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Bromocriptine in the management of peripartum cardiomyopathy: a review of current evidence

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Abstract. Peripartum cardiomyopathy (PPCM) is a severe form of heart failure that occurs during late pregnancy or early postpartum. Bromocriptine, a dopamine agonist that inhibits prolactin secretion, has been proposed as a disease-specific therapy due to its potential role in mitigating the cardiotoxic effects of the 16-kDa prolactin fragment. A comprehensive review of observational studies and clinical trials from PubMed and Google Scholar was conducted, with a focus on original research assessing bromocriptine therapy in PPCM. Data from ClinicalTrials.gov were also analyzed to identify ongoing research efforts. Key outcomes included changes in left ventricular ejection fraction (LVEF), heart failure recovery rates, thromboembolic events, and neonatal outcomes. Bromocriptine therapy was associated with significant improvement in LVEF and RVEF across studies. While an 8-week regimen suggested a numerically greater improvement compared to a 1-week course, the difference did not reach statistical significance in any trial. Bromocriptine treatment required concurrent anticoagulation due to thromboembolic risk, though no significant increase in adverse events was observed. Neonatal outcomes remained unaffected, but the necessity to discontinue breastfeeding remains a key limitation. Overall, bromocriptine improves myocardial recovery in PPCM. However, the lack of large randomized controlled trials limits definitive conclusions regarding optimal treatment duration and safety. Further research is needed to refine patient selection criteria and address long-term implications. Fig. 1, Tab. 2, Ref. 16, on-line full text (Free, PDF), www.cardiologyletters.sk

Keywords: peripartum cardiomyopathy – heart failure – Bromocriptine

Peripartum cardiomyopathy (PPCM) is a rare but serious form of heart failure that develops during the last trimester of pregnancy or within the first few months postpartum. It is characterized by left ventricular systolic dysfunction (LVEF <45%), leading to symptoms of heart failure in women without prior known cardiac disease.

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PPCM is increasingly recognized as a leading cause of maternal morbidity and mortality worldwide, with significant geographic and racial disparities (1). The reported incidence varies from 1 in 1000 to 1 in 4000 live births in the United States and can be as high as 1 in 100 deliveries in parts of Africa. These variations may reflect genetic predisposition, environmental factors, healthcare access, and underdiagnosis in some populations (2, 3).

Several factors increase the risk of developing PPCM, including ethnicity, advanced maternal age, hypertensive disorders of pregnancy, multiple gestation, obesity, diabetes mellitus, and genetic factors (3, 4).

However, the exact cause of PPCM remains multifactorial and incompletely understood. The recent research highlights a vascular and hormonal basis. One of the most significant findings in PPCM pathogenesis is the role of prolactin and its 16-kDa fragment, which has been identified as a key cardiotoxic factor. The cleavage of full-length prolactin into a 16-kDa pro-inflammatory, anti-angiogenic fragment is mediated by oxidative stress in the myocardium. This fragment contributes to endothelial dysfunction, increased apoptosis of cardiomyocytes, and reduced angiogenesis, leading to progressive heart failure (5).

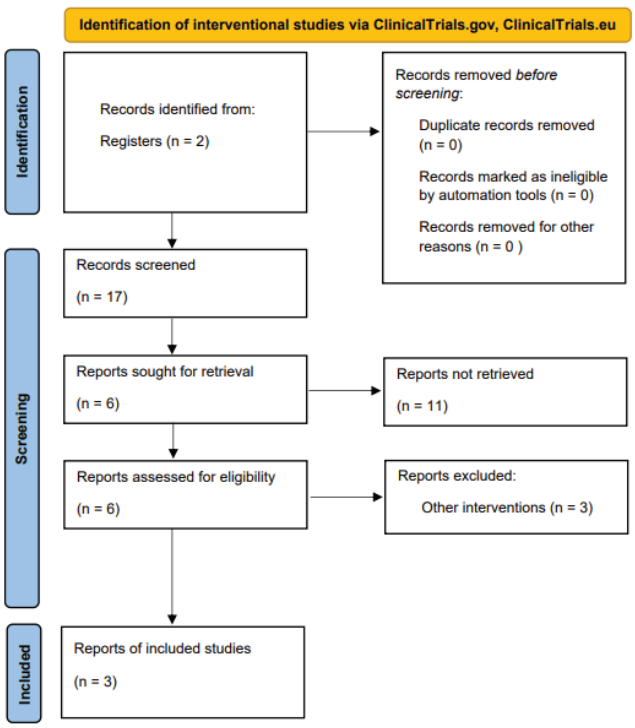

Figure 1 Identification of interventional studies in clinical trials.gov

Standard heart failure therapy includes ACE inhibitors or angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, beta-blockers, hydralazine, and nitrates. Diuretics can be also introduced (1, 6). Anticoagulation is recommended due to the increased risk of thromboembolism in PPCM, and it is always paired with bromocriptine therapy (7).

While these therapies help manage heart failure symptoms, they do not directly address the underlying vascular dysfunction seen in PPCM. This gap has led to increasing interest in bromocriptine as a disease-specific therapy due to its ability to inhibit prolactin secretion and prevent the formation of the cardiotoxic 16-kDa fragment. This integrated therapeutic approach has been conceptualized under the acronym BOARD, which encompasses bromocriptine, oral heart failure therapies, anticoagulants, vasorelaxing agents, and diuretics. The BOARD strategy aims to provide a comprehensive and structured treatment framework for PPCM, addressing both the underlying pathophysiology and symptomatic management to improve patient outcomes (8). This review will further explore the role of bromocriptine in PPCM treatment, examining its efficacy, safety, and ongoing clinical trials investigating its long-term benefits.

Methodology

This review is based on an analysis of observational studies and clinical trials retrieved from PubMed and Google Scholar, focusing on original research articles evaluating bromocriptine's role in PPCM treatment. Additionally, clinical trial data were extracted from ClinicalTrials.gov to assess ongoing research efforts related to bromocriptine therapy in PPCM. The search criteria included six original studies on "bromocriptine peripartum cardiomyopathy" on PubMed, where one of them wasn't investigated due to its different objective. Additionally, a search on Google Scholar, where study type selection is not possible, returned 5900 results, necessitating manual screening for relevant original research. The focus was on studies that evaluated bromocriptine's efficacy, safety, dosage regimens, and patient outcomes in PPCM patients.

Additionally, an overview of clinical trial data was extracted from ClinicalTrials.gov, revealing that out of 17 studies on PPCM, 3 were interventional trials investigating bromocriptine therapy. Notably, there are currently no ongoing PPCM interventional studies registered in ClinicalTrials.eu (**Figure 1**).

Data extraction included parameters such as study design, sample size, treatment duration, short-term and long-term clinical outcomes, and reported adverse effects. The primary outcomes analyzed included changes in left ventricular ejection fraction, rates of heart failure recovery, thromboembolic events, and mortality. Special attention was given to the necessity of anticoagulation during bromocriptine therapy due to its associated thromboembolic risk: information about infant outcomes was gathered as well.

Results

A total of five clinical studies and one large registry analysis evaluated the impact of bromocriptine therapy in patients with peripartum cardiomyopathy (PPCM), with particular focus on its effect on left ventricular (LV) and right ventricular (RV) recovery, mortality, thromboembolic events, and neonatal outcomes. Across the studies, bromocriptine was administered in different regimens, with most studies comparing short-term (1-week 2,5 mg/day, 1W) versus long-term (8-week, 5 mg/day (2 weeks) + 2,5 mg/day (6 weeks), 8W) therapy, alongside standard heart failure treatment.

A pronounced benefit of bromocriptine therapy was observed in studies that assessed bromocriptine against standard heart failure treatment alone. In a proof-of--concept study by Sliwa et all., patients receiving 8 weeks of bromocriptine showed a significant increase in LVEF from 27% at baseline to 58% after six months ($p = 0.012$), while those receiving only standard heart failure treatment had a more modest improvement from 27% to 36%. This study also found that significantly fewer patients in the bromocriptine group experienced adverse outcomes at six months, defined as death, NYHA functional class III/IV symptoms, or LVEF <35% (10% in the bromocriptine group vs. 80% in the standard therapy group, $p = 0.006$) (9). The retrospective BRO-HF cohort study further reinforced the potential benefits of bromocriptine by showing that patients treated with the drug had better mid-term LVEF recovery, with an increase from 23 ± 10% to 55 ± 12%, compared to 30 ± 12% to 45 ± 13% in the standard therapy group. A long-term follow-up of this study indicated a sustained benefit, as LVEF variation remained 9% higher in the bromocriptine group ($p < 0.01$) (10). Although these findings suggest that bromocriptine may contribute to improved myocardial recovery, the retrospective nature of the study limits the ability to draw firm conclusions regarding causality.

The EORP PPCM registry provided a broader perspective by including 552 patients with PPCM, of whom 85 received bromocriptine therapy. A complete case analysis showed that bromocriptine treatment was associated with a reduction in adverse maternal outcomes, with an odds ratio (OR) of 0.29 (95% confidence interval 0.10–0.83, $p = 0.021$), suggesting a significant protective effect. However, the registry also noted that patients receiving bromocriptine tended to have more severe disease at baseline, which raises the possibility of selection bias. While this finding aligns with smaller clinical trials demonstrating improved cardiac function with bromocriptine, it highlights the need for randomized controlled trials to confirm its efficacy in routine clinical practice (11).

The comparative analysis of 1W versus 8W bromocriptine therapy showed that left ventricular ejection fraction (LVEF) increased 21 ± 11% in the 1W group and 24 ± 11% in the 8W group in one study by Hilfiker--Kleiner et al. ($p = 0.381$), while Haghikia et al. reported LVEF increased 21 ± 11% in the W1 versus 27 ± 9% in the 8W ($p = 0.211$). Full LVEF recovery, defined as LVEF ≥50%, was observed in 52% and 50% of patients in the 1W group compared to 68% and 64% in the 8W group, respectively. Despite the numerically higher recovery rates in the 8W group, these differences did not reach statistical significance ($p = 0.678$) (12, 13). Similarly, right ventricular function appeared to improve more with bromocriptine therapy, as one study showed that full RV recovery was achieved in 40% of the 1W group versus 79% in the 8W group, though this difference was also not statistically significant ($p = 0.092$). The same study reported RV ejection fraction (RVEF) increase of 15% ± 12% in the 1W group compared to 23 ± 10% in the 8W group at 6 month

Table 1 Left ventricle ejection fraction (LVEF) recovery in PPCM patients with bromocriptine therapy in 6 month follow-up

Title, DOI	LVEF change in 6 month follow-up			Participants
	Standard	1W	8W	
Bromocriptine treatment in patients with peripartum cardiomyopathy and right ventricular dysfunction https://doi.org/10.1007/s00392-018-1355-7		ΔLVEF ↑ 21 ± 11%	ΔLVEF ↑ 27 ± 9%	24, 10 in the 1W group and 14 in the 8W group (p = 0.211)
Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study https://doi.org/10.1093/eurheartj/ehx355		ΔLVEF ↑ 21 ± 11%	ΔLVEF ↑ 24 ± 11%	63, 32 in the 1W group and 31 in the 8W group (p = 0.381)
Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy: A Proof-of-Concept Pilot Study https://doi.org/10.1161/circulationaha.109.901496	ΔLVEF ↑ 9 %		ΔLVEF ↑ 31 %	20, 10 treated with bromocriptine (p = 0.012)
The effect of bromocriptine on left ventricular functional recovery in peripartum cardiomyopathy: insights from the BRO-HF retrospective cohort study https://doi.org/10.1002/ehf2.12376	From 30 ± 12% to 45 ± 13%		From 23 ± 10% to 55 ± 12%	76, 8 treated with bromocriptine

ΔLVEF ↑ increase in left ventricular ejection fraction in 6 month follow-up compared to baseline
*Standard PPCM therapy
*1W bromocriptine 2.5 mg/day (7 days)
*8W bromocriptine 5 mg/day (2 weeks) + 2.5 mg/day (6 weeks)

follow-up (p = 0.118) (13). The overall trend in these studies suggested that long-term bromocriptine therapy may be associated with a greater likelihood of cardiac recovery function, yet the lack of statistical significance in these findings means that a definitive conclusion cannot be drawn (**Table 1**).

Thromboembolic events, a known concern with bromocriptine therapy, were variably reported across the studies. The EORP PPCM registry found no significant difference in the incidence of thromboembolic events between the bromocriptine (6.0%) and non-bromocriptine (5.6%) groups (p = 0.900), indicating that bromocriptine did not appear to increase thromboembolic risk in this large cohort (14). However, a single-centre study from North Africa reported a thromboembolism rate of 18.5%, though it was unclear whether this was directly associated with bromocriptine therapy (15). Given this variability, it remains uncertain whether bromocriptine independently increases thrombotic risk, but the potential for thromboembolic complications reinforces the recommendation for anticoagulation therapy when using bromocriptine in PPCM patients.

Neonatal outcomes were less frequently reported, but one study explicitly assessing the impact of bromocriptine therapy on infants found no significant differences in growth or survival between newborns of mothers treated with bromocriptine and those in the standard treatment group. However, the need to discontinue breastfeeding remains a critical limitation of bromocriptine therapy. The Hammami et al. study additionally reported a prematurity rate of 36% among newborns in patients who developed PPCM (15).

A review of clinical trial data from ClinicalTrials.gov identified 17 studies on PPCM, of which 3 were interventional trials specifically evaluating bromocriptine therapy. These 3 trials account for the half of interventional studies on PPCM, as only 6 interventional trials in total were identified in this field. The remaining

Table 2 ClinicalTrials.gov interventional studies involving bromocriptine therapy

Title	Study status	Date	Participants	Locations
Effect of Bromocriptine on Left Ventricular Function in Women With Peripartum Cardiomyopathy (PPCM)	Completed	2009-2020	64	1, Germany
Impact of Bromocriptine on Clinical Outcomes for Peripartum Cardiomyopathy (REBIRTH)	Recruiting	2021-	250	63, United States
Bromocriptine in the Treatment of Peripartum Cardiomyopathy (BRO-HF)	Withdrawn	2015-2023	0	1, Canada

three trials investigated taurine therapy, and screening programmes (**Table 2**).

Discussion

The findings of this review highlight the potential role of bromocriptine as a disease-modifying therapy in peripartum cardiomyopathy (PPCM), aligning with the current understanding of its pathophysiology. PPCM has been increasingly linked to prolactin dysregulation, particularly the formation of a cardiotoxic 16-kDa prolactin fragment, which contributes to endothelial dysfunction, oxidative stress, and myocardial apoptosis (5). The therapeutic rationale for prolactin inhibition with bromocriptine is therefore well-supported, as preclinical studies have demonstrated its ability to restore vascular function, reduce cardiac stress, and promote myocardial recovery.

In clinical studies, bromocriptine therapy has consistently shown trends toward improved left ventricular ejection fraction (LVEF) and functional outcomes, particularly when used for an extended 8W duration. While the comparison between short-term (1W) and long-term (8W) bromocriptine therapy suggested better right ventricular recovery and higher rates of full LVEF normalization in the 8W group, the differences did not always meet the threshold for statistical significance (12, 13). This suggests that while longer prolactin inhibition may offer greater myocardial protection, shorter regimens may still be beneficial in certain PPCM patients. Further studies are required to determine whether all PPCM patients require prolonged therapy or if treatment duration should be tailored based on clinical severity.

One of the concerns with bromocriptine therapy has been its potential association with thromboembolic complications. Early reports suggested that prolactin inhibition may increase vascular tone and platelet aggregation, raising concerns about an elevated risk of thrombosis. However, more recent data challenge this assumption. van der Meer et al. which included 552 PPCM patients, found no significant difference in thromboembolic events between those receiving bromocriptine (6.0%) and those managed with standard therapy alone (5.6%) (14). This suggests that bromocriptine itself may not independently increase thrombotic risk, but rather that PPCM patients as a whole are already at elevated risk due to endothelial dysfunction and hypercoagulability. Nonetheless, regional differences in reported thromboembolic rates remain, with a single-centre study in North Africa reporting an 18.5% thromboembolism rate in PPCM patients, raising the question of whether anticoagulation protocols, healthcare access, or patient selection differences influence these outcomes (15). Until further evidence is available, current guidelines recommending anticoagulation for PPCM patients receiving bromocriptine remain appropriate, particularly for those with LVEF ≤ 35% or other thrombotic risk factors.

The impact of bromocriptine on neonatal outcomes was less frequently addressed in the reviewed studies. Available data suggest that bromocriptine does not adversely affect neonatal survival or growth. However, a major limitation remains the necessity to discontinue breastfeeding, as bromocriptine suppresses lactation, which may limit maternal-infant bonding and present nutritional challenges in low-resource settings where alternative feeding options are scarce. This is a significant consideration in clinical decision-making, particularly for mothers who wish to breastfeed but require bromocriptine therapy for severe PPCM. While this is often cited as a limitation of treatment, it is important to recognize that many PPCM patients may already be unable to breastfeed due to the severity of their heart failure. Advanced heart failure symptoms, such as fatigue, dyspnea, and hemodynamic instability, can significantly impair a mother's ability to sustain lactation (16). Future research should investigate whether lower doses of bromocriptine or alternative prolactin inhibitors could allow for partial lactation preservation while maintaining cardiac benefits.

The fact that 3 out of the 6 interventional trials in PPCM research focus on bromocriptine underscores its perceived potential as a disease-modifying therapy. However, the limited number of interventional studies overall highlights the ongoing challenges in conducting prospective clinical trials in PPCM, particularly due to difficulties in patient recruitment, postpartum enrollment, and ethical considerations surrounding maternal health research. The prolonged completion times-with one trial taking 11 years to complete, another still ongoing since 2021, and one being withdrawn after 8 years-emphasize these barriers. This raises the question of whether al-

ternative study designs, such as registry-based analyses or multi-centre collaborations, may be necessary to generate robust clinical evidence for PPCM treatments.

Limitations

The primary limitation of current evidence on bromocriptine in PPCM is the lack of large-scale randomized controlled trials, as most studies are observational or retrospective, making it difficult to establish causality and optimal treatment duration.

Conclusions

Bromocriptine has emerged as a potential disease--modifying therapy in PPCM, showing promise in improving cardiac function and reducing adverse maternal outcomes, though definitive evidence favouring long--term over short-term therapy remains lacking. While thromboembolic risk remains a concern, recent data suggest that it may be more related to PPCM severity than bromocriptine itself, reinforcing the need for individualized anticoagulation strategies. The lack of large randomized controlled trials remains a major limitation, making definitive conclusions about treatment duration, safety, and patient selection difficult.

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