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Bromocriptine Use in Peripartum Cardiomyopathy: Review of Cases

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Abstract

Objective This study is to review published cases of peripartum cardiomyopathy (PPCM) treated with bromocriptine and outline pros and cons of the treatment strategy.

Data Sources Data were collected from PubMed/MedLine, ClinicalTrials.gov; the years 2007 to 2018 were searched for English-language articles. Search terms: “bromocriptine and peripartum cardiomyopathy”, “bromocriptine and cardiomyopathy.”

Methods of Study Selection This search strategy yielded 171 articles. After excluding duplicates, 86 studies were reviewed. Sixty-one articles involving the treatment of PPCMP were included, and of these, 17 were case reports of patients with PPCMP treated with bromocriptine; these studies were included in this review.

Tabulation, Integration, and Results Seventeen of these articles were case reports of patients with peripartum cardiomyopathy treated with bromocriptine that were included.

Conclusion Bromocriptine seems to be a promising treatment, there is currently insufficient evidence for universal utilization of bromocriptine for all patients with PPCMP. Addition of bromocriptine to the standard heart failure therapy should be individualized.

Keywords

- ▶ peripartum cardiomyopathy
- ▶ bromocriptine
- ▶ left ventricular function
- ▶ recovery
- ▶ pregnancy
- ▶ right ventricular function

Peripartum cardiomyopathy (PPCM) is a rare but potentially devastating form of cardiomyopathy occurring late in pregnancy or early postpartum period in previously healthy women.¹ Pregnancy associated heart failure was first described in the 1800s; however it was not until 1971 that Demakis and Rahimtoola who recognized the disease as a distinct entity and coined the term peripartum cardiomyopathy.^{1–3} According to the 2010 European Society of Cardiology (ESC), diagnosis of PPCM is made by echocardiography demonstrating ejection fraction of < 45% with or without the left ventricular dilation with no evidence of other potential etiologies of heart failure.⁴ Our goal is to provide brief overview of PPCM, review published cases of PPCM treated with bromocriptine and outline pros and cons of the treatment strategy.

Incidence and Risk Factors

Incidence of PPCM in the United States varies widely from 1 in 1,000 to 1 in 4,000 live births.⁵ The risk of PPCM is largely

influenced by ethnicity with African-American women at highest risk followed by Asians, whites, and Hispanic women.⁶ Geographically, the highest incidence is encountered in Haiti (1 in 300 pregnancies) and South Africa (1 in 1,000 pregnancies).^{7–9} Other risk factors include multiparity, multifetal gestation, preeclampsia, gestational hypertension, and advanced maternal age.⁸ In fact, greater than 50% of cases occur in women older than 30 years old.¹

Treatment Options for PPCM

Treatment of PPCM is similar to other types of heart failure with reduced ejection fraction. Mainstay of therapy is salt and fluid restriction, diuretics, vasodilators, and beta blockers. Anticoagulation may be indicated in selected cases. However, the use of angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers, (ARB) which have been shown to reduce morbidity and mortality are deferred until after delivery.^{7,10,11}

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Natural History of PPCM and Outcomes

Overall, outcomes of PPCM tend to be favorable compared to other types of cardiomyopathies as it is less likely to progress to end stage than heart failure caused by other etiologies.¹² With current treatment modalities, PPCM patients have a 50% rate of recovery and 98% chance of survival.¹³ Previously, it was thought that if PPCM were to resolve, it would do so within 6 months of diagnosis and it persisted past this time point; it was considered a poor prognostic factor.² However, more recently, Fett et al followed 116 Haitian patients with PPCM and only 27.6% achieved full recovery; of those who recovered, 53% did not achieve full recovery for at least 18 months.¹⁴ While this may be specific to the Haitian population, it appears that this disease may take a more significant amount of time to resolve than previously thought. Further, the risk of recurrence of PPCM is high and those who have had a pregnancy complicated by it are counseled to avoid future pregnancy.¹⁵

Theories for Causation

The exact etiology of PPCM remains unknown; however, significant advances have been made to elucidate causation of PPCM. The largest umbrella of hypotheses include the “oxidative stress–prolactin axis” and “antiangiogenic–signaling excess” hypotheses.⁷ The “oxidative stress–prolactin axis” hypothesis stems from the elevated markers of inflammation and apoptosis found in PPCM.^{16,17} A transgenic mouse model of PPCM was developed to investigate potential mechanisms of the disease. Using this mouse model, Sliwa et al showed that oxidative stress allows expression and activation of a lysosomal enzyme, cathepsin D which cleaves serum prolactin into an antiangiogenic and pro apoptotic 16-kDa prolactin sub fragment that incite and propagates myocardial damage.¹⁸ The study also showed that blocking the release of prolactin inhibited degeneration of the cardiac capillary network, thereby decreasing myocyte damage.¹⁸ Another study by Forster et al showed that increased levels of both prolactin and interferon- γ were associated with increased inflammatory status and adverse outcomes in PPCM.¹⁹ Recent data show that the “oxidative stress–prolactin axis” and the “antiangiogenic–signaling excess” probably converges in a final pathway of imbalanced cardiac remodeling in the peripartum phase, thereby causing myocardial injury secondary to metabolic “shortages.”⁸ Other proposed causative factors which will not be described here, include: selenium deficiency, viral myocarditis, and immune mediated cardiac damage.

Bromocriptine as a Therapy for PPCM

Bromocriptine is an ergot derivative with dopamine agonistic activity that inhibits the release of prolactin from the anterior pituitary. It is FDA approved for the treatment of hyperprolactinemia-associated endocrine dysfunction, acromegaly, Parkinson's disease, and to improve glycemic control in type 2 diabetes mellitus. In the past, it has also been used to inhibit lactation when medically indicated. Given the evidence to support the oxidative stress–prolactin hypothesis of PPCM, bromocriptine has been introduced as a potential beneficial addition to standard the treatment for PPCM.

Since the publications of the oxidative stress–prolactin axis model, there has been significant interest in the use of bromocriptine for prolactin inhibition in PPCM cases demonstrating a positive impact on left ventricular ejection fraction and NYHA (New York Heart Association) class. However, bromocriptine is not without risks. Serious adverse events have been reported in postpartum women using bromocriptine for lactation suppression including myocardial infarction, seizures, and stroke.²⁰ Among patients with adverse events after bromocriptine, many events may have been avoided if treatment was discontinued with the initial manifestations of adverse reaction.²¹ While a causal relationship remains unclear, routine use of bromocriptine for prevention of physiologic lactation is not recommended. Cessation of lactation may also pose significant disadvantage to the neonate; however, Sliwa et al showed normal growth and survival of neonates with mothers treated with bromocriptine.²² Bromocriptine is contraindicated in women with pregnancy-induced hypertension, as it can worsen blood pressures during pregnancy or postpartum periods. Therefore, the risk to benefit ratio of bromocriptine makes it a poor choice for lactation suppression but may be worth taking the risk of adverse events in PPCM as it may significantly improve cardiac outcomes (► **Table 1**).

Sources

Authors manually searched PubMed/MedLine and ClinicalTrials.gov for English-language articles written from 2007 to 2018 using the search terms “bromocriptine and peripartum cardiomyopathy,” “bromocriptine and cardiomyopathy.”

Study Selection

The Search strategy yielded 171 articles. After excluding duplicates, 86 studies were reviewed. Sixty-one articles involving the treatment of PPCM were included, and of these, 17

Table 1 Advantages and disadvantages of bromocriptine use in peripartum cardiomyopathy

Advantages	Disadvantages
FDA approved	Lactation suppression
Risk of serious adverse effects may be avoided with close monitoring	Worsening hypertension and may increase risk of neurologic events in those with pregnancy induced hypertension
May improve NYHA functional class at follow up	Reported risk of myocardial infarction
May improve systolic and diastolic function	Arterial thromboembolism

Abbreviation: FDA, Food and Drug Administration; NYHA, New York Heart Association.

Table 2 Case reports of bromocriptine use in peripartum cardiomyopathy—descriptive data

Author	Journal	Title	Maternal age	Mother's ethnicity	Gravidity and parity	GA	Onset (after delivery)	Delivery method
1	Hilfiker-Kleiner et al 2007 ²⁶	Recovery from postpartum cardiomyopathy in 2 patients by blocking prolactin release with bromocriptine	32	NR	NR	NR	3 wk	NR
		Same as above	41	NR	NR (twin gestation)	NR	At delivery	Elective C-section
2	Habedank et al 2008 ²⁷	Recovery from peripartum cardiomyopathy after treatment with bromocriptine	35	NR	G1 (twin gestation)	36/6	3 d	NSVD
3	Jahns et al 2008 ²⁸	Peripartum cardiomyopathy—a new treatment option by inhibition of prolactin secretion	43	NR	G1	34/4	8 d	C-section for maternal dyspnea
4	Abe et al 2010 ²⁹	Recovery from peripartum cardiomyopathy in a Japanese woman after administration of bromocriptine as a new treatment option	37	Japanese	G1	33/0	Prior to delivery	Emergency C-section for nonreassuring fetal status and maternal acute heart failure
5	Meyer et al 2010 ³⁰	Bromocriptine treatment associated with recovery from peripartum cardiomyopathy in siblings: two case reports	35	African	G3P3	NR	4 wk	Elective C-section
		Same as above	27	African	G2	NR	*During second pregnancy*	C-section for imminent fetal asphyxia and amniotic infection syndrome
6	Sliwa et al 2010 ²²	Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy	22	NR	P2	NR	8 d	NR
		Same as above	38	NR	P3	NR	14 d	NR
		Same as above	24	NR	P1	NR	26 d	NR
		Same as above	22	NR	P2	NR	7 d	NR
		Same as above	18	NR	P2	NR	24 d	NR
		Same as above	24	NR	P2	NR	7 d	NR
		Same as above	23	NR	P1	NR	4 d	NR
		Same as above	28	NR	P1	NR	30 d	NR
		Same as above	22	NR	P1	NR	2 d	NR
		Same as above	18	NR	P1	NR	3 d	NR
7	Emmert et al 2011 ³¹	Peripartum cardiomyopathy with cardiogenic shock: recovery after prolactin inhibition and mechanical support	33	NR	G2	NR	3 d	NR

(Continued)

Table 2 (Continued)

Author	Journal	Title	Maternal age	Mother's ethnicity	Gravidity and parity	GA	Onset (after delivery)	Delivery method
8 Ballo et al 2012 ³²	Case Reports in Medicine	Peripartum cardiomyopathy presenting with predominant left ventricular diastolic dysfunction: efficacy of bromocriptine	37	White	NR (twin gestation)	36	2 d	NSVD
9 Freerksen et al 2012 ³³	Hypertension in Pregnancy	Massive respiratory dysfunction as sign of fulminant peripartum cardiomyopathy (PPCM)	35	NR	G3P2	40/6	At delivery	Emergency Csection for maternal respiratory dysfunction
10 Hlilfiker-Kleiner et al 2012 ³⁴	Current Heart Failure Reports	16-kDa prolactin and bromocriptine in postpartum cardiomyopathy	41	NR	NR (IVF twin gestation)	NR	h	Csection
11 Schroeter et al 2012 ³⁵	Clinical Research in Cardiology	Prothrombotic condition in a woman with peripartum cardiomyopathy treated with bromocriptine and an impella lp 2.5 heart pump	39	White	G1	NR	4 d	NSVD
12 Kotlica et al 2016 ³⁶	Clinical and Experimental Obstetrics and Gynecology	Peripartum cardiomyopathy: a case report of a patient with triplet pregnancy	33	NR	NR (IUI triplet gestation)	35/0	1 d	Csection
13 Hamdan et al 2017 ³⁷	Journal of Critical Care	Peripartum cardiomyopathy, place of drug therapy, assist devices, and outcomes after left ventricular assistance						
		Same as above	25	NR	P1	NR	17 d	NR
		Same as above	35	NR	P3	NR	1 mo	NSVD
		Same as above	38	NR	P1	NR	3 wk	NR
14 Horn et al 2017 ³⁸	ESC Heart Failure	Complete recovery of fulminant peripartum cardiomyopathy on mechanical circulatory support combined with high-dose bromocriptine therapy	30	NR	NR	NR	4 mo	NR
15 Senanayake and Patabendige 2017 ³⁹	Journal of Medical Case Reports	Two potentially lethal conditions of probable immune origin occurring in a pregnant woman: a case report	33	Lankan	P1	38	2 wk	Csection
16 Kryczka et al 2018 ⁴⁰	American Journal of Case Reports	Severe course of peripartum cardiomyopathy and subsequent recovery in a patient with a novel ttn gene-truncating mutation	25	White	P1	36	N/A	Csection
17 Huang et al 2018 ⁴¹	Medicine	Successful management of fatal peripartum cardiomyopathy in a young pregnant woman: a case report	18	NR	P1	33	N/A	Csection

Abbreviations: ESC, European Society of Cardiology; GA, gestational age; IUI, intrauterine insemination; IVF, in vitro fertilization; NR, not applicable; N/A, not applicable; NR, not reported; NSVD, normal spontaneous vaginal delivery; PPCM, peripartum cardiomyopathy.

Table 3 Case reports of bromocriptine use in peripartum cardiomyopathy—treatment and outcome data

Author	LVEDd at diagnosis (mm)	LVEF at diagnosis (%)	NVHA class at diagnosis	Treatment (other than bromocriptine)	Bromocriptine dosing	LVEDd after treatment (mm)	LVEF after treatment	NVHA class after treatment
1 Hilfiker-Kleiner et al 2007 ²⁶								
	60	17	III	Standard heart failure therapy	Bromocriptine 5 mg/d for 2 wk, then 2.5 mg/d for 6 wk	59 at 2 wk; 51 at 4, 6 mo	29% at 2 wk, 57% at 4 mo, 60% at 6 mo	I at 12 mo
	55	30	IV	Standard heart failure therapy	Bromocriptine, unspecified	53 at 2 wk; 43 at 4 mo	50% at 2 wk, 49% at 4 mo	I at 4 mo
2 Habedank et al 2008 ²⁷	60	25	NR	Torsemide 5 mg, ramipril 2.5 mg, spironolactone 25 mg, bisoprolol 2.5 mg.	After 3 d of continued deterioration, started treatment with bromocriptine 2.5 mg twice daily and continued for 6 wk	56 at 2 mo	60% at 2 mo	I at 2 mo
3 Jahns et al 2008 ²⁸	NR	30	NR	Angiotensin-converting enzyme inhibitor, digoxin, beta blocker	Bromocriptine 2.5 mg/d for at least 3 mo	NR	43% at discharge; 50% at 6 mo	NR
4 Abe et al 2010 ²⁹	58	21.70	II	Dobutamine, furosemide; starting at 11 d given losartan 25 mg; bisoprolol 2.5 mg	Bromocriptine 5 mg/d beginning 11 d after diagnosis, continued for 12 wk	51 at 3 mo	60% at 3 mo	I at 3 mo
5 Meyer et al 2010								
	63	9	IV	Enoxaparin, Coumadin, and standard heart failure therapy	Bromocriptine 5 mg/d for 2 wk, 2.5 mg/d for 6 wk	NR	45% at 6 mo	II at 6 mo
	60	32	NR	Enoxaparin, standard heart failure therapy	Bromocriptine 5 mg/d for 2 wk, 2.5 mg/d for 6 wk	NR	59% at 8 mo	NR
6 Sliwa et al 2010 ²²								
	33	34	IV	Carvedilol, enalapril, furosemide, aldactone	Bromocriptine 2.5 twice daily for 2 wk followed by 2.5 mg/d for 6 wk	44	58%	I at 6 mo
	65	29	II	Carvedilol, enalapril, furosemide, aldactone	Same as above	59	37%	I at 6 mo
	68	30	II	Carvedilol, enalapril, furosemide, aldactone	Same as above	65	62%	I at 6 mo
	54	27	II	Carvedilol, enalapril, furosemide, aldactone	Same as above	51	72%	I at 6 mo
	56	30	II	Carvedilol, enalapril, furosemide, aldactone	Same as above	48	56%	I at 6 mo
	63	30	III	Carvedilol, enalapril, furosemide, aldactone	Same as above	51	58%	I at 6 mo
	55	33	IV	Carvedilol, enalapril, furosemide, aldactone	Same as above	47	60%	I at 6 mo
	49	32	II	Carvedilol, enalapril, furosemide, aldactone	Same as above	34	75%	I at 6 mo
	55	18	III	Carvedilol, enalapril, furosemide, aldactone	Patient died on index admission	N/A	N/A	Patient died on index admission

(Continued)

Table 3 (Continued)

Author	LVEDd at diagnosis (mm)	LVEF at diagnosis (%)	NYHA class at diagnosis	Treatment (other than bromocriptine)	Bromocriptine dosing	LVEDd after treatment (mm)	LVEF after treatment	NYHA class after treatment
	54	8	III	Carvedilol, enalapril, furosemide	Bromocriptine 2.5 mg twice daily for 2 wk followed by 2.5 mg/d for 6 wk	56	48%	I at 6 mo
7 Emmert et al 2011 ³¹	77	23	NR	Cabergoline 1 mg, acute heart failure treatment, intra-aortic balloon pump, left ventricular assist device,	Bromocriptine 2.5 mg/d for 6 wk	50 at 14 mo after LVAD removal	After surgery 42%; 14 mo after LVAD removal 47%	I at 14 mo after LVAD removal
8 Ballo et al 2012 ³²	NR	35	II	Ramipril, bisoprolol, furosemide	Bromocriptine 2.5 mg twice daily 2 wk after diagnosis	NR	45% at 6 wk; 60% at 18 mo	I at 6 wk and 18 mo
9 Freerksen et al 2012 ³³	NR	15	IV	Levosimendan; required left ventricular assist device on d 7 postpartum	Bromocriptine 2.5 mg/d at d 1; 1.5 mg/d from d 2 onwards	NR	Stabilized but LVEF NR	NR
10 Hilfiger-Kleiner et al 2012 ³⁴	NR	26	IV	Bisoprolol, enalapril, spirinolactone, torsemide, phenprocoumon	Bromocriptine 5 mg/d	NR	62% at 6 mo	NR
11 Schroeter et al 2012 ³⁵	59	45	NR	Levosimendan 8µg/min, Impella LP 2.5 percutaneous micro-axial pump assist device	Bromocriptine 2.5 mg twice daily	49 at discharge on d 21	NR	NR
12 Kotlica et al 2016 ³⁶	55	25–30	NR	Dobutamine, furosemide, manitol, low molecular weight heparin, magnesium sulfate, ACE inhibitors, xylocaine, digitalis, antibiotics	Bromocriptine, dose NR	"Normal dimension"	64% at d 18	NR
13 Hamdan et al 2017 ³⁷	NR	15–20	NR	ECMO, inotropes, diuretics, HVAD	Bromocriptine 2.5 mg/d for 3 d	NR	45% at 6 mo	NR
	NR	30	NR	Beta blockers, ACE inhibitor, aldosterone agonist, diuretics	Bromocriptine 2.5 mg/d for 7 d	NR	35% at 10 d; 60% at 2 y	I at 2 y
	NR	25	III	Diuretics, "conventional (heart failure) treatment"	Bromocriptine 2.5mg/d for 10 d	NR	40% within "d;" 55% at 9 mo	NR
14 Horn et al 2017 ³⁸	NR	NR	NR	ECMO, "optimal medical heart failure therapy"	Bromocriptine 5 mg/d via gavage; increased to 10 mg daily for 8 wk	NR	"Normal" at 3 mo	I at 1 y
15 Senanayake and Patabendige 2017 ³⁹	NR	45	NR	Warfarin, "heart failure regimen"	Bromocriptine, unspecified	NR	60% at 6 wk postpartum	NR
16 Kryczka et al 2018 ⁴⁰	NR	25–0	NR	NR	Bromocriptine, unspecified for 12 mo	NR	32% at 10 wk	NR
17 Huang et al 2018 ⁴¹	NR	40	NR	Digoxin, furosemide, losartan	Bromocriptine 5 mg/d for 3 mo	NR	51% at 3 mo; 62% at 6 mo	NR

Abbreviation: ACE, angiotensin converting enzyme; ECMO, extracorporeal membrane oxygenation; HVAD, HeartWare® ventricular assist device; LVAD, left ventricular assist device; LVEDd, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; NR, not report; NYHA, New York Heart Association.

were case reports of patients with PPCMP treated with bromocriptine; these studies were included in this review.

Tabulation, Integration, and Results: Seventeen of these articles were case reports of patients with peripartum cardiomyopathy treated with bromocriptine that were included.

Results

We describe a review of the existing case studies from 2007 to 2018 that discusses use of bromocriptine in patients with PPCM (► **Table 2** and **3**). These case reports describe the use of bromocriptine in 30 individual women, ranging in age from 18 to 43 years. The study subjects vary with respect to their country of origin, gravidities and parities, and gestational age. The onset of PPCM ranged from prior to delivery to as late as a month after delivery. The majority of these women recovered their left ventricular ejection fraction after receiving bromocriptine, typically dosed from 2.5 to 5 mg daily, in conjunction with the standard heart failure therapy. Though many women presented with low ejection fractions, (range: 8–45%), many were able to report NYHA classes II and I at time of follow-up.

While most of these are individual, heterogeneous case reports, 10 of these cases came from a pilot study comparing women with newly diagnosed PPCM receiving standard heart failure care ($n = 10$) versus standard care and bromocriptine ($n = 10$). This study demonstrated that the addition of bromocriptine to standard heart failure therapy improved NYHA functional class, left ventricular systolic and diastolic function, and degree of functional mitral regurgitation in women with PPCMP. Though this trial was small and far from definitive, the data appeared to show greater improvement in the group that received bromocriptine. Subsequently, a multicenter randomized controlled trial evaluated outcomes of 63 patients with PPCM who were treated with 1 or 8 weeks of bromocriptine in addition to standard therapy revealed that patients treated with bromocriptine was associated with higher rate of left ventricular recovery and had low morbidity and mortality.²³ Post hoc analysis of this study demonstrated an improvement of the right ventricular function in addition to the left ventricular function at 6 month follow-up in women treated with bromocriptine.²⁴ Bromocriptine may have a role in PPCMP patients with biventricular dysfunction. Addition of bromocriptine to the standard heart failure therapy, i.e. BOARD (Bromocriptine, Oral heart failure drugs, Anticoagulation, Relaxants [vasodilators for SBP > 110 mm Hg], Diuretics) has been proposed. Of note, prophylactic anticoagulation should be used when using bromocriptine to reduce the risk of thromboembolic complications.²⁵

Conclusion

There is currently insufficient evidence for universal use of bromocriptine in addition to the standard treatment of PPCM. However, there are data to suggest that bromocriptine improves clinical outcomes. We recommend consideration of bromocriptine in selected cases of PPCMP. Future studies are indicated to elucidate its role as a standard therapy.

Précis

Bromocriptine seems to be a promising treatment for peripartum cardiomyopathy but there is a need for further clinical trials.

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