—Case Reports—

# Recovery from Peripartum Cardiomyopathy in a Japanese Woman after Administration of Bromocriptine as a New Treatment Option

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**Abstract**

Peripartum cardiomyopathy (PPCM) is a form of heart failure that occurs in women within 1 month before delivery and 5 months after delivery. The outcome of PPCM is variable but improves significantly when appropriate medication is administered in the acute phase; furthermore, the outcome does not worsen even after discontinuation of therapy in the chronic phase. The symptoms and signs of PPCM are similar to those of idiopathic dilated cardiomyopathy. The medical management of patients with PPCM is similar to that for other other forms of heart failure. Recent experimental data implicate a casual role of prolactin in the development of PPCM. Prolactin secretion can be reduced with bromocriptine which had benefitical effects in a small study. We present a Japanese woman with acute PPCM treated with bromocriptine as a therapeutic option. Following treatment, the serum prolactin levels dropped swiftly. Concurrently, LV function improved, and heart failure symptoms decreased, accompanied by a decrease in the BNP level.
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**Key words:** heart failure, peripartum cardiomyopathy, bromocriptine

## Introduction

Peripartum cardiomyopathy (PPCM) is a rare disease of unknown etiology, characterized by an acute onset of heart failure in women with in 1 month before delivery and 5 months after delivery[1,2]. It is common in some coutries and rare in others. Clinical presentation includes usual signs and symptoms of heart failure. Treatment of PPCM includes medical pharmacotherapy for heart failure with angiotensin converting enzyme (ACE) inhibitors, β-blockers, vasodilators, and diuretics (standerd therapy for heart failure)[1]. Little is known about the pathophysiology of peripartum cardiomyopathy, and suitable animal models to study the disease are rare. There have been speculations about the involvement of inflammation, myocarditis, autoimmune reactions, and apoptosis[3]. Recent evidence suggests that oxidative stress mediated generation of anti-angiogenic and proapoptotic 16-kDa prolactin, and subsequent

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impaired cardiac microvascularization has been related to PPCM. In turn, prolactin blockade with bromocriptine was successful in preventing onset of PPCM in mice and in patients at high risk for the disease[4]. Here, we present a Japanese woman with acute PPCM treated with bromocriptine as a therapeutic option.

## Case Report

A 37-year-old primigravida with an unremarkable history and a negative family history was transferred to our facility at 33 weeks' gestation for treatment of preeclampsia and severe dyspnea (New York Heart Association functional class II). The following were noted: slightly elevated blood pressure (152/64 mm Hg); sinus tachycardia (127 bpm); proteinuria (5,731 mg/dL); systemic massive edema; and bilateral pleural effusions plus pulmonary edema (**Fig. 1**). Brain natriuretic peptide (BNP; 1,987 pg/dL) was markedly elevated (normal range, <18.4 pg/mL), creatine kinase-MB fraction (11.8 ng/mL) was mildly elevated (normal range, 0.0–7.5 ng/mL), C-reactive protein (2.04 mg/dL) was mildly elevated (normal range, <0.3 mg/mL), and troponin T was within normal limits. Echocardiography revealed severely decreased left ventricular (LV) function with an estimated ejection fraction of 21.7%, LV dilatation (LV end-diastolic diameter, 58 mm; LV end-systolic diameter, 50 mm), and mitral valve regurgitation of grade II to III (**Fig. 2**). The patient had no pre-existing cardiac disease, no exposure to cardiotoxic agents, and no family history of pregnancy-related heart disease. Up to the time of admission, the pregnancy had been uncomplicated; there was no history of hypertension, proteinuria, or placental insufficiency. Therefore, peripartum cardiomyopathy (PPCM) was diagnosed.

Transabdominal sonography revealed decreased fetal movement, increased maternal uterine artery pulsatility index (PI), decreased fetal middle cerebral artery PI compared with umbilical artery PI as "brain-sparing effects," fetal growth restriction, and normal levels of amniotic fluid. Cardiotocography showed a loss of variability, decreased acceleration, and variable decelerations. On the day of admission, an emergency cesarean section was performed under intubation; the indications were nonreassuring fetal status and maternal acute heart failure. A male newborn was delivered with the following findings: Apgar score, 2/9; umbilical artery pH, 7.155; and birth weight, 1,350 g (small for dates). During the cesarean section, the patient's LV ejection fraction decreased to 10%; however, after dobutamine was administered, the ejection fraction increased to 25% to 30%.

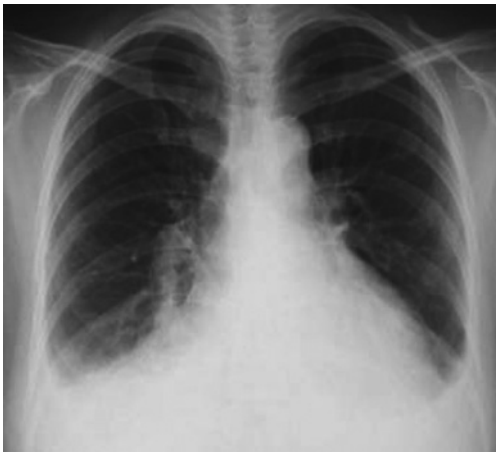

Fig. 1 A chest X-ray film obtained on the day of admission showed bilateral pleural effusions and pulmonary edema.

Infusions of dobutamine and furosemide were started to treat the heart failure; this treatment markedly decreased the symptom of dyspnea. The white blood cell count and levels of C-reactive protein and creatine kinase-MB fraction had also decreased to within the normal limits by postpartum day 5. However, on postpartum day 11, the LV ejection fraction remained low at 35% to 40%, and the BNP level remained elevated. After written informed consent was obtained, the patient was given the angiotensin II receptor blocker losartan potassium (25 mg/day) and the β-blocker bisoprolol fumarate (2.5 mg/day); lactation was prevented with bromocriptine (5 mg/day). After bromocriptine was administered, the serum prolactin levels decreased from 46.5 ng/mL to less than 1.0 ng/mL (postpartum day 8). Concurrently, LV function improved, and heart failure symptoms decreased, accompanied by a decrease in the BNP level (**Fig. 3**). Blood pressure had normalized by postpartum day 1, and proteinuria had markedly decreased (72 mg/dL) by

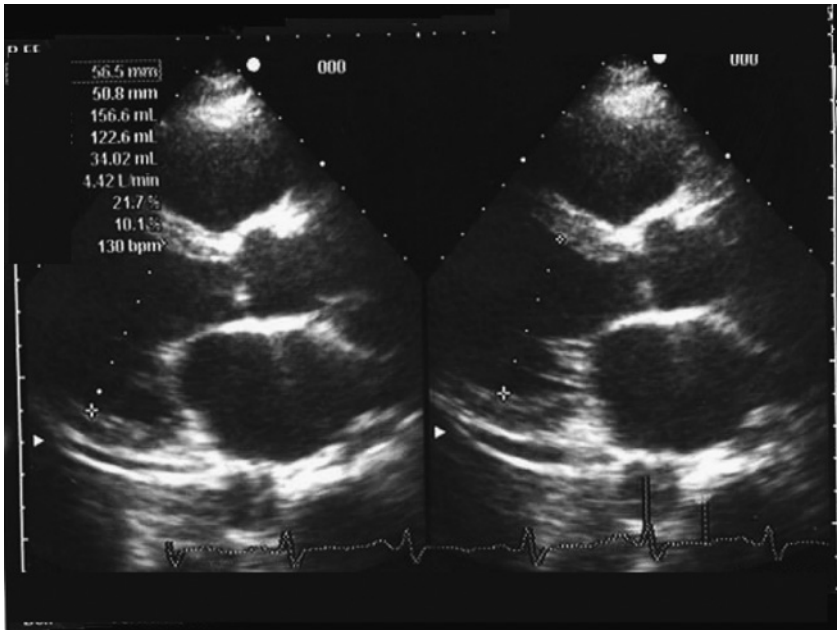


Fig. 2 Echocardiography on the day of admission revealed severely decreased LV function with an estimated ejection fraction of 21.7%, LV dilatation (LV end-diastolic diameter, 58 mm; LV end-systolic diameter, 50 mm), and mitral valve regurgitation of grade II to III.

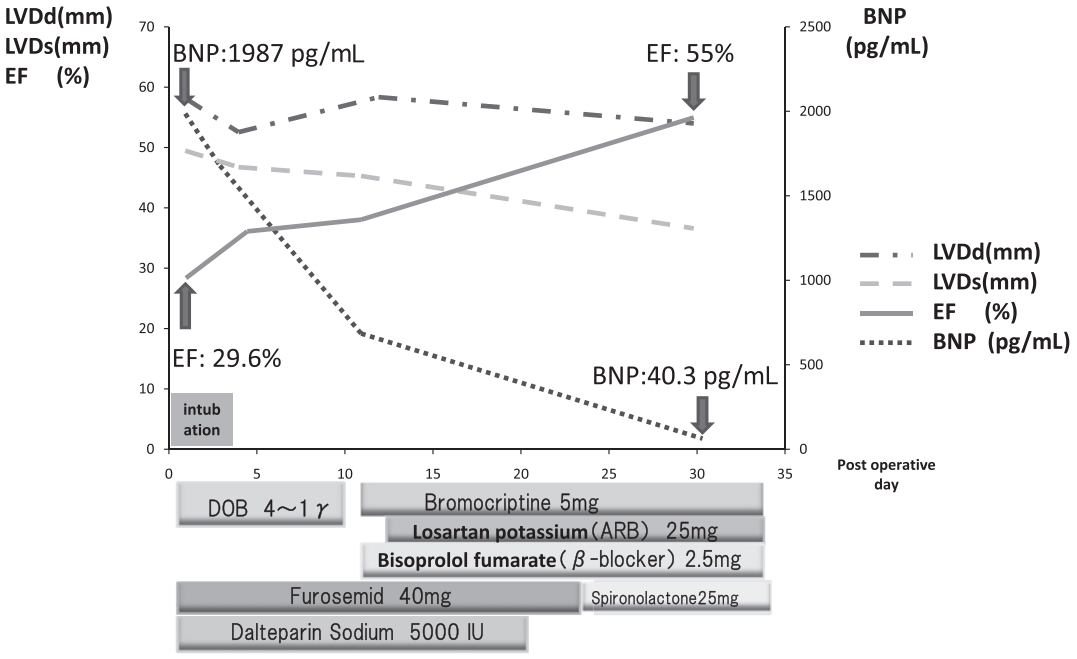


Fig. 3 Time course of echocardiographic data and BNP levels

Infusions of dobutamine and furosemide were started to treat heart failure. However, 11 days after delivery, the ejection fraction remained low at 35% to 40%, and the BNP level remained elevated. The patient received an angiotensin II receptor blocker and a β-blocker; lactation was prevented with bromocriptine (5 mg/day). Concurrently, LV function improved, and the symptoms of heart failure decreased (ejection fraction: 55%) and were accompanied by a decrease in the BNP level.

LVDd = LV end-diastolic diameter; LVDs = LV end-systolic diameter; EF = ejection fraction; BNP = brain natriuretic peptide

postpartum day 9. Bromocriptine was continued for 12 weeks at a dosage of 5 mg/day. By 3 months postpartum, the function and dimensions of the LV had completely normalized (ejection fraction: 60%; LV end-diastolic diameter, 51 mm; LV end-systolic diameter, 36 mm), and cardiac function was classified as New York Heart Association class I.

## Discussion

PPCM is defined as the onset of cardiac failure with no identifiable cause in the last month of pregnancy or within 5 months following delivery, in the absence of heart disease before the last month of pregnancy[5]. The incidence of PPCM has been estimated to be 1 in 100 live births in a small region of sub-Saharan Africa[6], 1 in 299 live births in Haiti[1], and 1 in 2,289 live births among Hispanics in the United States[7]. The reason for these variations among different geographic regions and ethnic groups is unknown; however, the variations may be related to African ancestry, lifestyle, or cultural habits.

Little is known about the pathophysiology of PPCM. There have been hypotheses based on the involvement of inflammation, myocarditis, autoimmune reactions, and apoptosis[3]. Recently, Hilfiker-Kleiner et al.[4,8] have shed new light on the pathogenesis of PPCM. They observed that PPCM readily develops in signal transduction and activator of transcription 3 (STAT3) knock-out mice. STAT3 has several cardioprotective functions, including protection against oxidative stress. Oxidative stress can result in cleavage of prolactin into an antiangiogenic 16-kDa form. In these STAT3 knock-out mice, cardiac cathepsin D expression and activity is enhanced and associated with generation of a cleaved antiangiogenic and proapoptotic 16-kDa form of the nursing hormone prolactin. The 16-kDa prolactin derivative promotes endothelial cell apoptosis, disrupts capillary structures, and impairs cardiomyocyte metabolism and contractility[4,9,10]. Hilfiker-Kleiner et al. have shown that this 16-kDa prolactin induces cardiomyopathy in these mice and that myocardial STAT3 protein levels are reduced and serum levels of activated cathepsin D and 16-kDa prolactin are elevated in patients with PPCM.

In the present patient, blood pressure and the severity of preeclampsia and proteinuria decreased markedly after delivery. One paper has reported PPCM with preeclampsia and the syndrome of hemolysis, elevated liver enzymes, and low platelet count[11], but there have been no reports of a relationship between PPCM and preeclampsia.

The treatment for PPCM is similar to that for other forms of heart failure and has been reviewed in detail[10]. Angiotensin-converting enzyme inhibitors are usually used to reduce afterload by vasodilation if PPCM occurs after pregnancy. Moreover, β-blockers are used, because tachycardia, arrythmias, and sudden death often occur in patients with PPCM. Diuretics are also safe and are used to reduce preload and relieve symptoms. Because of a high incidence of thromboembolism in patients with PPCM, the use of heparin is also deemed necessary, followed by warfarin in patients with an LV ejection fraction of less than 35%[1]. Where resources exist, LV assist devices and heart transplantation may be used if indicated[12,13].

Several recent reports have noted the beneficial effects of bromocriptine and the prolactin antagonist cabergoline[9]; these substances preserve LV function in PPCM. In one reported series, 12 women had had PPCM during a previous pregnancy and were, therefore, at increased risk for PPCM; 6 were treated with bromocriptine. All 6 women treated with bromocriptine survived with preserved LV function, whereas the 6 women not treated with bromocriptine had decreased LV function, and 3 of these women died[4].

Reported 5-year survival rates for PPCM are 85% and 94%[1,14]. These high survival rates are probably due to the high rate of spontaneous resolution of PPCM. However, the mortality rate for patients who do not recover normal or near-normal function is reported to be only 15%. Full recovery of LV function is reported to occur in only 23% of patients with PPCM, whereas continuous deterioration is reported in up to 50% of cases despite optimal medical treatment[2,15–18]. The prognosis of PPCM is related to the recovery of ventricular function. About 50% of patients with PPCM are reported to

recover baseline ventricular function within 6 months postpartum[19,20].

Our present patient was a Japanese woman with acute PPCM in whom bromocriptine was administered in addition to standard heart failure therapy and was associated with recovery and the prevention of chronic heart failure. However, while receiving bromocriptine the patient also received the angiotensin II receptor blocker furosemide and a β-blocker, which may have limited the described effects of bromocriptine on LV function and hemodynamics. Nevertheless, it is possible that a multifactorial role of bromocriptine might ultimately account for its beneficial effects.

Our patient fully recovered by 3 months postpartum; however, subsequent pregnancies in women with PPCM carry a high risk of relapse if LV systolic function has not fully recovered. Even with full recovery, some additional risk of relapse remains[21–23]. On the basis of experimental and initial clinical findings, bromocriptine may be a therapeutic option. Therefore, controlled, randomized studies are indicated to evaluate the efficacy of bromocriptine in the treatment of PPCM.

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