Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1537-18
Intern Med 58: 541-544, 2019
http://internmed.jp

【 CASE REPORT 】

The Use of Bromocriptine for Peripartum Cardiomyopathy after Twin Delivery via Oocyte Donation

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Abstract:
Peripartum cardiomyopathy (PPCM) is rare but life-threatening. We herein report the case of a 48-year-old woman with PPCM after oocyte donation and delivery of twins. Two weeks after delivery, she suffered from severe symptoms of heart failure [orthopnea, New York Heart Association (NYHA) class IV, pulmonary edema and a reduced left ventricular ejection fraction of 18%]. Although standard heart failure therapy was effective for diminishing the congestion, it was not sufficient to improve her symptoms or left ventricular systolic dysfunction. During admission, we added bromocriptine. A year later after the onset, she was in a good state with an improved left ventricular systolic function.

Key words: peripartum cardiomyopathy, assisted reproductive technique, bromocriptine

(Intern Med 58: 541-544, 2019)
(DOI: 10.2169/internalmedicine.1537-18)

Introduction

Peripartum cardiomyopathy (PPCM) is a rare form of cardiomyopathy occurring in women between one-month antepartum and five-months postpartum (1, 2). Although the precise mechanisms remain unknown, several risk factors or associated conditions have been suggested, including older age (1), multiparity (3), lower parity (4), infectious diseases, autoimmune diseases (5), pregnancy-associated hypertensive diseases (4, 6), cesarean section, volume overload, multifetal pregnancies (4), and the use of tocolytic therapy (4).

For women with diminished ovarian reserve, premature ovarian failure, genetic disorders and surgical menopause, oocyte donation, which was first introduced in the early 1980s, improves the chances of achieving pregnancy and live birth (7-9). In the United States and other countries, assisted reproductive technologies (ARTs) including oocyte donation are increasingly used to overcome infertility. There were approximately 20,000 attempts at achieving pregnancy with the use of oocyte donation in the United States in 2015 (10). ART using donor eggs or embryos is much more common among older women than among younger women and the percentage of cycles performed with donor eggs increases sharply after 40 years of age. Likewise, the number of pregnancies achieved using ART has been increasing in line with the aging of pregnant women, even in Japan (11, 12). However, the prevalence of obstetric complications of ART, including PPCM, has not obviously been reported. We herein report a rare case of a patient, who developed PPCM after donor oocyte gestation and delivery. This case report was approved by the Ethics Committee of Kurume University Hospital and the patient gave her informed consent for the publication of this report.

Case Report

A 48-year-old Japanese woman was admitted to our hospital due to dyspnea and orthopnea two weeks after an elective cesarean section after achieving pregnancy by ART using donor oocytes (three frozen-thawed embryos were transferred and live births were achieved). It was her first preg-

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Received: May 15, 2018; Accepted: July 2, 2018; Advance Publication by J-STAGE: December 18, 2018
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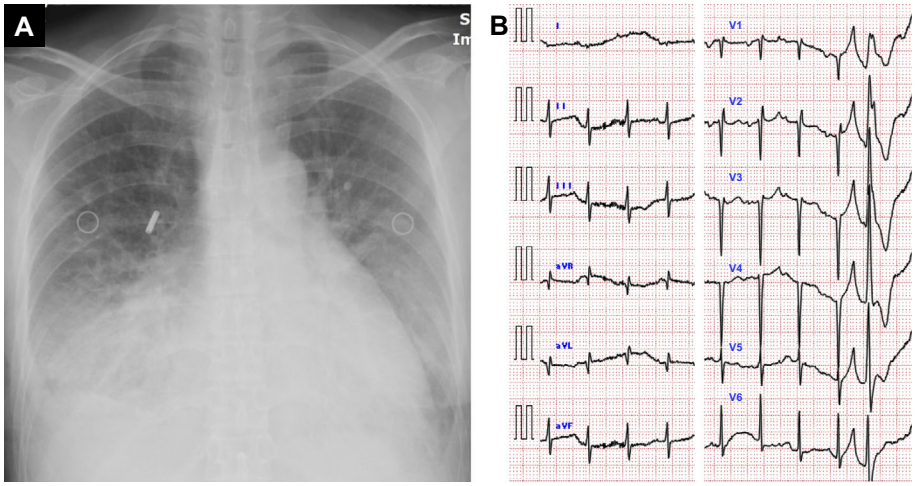

Figure 1. **Chest X-ray (A) and electrocardiography (B) findings on admission.**

nancy and she had twins. She had no pre-existing cardiovascular disease, gestational hypertension, proteinuria or preeclampsia during pregnancy. At the 38th week of gestation, a planned cesarean section was performed without problems and both newborns were delivered in a good condition. She was free from cardiovascular symptoms after delivery.

On admission, chest X-ray demonstrated pulmonary edema (Fig. 1A). Electrocardiography (ECG) showed sinus tachycardia (heart rate, 120 beats/min) with poor R-wave progression in V1-V4 and premature ventricular contraction (PVC) (Fig. 1B). Echocardiography revealed severe left ventricular dysfunction with a reduced left ventricular ejection fraction (LVEF) of 18% (severe hypokinesis outside of the lateral region) and left ventricular dilatation [left ventricular end diastolic diameter (LVEDD) 59 mm] (Supplementary material 1). A blood test showed an elevated level of N-terminal pro-brain natriuretic peptide (NTpro-BNP) (8,298 pg/mL) and normal levels of troponin T (0.021 ng/mL) and creatine kinase (CK) (129 U/L). We diagnosed her with PPCM and transferred her to our intensive care unit (ICU). On the 6th day, we started anti-coagulation therapy using edoxaban (30 mg, once a day), due to a suspected venous thromboembolism. She was treated with intravenous nitroglycerin (1 mg/min), furosemide (20 mg, intravenous, twice a day), spironolactone (200 mg, intravenous, once a day) and non-invasive positive pressure ventilation (NIPPV), to which she responded very well. In the chronic phase, she received an angiotensin-converting enzyme (ACE)-inhibitor (enalapril maleate 5 mg twice a day) and a beta-blocker (bisoprolol fumarate 1,25 mg once a day). Despite optimal therapy and decreased NTpro-BNP levels (156 pg/mL), her symptom remained New York Heart Association (NYHA) class III and her left ventricular (LV) contractility was still reduced (LVEF 23.8%). Thus, after receiving ethics committee approval from Kurume University Hospital and obtaining written informed consent, we started the administration of a dopamine-D2-receptor agonist, bromocriptine (5 mg/day for 2 weeks and 2.5 mg/day for the next 6 weeks) (13) on the 41st day after cesarean section (25th day after the onset of heart failure) in addition to cardiac rehabilitation. On day 28, we performed cardiac catheterization, which indicated normal hemodynamics, normal coronary angiography, and a reduced LVEF of 34% (Fig. 2A). Cardiac biopsy indicated mild cardiac fibrosis without inflammatory cells, which was also compatible with PPCM (Fig. 2B). She was discharged to return home on the 44th day and bromocriptine was continued for a total of 8 weeks. In an examination at an outpatient clinic, she was in a good state (NYHA class II, NTpro-BNP levels; 152 pg/mL 3 months later and 90 pg/mL one year later). Echocardiography showed a smaller LVEDD (53 mm both 3 months and one year later) and an improved LVEF (44% 3 months later and 47% one year later) (Supplementary material 2, 3).

Discussion

Generally, several risk factors, including older age (1) and multifetal pregnancies (4), as were present in this case, are known to increase the risk of PPCM; these factors are also apparently associated with ART. Thus, it is possible that PPCM often occurs in women who have received ART or that ART itself causes PPCM. A retrospective cohort of 36 women with PPCM by Shani et al. showed that 36% of PPCM patients conceived with *in vitro* fertilization (IVF) and that 16% of PPCM cases occurred in women who received ovum donation; this prevalence was significantly higher in comparison to controls without PPCM (14). In the cohort study, Shani et al. presented the demographics and the pregnancy characteristics (ART vs. non-ART PPCM subgroups), indicating that the ART group showed a higher maternal age and had a higher prevalence of primipara, multifetal pregnancies and cesarean delivery in comparison to the non-ART group. The cardiac function at the time of the diagnosis and the follow-up phase was comparable between the 2 subgroups. Nevertheless, the regression analyses of Shani et al. also demonstrated that ART was not an independent risk factor for PPCM, even after adjustment for

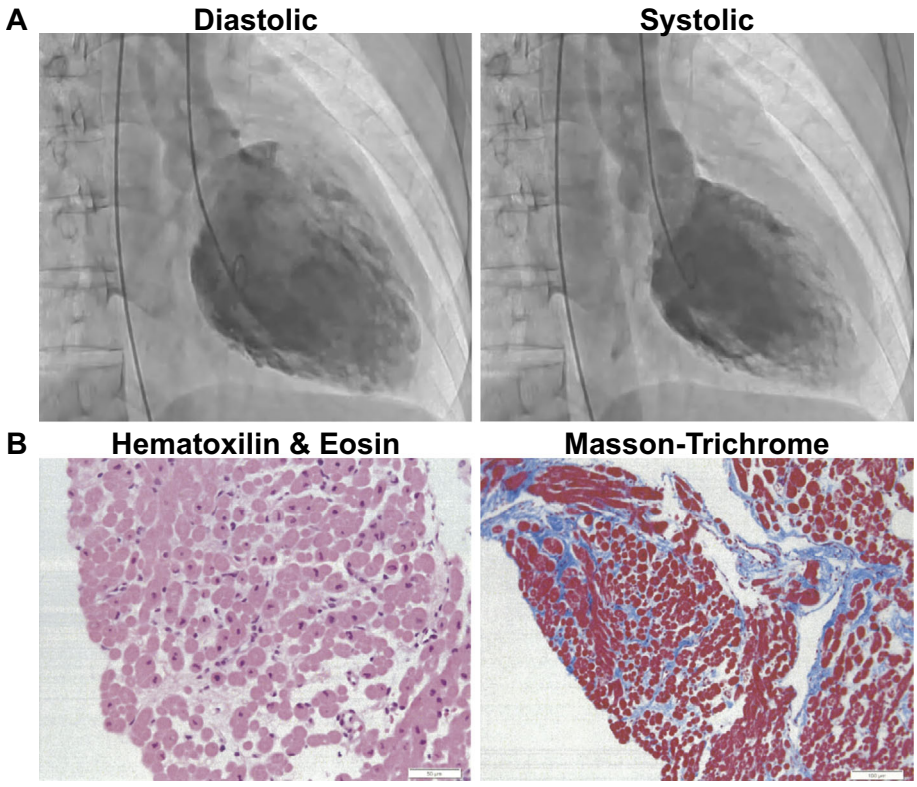

Figure 2. **Left ventricular angiocardiography (A) and the pathological findings of an endomyocardial biopsy specimen (B).**

other risk factors (maternal age, parity and number of fetuses) (OR 1.802, 0.59-5.875) (14).

In contrast, some previous studies demonstrated that ART was associated with an increased risk of pregnancy complications (15-17). Levron, et al. (18) suggested that the rate of hypertensive diseases of pregnancy in donor oocyte (IVF-DO) recipients was significantly higher than that in patients who conceived with autologous oocytes (IVF-AO) (25% vs 10%). Interestingly, even after adjustment for maternal age, gravidity, parity, and the presence of chronic hypertension, oocyte donation was independently associated with a higher rate of hypertensive diseases of pregnancy (18). It has been hypothesized that preeclampsia might result from an abnormal maternal immune response to novel paternally derived fetal antigens (19-22) and the difference between IVF-DO and IVF-AO might support the immunologic theory. Future studies are necessary to investigate whether donor oocytes are potential risk factor for not only hypertensive disease but also PPCM.

In this case, we added bromocriptine to the optimal heart failure therapy. After bromocriptine therapy, the left ventricular systolic function of our patient improved. However, it is unclear whether or not this was a direct effect of bromocriptine. Whether the use of bromocriptine has a prognostic benefit in patients with PPCM remains controversial. Experimental studies have suggested that 16 kDa prolactin reduced the myocardial capillary density, reduced the cardiac function and promoted endothelial cell apoptosis (23-25). Then, the suppression of prolactin secretion by bromocriptine prevented PPCM in these mice (23). In a clinical pilot study, bromocriptine prevented the expected deterioration of LV dimensions and the systolic function when administered in addition to standard heart failure therapy to patients with subsequent pregnancy after known PPCM (13). However, concerns have been raised about the potential risk of cerebral and cardiovascular complications, such as stroke (26, 27), seizure (28), coronary artery thrombosis (28), and coronary artery vasospasm (29, 30). Caution is therefore needed in drawing conclusions about the effectiveness of bromocriptine in patients with PPCM. In fact, a recent prospective, randomized, and multicenter trial demonstrated that both long-term and short-term bromocriptine in addition to standard therapy for heart failure is associated with a high recovery rate and very low rate of adverse outcome in patients with severe forms of PPCM; in the studies, attention was paid to ensure sufficient anticoagulant therapy during treatment (31, 32). Indeed, bromocriptine is suspected to be associated with thrombotic events (32). Thus, anticoagulation therapy is recommended-at least at a prophylactic dose (32). The optimal dosage and duration of therapy to achieve the maximum cardioprotective effects still remains a matter of investigation. Further research is required to prove the efficacy of bromocriptine in the treatment of PPCM.

Conclusion

We reported the case of a woman with a history of ART who developed PPCM. Pregnant women who conceive via

ART should be carefully monitored to detect the onset of heart failure during pregnancy and in the peripartum period.

The authors state that they have no Conflict of Interest (COI).

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