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【 ORIGINAL ARTICLE 】

# Risk Factors for Cardiovascular Events among Pregnant Women with Cardiovascular Disease

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**Abstract:**

**Objective** Cardiovascular disease increases the risk of maternal mortality. This study examined the risk factors for cardiovascular events in pregnant women with cardiovascular disease.

**Methods** This was a case-control study conducted in 2 phases at Japanese maternal and fetal care centers. The primary survey, using an interviewer-administered questionnaire, investigated whether the institutions had managed pregnant women with cardiovascular disease from April 2014 to March 2016. From 424 individual facilities surveyed, 135 facilities were found to have experience in managing pregnant women. In the secondary survey, the 135 institutions were asked to complete a web-based questionnaire, which collected detailed clinical information about cases, including cardiovascular disease, cardiovascular events, maternal background, and the perinatal outcome.

**Results** Information on 302 pregnant women with cardiovascular disease was collected. None of the 302 patients died. There were 25 women with cardiovascular events (cardiovascular event group) and 277 women without cardiovascular events (non-cardiovascular event group); the two groups were compared. No significant differences were found in the perinatal outcomes. Medication use before pregnancy was identified as a risk factor for cardiovascular events (adjusted odds ratio, 23.28; 95% confidence interval, 8.15-66.47; $p< 0.001$). In pregnant women with cardiovascular disease, New York Heart Association (NYHA) functional class II or III before pregnancy was associated with a higher risk of cardiovascular events in comparison to NYHA functional class I ($p<0.001$ for both).

**Conclusion** Medication use before pregnancy and NYHA functional class >I were risk factors for cardiovascular events in pregnant women with cardiovascular disease.

**Key words:** pregnancy, cardiovascular disease, maternal death, cardiovascular event

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## Introduction

Cardiovascular disease in pregnant women is a well-recognized complication because it is associated with high maternal mortality rates. Cardiovascular disease is the leading cause of maternal death in the UK and the fourth leading cause in Japan (1, 2). Managing pregnant women with cardiovascular disease is difficult. In Japan, approximately 1 million deliveries are reported each year, and the proportion of pregnant women with cardiovascular disease ranges from 0.5% to 1.0% overall; the proportion increases to 2-3% in pregnant women with cardiovascular disease and arrhythmia (3, 4). Generally, the number of pregnant women with cardiovascular disease is high; this number varies per institution and for pregnant women with different types of cardiovascular diseases. Thus, although the Japanese Circulation Society published the first official Guidelines for Indication and Management of Pregnancy and Delivery in Women with Heart Disease in 2010 (5), evidenced-based standard man-

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agement and therapy are difficult to formulate. However, few studies have documented the occurrence of cardiovascular diseases in pregnant women in Japan. Recently, increasing age at pregnancy, advances in fertility treatments and advanced medications and operations for cardiovascular disease, have led to an increase in the number of women of childbearing potential, resulting in an increase in the number of pregnant women with cardiovascular disease (6). Thus, a survey of all maternal and fetal care centers in Japan regarding pregnant women with cardiovascular disease was planned in 2014-2015. This study aimed to investigate the status, including the prevalence, trends, and outcomes, of pregnant women with various types of cardiovascular disease and to contribute to their management in Japan.

## Materials and Methods

This was a case-control study conducted using an interviewer-administered questionnaire sent to maternal and fetal care centers in Japan. This study was conducted in 2 phases. The aim of the primary survey was to determine whether the facilities had managed pregnant women with cardiovascular diseases from April 2014 to March 2016. In this study, cardiovascular disease was defined as the presence of congenital heart disease, pulmonary hypertension, aortic disease (including Marfan syndrome), valvular heart disease, acute coronary syndromes, coronary artery aneurysm due to Kawasaki disease, cardiomyopathies, and arrhythmias diagnosed before pregnancy, during pregnancy, or within one month postpartum. Subsequently, in the secondary survey, institutions with experience in managing pregnancy in women with cardiovascular disease were asked to complete a web-based questionnaire that requested detailed clinical information about cases, without any personally identifying information. Data were collected from October 2014 to September 2016. The parameters considered in the analysis were maternal characteristics, including age, the New York Heart Association (NYHA) functional classification, the cardiac function (including the ejection fraction), the presence or absence of an implantable cardiac defibrillator, mechanical valve replacement, the presence or absence of a pacemaker, medication use before pregnancy or early in pregnancy, the diagnosis of cardiovascular disease, and the perinatal outcome. A cardiovascular event in this study was defined as new or worsening of arrhythmia, heart failure, endocarditis, cerebrovascular events, acute myocardial infarction, or thromboembolic events that required medication use or hospitalization during pregnancy or within one month postpartum. Pregnant women with cardiovascular disease were divided into a cardiovascular event group, defined as women with cardiovascular events, and a non-cardiovascular event group, defined as women without cardiovascular events. The two groups were then compared.

### Data analyses

All analyses were performed using IBM SPSS Statistics 20.0 (IBM, Armonk, USA). Data were summarized using descriptive statistics. The number (percentage) and mean ± standard deviation (SD) were used to report demographic and clinical characteristics. We compared the two groups using the chi-squared test, Student's *t*-test, and a multivariate logistic regression analysis to assess associations between risk factors and cardiovascular events. Two-sided p values of $<0.05$ were considered to indicate statistical significance. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were reported.

### Ethics statement

The study was approved by the ethics committee of Sakakibara Heart Institute. We clearly announced that the opportunity to withdraw from the study was always available by posting information at the hospital or on the hospital website. This study was conducted in accordance with the Declaration of Helsinki.

## Results

The study flowchart is shown in Figure. Among the 424 institutions who received the primary questionnaire, 278 (65.5%) provided valid responses. Of these, 135 (48.5%) had experience managing pregnant women with cardiovascular disease. The secondary questionnaire was then sent to the 135 institutions, of which 49 (36.3%) provided detailed clinical information about cases. Consequently, the details of the cases of 302 pregnant women with cardiovascular disease were collected. Of these, 25 (8.3%) and 277 (91.7%) were included in the cardiovascular and non-cardiovascular event groups, respectively.

The demographic and clinical characteristics of the women in each group are summarized in Table 1. With the exception of the perinatal outcomes, the parameters presented in Table 1 were assessed before pregnancy. No significant differences in age or the rate of hypertension before pregnancy were found between the two groups. The proportion of women with NYHA functional class I before pregnancy was significantly lower in the cardiovascular event group than in the non-cardiovascular event group ($p<0.001$), while the proportion of women with NYHA functional class II was significantly higher in the cardiovascular event group ($p<0.001$). Thus, there was a significant difference between the two groups with regard to the distribution of women with different NYHA functional classes ($p<0.001$).

The ejection fraction of all women in the non-cardiovascular event group was >40%. Even in the cardiovascular event group, only 3 women (12%) had an ejection fraction of ≤40%. The perinatal outcomes were not significantly different, with 1 stillbirth and 5 miscarriages in the non-cardiovascular event group.

Although small, the proportions of women who underwent mechanical valve replacement and with medication use before pregnancy were significantly higher in the cardiovascular event group than in the non-cardiovascular event group

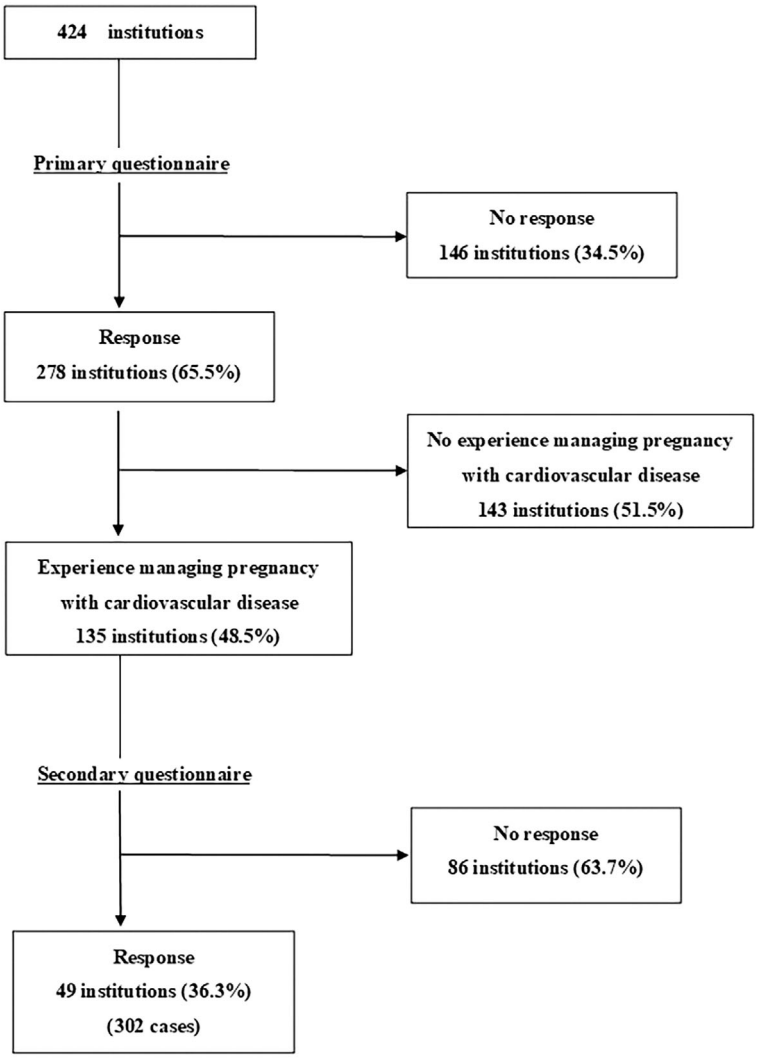


**Figure.** **Study flowchart.**

(p<0.001 vs. p<0.001). Table 2 shows the types of cardiovascular diseases and the proportion of women with different cardiovascular disease in the cardiovascular and non-cardiovascular event groups. In both groups, congenital heart disease was the most frequent (52% in the cardiovascular event group and 58% in the non-cardiovascular event group), followed by arrhythmia or valvular heart disease. Overall, the proportion of patients with each disease was not very different. Table 3 shows the types and numbers of cardiovascular events for each disease in the cardiovascular event group. The number of events and the number of cases were the same, without duplication. Arrhythmia was the most common event, followed by heart failure. No endocarditis, cerebrovascular events, or acute myocardial infarction was noted.

We analyzed the following parameters in the multiple logistic regression model: hypertension before pregnancy, ejection fraction ≤40%, presence or absence of an implantable cardiac defibrillator, mechanical valve replacement, presence or absence of a pacemaker, and medication use before pregnancy. These parameters had a high response rate and might be involved in the onset of events; some were also included in the risk score for maternal cardiovascular events during pregnancy in previous studies, such as the Cardiac Disease in Pregnancy (CARPREG) study and ZAHARA study (7, 8).

Medication use before pregnancy was associated with a 23-fold increase in cardiovascular events in comparison to no medication use before pregnancy (aOR, 23.28; 95% CI, 8.15-66.47; p<0.001; Table 4).

Table 5 shows the association of the pre-pregnancy NYHA functional class and cardiovascular events. A pre-pregnancy NYHA functional classification of II or III was associated with a significantly increased incidence of cardiovascular events in comparison to NYHA functional class I (p<0.001 for both).

## Discussion

We made the following 2 important clinical observations in this study. First, we identified the incidence of cardiovascular events in pregnant women with cardiovascular disease and the type and incidence of cardiovascular disease in the cardiovascular and non-cardiovascular event groups, despite

**Table 1. Maternal Background Characteristics of the 302 Pregnancies of Women with Cardiovascular Disease and Perinatal Outcome.**

| | Cardiovascular event group (n=25) | Non-cardiovascular event group (n=277) | p value |
|---|---|---|---|
| **Maternal background** | | | |
| Maternal age (y) | 30.6±3.2 | 30.2±5.1 | 0.87 |
| Hypertension | 1(4%) | 1(0.3%) | 0.16 |
| Hypertensive disorders of pregnancy | 2(8%) | 0(0%) | N.A. |
| NYHA functional classification | | | |
| Class I | 6 (24%) | 254 (92%) | <0.001 |
| Class II | 14 (56%) | 23 (8%) | <0.001 |
| Class III | 5 (20%) | 0 (0%) | N.A. |
| Class IV | 0 (0%) | 0 (0%) | N.A. |
| Cardiac function (ejection fraction ≤ 40%) | 3 (12%) | 0 (0%) | N.A. |
| Implantable cardiac defibrillator | 0 (0%) | 5 (2%) | N.A. |
| Mechanical valve replacement | 6 (7%) | 1 (0.4%) | <0.001 |
| Pacemaker | 0 (0%) | 3 (1%) | N.A. |
| Medication before pregnancy | 12 (48%) | 20 (7%) | <0.001 |
| **Perinatal outcome** | | | |
| Live birth | 25 (100%) | 271 (98%) | 1.00 |
| Still birth | 0 (0%) | 1 (0.4%) | N.A. |
| Miscarriage | 0 (0%) | 5 (2%) | N.A. |

NYHA: New York Heart Association, N.A.: not available

**Table 2. Cardiovascular Disease Groups.**

| | Cardiovascular event group (n=25) | Non-cardiovascular event group (n=277) |
|---|---|---|
| Congenital heart diseases | 13 (52%) | 162 (58%) |
| Pulmonary hypertension | 2 (8%) | 0 (0%) |
| Aortic diseases (including Marfan's syndrome) | 1 (4%) | 9 (3%) |
| Valvular heart diseases | 2 (8%) | 53 (19%) |
| Acute coronary syndromes | 1 (4%) | 0 (0%) |
| Coronary artery aneurysm due to Kawasaki disease | 3 (12%) | 1 (0.3%) |
| Cardiomyopathies | 0 (0%) | 6 (2%) |
| Arrhythmias | 3 (12%) | 46 (16%) |

**Table 3. Cardiovascular Events for Each Disease in Cardiovascular Event Group.**

| | Arrhythmia | Heart failure | Thromboembolic event | Others |
|---|---|---|---|---|
| Congenital heart disease | 9 | 3 | 1 | 0 |
| Pulmonary hypertension | 0 | 2 | 0 | 0 |
| Aortic diseases (including Marfan's syndrome) | 1 | 0 | 0 | 0 |
| Valvular heart diseases | 1 | 1 | 0 | 0 |
| Acute coronary syndromes | 0 | 0 | 1 | 0 |
| Coronary artery aneurysm due to Kawasaki disease | 2 | 1 | 0 | 0 |
| Cardiomyopathies | 0 | 0 | 0 | 0 |
| Arrhythmias | 3 | 0 | 0 | 0 |

Others: endocarditis, cerebrovascular events and acute myocardial infarction.

the selection bias. Second, medication use before pregnancy and NYHA functional class >I were significantly associated with cardiovascular events in pregnant women with cardiovascular disease.

The incidence of cardiovascular events in the present study (8.3%) is nearly the same as that reported in a retro-

**Table 4. Multivariate Analysis of Risk Factors Related to Cardiovascular Events in Maternal Background.**

| | Cardiovascular event group (n=25) | Non-cardiovascular event group (n=277) | Odds ratio | 95% Cl | p value |
|---|---|---|---|---|---|
| Medication before pregnancy | 12 (48%) | 20 (7%) | 23.28 | 8.15-66.47 | <0.001 |

**Table 5. Pre-pregnancy NYHA Classification and Cardiovascular Event.**

| Pre-pregnancy NYHA classification | I (n=260) | II (n=37) | III (n=5) |
|---|---|---|---|
| Cardiovascular event | 6 (2.3%) | 14 (37.8%)* | 5 (100%)* |

*significantly increase cardiovascular event compared with class I (p<0.001)

spective study (13%) (7). When the subtypes of cardiovascular disease were assessed in our study, congenital heart disease was the most frequent in both groups; this is consistent with the finding of a previous report (9). No marked change in the incidence of other diseases was observed. Thus, improving the management of women with congenital heart disease is the key to reducing the incidence of cardiovascular events and maternal mortality in pregnant women with cardiovascular disease.

Medication use before pregnancy and the pre-pregnancy NYHA functional class were significantly related to the incidence of cardiovascular events in pregnant women with cardiovascular disease. These risk factors are consistent with the ZAHARA score, which was developed for congenital heart disease (8).

Medication use before pregnancy is a risk factor for cardiovascular events other than arrhythmia. Women with cardiovascular diseases other than arrhythmia who required medication use before pregnancy were considered to have a poor cardiac function. On the other hand, medication use before pregnancy led to a good outcome in women with arrhythmia. This is because women with arrhythmia usually have a normal cardiac function and arrhythmias occur suddenly; thus, prophylactic medication is important. Sudden arrhythmic death syndrome is the leading cardiovascular cause of sudden maternal death in the UK (10). Another cause is long QT syndrome, which may result in torsades de pointes during delivery. In the present study, no cardiovascular events occurred in women with arrhythmias who were on medication from before pregnancy, which is consistent with a previously reported result (11).

The NYHA functional class is a prominent predictor of the occurrence of pregnancy complications in women with all types of cardiovascular disease (7). Parloff et al. reported that the maternal mortality rate was 0.4% in women with NYHA classes I and II and 6.8% in women with NYHA functional classes of III and IV; the fetal mortality rate was 30% for women with NYHA functional class IV (12). In the present study, most women had an NYHA functional class of ≤II, and pregnancy is usually permitted in many such cases. However, more women with NYHA functional class II were found in the cardiovascular event group than in the non-cardiovascular event group, and some women with NYHA class II may have fatal outcomes depending on the type of cardiovascular disease. Thus, sometimes, outcomes cannot be judged by the NYHA functional class alone.

Mechanical valve replacement was not a significant risk factor for cardiovascular events in the present study. The reason is that only a small number of women had mechanical heart valves. Women who have undergone mechanical valve replacement are classified as World Health Organization class III and have a significantly increased risk of maternal mortality and morbidity (1, 13, 14). Pregnancy is associated with the increased production of procoagulant factors, a reduction in the level of protein S, acquired protein C resistance, and impaired fibrinolysis, which lead to an increased risk of thrombotic events (15). These changes make pregnant women particularly vulnerable to thrombosis and mechanical heart valve failure (16), which leads to poor perinatal outcomes. Thus, anticoagulation is important for the management of pregnant women who have undergone mechanical valve replacement. The American College of Cardiology and American Heart Association guidelines recommend the use of low-dose warfarin over either low-molecular-weight or unfractionated heparin for women who can maintain therapeutic international normalized ratios during the first trimester (17). However, no single method of anticoagulation has been determined, and various methods are used depending on the institution. Although the results of the present study indicated that mechanical valve replacement was not a risk factor for cardiovascular events, women who underwent mechanical valve replacement must nevertheless be managed at tertiary centers with expertise in managing pregnant women with cardiovascular disease.

This present study was associated with two limitations. First, the response rates to the primary and secondary questionnaires were low, which led to a small sample size and even fewer cases with cardiovascular disease. The specific risk factors for each type of cardiovascular disease could not be identified. Second, details-such as the cardiac function parameters before and during pregnancy and the neonatal prognosis-could not be collected because only a simple questionnaire was used. Although these were observational and retrospective case-control investigations, the challenges involved in conducting randomized clinical trials among pregnant women with cardiovascular disease are significant. Conducting multicenter prospective studies to obtain more

data about cardiovascular diseases and to gather evidence regarding the characteristics and management of individual cardiovascular diseases will be important in the future.

Only a few investigations of the trends and outcomes in heart disease and pregnancy have been conducted in Japan. In recent decades, the number of women of child-bearing age with cardiovascular diseases and the incidence of pregnancy among relatively older women have significantly increased because of advances in fertility treatments and advanced medications and operations for cardiovascular disease. As a result, the rate of maternal death due to cardiovascular disease has increased 3-fold in Japan in the past 20 years (6). Understanding the prevalence, trends, and outcomes in pregnant women with cardiovascular disease in Japan is important, which is why this investigation is significant. Although the types of cardiovascular disease vary, the risk of pregnancy for women with cardiovascular disease depends on the specific cardiac condition, and the therapies for each cardiovascular disease are diverse. This study will contribute to focusing the attention obstetricians on transferring women with cardiovascular disease and the identified risk factors to tertiary institutions at an earlier stage. In conclusion, medication use before pregnancy and NYHA functional class > I were risk factors for cardiovascular events in pregnant women with cardiovascular disease. Pregnant women with cardiovascular disease and corresponding risk factors should be managed at institutions with cardiologists, anesthetists, and obstetricians who have broad knowledge in managing pregnant women with cardiovascular disease.

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

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