 months compared to standard therapy alone. In addition, no thromboembolic events were reported in any of the 263 patients.

Conclusion: Peripartum cardiomyopathy is a rare but serious condition that affects childbearing women. The present study showed that bromocriptine has a therapeutic effect in the clinical outcomes of women with PPCM.

Keywords: Peripartum cardiomyopathy; Bromocriptine; Ejection fraction

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Introduction

Peripartum cardiomyopathy (PPCM) is a pregnancy-associated cause of heart failure (HF) that is characterized by left ventricular (LV) systolic dysfunction in previously healthy young women [1]. Although rare, its incidence is increasing, and it continues to be an important cause of cardiac-related maternal morbidity and mortality worldwide [2]. Treatment of PPCM is largely similar to treatment for other types of HF [3,4]. Furthermore, with early diagnosis and treatment, much of the patients demonstrate recovery. Nevertheless, many PPCM patients who do not recover cardiac function will require advanced heart failure therapies such ventricular assist device and heart transplantation as only 23% to 54% of patients show recovery of cardiac function within 6 months [5-8].

Although the cause of PPCM remain unknown and maybe be multifactorial, in recent years several contributory mechanisms have been recognized to initiate and propagate the disease. Prolactin is cleaved into an antiangiogenic and pro-apoptotic 16 kDa prolactin fragment (16K PRL) which in turns induces microRNA-146a expression which promotes endothelial damage and myocardial dysfunction **(Figure 1)**. MicroRNA-146a expression has been found in higher levels in women with cardiomyopathies compared with healthy postpartum women [9]. If full-length prolactin promotes inflammation in PPCM, therefore inhibition of prolactin release by the dopamine-D2-receptor agonist bromocriptine could help prevent onset or reverse disease process of PPCM.

Previous studies have shown that bromocriptine in addition to standard heart failure therapy appeared to improve LVEF and clinical outcomes in patient with PPCM. However, the impact of bromocriptine on clinical outcomes in patients with PPCM have not been well characterized and mostly because the sample size of the population study was too small for the previous results to be considered definitive and its overall prognostic significance has not been clearly determined.

Therefore, we conducted a systematic review and meta-analysis to determine the overall therapeutic effect and impact of bromocriptine on heart function and clinical outcomes of women with PPCM.

Materials and Methods

The main objective of this review was to find out if left ventricular function and clinical outcomes improve after adding bromocriptine to standard optimal heart failure treatment in patients with PPCM. We used the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statement extension for network meta-analysis. The PRISMA flow diagram was used to depict the four phases of the review including identification, screening, eligibility and inclusion as seen in **Figure 2**.

Search strategy

Searches were limited to peer-reviewed primary research articles published in English, French and Spanish up to July 31st, 2017. This research involved human subjects in reproductive age and described the effects of bromocriptine with standard heart failure treatment on patients with PPCM to improve left ventricular function and clinical outcomes in comparison to standard heart failure therapy alone. We developed the search strategy according to available guidance from the Cochrane Collaboration.

The search strategy in MEDLINE explored Medical Subject Heading (MeSH) terms in all the databases as shown in **Table 1**, related to patients with PPCM with terms to identify the use of bromocriptine as part of optimal medical management. The articles found to be relevant during the hand search were stored in End Note. Selected articles underwent full evaluation to assess their potential inclusion in the systematic review.

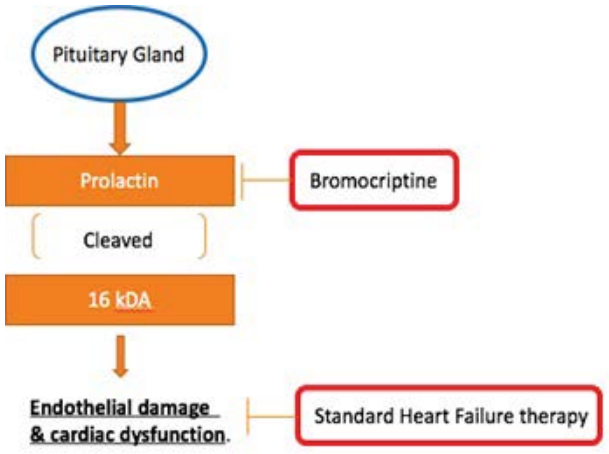


Figure 1 Disease specific therapy with bromocriptine.

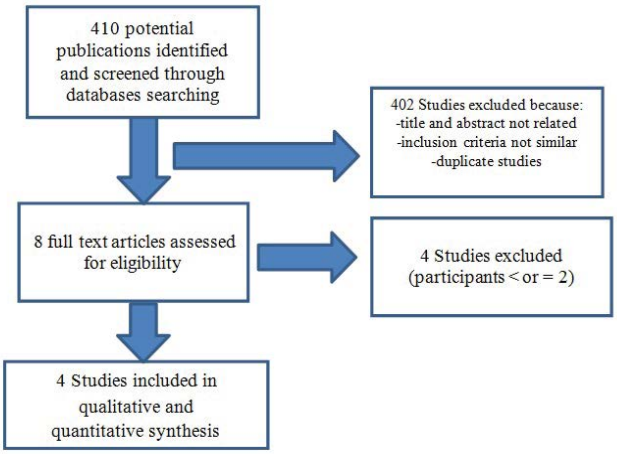


Figure 2 PRISMA flow diagram of study screening and selection.

Table 1 Inclusion criteria.

Sex	Female
Race	All
Age	Reproductive age
Diagnosis with echocardiographic evidence	PPCM with Ejection Fraction less than 45%
Control Group Treatment	Standard Heart failure therapy
Intervention group	Bromocriptine and standard heart failure therapy
Echocardiographic follow up	At least 3 months to 6 months
Clinical outcomes	New York Heart Classification

Study selection

Articles were selected for inclusion based on predefined criteria which included age, sex, ethnicity and the primary or secondary outcome being left ventricular functions and clinical outcomes seen in **Table 2**. Exclusion criteria were management of other causes of heart failure.

We excluded case reports and studies with equal or fewer than

Table 2 Characteristics of studies included in the systematic review.

Author	Year	Country	Size	Age (y)	Ethnicity	Design	f/u months	Baseline LVEF (EF%) n:patients		Baseline classification NYHA /n: patients	
Sliwa K et al. [1]	2010	South Africa	20	26 ± 8	Black	RCT	6	Br(+) 10	Br(-)10	Br(+)	Br(+)
								27.2 ± 8.1 (0.87)	26.9 ± 7.6 p (0.87)	II: 10	III-IV: 10
Haghikia et al. [13]	2013	Germany	115	34 ± 6	White	Prosp.	6 ± 3	Br(+)64	Br(-)32	II, III, IV	
								LVEF: 27 ± 9%.			
Marquis- Gravel G et al. [15]	2015	Canada	51	32 ± 7	White	Prosp.	6	Br(+) 11	Br(-) 41	None reported	
								20%	29%		
Yameogo et al. [14]	2016	Burkina Faso	96	31 ± 5	Black	RCT	3, 6, 12	Br(+)48	Br(-)48	Br(+)	Br(-)
								37.2 ± 6.6	37.5 ± 4.8	14: III	13: III
								(22.3 and 44.4)	(22.3 and 44.0) p:0.123	34: IV	35: IV

2 subjects. We did a thorough systematic review of clinical studies that mentioned treatment of PPCM with bromocriptine that included more than 10 women. We were able to identify and screen 410 potentially eligible publications through the databases. Based on our inclusion and exclusion criteria, 4 studies for a total of 263 patients were included in this analysis: two (2) randomized control trials and two (2) prospective studies that investigated the effect of bromocriptine in the management of acute PPCM.

Data collection

The information extracted for each study was: a) publication details (first author's last name, journal, year of publication), b) general characteristics of the study (country of origin, study design, single or multi-center, enrollment period, follow-up duration, number of patients included), and c) characteristics of the study population [age, gender, type of cardiomyopathy, LVEF, New York Heart Association (NYHA) HF classification, the results reported in the study [adjusted hazard ratio (HR), relative risk (RR), odds ratio (OR) with 95% confidence intervals (CI)] regarding the impact of baseline cardiac function on all-cause mortality.

Statistical analysis

Data were analyzed using Review Manager software 5.3. We did a thorough systematic review of clinical studies that mentioned treatment of PPCM with bromocriptine. Randomized and nonrandomized studies were identified by searching the electronic databases including MEDLINE, EMBASE, SCOPUS, COCHRANE, DARE from January 2000 to July 2017. The following search strategy was applied to search MEDLINE and we adapted it for the other databases: Bromocriptine OR "Bromocriptine"[Mesh])))) AND (cardiomyopathy OR cardiomyopathies OR heart failure OR "Cardiomyopathies"[Mesh] OR "Heart Failure"[Mesh])) AND ((pregnancy OR pregnant OR "Pregnancy"[Mesh] OR "Pregnancy Complications, Cardiovascular"[Mesh]))))) OR (((((Bromocriptine OR "Bromocriptine" [Mesh])))) AND (cardiomyopathy OR cardiomyopathies OR heart failure OR "Cardiomyopathies"[Mesh] OR "Heart Failure"[Mesh])) AND ((peripartum OR "Peripartum Period"[Mesh] OR post pregnancy OR postpartum)). The analysis included articles and abstracts published in English, French and Spanish and no restrictions to publication date were imposed.

Two authors (MI, GS) independently read the trials and screened the abstracts to choose potentially relevant articles. Risk of bias in the studies was assessed at an individual level of each study. Selected articles underwent full evaluation to assess their potential inclusion in the systematic review. We used fixed-effects to assess the combined risk estimates per I2 statistics. Analysis to determine sensitivity and publication bias was detected by funnel plots. P<0.05 was considered statistically significant.

Results

Compared with the control (standard therapy for heart failure alone), bromocriptine when combined with standard therapy improved the left ventricle ejection fraction by 11.37% (MD 11.37, 95% confidence interval [CI]: 9.55-13.19 p=0.001) after 6 months compared to standard therapy alone as demonstrated in the Forrest plot in **Figure 1**. In addition, no thromboembolic events were reported in any of the 263 patients. A summary of the systematic review results is presented in **Tables 2-5**. All the studies showed the benefit of bromocriptine except one study done in Canada by Marqui-Gravel that concluded no statistical or clinical significant.

No cardiovascular adverse events including stroke, thrombotic and vasospastic infarctions were reported during follow-up of all the patients included in these studies although the postpartum period, not the pregnancy itself, is associated with an increased risk of recurrent stroke [10]. This is important to mention given bromocriptine is known to increase risk of thrombosis because of its deleterious effects on the vessel endotheliums [11]. Although in all the mentioned studies [12-15] except for Marques Gravel G et al. used some form anticoagulation in patients with LVEF equal or less than 25% and furthermore highlights the importance of anticoagulation specially if patients are at risk for potential thromboembolism risk including deep vein thrombosis, pulmonary embolism and stroke and myocardial infarction.

None of the 9 patients receiving bromocriptine mentioned in the studies [12-15] died from side effect of medication but from severity and complication of disease. Thus, according to our findings, bromocriptine was found to be relatively safe.

In their pilot study, Silwa K et al. [12] recruited 20 consecutive patients with confirmed PPCM who were HIV negative and presented with heart failure symptoms during the last month of pregnancy to within 1 month postpartum and with LVEF 35% or

Table 3 Characteristics of studies included in the systematic review.

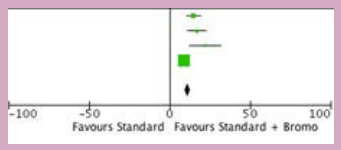
Author	Thromboembolism(n)%	Advanced Heart Failure therapies (n)	Death/Lost to follow		NYHA Classification after treatment	End-point including LVEF after treatment
Sliwa K et al. [1]	0	0	Br (+) 1	Br (-) 4	Br (+): 9 Class 1;	Br (+): 58 +/-11p(0.0007)
					Br (-): 3 class II; 3 Class III	Br (-)36 +/- 9 &11 p (0.0007)
Haghikia et al. [13]	None reported		2 death 19 lost to follow		I-II	Br (+): 92% showed LVEF improvement Br (-): 72% showed LVEF improvement. Br (+) Br (-) = 47 ± 19 %.
		1: LVAD				LVEF improvement in 85% of cases, Full
		7: heart transplant				recovery in 47%, 15% failed to recover, 2% death
Marquis-Gravel G et al. [15]	None reported	3:Heart Transplant (Br-)	Br (+)	Br (-)	None Reported	No differential effect (LVEF in BRO+ from 20% to 55% vs from 29% to 47% in BRO-)
			1	1		
Yameogo et al. [14]	0	0	Br (+) 8	Br(-) 14	None reported	Br(+) 49.9 +/- 2.1 Br+ p: 0.001
						Br(-) 40.9 +/- 5.9 p (0.001)

Table 4 Characteristics of studies included in the systematic review.

Author	Bromocriptine	Standard Heart failure therapy	Anticoagulation
Sliwa K et al. [1]	2.5 mg BID 2 weeks	Enalapril Carvedilol	EF <25% + or – LV thrombus: Warfarin
	2.5 mg daily for 4 weeks.	Lasix	
Haghikia et al. [13]	Bromocriptine 2.5 mg -5 mg daily for at least 4 weeks	Beta-Blocker ACE inhibitor	No anticoagulation documented been given.
		Angiotensin Receptor Blocker (ARB)	
		Mineral corticoid Antagonists	
Marquis-Gravel G et al. [15]	Bromocriptine unspecified dosage and	Was not mentioned in article	Was not mentioned in article
	length of treatment		
Yameogo et al. [14]	2.5 mg BID for 4 weeks	Captopril Furosemide	Fluindione for 6 months EF <25% or LV thrombus

Table 5 Forrest plot.

Study or Subgroup	Standard Therapy			Standard + Bromocriptine			weight	Mean difference IV, Fixed, 95% CI	Mean difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Haghikia et al. [13]	39	11	32	24	7	64	19.0%	15.00 [10.82, 19.18]	
Marquis-Gravel G et al. [15]	35	9	11	18	8	40	9.6%	17.00 [11.13, 22.87]	
Sliwa K et al. [1]	31	11	10	9	11	10	3.6%	22.00 [12.36, 31.63]	
Yameogo et al. [14]	13	5	48	4	6	48	67.9%	9.00 [6.79, 11.21]	
Total (95% CI)			101			162	100.0%	11.37 [9.55, 13.19]	
Heterogenity Chi²=15.52, df=3(p=0.001); I2=81%									
Test for overall effect: Z=12.25 (P<0.00001)									



less and no other identifiable cause for heart failure. Half of them received standard heart failure therapy with enalapril, furosemide and carvedilol in addition to bromocriptine 2.5 twice daily for 2 weeks followed by 2.5 mg daily for 6 weeks and the other half standard heart failure therapy alone. The baseline characteristics of patients in both 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, LVEF. Recovery of LVEF between baseline and 6 months was greater in the treatment group receiving bromocriptine (31%) than in the group receiving standard heart failure therapy alone (9%). All 9 surviving patients in the group receiving bromocriptine recovered to NYHA functional class I at 6 months. In contrast, all patients group receiving standard heart failure therapy alone group that survived 6 months were in NYHA functional class II or III. The single patient who died in the bromocriptine group presented with severe heart failure and survived only 7 days. All 9 remaining patients in that group survived 6 months. Four patients in the group receiving standard heart failure 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. The combined measure of poor outcome that included LVEF 35%, NYHA functional class III/IV at 6 months or death within 6 months revealed that the patients receiving bromocriptine had better outcome than the patients receiving standard heart failure treatment alone. No thromboembolic events were reported.

Haghikia et al. performed a prospective cohort study with 115 patients who met diagnostic criteria set by Silwa et al. [1] for PPCM. Mean LVEF at the time of diagnosis was 27 ± 9%. Follow-up data for 6 ± 3 months on LVEF were available for 96 patients while 19 patients were lost to follow up. The mean follow-up LVEF increased from 27 ± 9 to 47 ± 19%. 1 patient needed a left ventricular assist device (LVAD), and 7 patients obtained heart transplantation. 1 patient died of them after transplantation and 1 due to sudden cardiac death. 67% of patients (64/96) obtained standard therapy for heart failure in addition to bromocriptine. 92% of these patients (59/64) show improvement in LVEF and functional class. 8% of patients receiving Bromocriptine (5/64) did not show improvement. The percentage of patients experiencing full recovery (LVEF of 55% with NYHA class I to II) was similar in both groups with no difference in baseline characteristics. The study did note that the patients who did not improve regardless of the fact they received bromocriptine in addition to standardized heart failure regimen have a baseline EF equal to or lower than 25%.

In the study of Marquis-Gravel G et al. [15], a total of 51 patients were diagnosed with PPCM, of which 11 were treated with bromocriptine. Cardiovascular events were similar in the two groups, but there was a significant greater improvement in LVEF in patients with bromocriptine in addition to standard heart failure therapy at 6 months that was no longer significant at follow-up. Data analysis was limited because could not use the full article could not be found. The abstract was used to perform the systematic review.

Nobiga Yamego et al. [14] included 96 women with at least stage III NYHA dyspnea developed in the last month of pregnancy or during the five months postpartum, with no other identifiable cause for heart failure, and left ventricle ejection fraction (LVEF) < 45% by transthoracic echocardiography. 69.7% presented a stage IV NYHA dyspnea and stage III was found in 30.3% The mean LVEF was 37.2 ± 6.6% (22.3 and 44.4%) in patients treated with standard heart failure in addition to bromocriptine and 37.5 ± 4.8% (22.3 and 44.0%) in patients treated with bromocriptine alone Br- (p=0.129). There were no significant differences in baseline characteristics. All patients received standard heart failure treatment with the diuretic furosemide and the angiotensin-converting enzyme (ACE) inhibitor captopril. Patients with an LVEF < 35% or ventricular thrombus received anticoagulation therapy with fluindione (vitamin K antagonist like Coumadin) for 6 months. At six months follow up cumulative death was reported to be 8 (16.6%) in patient that received Bromocriptine but 14 (29.1%) in patient that did not receive bromocriptine (p=0.0001). Echocardiographic findings demonstrated better improvement in ventricles function in those treated with bromocriptine in addition to standard heart failure therapy. The mean LVEF was 49.9 ± 2.1% (43.1 and 52.7%) in patient's treatment with bromocriptine and 40.9 ± 5.9% (32.2 and 48.9%) in patients treated with standard heart failure alone (p=0.001). Given symptoms onset, ventricles systolic function improvement was better when onset occurred before delivery and more preferably within 1 month after delivery. There was no publication bias as shown in **Figure 3**.

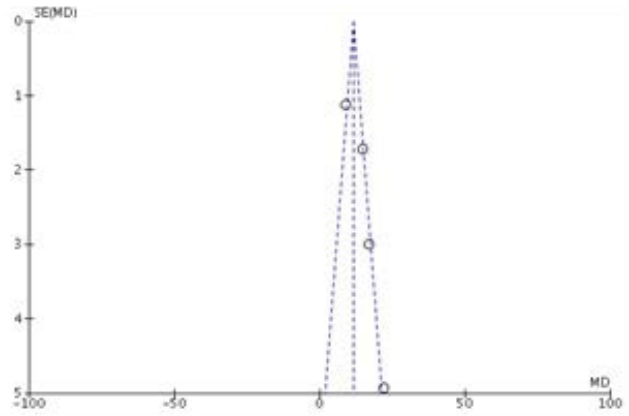


Figure 3 Funnel plot analysis shows no evidence of publication bias.

Discussion

This study is the first meta-analysis and systematic review of the scientific literature and it confirms the positive effect of the use of bromocriptine for PPCM given the fact there is an improvement of the left ventricle ejection fraction (LVEF) by 11.37% after 6 months. In Haghikia A et al. [15] prospective study, patient's with very low baseline LVEF equal or less than 25% had poor prognosis compared to patients with higher baseline LVEF despite adherence to standard heart failure regimen with or without bromocriptine. Hence, suggesting LVEF is an important factor of prognosis. It is important to note that this was the only study that documented the use of mineralocorticoids antagonist. 19 patients were subsequently lost to follow up an as they mentioned, there were minimal requirement for enrolment in this which included a baseline LVEF around the area of pregnancy and some patients did not agree to blood work or providing additional clinical data. Therefore there is a need to have better baseline data for diagnosis of PPCM and study inclusion including more echocardiographic data at baseline and follow up in correlation with NYHA functional class. In this study, time line of diagnosis was not clearly defined. If we our hypnotizing that prolactin plays a major role in PPCM, question remains how much effect would prolactin have several months after myocardial damage? This question can somewhat be answered in Silwa K et al. pilot study in which case showed NYHA functional class improvement and improvement in LVEF in patients with PPCM receiving bromocriptine. In this case, patient's presentation was more acute as patients included in the study were presenting with signs and symptoms of heart failure between last month of pregnancy up to 4 weeks postpartum which might correlate more with high levels of prolactin then and therefore using an antagonist such as

bromocriptine could play a impactful role in treatment. However, the study was very small, and findings mentioned in **Table 1** are in no way definitive. Nobiga Yamego et al. [14] showed that Bromocriptine associated with standard treatment of heart failure leads to a rapid and almost complete recovery of left and right ventricular function and reduces mortality associated with this disease but most importantly that the drug is more effective in patients whose symptoms on set occurred before delivery or in the first month following this event. However, safety issues were raised for patients taking Bromocriptine in the early postpartum phase: a few case reports describe an increased risk of thrombotic events, such as myocardial infarction and retinal vein occlusion, in these patients [16-18]. But in fact, never thrombotic events in peripartum cardiomyopathy patients treated with Bromocriptine and heparin have been observed [13]. Our analysis of Marquis-Gravel G et al. [15] study was limited as we were not able to find the full article and we could only obtain date from the abstract, a total of 51 patients were diagnosed with PPCM, of which 11 were treated with bromocriptine. From data obtained, there was a statistical difference between patients receiving bromocriptine in addition to standard heart failure therapy versus standard heart failure therapy alone. Other limitations of the previous mentioned studies are in fact.

Study limitations

This study has several limitations. Most notably, the included studies involved different doses (2.5mg daily to 5 mg BID) of bromocriptine between the studies some differences in methods, differences in patient selection, and small differences in outcomes definitions, which resulted in a substantial amount of heterogeneity. In addition, there were only 2 RCTs included, and the absence of patient-level data (common in meta-analysis) prevented more detailed subgroup analysis. Finally, this study was not registered prospectively, which prevented feedback from the protocol.

Recommendations

In view of findings on previous studies [12-15], considering strengths and limitations, there is a need for a larger-scale multicenter and blinded studies to help make a stronger case for the use of bromocriptine in the management of PPCM. It is important to consider in future trials patients with more severe presentations of PPCM with NYHA class III or higher and/or LVEF< 35%. It also is important to try to consider time of presentation as a factor to help answer the question whether or not patient's being treated acutely within the first 4 weeks of postpartum period will benefit more from the use of bromocriptine therapy given the possibility that prolactin might have its strong effects on the heart during this time. As noted by Haghikia A et al. [13] study, LVEF equal or less than 25% is a poor prognosis, hence earlier diagnosis and treatment of PPCM with standard heart failure therapy is essential for the overall prognosis regardless of the use of Bromocriptine. Bromocriptine has not been shown to be unsafe in women with PPCM, thus the decision to start a patient a bromocriptine in addition to standard guideline directed medical therapy for heart failure could be more beneficial than harmful and should be considered in all women with PPCM. Patients with PPCM to be started on bromocriptine should be on anticoagulation if they have history thromboembolism event or if LVEF is less than 35% as described in our systematic review.

Conclusion

Peripartum cardiomyopathy is a rare but serious condition that affects childbearing women. Bromocriptine associated with standard treatment of heart failure leads to a rapid and almost complete recovery of left and right ventricular function and reduces mortality associated with this disease. In view of these results, bromocriptine should be the central molecule in the treatment of peripartum cardiomyopathy, in addition of course to conventional treatment of heart failure.

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