Echocardiographic Assessments for Peripartum Cardiac Events in Pregnant Women with Low-Risk Congenital Heart Disease

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Summary
This retrospective cohort study aimed to explore the relationship between temporal changes in the cardiac function and peripartum cardiac events in pregnant women with low-risk congenital heart disease.

We performed echocardiography at early and late pregnancy and postpartum in 76 pregnant women with low-risk congenital heart disease, and compared echocardiographic parameters between subjects with and without peripartum cardiac events. Median age at delivery was 27 (range, 24-31) years. The ZAHARA and CAR-PREG II scores suggested that most women were found to be at low-risk for pregnancy. Fifteen subjects had cardiac events that included heart failure in 10, arrhythmia in 4, and pulmonary hypertension in one subject. The left ventricular and atrial volumes significantly increased from early pregnancy toward late pregnancy, and the E/A ratio and global longitudinal strain significantly decreased from early pregnancy toward late pregnancy. The left atrial volume (67 [53-79] versus 45 [35-55] mL, P = 0.002) and plasma brain natriuretic peptide level (58 [36-123] versus 34 [18-48] pg/mL, P = 0.026) at late pregnancy were significantly higher in subjects with cardiac events than in those without cardiac events.

An increase in the left atrial volume followed by mild left ventricular diastolic dysfunction is related to peripartum cardiac events in women with congenital heart disease who are at low risk for cardiac events during pregnancy.

(Key words: Maternal cardiac function, Diastolic dysfunction, Hemodynamics, Pregnancy)

Pregnant women with congenital heart disease (CHD), regardless of whether they received corrective surgery or not, are at risk for heart failure, arrhythmia, and thromboembolic complications during pregnancy, delivery, and postpartum because of their profound hemodynamic changes during pregnancy and the postpartum period. Maternal hemodynamic changes are characterized by a 30-50% increase in cardiac output and plasma volume and a 30% reduction in systemic vascular resistance during pregnancy. During delivery, cardiac output is further increased as a result of uterine contractions and maternal effort. These hemodynamic changes reverse in the first 2 weeks after delivery and normalize toward preconception values after 3-12 months.

Previous studies such as the Zwangerschap bij Aangeboren Hartafwijking (ZAHARA) and Cardiac Disease in Pregnancy (CARPREG) studies have shown that pregnancy-related complications are associated with maternal cardiac function. In women with CHD, as the primary diseases and status are extremely variable, maternal cardiac function should be individually evaluated. Although exercise stress testing and cardiac magnetic resonance imaging are useful to evaluate the cardiopulmonary functional status in pregnant women, these modalities are not suitable for repetitive cardiac evaluation during pregnancy and postpartum. Therefore, transthoracic echocardiography is still a mainstay of cardiac evaluation because of its noninvasive and repetitive nature. Normal pregnant women exhibit left ventricular remodeling from early pregnancy toward late pregnancy, including increases in the left ventricular longitudinal and transverse chamber dimensions as well as left ventricular wall thickness. The patterns of change in cardiac function and dimension in pregnant women with CHD are similar to those observed in normal pregnant women. In women with right-sided heart disease, the pattern of right ventricular systolic function over time differed from that of normal subjects, and in women with left-sided heart disease, the left ventricular end-diastolic diameter tended to increase compared with that in normal subjects. However, there is still a lack of information about the relationship between maternal cardiac function and peripartum cardiac events. Therefore,
the aim of the present study was to explore the relationship between temporal changes in left ventricular function and peripartum cardiac events in pregnant women with CHD.

Methods

Subjects: This study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional ethics committee (approval number 381). Informed consent was obtained from all participants. Between 2008 and 2018, 153 pregnant women with congenital heart disease (CHD) were referred for transthoracic echocardiography to Kyushu Hospital, Japan Community Healthcare Organization. We excluded 4 subjects with ZAHARA scores 3.5 or above since our aim was to study women with CHD at a low risk for pregnancy. We excluded 5 subjects with single-ventricle physiology and systemic right ventricle because we wanted to focus on left ventricular function. We also excluded 5 subjects with cardiomyopathy because the pathophysiology of cardiomyopathy differed from that of congenital heart disease. Thus, our cohort consisted of 76 subjects with low-risk congenital heart disease (CHD). Women with isolated valvular disease who were diagnosed and followed up since childhood were assigned to the CHD group. We extracted maternal and neonatal profiles from clinical records. All subjects were followed up during pregnancy and the postpartum period at our hospital. To evaluate cardiac function, we performed transthoracic echocardiography at 3 points: at early pregnancy, late pregnancy, and postpartum. Early and late stages of pregnancy were defined as less than 20 gestational weeks and more than 28 gestational weeks, respectively, and postpartum was defined as within a week after delivery. Cardiac events were defined as heart failure related to symptoms, notable arrhythmia (either atrial or ventricular), systemic and pulmonary hypertension, and thromboembolic complications. We compared the patient characteristics and echocardiographic data between women with and without cardiac events.

Echocardiographic assessments of left ventricular diastolic function: All subjects underwent standard transthoracic echocardiography using a GE Vivid 7 (GE Healthcare, Chicago, USA), Vivid E9 (GE Healthcare, USA), Philips iE33 (Koninklijke Philips N.V., Amsterdam, The Netherlands), EPIQ7 (Koninklijke Philips N.V., The Netherlands), or Siemens Acuson Sequoia 512 (Siemens Healthineers AG, Erlangen, Germany) according to the American Society of Echocardiography guidelines. We obtained 2-dimensional images from the apical 4-chamber view and 2-chamber view while the subjects were in the left lateral decubitus position. From these acquisitioned images, we measured left ventricular and atrial volumes using a commercial echocardiographic analysis software program (TomTec-Areaana™, TomTec Imaging Systems GmbH, München, Germany). The left ventricular end-diastolic, end-systolic, and left atrial volumes were calculated using the modified Simpson’s method. Pulsed wave Doppler and tissue Doppler analyses were also performed to assess the left ventricular diastolic function from the apical 4-chamber view. In pulsed wave Doppler analysis, the sample volume was placed between the mitral leaflet tips, the size was set at 3 mm, and the following variables were measured: peak flow velocity during early diastole (E) and during atrial contraction (A) and the E-to-A wave ratio (E/A). In tissue Doppler analysis, samples with volumes of 10 mm were placed at the mitral annular of the septal wall site from the apical 4-chamber view. From the myocardial velocity patterns obtained, peak myocardial velocities during early diastole (e’) and atrial contraction (a’) were measured, and the ratio of early diastolic transmural inflow E velocity to mitral annular velocity e’ (E/e’) was calculated. The average peak early diastolic relaxation velocity of the septal mitral annulus was computed, and the ratio of transmural peak early velocity to average e’ was calculated as LV ventricular filling. Moreover, the global longitudinal strain (GLS) of the left ventricle was also calculated. The borders defined in the left ventricular mass are propagated to end systole, using the conservation of mass as a restriction, and to define a region of interest encompassing the left ventricular myocardial wall. All areas inside the region of interest were tracked, and GLS was generated from the tracking results.

Statistical analysis: Values are expressed as the median and interquartile ranges. Statistical analysis was performed using EZR on R Commander (ver. 1.33). Unless otherwise noted, category variables are expressed as percentages (%), and continuous values are expressed as the median following the first and third quartiles. To compare the patient characteristics and echocardiographic data between subjects with and without peripartum cardiac events, the unpaired t-test and Fisher exact test were used for continuous variables and categorical variables, respectively. The Friedman test was used to compare continuous variables in the left atrial and ventricular volumes and parameters relevant to systolic and diastolic functions during early pregnancy, late pregnancy, and postpartum. For all statistical analyses, P < 0.05 was considered to indicate statistical significance.

Results

Maternal and neonatal problems: Among 139 pregnant women with CHD, we excluded 63 with CHD because the complete data sets were not obtained. Thus, we studied a total of 76 subjects with low-risk CHD (Figure 1).

A summary of the maternal and neonatal characteristics is shown in Table I. Age at delivery was 27 (24-31) years. There were 54 transvaginal deliveries and 22 cesarean section deliveries. Other comorbidities before pregnancy included hypertension in 2 women and hyperglycemia in 4 women. The ZAHARA scores were 0.00-0.50 in 56, 0.51-1.50 in 13, 1.51-2.50 in 3, and 2.51-3.50 in 4 subjects, while the CARPREG II scores were 0-1 point in 67, 2 points in one, 3 points in 6, and 4 points in 2 subjects. The modified WHO classification included class I in 51, class II in 20, and class II-III in 5 subjects. These findings suggested that the majority of pregnant women in our cohort had low risk for peripartum cardiac events. Regarding neonatal data, gestational age and weight at birth were 38 (37-39) weeks and 2,755 (2,470-3,050) g, respec-
Neonatal problems included low birthweight in 6, CHD in 3, asphyxia in 2, and hyperbilirubinemia in 1.

There were 15 pregnant women with cardiac events; heart failure that required treatment in 10, new-onset arrhythmias in 4, and pulmonary hypertension at postpartum in 1. Subjects with arrhythmias required no additional treatment. Subjects with peripartum cardiac events had a higher modified WHO classification compared to those without peripartum cardiac events (class II-III, 20% versus 3%, \( P = 0.049 \)), although there was no significant difference in other maternal and neonatal characteristics.

**Echocardiographic findings:** The temporal changes in echocardiographic data are shown in Table II. The left ventricular end-diastolic volumes at early pregnancy, late pregnancy, and postpartum were 81 (69-103) mL, 95 (78-107) mL, and 83 (76-104) mL, respectively, while the left atrial volumes at early and late pregnancy and postpartum were 42 (37-53) mL, 53 (42-68) mL, and 45 (33-62) mL, respectively. The temporal changes in echocardiographic data between subjects with and without cardiac events are shown in Figure 2. The left ventricular end-diastolic volume increased from early pregnancy toward late pregnancy and reverted during postpartum in both subjects with and without cardiac events, which did not differ between them. The left atrial volume also increased from early pregnancy toward late pregnancy in both subjects. However, the left atrial volume at late pregnancy in subjects with cardiac events was significantly higher than that in subjects without cardiac events (67 [53-79] versus 45 [35-55] mL, \( P = 0.002 \)).

Regarding left ventricular diastolic function, the E/A ratio significantly decreased from early pregnancy to late pregnancy in both groups, but there was no significant difference in the E/A ratio between the groups. The E/e’ ratio and the left ventricular ejection fraction (LVEF) remained unchanged in both groups during pregnancy and postpartum. In subjects with cardiac events, the left ventricular GLS at early and late pregnancy and postpartum was 21.1% (17.9-22.9), 18.6% (16.0-19.8), and 19.3% (15.7-22.5), respectively, which showed a significant decrease in GLS from early pregnancy to late pregnancy (\( P = 0.045 \)). GLS in subjects without cardiac events remained unchanged throughout pregnancy and postpartum (19.9% [17.8-21.3] versus 20.1% [16.7-20.9] versus 20.2% [18.7-22.3], \( P = 0.247 \)).

The plasma BNP level at late pregnancy in subjects with cardiac events was significantly higher than that in subjects without cardiac events (58 [36-123] versus 34 [18-48] pg/mL, \( P = 0.026 \)) (Figure 2).

**Discussion**

The major finding of the present study was that an increase in the left atrial volume at late pregnancy predicted peripartum cardiac events in women with CHD who had been recognized at low risk for these events during pregnancy. We also suggested that an increase in the left atrial volume at late pregnancy might reflect mild left ventricular dysfunction, represented by decreases in the left ventricular GLS at late pregnancy. The echocardiographic assessment of the left atrial volume is simple and feasible for screening pregnant women with CHD who are at risk of peripartum cardiac events. Previous reports have shown that maternal cardiovascular and offspring events occur in 10% and 37% of pregnant women with CHD, respectively.\(^1\) Our cohort showed as high as 20% of pregnant women had peripartum cardiac events because peripartum cardiac events included new-onset notable arrhythmia either needing treatment or not. Predictive factors for these complications associated with pregnancy have been identified in numerous studies and with the use of specific scores. A ZAHARA risk score more than 3.50 and a CAPREG II score more than 5 points can predict maternal cardiovascular events among women with CHD. Although our cohort consisted of women with CHD who were at a low risk for pregnancy, there was no sig-
### Table 1. Summary of Maternal and Neonatal Backgrounds

| Total | With cardiac events | Without cardiac events | P  |
|-------|---------------------|------------------------|----|
|       | n = 76              | n = 15                 | n = 61 |   |
| **Maternal characteristics** |                      |                        |     |
| Age at delivery, years       | 27 (24-31)           | 27 (26-31)             | 27 (23-31) | 0.556 |
| Delivery                      |                      |                        |     |
| Transvaginal                  | 54 (71%)             | 10 (67%)               | 44 (72%) | 0.754 |
| Cesarean section              | 14 (18%)             | 4 (27%)                | 10 (16%) | 0.457 |
| Emergency                     | 8 (11%)              | 1 (7%)                 | 7 (12%) | 1.000 |
| Past delivery                 | 1.0 (1.0-2.0)        | 1.0 (1.0-2.0)          | 1.0 (1.0-2.0) | 0.296 |
| **Risk factors**              |                      |                        |     |
| Hypertension                  | 2 (3%)               | 1 (7%)                 | 1 (2%) | 0.358 |
| Hyperglycemia                 | 4 (5%)               | 0 (0%)                 | 4 (7%) | 0.579 |
| **Risk assessment**           |                      |                        |     |
| ZAHARA score                  |                      |                        |     |
| 0-0.50                        | 56 (74%)             | 9 (60%)                | 47 (77%) | 0.201 |
| 0.51-1.50                     | 13 (17%)             | 3 (20%)                | 10 (16%) | 0.713 |
| 1.51-2.50                     | 3 (4%)               | 3 (20%)                | 0 (0%) | 0.006* |
| 2.51-3.50                     | 4 (5%)               | 0 (0%)                 | 4 (7%) | 0.679 |
| CARPREG II score              |                      |                        |     |
| 0-1                            | 67 (88%)             | 13 (87%)               | 54 (89%) | 1.000 |
| 2                              | 1 (1%)               | 0 (0%)                 | 1 (2%) | 1.000 |
| 3                              | 6 (8%)               | 2 (13%)                | 4 (7%) | 0.338 |
| 4                              | 2 (3%)               | 0 (0%)                 | 2 (3%) | 1.000 |
| Modified WHO classification   |                      |                        |     |
| I                              | 51 (67%)             | 10 (67%)               | 41 (67%) | 1.000 |
| II                             | 20 (26%)             | 2 (13%)                | 18 (30%) | 0.328 |
| II-III                         | 5 (7%)               | 3 (20%)                | 2 (3%) | 0.049* |
| **Maternal heart disease**    |                      |                        |     |
| Congenital heart disease      | 51 (67%)             | 9 (60%)                | 42 (69%) | 0.549 |
| Unrepaired                    | 13 (17%)             | 2 (13%)                | 11 (18%) | 1.000 |
| VSD                           | 8                    | 1                      | 7     |
| ASD                           | 2                    | 1                      | 1     |
| PAPVC                         | 1                    | 0                      | 1     |
| Coronary-pulmonary artery fistula | 1              | 0                      | 1     |
| Cor triatriatum               | 1                    | 0                      | 1     |
| Repaired                      | 38 (50%)             | 7 (47%)                | 31 (51%) | 1.000 |
| VSD                           | 11                   | 2                      | 9     |
| AVSD                          | 9                    | 3                      | 6     |
| TOF                           | 7                    | 0                      | 7     |
| ASD                           | 5                    | 1                      | 4     |
| TGA                           | 4                    | 1                      | 3     |
| TAPVC                         | 2                    | 0                      | 2     |
| Valvular disease              | 21 (28%)             | 5 (33%)                | 16 (26%) | 0.748 |
| MR                            | 15                   | 2                      | 13    |
| PS                            | 2                    | 0                      | 2     |
| ASR                           | 2                    | 2                      | 0     |
| AR                            | 1                    | 0                      | 1     |
| PR                            | 1                    | 1                      | 0     |
| Others                        | 4 (5%)               | 1 (7%)                 | 3 (5%) | 1.000 |
| Marfan                        | 3                    | 1                      | 2     |
| IVCD                          | 1                    | 0                      | 1     |
| **Neonatal characteristics**  |                      |                        |     |
| Number of births              | 77 (Twin 1)          | 16 (Twin 1)            | 61    |
| Gestational, weeks            | 38 (37-39)           | 38 (38-40)             | 38 (37-39) | 0.746 |
| Birth weight, g               | 2755 (2470-3050)     | 2750 (2635-2904)       | 2760 (2386-3196) | 0.989 |
| Complications                 | 12 (16%)             | 0 (0%)                 | 12 (20%) | 0.109 |
| Low birth weight              | 6                    | 0                      | 6     |
| Cardiac anomaly               | 3                    | 0                      | 3     |
| Asphyxia                      | 2                    | 0                      | 2     |
| Hyperbilirubinemia            | 1                    | 0                      | 1     |

VSD indicates ventricular septal defect; ASD, atrial septal defect; PAPVC, partial anomalous pulmonary venous connection; AVSD, atrioventricular septal defect; TOF, Tetralogy of Fallot; TGA, transposed great arteries; TAPVC, total anomalous pulmonary venous connection; MR, mitral valvular regurgitation; PS, pulmonary stenosis; ASR, aortic valvular stenosis/regurgitation; AR, aortic valvular regurgitation; PR, pulmonary valvular regurgitation; and IVCD, inferior vena cava defect. Mann–Whitney U test was used to compare continuous variables and Fisher’s exact test was used to compare categorical variables. *P < 0.05.
Normal pregnancy promotes reversible and physiological hypertrophy without long-term effects on cardiac function. Recent echocardiographic studies have shown that left ventricular systolic and diastolic function remains almost constant during pregnancy despite profound cardiac remodeling of the left ventricle. Our recent study on ventricular-arterial coupling in pregnant women with normal pregnancy, it is also important to evaluate the left ventricular GLS changes in women with CHD. Further, the assessment of left atrial volume is strikingly simple and useful to predict peripartum cardiac events in pregnant women with CHD, even though they are at low risk for cardiac events based on the ZAHARA and CARPEG II scores.

The present study has several limitations. First, our cohort consists of a limited number of patients, and the number of pregnant women with peripartum cardiac events was quite small. For retrospective studies, assessing the postpartum period in a group of women with cardiac events also includes assessing the condition when treatment has already started. Second, our study lacks echocardiographic data during the second trimester. We measured ventricular diastolic function based on transmitral Doppler velocity and strain measurements during pregnancy and postpartum. Previous studies on cardiac function in normal pregnant women have shown a decrease in the E/A ratio and left ventricular GLS from early pregnancy toward late pregnancy, which was consistent with our present study. Although strain measurements may detect subtle changes more sensitively than other echocardiographic parameters, GLS reflects myocardial function modulated by not only the ventricular loading but also chamber size and wall thickness. Therefore, the observed changes in GLS may not be an indicator of the adverse effects of pregnancy on the global cardiac function or clinical status in women with CHD. Moreover, the structural nature according to the primary diagnosis of CHD and the presence of a left-to-right or right-to-left shunt would make it difficult to understand the left ventricular GLS changes in women with CHD. Further, the assessment of left atrial volume is strikingly simple and should be recommended for women with CHD, regardless of whether it is repaired or unrepaired, who are at risk of peripartum cardiac events.

Our finding that mild diastolic dysfunction occurs at late pregnancy in pregnant women with cardiac events is likely to be similar to the findings observed in patients with heart failure with preserved ejection fraction (HFpEF). HFpEF is an important issue in contemporary cardiology, given its growing prevalence, high morbidity and mortality burden, and lack of proven therapy. It is characterized by impaired diastolic function due to eccentric remodeling of the heart along with increased stiffness of both the extracellular matrix and myofibrils. Pregnancy also exposes women to unique physiological challenges, which affects myocardial structure and function. Estrogen and progesterone levels extraordinarily increase from early pregnancy toward late pregnancy. Both estrogen and progesterone modulate the mechanical properties of titin, which is one of the key structural proteins determining cardiomyocyte stiffness. The assessments of echocardiographic parameters including e', E/e', GLS, and left atrial volume are important in the management of pregnant women with CHD.

The present study has several limitations. First, our cohort consists of a limited number of patients, and the number of pregnant women with peripartum cardiac events was quite small. For retrospective studies, assessing the postpartum period in a group of women with cardiac events also includes assessing the condition when treatment has already started. Second, our study lacks echocardiographic data during the second trimester. We measured the left ventricular diastolic function at only two points: at early pregnancy (less than 20 gestational weeks) and at late pregnancy (more than 28 gestational weeks). It may be possible that an increase in the left atrial volume occurs prior to 28 weeks of gestation. Third, there were a significant number of subjects, as high as 45%, in whom the complete data set was not obtained. This suggested that the majority of cardiologists might not recognize the necessity of temporal and repetitive assessments of mater-
Figure 2. Pregnancy and postpartum and comparison between groups. LVEDV indicates left ventricle end diastolic volume; LVESV, left ventricle end systolic volume; LAV, left atrial volume; E, early diastolic mitral flow velocity; A, late diastolic mitral flow velocity; e’, early diastolic septal annular velocity; GLS, global longitudinal strain; LVEF, left ventricle ejection fraction; and BNP, brain natriuretic peptide. *P < 0.05, Mann-Whitney U test was used to compare continuous variables. **P < 0.05, the Friedman test was used to compare continuous variables.
nal cardiac function among women with CHD. It is important to educate obstetricians and cardiologists who treat such pregnant women.

Conclusions

An increase in the left atrial volume followed by mild left ventricular diastolic dysfunction is related to peripartum cardiac events in women with CHD who are at low risk for these events during pregnancy. Temporal and repetitive assessments of maternal cardiac function based on the left atrial volume are important in the management of pregnant women with CHD.

Acknowledgments

We would like to thank Editage (www.editage.com) for their assistance with the editing of an earlier version of this paper.

Disclosure

Conflicts of interest: The authors have no conflicts of interest to declare.

Ethical Standards: This work does not involve any human or animal experimentation.

IRB information: This study was approved by the Ethics Committee of Kyushu Hospital, Japan Community Healthcare Organization (number: 381).

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