

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



## **Bromocriptine for the Treatment of Peripartum Cardiomyopathy**

Uri Elkayam and Sorel Goland

*Circulation* 2010;121;1463-1464; originally published online Mar 22, 2010;

DOI: 10.1161/CIR.0b013e3181db2f07

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

Copyright © 2010 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/121/13/1463>

Subscriptions: Information about subscribing to *Circulation* is online at  
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

## Bromocriptine for the Treatment of Peripartum Cardiomyopathy

Uri Elkayam, MD; Sorel Goland, MD

Peripartum cardiomyopathy (PPCM) is a pregnancy-associated idiopathic cardiomyopathy presenting during pregnancy or within few months after delivery<sup>1,2</sup> with signs and symptoms of heart failure caused by marked depression of left ventricular (LV) systolic function. Although the disease is uncommon, it is increasing in frequency<sup>3</sup> and represents an important cause of pregnancy-related morbidity and mortality.<sup>1,2,4</sup> The incidence of PPCM has recently been estimated to be 1 in 2000 to 4000 deliveries,<sup>1,3,5</sup> thus affecting ≈1000 to 2000 women per year in the United States alone. Data from South Africa and Haiti suggest a significantly higher incidence of PPCM in these countries, affecting 1 in 1000 (Africa) and 1 in 300 (Haiti) pregnant women.<sup>1</sup>

### Article see p 1465

Although early recovery of LV function frequently occurs, failure to recover has been reported in one third to two thirds of the patients in the United States<sup>2,4,6,7</sup> and in an even larger number of patients in other populations.<sup>8,9</sup> A strong relationship has been demonstrated between the severity and persistence of LV dysfunction and the incidence of morbidity and mortality.<sup>4,8</sup> Although the use of evidence-based therapies, proven effective in patients with heart failure with other origins, makes good clinical sense, there is no clear evidence for the effect of these therapies on the recovery of cardiac function in patients with PPCM, and the rate of recovery reported in early studies, before the current therapeutic era,<sup>10</sup> seems comparable to that published more recently. Because the cause of PPCM is still unknown, no specific therapy has been established to treat this condition.

On the basis of the hypothesis that abnormal maternal immunologic response may cause PPCM, Bozkurt et al<sup>11</sup> attempted the use of intravenous immune globulin, which has a significant immune modulator properties, in 6 women with PPCM and reported a significantly greater improvement in LV ejection fraction in these women compared with 11 historical control patients who received conventional therapy alone. Although the results seemed encouraging, the study was limited by a small number of patients and by the lack of a blindly randomized, well-matched control group. The failure of immune

globulin treatment to improve LV function in another study of women with recent-onset dilated cardiomyopathy may have discouraged further investigation of this therapy in PPCM.

More recent studies emphasized the potential role of cytokine-mediated inflammation in the progression of PPCM.<sup>12</sup> Sliwa et al<sup>13</sup> therefore investigated the effect of pentoxifylline, a xanthine agent known to inhibit the production of tumor necrosis factor and to prevent apoptosis. These investigators reported on 59 patients with PPCM, 30 of whom were randomized to receive pentoxifylline 400 mg TID for 6 months in addition to conventional therapy, including diuretics, digoxin, enalapril, and carvedilol. The results of the study demonstrated a significant improvement in a combined end point of poor outcome defined as death, failure to improve LV ejection fraction >10 absolute points, or persistence of New York Heart Association functional class III to IV at the latest follow-up (52% versus 27%;  $P=0.03$ ). Despite these positive results, no further studies have been conducted, and this therapy has not been widely adopted to treat PPCM.

In this issue of *Circulation*, Sliwa and coworkers<sup>14</sup> report the preliminary results of another therapy based on the concept of enhanced oxidative stress-mediated cleavage of the nursing hormone prolactin into an antiangiogenic and proapoptotic 16-kDa form that may be responsible for the development of PPCM.<sup>15</sup> This prospective single-center, proof-of-concept pilot study performed in South Africa evaluated the effect of prolactin blockade with bromocriptine. Treatment with this drug given after diagnosis at a dose of 2.5 mg twice daily for 2 weeks, followed by 2.5 mg daily for 6 weeks, in addition to standard heart failure therapy in 10 patients with PPCM resulted in a significantly larger rate of LV recovery at 6 months compared with a comparable group of 10 women with PPCM treated with standard heart failure therapy alone ( $\pm 31\%$  versus  $\pm 9\%$ ;  $P=0.012$ ). In addition, there was a lower rate of mortality in the treatment group (1 versus 4 patients) and of an index of poor outcome defined as a combined end point of death, New York Heart Association functional class III/IV, or LV ejection fraction <35% at 6 months.

The results of this study are exciting and may represent breakthroughs in the understanding of the mechanism causing PPCM and in the development of a new specific therapy for this condition. At the same time, however, the study suffers from important limitations that are mentioned by the authors but need to be further emphasized. Similar to other pilot studies, the small number of patients included in each arm of the study may lead to erroneous results and conclusions. This concern is further supported by the excessive mortality rate reported in the control group, which far exceeds mortality rates reported by other investigators<sup>2,4-7</sup> and even previously

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Medicine, Division of Cardiology, and Department of Obstetrics and Gynecology, University of Southern California, Los Angeles (U.E.), and Department of Cardiology, Kaplan Medical Center, Rehovot, Israel (S.G.).

Correspondence to Uri Elkayam, MD, LAC+USC Medical Center, 2020 Zonal Ave, Los Angeles, CA 90033. E-mail Elkayam@usc.edu (*Circulation*. 2010;121:1463-1464.)

© 2010 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>  
DOI: 10.1161/CIR.0b013e3181db2f07

by the same investigators.<sup>1,12</sup> This high mortality rate may be coincidental and could have importantly affected the results of the study. Another potential limitation of the study is related to the fact that African patients with PPCM demonstrate important phenotypic differences compared with patients in other geographical areas<sup>1,2</sup>; thus, the results of this study may not be applicable to non-African populations of patients with PPCM. This assumption may be supported by our preliminary experience with 2 Israeli women who were diagnosed with PPCM in the first week after delivery and failed to show an improvement in markedly depressed LV function with bromocriptine at the regimen used by the investigators and described in other cases.<sup>16,17</sup> It should also be noted that although the use of bromocriptine may be safe in most patients, the safety of bromocriptine as a drug of choice in the suppression of lactation has been questioned, and important complications, including stroke, seizures, and myocardial infarction, have been reported in isolated cases.<sup>18,19</sup> For all the above reasons, the promising preliminary results of the study by Sliwa et al<sup>15</sup> should be viewed with caution and should serve only as a basis for further studies aimed at clearly establishing the efficacy and safety of bromocriptine therapy.

Performing an adequate study to evaluate this therapy for PPCM patient may be challenging. The relatively low incidence of the disease and the possible reluctance of women to use bromocriptine and deprive themselves and their newborn babies of the emotional and physical benefits of breastfeeding may limit the number of patients randomized. For these reasons, only a large, multicenter trial will enable the enrollment of enough patients to answer the clinical questions at hand at a reasonable time period. Because of significant variability in the clinical presentation of PPCM in different populations,<sup>1</sup> a multinational study is preferred to capture potential heterogeneous responses to therapy. Because a significant number of patients demonstrate improvement in LV function either spontaneously or after standard therapy, the effect of bromocriptine may be better tested in patients at high risk of failure to recover. This should include patients with more severe myocardial insult at presentation as reflected by a larger degree of LV dilatation and systolic dysfunction, as well as hemodynamic compromise and elevation of troponin levels.<sup>20–22</sup>

Despite these potential difficulties, the promising results of the study by Sliwa et al published in this issue of *Circulation* should provide a strong incentive for physicians and funding institutions to perform a large, well-designed, prospective study aimed at evaluating the therapeutic potential of bromocriptine as the first specific therapy for patients with PPCM.

## Disclosures

None.

## References

1. Sliwa K, Fett J, Elkayam U. Current understanding of the epidemiology, etiology, clinical profile, and management of PPCM. *Lancet*. 2006;368:687–693.
2. Elkayam U, Akhter MW, Singh H, Khan S, Bitar M, Hameed A, Shotan A. Pregnancy-associated cardiomyopathy: clinical characteristics and a

- comparison between early and late presentation. *Circulation*. 2005;111:2050–2055.
3. Mielniczuk LM, Williams K, Davis DR, Tang A, Lemery R, Green MS, Gollob MH, Haddad H, Birnie D. Frequency of peripartum cardiomyopathy. *Am J Cardiol*. 2006;97:1765–1768.
4. Goland S, Modi K, Bitar F, Janmohamed M, Mirocha J, Czer L, Illum S, Hatamizadeh P, Elkayam U. Clinical profile and predictors of complications in peripartum cardiomyopathy. *J Card Fail*. 2009;15:645–650.
5. Brar SS, Khan SS, Sandhu GK, Jorgensen MB, Parikh N, Hsu JW, Shen A. Incidence, mortality, racial differences in peripartum cardiomyopathy. *Am J Cardiol*. 2007;100:302–304.
6. Amos AM, Jaber WA, Russell SD. Improved outcomes in peripartum cardiomyopathy with contemporary. *Am Heart J*. 2006;152:509–513.
7. Modi KA, Illum S, Jariatul K, Caldito G, Reddy P. Poor outcome of indigent patients with peripartum cardiomyopathy in United States. *Am J Obstet Gynecol*. 2009;201:171–172.
8. Sliwa K, Förster O, Libhaber E, Fett J, Sundstrom JB, Hilfiker-Kleiner D, Ansari A. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J*. 2006;27:441–446.
9. Fett JD, Sannon H, Thélisma E, Sprunger T, Suresh V. Recovery from severe heart failure following peripartum cardiomyopathy. *Int J Gynaecol Obstet*. 2009;104:125–127.
10. Demakis JG, Rahimtoola SH, Sutton GC, Medows WR, Szanto PB, Tobin JR, Gunnar RM. Natural course of peripartum cardiomyopathy. *Circulation*. 1971;44:1053–1061.
11. Bozkurt B, Villaneuva F, Holubkov R, Tokarczyk T, Alvarez RJ Jr, MacGowan GA, Murali S, Rosenblum WD, Feldman AM, McNamara DM. Intravenous immune globulin in the therapy of peripartum cardiomyopathy. *J Am Coll Cardiol*. 1999;34:177–180.
12. Sliwa K, Skudicky D, Bergemann A, Candy G, Puren A, Sareli P. Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma levels of cytokines and Fas/APO-1. *J Am Coll Cardiol*. 2000;35:701–705.
13. Sliwa K, Skudicky D, Candy G, Bergmann A, Hopley M, Sareli P. The addition of Pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. *Eur J Heart Fail*. 2002;4:305–309.
14. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema J-P, Becker A, McMurray J, Yamac H, Labidi S, Struhman I, Hilfiker-Kleiner D. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation*. 2010;121:1465–1473.
15. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, Forster O, Quint A, Landmesser U, Doerries C, Luchtefeld M, Poli V, Balligand JL, Desjardins F, Ansari A, Struman I, Nguyen N, Zschemisch NH, Klein G, Heusch G, Schulz R, Hilfiker A, Drexler H. A cathepsin D-cleaved 16kDa form of prolactin mediates postpartum cardiomyopathy. *Cell*. 2007;128:589–600.
16. Hilfiker-Kleiner D, Meyer G, Schieffer E, Goldmann B, Podewski G, Struman I, Fischer P, Drexler H. Recovery from postpartum cardiomyopathy in 2 patients by blocking prolactin release with bromocriptine. *J Am Coll Cardiol*. 2007;50:2354–2356.
17. Habedank D, Kühnle Y, Elgeti T, Dudenhausen JW, Haverkamp W, Dietz R. Recovery from peripartum cardiomyopathy after treatment with bromocriptine. *Eur J Heart Fail*. 2008;10:1149–1151.
18. Katz M, Kroll D, Pak I, Osimoni A, Hirsch M. Puerperal hypertension, stroke and seizures after suppression of lactation with bromocriptine. *Obstet Gynecol*. 1985;66:822–823.
19. Dutt S, Wong F, Spurway JH. Fatal myocardial infarction with bromocriptine for postpartum lactation suppression. *Aust NZ J Obstet Gynaecol*. 1998;38:116–117.
20. Duran N, Günes H, Duran I, Biteker M, Ozkan M. Predictors of prognosis in patients with peripartum cardiomyopathy. *Int J Gynaecol Obstet*. 2008;101:137–140.
21. Chapa JB, Heiberger HB, Weinert L, DeCara J, Lang RM, Hibbard JU. Prognostic value of echocardiography in peripartum cardiomyopathy. *Obstet Gynecol*. 2005;105:1303–1308.
22. Hu Cl, Li Yb, Zhang JM, Chen JB, Liu J, Tang YH, Tang QZ, Huang CX. Troponin T measurement can predict persistent left ventricular dysfunction in peripartum cardiomyopathy. *Heart*. 2007;93:488–490.

KEY WORDS: Editorial ■ cardiomyopathy ■ pregnancy