Different Characteristics of Peripartum Cardiomyopathy Between Patients Complicated With and Without Hypertensive Disorders

– Results From the Japanese Nationwide Survey of Peripartum Cardiomyopathy –

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Background: There has been no nationwide survey concerning peripartum cardiomyopathy (PPCM) among the Asian population, and clinical profiles of PPCM complicated with hypertensive disorders complicating pregnancy (HD) as the major risk factor of PPCM have not been characterized.

Methods and Results: A retrospective, nationwide survey of PPCM in 2007 and 2008 all over Japan was performed and the clinical characteristics were compared between patients with and without HD. We obtained data for 102 patients. HD during pregnancy occurred in 42 patients (41%). Patients with HD were older than those without HD (33.8 vs. 31.9 years old, P<0.05) and babies were delivered more frequently by Caesarean section (81% vs. 52%, P<0.01). Although cardiac parameters at diagnosis were similar in patients with and without HD, patients with HD were hospitalized for a shorter period and had better cardiac function after 7 months. Multivariate regression analysis revealed that HD was independently associated with a shorter hospital stay and a higher left ventricular ejection fraction at last follow up.

Conclusions: PPCM complicated with HD had different clinical characteristics from those without HD. This condition might be a unique subset of PPCM that is characterized by relatively swift recovery except in the cases of death. In order to prevent severe heart failure and maternal death, peripartum women should be treated with HD cautiously and must immediately undergo a cardiac examination as needed. (*Circ J* 2011; **75:** 1975–1981)

Key Words: Cardiomyopathy; Heart failure; Hypertension; Pregnancy; Prognosis

P eripartum cardiomyopathy (PPCM) and pregnancy-associated cardiomyopathy are rare but life-threatening conditions that occur during the peripartum period in previously healthy women. Although its etiology remains unknown, potential risk factors include advanced maternal age, multiparity, multiple gestation, African descent, use of tocolytic agents, preeclampsia, and chronic hypertension.[1–3] Next to African descent, Asian populations showed the second highest incidence of PPCM in a study performed in Southern California,[4] but there was no nationwide survey about PPCM in Asian counties. Hypertensive disorders complicating pregnancy (HD) are observed in up to 60% of PPCM patients,[5] but few studies have analyzed the differences in clinical characteristics between PPCM patients with and without HD. Therefore, this study was performed: (1) to characterize PPCM in Japanese women; and (2) to evaluate whether complications of PPCM with hypertension affects the prognosis for this condition.
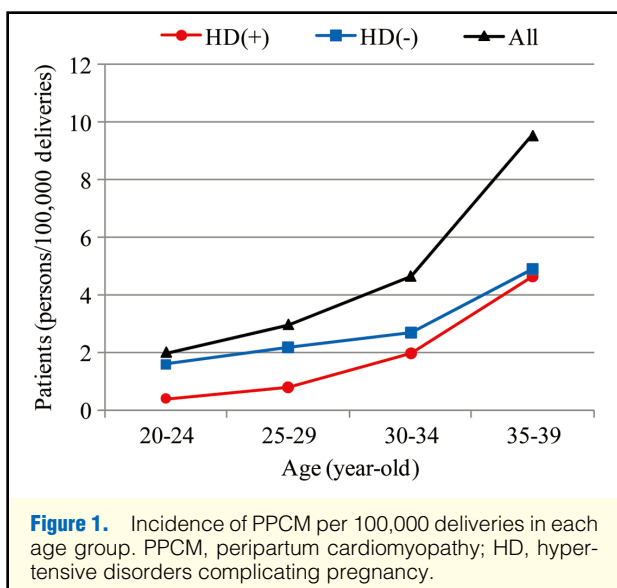
Figure 1. Incidence of PPCM per 100,000 deliveries in each age group. PPCM, peripartum cardiomyopathy; HD, hypertensive disorders complicating pregnancy.

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Methods

A questionnaire survey of 1,444 professional medical organizations in Japan, including 1,030 departments of cardiology, 1,025 departments of obstetrics, and 431 emergency departments, was performed to identify patients with PPCM who were newly managed from January 2007 to December 2008. The diagnosis of PPCM was based on the following criteria: (1) development of heart failure during pregnancy or within the first 5 postpartum months; (2) no determinable etiology for cardiac failure; (3) no history of heart disease prior to pregnancy; (4) reduced left ventricular contraction based on a left ventricular ejection fraction (LVEF) <50% and/or a percent fractioning shortening (%FS) <30%. We modified the criteria established by Demakis and Rahimtoola[1] and those recommended by a workshop convened by the National Heart Lung and Blood Institute and the Office of Rare Diseases of the National Institute in Health.[6] Although classic diagnostic criteria of PPCM by Demakis and Rahimtoola limited the diagnosis to the last gestational month and first 5 months after delivery, Elkayam et al reported that clinical presentation and outcome of patients diagnosed early in pregnancy were similar to those of patients with traditional PPCM.[7] We included patients who developed heart failure during pregnancy and during the first 5 months after delivery in the present study, which was based on the report by Elkayam et al.

Age, parity, complications of pregnancy, time of diagnosis, symptoms, time and route of delivery, outcomes of mother and infant, length of hospital stay, and therapeutic information were collected as background data. Echocardiographic parameters and serum brain natriuretic peptide (BNP) levels at diagnosis, at hospital discharge, and at the last follow up were also obtained. If the patients were complicated with HD, the type and severity of hypertension, and the duration between the onset of HD and diagnosis of PPCM were also recorded.

HD were categorized according to the National High Blood Pressure Education Program Working Group Report on high blood pressure (BP) in pregnancy as: (1) gestational hypertension: systolic BP≥140mmHg or diastolic BP≥90mmHg for the first time during pregnancy, and no proteinuria (PU); (2) preeclampsia: systolic/diastolic BP≥140/90mmHg after 20 weeks' gestation and PU≥300mg/day or ≥1+dipstick; (3) eclampsia: seizures that cannot be attributed to other causes in a woman with preeclampsia; (4) preeclampsia superimposed on chronic hypertension: new-onset PU≥300mg/day in hypertensive women without PU before 20 weeks' gestation or a sudden increase in PU or BP in women with hypertension and PU before 20 weeks' gestation; and (5) chronic hypertension: systolic/diastolic BP≥140/90mmHg before pregnancy or diagnosed before 20 weeks' gestation.[8] The severity of preeclampsia was defined as mild for systolic/diastolic BP ≥140/90mmHg and severe for systolic/diastolic BP≥160/110mmHg. PU was defined as mild for >300mg/day and severe for >2.0g/day. The number of deliveries in Japan in
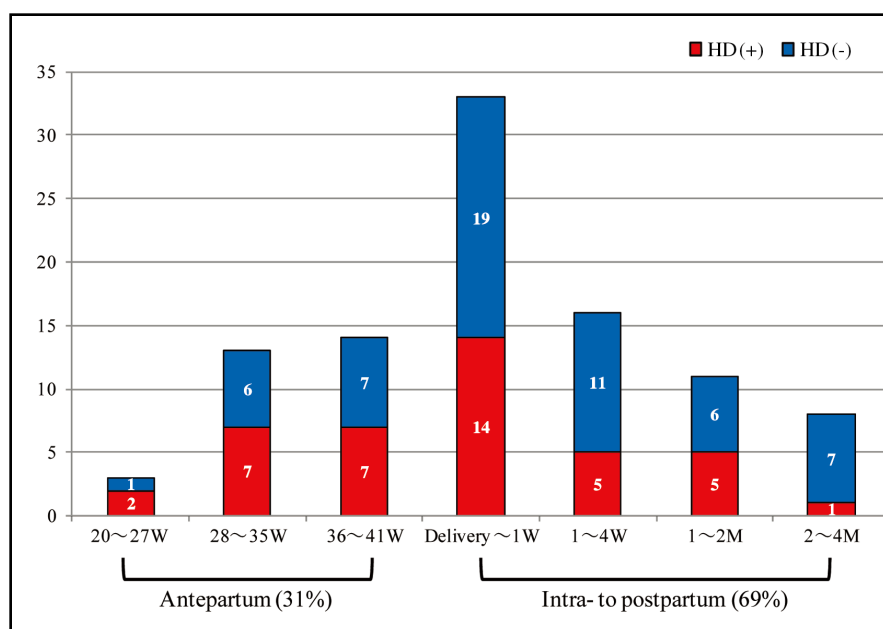

Figure 2. Time of diagnosis. HD, hypertensive disorders complicating pregnancy.

Table 1. Comparison of Patients' Background and Use of Medications at Discharge Between PPCM Patients Complicated With and Without HD

	HD (+) (n=42)	HD (−) (n=60)	P value*
Age (years)	33.8±4.2	31.9±4.1	<0.05
Parity	1.62±1.17	1.67±0.78	NS
Tocolytic therapy	6	8	NS
Twin pregnancy	7	8	NS
HD	42 (100%)	0	<0.0001
Gestational weeks of delivery (weeks)	36.4±3.7	37.5±2.4	NS
Route of delivery			
Vaginal delivery	8	27	<0.01
Cesarean section	34	29	
Medications at discharge			
ACE-I/ARB	26 (67%)	33 (63%)	NS
β-blocker	22 (56%)	30 (58%)	NS
Diuretics	26 (67%)	29 (56%)	NS
Anticoagulant	11 (28%)	11 (21%)	NS

PPCM, peripartum cardiomyopathy; HD, hypertensive disorders complicating pregnancy; NS, not significant; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
*P value for comparison of the HD (+) and HD (−) groups.
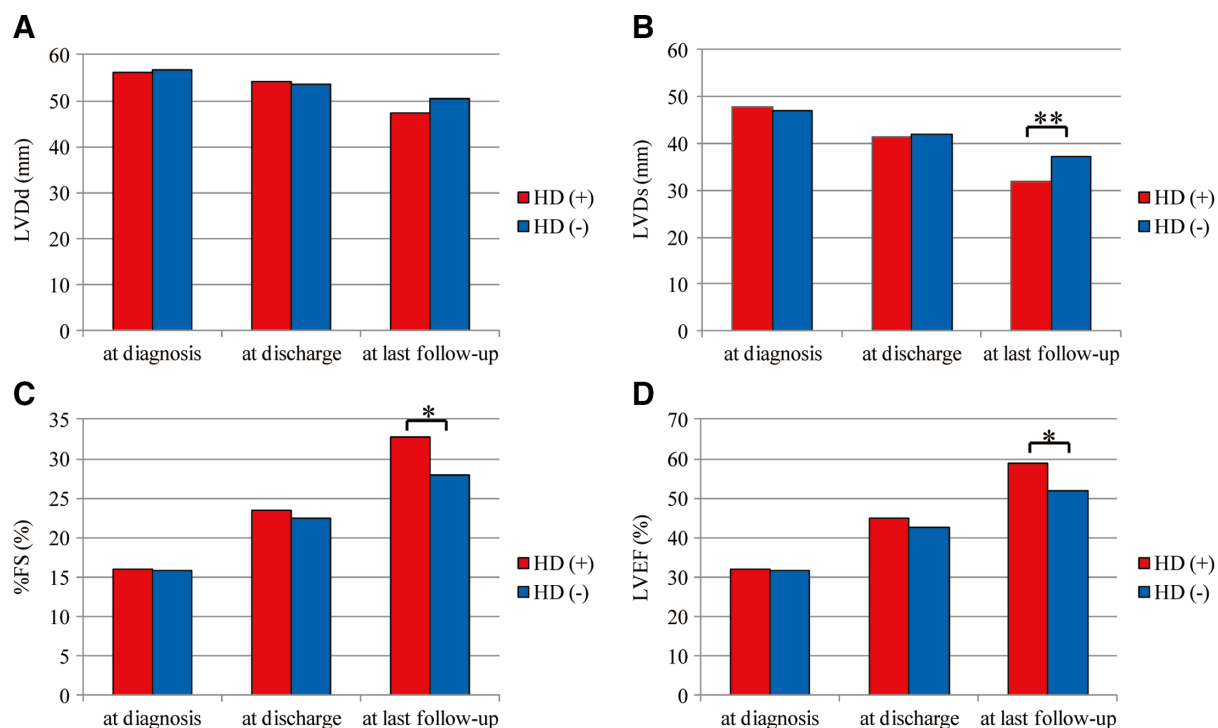
Figure 3. Changes of (**A**) LVDd, (**B**) LVDs, (**C**) %FS, and (**D**) LVEF in HD (+) and HD (−) groups. LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; %FS, % fractional shortening; LVEF, left ventricular ejection fraction; HD, hypertensive disorders complicating pregnancy. *P<0.05 for comparison of the HD (+) and HD (−) groups. **P<0.01 for comparison of the HD (+) and HD (−) groups.

each age group were taken from national statistics published by the Ministry of Health, Labour and Welfare.

Statistical significance was evaluated using paired and unpaired Student t-tests for comparisons between means. A chi-square test and a Fisher exact test were used for categorical data. Two-way ANOVA and correlation coefficient anal-

ysis were also used. Multivariate analysis was done to examine the correlations of length of hospital stay and LVEF at last follow up with variables such as age, parity, time of diagnosis, tocolytic therapy, twin pregnancy, HD and LVEF at diagnosis, which are considered as risk factors. All data were expressed as the mean±standard deviation. Statistical signifi-
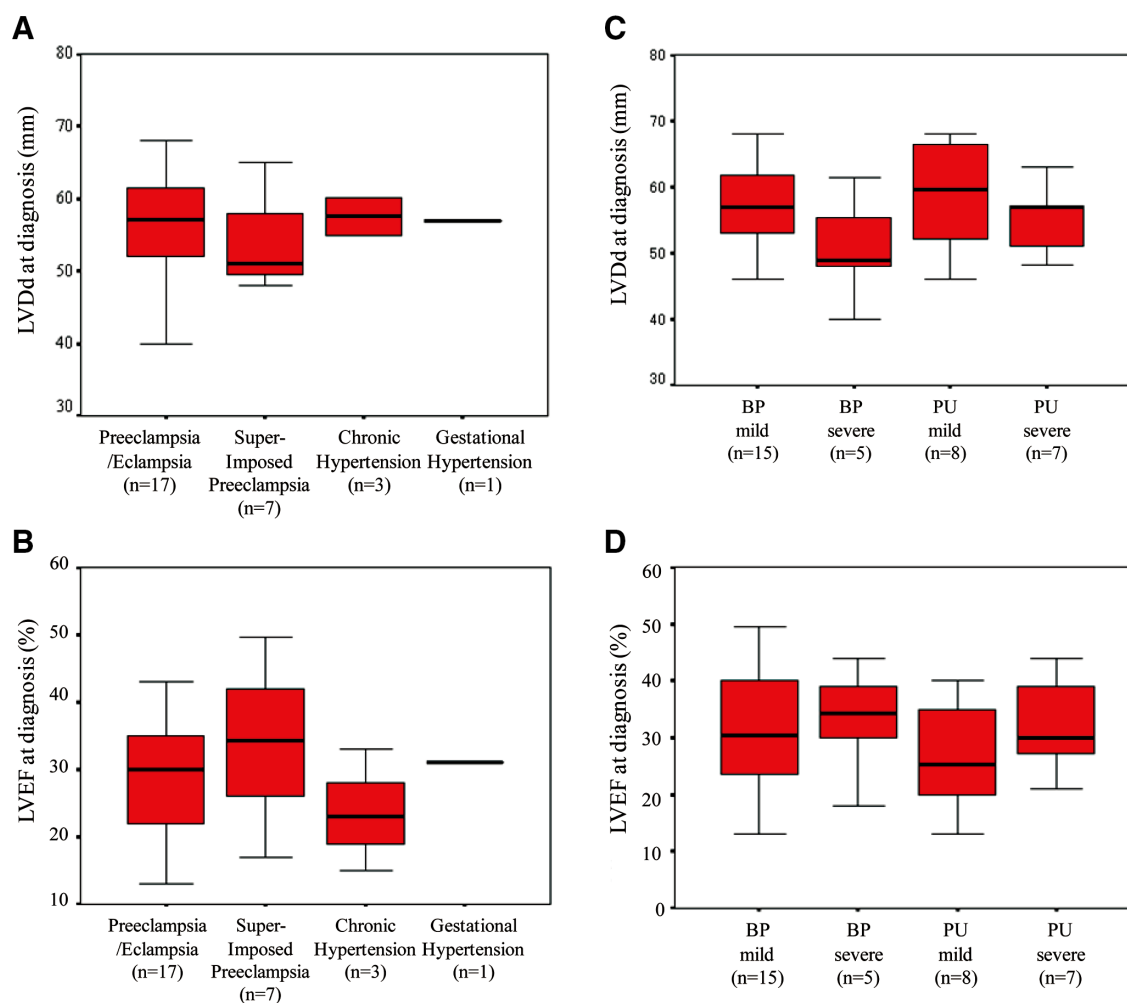
Figure 4. (**A**) LVDd and (**B**) LVEF at diagnosis in each type of HD, and (**C**) LVDd and (**D**) LVEF at diagnosis in preeclampsia patients with different severities of BP and PU. HD, hypertensive disorders complicating pregnancy; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; BP, blood pressure; PU, proteinuria.

cance was defined as a P value <0.05. A software package (SPSS 11.0; SPSS, Chicago, IL, USA) was used for statistical analysis.

The Ethics Committee at the National Cerebral and Cardiovascular Center in Osaka, Japan approved the study in November 2008.

Results

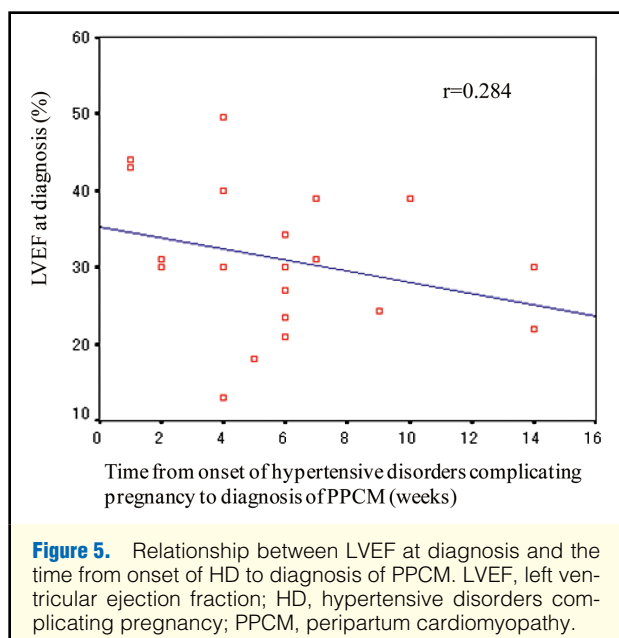### Clinical Characteristics of All Patients

Out of 1,444 institutes, 1,049 (73%) responded. These responses included 102 cases fulfilling the inclusion criteria for PPCM. The estimated incidence of PPCM in Japan was 1/20,000 births. The mean age of the patients was 32.7 years old, with a range of 22–43 years old. Fifty-four percent of patients were primiparous women and the mean parity was 1.65±0.96. Tocolytic agents were used during pregnancy in 14%, twin pregnancy occurred in 15%, and HD was present in 42% of PPCM patients.

Diagnosis of PPCM was established antepartum in 31% and intra to postpartum in 69%. One-third of patients were diagnosed intrapartum to within 1 week after delivery. The major symptoms at onset were dyspnea in 80%, cough in 37%, and edema in 37%. With those complaints, 63% of patients were initially seen by an obstetrician and 12% of patients were seen by a general physician, and then referred to cardiologists. Only 9% were primarily seen by a cardiology specialist.

At diagnosis, an echocardiography showed the following mean values: left ventricular end-diastolic dimension (LVDd) 56.5±7.1 mm, left ventricular end-systolic dimension (LVDs) 47.8±8.1 mm, %FS 15.8±7.0%, and LVEF 31.6±12.0%. The mean serum BNP level was elevated to 1,258±1,028 pg/ml. There were only 4 patients whose serum BNP level was under 100 pg/ml.

The mortality rate was 4%. One patient who was at 34 weeks' gestation died from pulmonary edema on the day of admission, 1 patient died from acute heart failure 1 day after an emergency Caesarean section was performed because of obstructed labor at 37 weeks' gestation, 1 died from cardiac arrest 2 days after vaginal delivery despite implementation of percutaneous cardiopulmonary support, and another died

Figure 5. Relationship between LVEF at diagnosis and the time from onset of HD to diagnosis of PPCM. LVEF, left ventricular ejection fraction; HD, hypertensive disorders complicating pregnancy; PPCM, peripartum cardiomyopathy.

Table 2. Factors Correlated With the Length of Hospitalization

	Standardized coefficient	P value*
Age	0.074	0.509
Parity	−0.088	0.418
Antepartum onset	−0.002	0.988
Tocolytic therapy	0.134	0.219
Twin pregnancy	−0.199	0.072
HD	−0.248	0.027
LVEF at diagnosis	−0.420	<0.001

HD, hypertensive disorders complicating pregnancy; LVEF, left ventricular ejection fraction.
*P value for comparison of the HD (+) and HD (−) groups.

Table 3. Factors Correlated With LVEF at Last Follow up

	Standardized coefficient	P value*
Age	0.214	0.420
Parity	−0.069	0.116
Antepartum onset	−0.079	0.552
Tocolytic therapy	−0.101	0.476
Twin pregnancy	0.131	0.353
HD	0.277	0.042
LVEF at diagnosis	0.335	0.011
Follow-up period	0.054	0.686

Abbreviations as per Table 2.
*P value for comparison of the HD (+) and HD (−) groups.

from worsening chronic heart failure more than 6 months after diagnosis.

Additionally, 2% of patients had severely deteriorated left ventricular function that required treatment with a left ventricular assist system (LVAS); 3% were transferred to other hospitals and no data were available for their prognosis; and further prognostic data for another 2% were not available. For the other 89% (91 patients), discharge from hospital occurred after a mean stay of 34.6 days. The clinical findings at discharge included mean values of LVDd 53.7±7.7 mm, LVDs 41.8±9.7 mm, %FS 22.8±8.9%, and LVEF 43.6±14.1%. The mean serum BNP at discharge was 211±277 pg/ml.

The mean follow-up period was 9.6±6.5 months for the 82 of 91 discharged patients. Echocardiography improved significantly, with values of LVDd 49.0±6.1 mm, LVDs 34.8±8.2 mm, %FS 29.6±8.3%, and LVEF 54.6±13.6%, and the mean serum BNP level had significantly decreased to 44±103 pg/ml. Sixty-three percent of patients recovered their LVEF over 50% after 6 months.

Comparison Between Patients With and Without HD

A total of 42 patients were complicated with HD in pregnancy [HD (+) group] and 60 patients did not have this complication [HD (−) group]. Hypertensive subcategories of PPCM patients are as follows: 18 patients with preeclampsia, 11 with preeclampsia superimposed on chronic hypertension, 3 with chronic hypertension, 1 with gestational hypertension, 1 with eclampsia, and 8 with an unknown subcategory. The incidence of PPCM per 100,000 deliveries (**Figure 1**) increased with maternal age, especially in the HD (+) group. This incidence was more than 10 times higher in 35- to 39-year-old women than in 20- to 24-year-old women in the HD (+) group (4.7 vs. 0.4 per 100,000 births, respectively), but only 3 times higher in the HD (−) group (4.91 vs. 1.59 per 100,000 births, respectively). The time of diagnosis of PPCM in the HD (+) and HD (−) groups showed a similar tendency (**Figure 2**). The clinical backgrounds of the HD (+) and HD (−) groups are compared in **Table 1**. Patients in the HD (+) group were significantly older and underwent a Caesarean section more frequently than those in the HD (−) group. At diagnosis, the

2 groups had similar cardiac dimensions, systolic functions, and BNP levels; LVDd were 56.1±6.7 mm vs. 56.8±7.3 mm, LVDs were 47.1±7.3 mm vs. 48.3±8.6 mm, %FS were 16.0±6.7% vs. 15.8±7.2%, LVEF were 31.9±10.2% vs. 31.5±13.2%, and serum BNP were 1,114±884 pg/ml vs. 1,353±1,112 pg/ml in each HD (+) and HD (−) group, respectively.

Two deaths occurred in both the HD (+) and the HD (−) groups and 2 patients with LVAS in the HD (−) group also died. Among the discharged patients, the hospitalization period was shorter in the HD (+) group than in the HD (−) group (26.9 vs. 40.9 days). Use of medications at discharge was similar in the 2 groups (**Table 1**).

The mean observation periods were 7.9 months in the HD (+) group and 10.9 months in the HD (−) group. In a shorter period, cardiac parameters such as LVDs, %FS, and LVEF showed significantly greater improvement in the HD (+) group compared to the HD (−) group (**Figure 3**).

Both LVDd and LVEF at diagnosis, reflecting the degree of cardiac dysfunction, showed no significant relationship with the type of hypertension or severity of BP and PU (**Figure 4**). There was also no significant relationship of LVEF at diagnosis with the duration from onset of preeclampsia or superimposed preeclampsia to onset of heart failure, but there was a weak correlation of a longer duration of preeclampsia with a lower LVEF at diagnosis (r=0.284: **Figure 5**).

Factors Associated With the Length of Hospitalization and LVEF at Last Follow up

Table 2 shows the factors that correlate with the length of hospitalization among discharged patients. The better LVEF at diagnosis strongly predicts shorter hospitalization. HD is also associated with shorter hospital stay. Other risk factors such as age, parity, twin pregnancy, tocolytic therapy show no significant effect on the length of hospitalization. **Table 3**

shows the factors that correlate with LVEF at last follow up. Both LVEF at diagnosis and HD predict LVEF at last follow up.

Discussion

This nationwide study of PPCM in Japan is the first performed on an Asian population. The current study covered specialized obstetrics, cardiology and emergency departments from all over Japan, which suggests that our data are representative of the clinical features of PPCM. Interestingly, the background, risk factors, and prognosis of all cases were similar to a report from the USA in 2005.[7] This suggests that the etiology of PPCM might be similar in the USA and Japan beyond the difference of ethnicity, and we consider that this may be because both countries have similar medical standards and trend of pregnancy such as increased maternal age and a rate of artificial fertilization. However the incidence of PPCM in Japan is lower than that in the USA (1/20,000 births vs. 1/3,000–4,000 births).[7] Several reasons like ethnicity and lifestyle might attribute to this discrepancy, and there is a possibility that some patients are undiagnosed in Japan.

In our patient population, HD in pregnancy was the major complication of PPCM. Previous studies have found incidences of hypertensive states in PPCM ranging from 2 to 68%.[5,9,10] The incidence in this study was 41%, which is similar to the rates of 43% for HD found in the study by Elkayam et al,[7] 46% for hypertension in the study by Modi et al,[11] and 22% for preeclampsia in the study by Demakis et al,[12] respectively, and quite different from those found in Haiti (4%)[13] and South Africa (2%).[10] This might be explained by differences in race, lifestyle, and medical standards.

It remains controversial as to whether patients complicated with preeclampsia should be included in cases of PPCM. It is well known that preeclampsia affects organs including the brain, liver, kidney, and the hematopoietic system, and that these effects are usually reversible. However, it is generally thought that the heart is spared from deterioration in hypertension in pregnancy. In cases of preeclampsia, cardiac function is generally well maintained, based on previous studies using echocardiography (the findings include an increased afterload caused by hypertension and a diminished preload that is changeable depending on the degree of hydration).[14–16] A recent echocardiographic study by Rafik Hamad et al[17] showed that the E/E' ratio (where E is the early transmitral diastolic flow velocity, and E' is the early diastolic myocardial velocity) was elevated in preeclampsia patients compared with normal pregnant controls, indicating impaired diastolic left ventricular function. This impairment on echocardiography was accompanied by increased blood levels of amino-terminal pro-BNP, cystatin C, and several other cardiovascular biomarkers. It seems reasonable to hypothesize that impairment of diastolic function precedes impairment of systolic function, which is characteristic of PPCM, as in hypertensive cardiomyopathy aggravated to the end-stage dilated phase. However, our data showed no relationship between the severities of cardiac systolic dysfunction and hypertension, which appears contradictory. Because our data showed severe deterioration of left ventricular function in patients with HD as well as those without HD, it is reasonable to consider that these patients were suffering from cardiomyopathy. Also, a weak correlation of a longer duration of preeclampsia with a lower LVEF at diagnosis might suggest that hypertension might increase the severity of PPCM in the acute phase.[18]

Several theories have been proposed for the pathophysiological mechanism underlying the development of PPCM; this includes an autoimmune disorder,[19,20] viral myocarditis,[21] pregnancy-induced cardiac stress (hypervolemia, elevated heart rate, and thrombophilia[22]), and ethnic susceptibility.[2,6] In a recent study, van Spaendonck-Zwarts et al reported that a subset of PPCM is an initial manifestation of familial DCM.[23] Morales et al also reported that a proportion of PPCM and pregnancy-associated cardiomyopathy cases results from a genetic cause.[24] Heterogeneity is a common element in the pathogenesis of PPCM. In this study, the PPCM patients with HD had a shorter hospital stay than those without HD. The 2 groups of patients had the same left ventricular size and systolic dysfunction at diagnosis and at discharge. In contrast, parameters such as LVDs, %FS, and LVEF at the last follow up showed greater improvement in the hypertensive patients. Ntusi and Mayosi reviewed the etiology and risk factors of PPCM and mentioned that PPCM patients with HD showed good left ventricular recovery at 6 months.[25] But there has been no data to prove this concept except the current study. As supported by these data, PPCM with HD seems to be a characteristic subset of PPCM.

Recent data have shown that increased oxidative stress is proposed to aggravate proteolysis of full-length prolactin, and subsequently the 16 kDa prolactin fragment, a cardiotoxin and endotheliotoxin, might contribute to the deterioration of PPCM.[26] Moreover, urinary prolactin and their isoforms of 14 and/or 16 kDa prolactin are increased in preeclampsia patients.[27] Reuwer et al proposed a recent hypothesis for the increased co-existence of PPCM and preeclampsia based on the pathophysiology of the 2 conditions sharing the same molecular pathway.[28] The current study might suggest that hypertension in pregnancy is not causative in the development of PPCM, but that a hypertensive state and PPCM are associated with other common factors.

In our study, the rate of death was similar between PPCM patients with and without HD. Goland et al reported predictors of major adverse events (MAE; death, heart transplantation, temporary circulatory support, cardiopulmonary arrest, request for intensive care, thromboembolic complication, or implantation of pacemaker and implantable cardioverter) among PPCM patients, and only baseline LVEF and non-Caucasian background were significant predictors.[29] This result can apply to the current study. We cannot prevent PPCM in patients complicated with HD because of MAE at the acute phase because their cardiac functions were severely deteriorated; this was also the case for those patients without HD. Thus, identification of patients who might develop PPCM might allow early intervention or prevention of the condition.

It is often difficult to diagnose whether a pregnant woman complaining of dyspnea or edema has heart failure or not. From a practical clinical point of view, we might suggest the use of the serum BNP level to diagnose heart failure in PPCM patients, as well as a chest X-ray. Moreover, we should treat peripartum women, especially those who are older in age, with HD cautiously and they should immediately undergo a cardiac examination to rule out PPCM as needed.

Disclosures

None.

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