



# Cabergoline as an adjuvant to standard heart failure treatment in peripartum cardiomyopathy: A case report and review of the literature

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## ABSTRACT

**Introduction:** Peripartum cardiomyopathy (PPCM) is a rare and idiopathic form of dilated cardiomyopathy presenting late in pregnancy or early postpartum. Since the 16-kDa fragment of prolactin has been identified as a key factor in the pathophysiology of PPCM, prolactin inhibitors have been used as an adjuvant to standard heart failure treatment. Although bromocriptine is the current first choice, promising results have been reported with cabergoline, albeit scant.

**Case Presentation:** We presented the case of a 41-year-old woman who received a diagnosis of PPCM one week after delivery and was successfully treated with cabergoline, finally experiencing a complete recovery.

**Conclusion:** The case adds to the scant evidence supporting the use of cabergoline in PPCM patients. We argue that the favorable pharmacokinetic and metabolic profiles of this drug should prompt its consideration as a valid alternative prolactin inhibitor in these critical patients.

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## 1. Introduction

Peripartum cardiomyopathy (PPCM) is an idiopathic and life-threatening form of left ventricular systolic dysfunction occurring in the early postpartum period (60–70% of cases) or late in pregnancy, with a reported incidence of 1/15,000 live births worldwide [1–3]. In 2019, the European Society of Cardiology defined PPCM as an idiopathic cardiomyopathy with a left ventricular LVEF <45% occurring towards the end of pregnancy or in the months following delivery, with no other identifiable cause of heart failure [13].

The pathogenesis of PPCM is still unclear but apparently linked to a “two-hit” model where vasculo-hormonal pathways (secretion of prolactin, upregulation of endothelial miRNA-146a, placental secretion of sFlt-1) and autoimmune mechanisms lead to endothelial dysfunction and cardiomyocyte death in the presence of a genetic predisposition (e.g., sarcomere gene mutations) [4].

Since PPCM symptoms largely overlap those of term pregnancy or early postpartum, this unpredictable condition is mainly evaluated according to echocardiographic criteria. These include hampered

left ventricular ejection fraction (LVEF) (<45%), reduced fractional shortening (<30%), and left ventricular end-diastolic dimension >2.7 cm/m<sup>2</sup> [5,6].

More than 10 years ago, Hilfiker-Kleiner (2007) evidenced that pregnancy-associated oxidative stress stimulates cathepsin D expression within the cardiomyocytes. This lysosomal enzyme cleaves the 23-kDa prolactin (PRL) into a 16-kDa fragment that displays vasoconstrictor, antiangiogenic, and proinflammatory effects and may lead to myocardial damage [7].

The use of prolactin inhibitors (dopamine D2 receptor agonists) has received increasing attention as a potential addition to standard heart failure treatment in cases of PPCM. Currently, bromocriptine is the first-choice drug for suppressing prolactin production in PPCM patients. However, its use is possibly associated with serious thrombotic complications, including myocardial infarction and ischemic stroke [8–10]. Conversely, the alternative use of cabergoline has been reported in only a few PPCM cases [11,12].

In this report, we discuss the role of cabergoline as a safe and effective alternative to bromocriptine for the treatment of PPCM.

## 2. Case Presentation

A 41-year-old Caucasian woman at 29 weeks and 5 days of gestation of her first pregnancy was admitted to the emergency ward with an assigned diagnosis of severe preeclampsia, on the basis of epigastric pain, hypertension (165/100 mmHg), and massive proteinuria at dipstick analysis. Non-stress test (NST), obstetric examination, and

**Abbreviations:** CPAP, continuous positive airway pressure; CRP, C-reactive protein; FFA, free fatty acids; ICU, intensive care unit; IGF-1, insulin-like growth factor 1; LVEF, left ventricular ejection fraction; NST, non-stress test; PPCM, peripartum cardiomyopathy; PRL, prolactin; SHFT, standard heart failure treatment; TTE, transthoracic echocardiogram.

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ultrasound findings were unremarkable. An electrocardiogram revealed sinus rhythm with normal conduction and diffuse ST-T segment abnormalities.

Antihypertensive medications were started including e.v. urapidil, i.e. an  $\alpha$ 1-adrenoceptor antagonist and 5-HT1A receptor agonist (bolus at a dose of 12.5 mg followed by a continuous infusion at a rate of 9 mg/h) and oral administration of labetalol (100 mg b.i.d) and methyldopa (500 mg b.i.d.). Corticosteroids were used to improve fetal lung maturation. Magnesium sulphate was administered.

Following the inpatient stabilization, a cesarean section was performed at 30 weeks and 0 days of gestation, because of fetal distress and maternal clinical deterioration. A male newborn of 1124 g was delivered, with low Apgar scores at 1 and 10 min (1 and 5, respectively). During postpartum day 1, the patient's blood pressure remained scarcely controlled (170/110 mmHg) despite increasing doses of labetalol (100 mg three times a day), methyldopa (750 mg b.i.d.), and urapidil (infusion rate of 16 mg/h) and the addition of clonidine (e.v. bolus of 150  $\mu$ g b.i.d.) and furosemide (e.v. bolus dose of 20 mg b.i.d.). Late on that day, the patient started experiencing fatigue, shortness of breath, coughing, and tachypnea. Doppler investigation of the great veins and thoracic computed tomography angiography excluded the presence of thrombosis/embolism. Hemogasanalysis indicated the presence of combined metabolic acidosis/respiratory alkalosis and a severely decreased oxygen saturation (81%). At physical examination, lung auscultation revealed wheezing and crackles; a chest X-ray had signs of pulmonary edema. Transthoracic echocardiogram (TTE) showed a LVEF severely decreased to 26% together with mild mitral regurgitation and left atrial dilation. Cardiac MRI confirmed a reduced LVEF (28%) and did not show Takotsubo cardiomyopathy (broken-heart syndrome).

On postpartum day 2, the patient was transferred to the intensive care unit (ICU) under continuous positive airway pressure (CPAP). D-dimer and B-type natriuretic peptide (BNP) plasma levels were elevated (4245 pg/mL and 10,365 pg/mL, respectively). Myoglobin and troponin T values were normal (21 ng/mL and 0.021 ng/mL, respectively), thus excluding myocardial ischemia. Viral myocarditis was also excluded. The serology was negative for the following: parvovirus B19, coxsackievirus, rubella virus, influenza A/B, *Mycoplasma pneumoniae*, Epstein-Barr virus, and enterovirus.

On postpartum day 3, the patient was assigned a final diagnosis of PPCM. With reference to the putative risks of bromocriptine use in severe preeclampsia, PRL inhibition was achieved using a single dose of cabergoline 1 mg orally, which resulted in a reduction of PRL and BNP levels from 279 ng/mL and 10,365 pg/mL, respectively, on postpartum day 3 to 13.5 ng/mL and 75 pg/mL, respectively, on postpartum day 14. Heart failure treatment included digoxin (0.125 mg orally and 0.25 mg intravenously daily) and low-molecular-weight heparin (4000 IU subcutaneously daily). The patient's clinical condition rapidly improved. On postpartum day 16, LVEF evaluated by TTE was significantly increased up to 45%. Nineteen days after delivery, the patient was discharged with the following daily medications: acetylsalicylic acid 100 mg, carvedilol 25 mg, furosemide 25 mg, irbesartan 150 mg, digoxin 0.125 mg, which were gradually discontinued over two months.

LVEF recorded at the scheduled 1-month and 1-year follow-ups was in the normal range (50% and 55%, respectively). The baby was followed up until age one and no complications were noted.

### 3. Discussion and Conclusion

We present an illustrative case of PPCM managed with standard heart failure treatment and cabergoline that resulted in full clinical recovery. PPCM poses acute clinical challenges, a minority of patients requiring mechanical support, and has long-term prognostic implications, incomplete recovery being reported in up to 35–40% of cases [4].

After the identification of a 16-kDa fragment of prolactin as a key factor in the PPCM pathophysiology leading to cardiomyocytes apoptosis, heart chamber dilation, and myocardial dysfunction, many reports outlined the positive impact of bromocriptine on PPCM treatment. Its use increases the number of patients who experience a greater recovery of LVEF and of their New York Heart Association class and reduces the death rate from 15% to 0% [8–10,14]. Therefore, bromocriptine is currently considered the first-choice prolactin inhibitor in the management of PPCM. However, bromocriptine-related serious adverse events, such as myocardial infarction, seizures, and ischemic stroke [15], make it a poor choice as an adjuvant therapy for PPCM in women with pregnancy-induced hypertension or adverse metabolic profile. The mechanisms underlying these major complications are still poorly characterized but possibly include individual hyperactivity of alpha-adrenergic receptors [16,17] and metabolic pathways prompting ergotism instead of vasodilation [18].

Cabergoline displays a higher affinity for D2 receptors, thus being even more effective than bromocriptine as a PRL inhibitor [19]. Due to its long half-life (65 h), cabergoline can be administered once or twice weekly, favoring a greater adherence to treatment when compared with the multiple administrations required for bromocriptine [19]. Furthermore, it positively impacts different metabolic and cardiovascular risk factors as it activates the central nervous system dopaminergic pathways involved in insulin resistance, food intake, and energy expenditure [20,21]. Indeed, treatment with cabergoline reduces the circulating levels of triglycerides, insulin-like growth factor 1 (IGF-1), free fatty acids (FFA), uric acid, C-reactive protein (CRP), homocysteine, and fibrinogen, while increasing HDL cholesterol and 25-hydroxyvitamin D levels, and favorably impacts 2-h post-challenge plasma glucose [22,23]. Finally, cabergoline has less adverse effects than bromocriptine and is better tolerated. Two recent meta-analyses [23,24] reported significantly more adverse effects, especially nausea and vomiting, associated with the use of bromocriptine compared with cabergoline for the treatment of hyperprolactinemia. As with other ergot derivatives, cabergoline should not be used in women with preeclampsia or post-partum hypertension, unless the potential benefit is judged to outweigh the possible risk. In our case, breastfeeding was contraindicated for the patient due to her precarious clinical condition; thus, the benefit of suppressing lactation using cabergoline was considered superior to the concerns regarding its use in preeclampsia.

Despite these favorable theoretical considerations, the evidence on the use of cabergoline to manage PPCM is still anecdotal [11,12]. We describe another case of a satisfactory resolution of PPCM treated with cabergoline in order to support the scant evidence on its efficacy in this high-risk clinical condition.

In short, we suggest that cabergoline, due to its greater therapeutic efficacy, safer profile and favorable pharmacokinetics, should be considered as an alternative treatment option for PRL inhibition in cases of PPCM complicated by preeclampsia or unfavorable metabolic profile.

### Contributors

Giuseppe Caruso contributed to conception, design, and coordination of the project, collection and assembly of data, and drafting of the manuscript.

Annalisa Scopelliti contributed to conception, design, and coordination of the project, collection and assembly of data, and drafting of the manuscript.

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Roberto Brunelli contributed to contributed to review and editing and critical revision of the manuscript.

### Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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### Patient Consent

Obtained.

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