



## Left Ventricular Diastolic Function During the Normal Peripartum Period

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**Background:** Because cardiovascular function and hemodynamics markedly change during pregnancy, our aim was to elucidate left ventricular (LV) diastolic function in pregnant women.

**Methods and Results:** We prospectively collected the data of 397 pregnant women treated between 2012 and 2013. We evaluated their LV systolic and diastolic functions via echocardiography during the 3rd trimester (28–30 weeks' gestation) and within 4 days of delivery. Additionally, we analyzed the cardiac geometry: relative wall thickness and LV mass index (LVMI). Diastolic dysfunction was defined as early diastolic mitral annulus velocity ( $e'$ )  $<7$  cm/s and peak early filling velocity ( $E/e'$ ) ratio  $>15$ . The pregnant women were  $33.7 \pm 5.0$  years old and the prevalence of hypertensive disorders in pregnancy (HDP) was 4.0%. LV systolic function was preserved in all pregnant women. However, diastolic function significantly decreased after delivery (mean  $e'$ : 12.6 vs. 11.6 cm/s,  $P < 0.0001$ ; median  $E/e'$  ratio: 6.4 vs. 7.3,  $P < 0.0001$ ). Diastolic function after delivery was associated with the prevalence of HDP ( $P = 0.035$ ) and was correlated with age ( $R = -0.17$ ,  $P = 0.0009$ ) and LVMI ( $R = -0.30$ ,  $P < 0.0001$ ). However, these changes in diastolic function remained within the normal range and only 1 woman (1/397, 0.3%) had LV diastolic dysfunction after delivery.

**Conclusions:** LV diastolic function decreased after delivery in pregnant women but was within the normal range.

**Key Words:** Cardiac geometry; Echocardiography; Left ventricular diastolic function; Peripartum period; Pregnancy

Maternal cardiovascular functions change markedly during pregnancy and adapt to fluctuating hemodynamics to aid the development of the fetus and to protect the mother from the risks of delivery.<sup>1</sup> For instance, the left ventricular (LV) chamber size and LV mass enlarge with preserved LV contraction.<sup>1–3</sup> These changes begin early in pregnancy and reach their peak during the 2nd and 3rd trimesters (14–27 weeks and 28 weeks–delivery, respectively).<sup>4</sup> However, the change in cardiac diastolic function during pregnancy is not well known.<sup>5,6</sup> In women with a previous history of preeclampsia, cardiac diastolic function was reported to worsen in middle age.<sup>7,8</sup> Additionally, Aggarwal et al indicated that high parity was a risk factor for diastolic dysfunction despite the absence of a history of preeclampsia.<sup>9</sup> These findings suggest that cardiac diastolic function may be impaired during the normal peripartum period. Thus, we aimed to elucidate the changes in cardiac diastolic function during pregnancy and early after delivery.

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#### Methods

##### Patient Population

We prospectively enrolled 405 pregnant women during the 3rd trimester (28–30 weeks of gestation) at Tazuke Kofukai Medical Research Institute, Kitano Hospital between February 2012 and February 2013. The women underwent cardiac echocardiography during the 3rd trimester and within 4 days of delivery. We excluded those whose parameters of cardiac diastolic function were not assessed via echocardiography during the 3rd trimester ( $n = 3$ ) or within 4 days of delivery ( $n = 5$ ). Finally, we included 397 pregnant women.

##### Data Collection

The following peripartum characteristics were assessed:

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**Table 1. Characteristics of the Pregnant Women During the Peripartum Period**

	All patients (n=397)
<b>Prenatal characteristics</b>	
Age (years)	33.7±5.0
Advanced maternal age* [n (%)]	184 (46)
Body mass index (kg/m <sup>2</sup> )	23.1±2.9
Smoking [n (%)]	20 (5)
Gravidity (times)	1.43±0.72
Parity (times)	1.41±0.70
Primipara [n (%)]	255 (64)
<b>Comorbidities</b>	
Past medical history [n (%)]	
Hypothyroidism	10 (2.5)
Bronchial asthma	4 (1.0)
Renal disease	7 (1.8)
Connective tissue disease	4 (1.0)
Uterine myoma	28 (7.5)
Ovarian cystoma	5 (1.3)
Perinatal comorbidities [n (%)]	
HDP	16 (4.0)
Gestational hypertension	13 (3.3)
Chronic hypertension	2 (0.5)
Preeclampsia	1 (0.2)
Eclampsia	0 (0)
Diabetes mellitus	9 (2.3)
Placental abnormality	8 (2.0)
Threatened premature delivery	11 (2.8)
Intrauterine infection	1 (0.3%)
<b>Fetal status</b>	
Duration of pregnancy (weeks)	38.8±2.6
Birth weight (g)	2,986±471
Twin gestation [n (%)]	13 (3.3)
FGR [n (%)]	8 (2.0)
NRFS [n (%)]	4 (1.0)
<b>Delivery</b>	
Cesarean delivery [n (%)]	63 (17)
Method of labor induction [n (%)]	
Oxytocin	118 (32)
Dinoprost	9 (2.4)
Balloon catheter	38 (10)
Blood loss during delivery [median (IQR), mL]	392 (250–610)
Transfusion [n (%)]	0 (0)
Retained placenta with manual removal [n (%)]	6 (1.5)
Duration of delivery [median (IQR), h]	7.2 (4.2–12.2)
Maternal death [n (%)]	0 (0)

\*Maternal age ≥35 years. FGR, fetal growth restriction; HDP, hypertensive disorders in pregnancy; IQR, interquartile range; NRFS, non-reassuring fetal status.

age, body mass index, smoking status, history of gravidity or parity, comorbidities, duration of pregnancy and delivery, fetal status, delivery method, amount of bleeding, blood transfusion, and maternal death. The amount of bleeding was assessed by an obstetrician, gynecologist, and registered nurses.

## Echocardiography

Cardiac function was evaluated by 2 cardiac sonographers with experience in research echocardiography during the 3rd trimester and within 4 days of delivery. All echocardiographic findings [LV ejection fraction (LVEF), LV diastolic dimension (LVDd), LV systolic dimension, interventricular septal thickness (IVST), posterior wall thickness (PWT), left atrial dimension, left atrial volume index (LAVI), mitral peak E-wave velocity (E), mitral peak A-wave velocity (A), mitral E/A ratio, E velocity deceleration time, early diastolic mitral annulus velocity (e'), and E/e' ratio] were analyzed using the standardized protocol recommended by the American Society of Echocardiography.<sup>10</sup> LVEF was measured using the Teichholz method and the tissue Doppler indices of e' were measured at the septal basal region. Diastolic dysfunction was defined as e' <7 cm/s and E/e' ratio >15.<sup>11</sup>

## Cardiac Geometry

We analyzed the cardiac geometry in pregnant women whose body surface area (BSA) was recorded (n=302). LV geometry was classified according to relative wall thickness (RWT) and LV mass index (LVMI) as follows: normal geometry (RWT ≤0.42 and LVMI ≤95 g/m<sup>2</sup>), concentric remodeling (RWT >0.42 and LVMI ≤95 g/m<sup>2</sup>), concentric hypertrophy (RWT >0.42 and LVMI >95 g/m<sup>2</sup>), and eccentric hypertrophy (RWT ≤0.42 and LVMI >95 g/m<sup>2</sup>).<sup>12</sup> RWT was measured at diastole as the ratio of 2×(PWT/LVDd).<sup>13</sup> LVMI was calculated at end-diastole using the formula of Devereux et al: (0.8×{1.04×[(LVDd+IVST+PWT)<sup>3</sup>–LVDd<sup>3</sup>]}+0.6)/BSA.<sup>14,15</sup>

## Ethics

Written informed consent was given by all participants. The research protocol was approved by the Review Board of Kitano Hospital according to the ethical guidelines of the 1975 Declaration of Helsinki and its amendments (P12-12-002). The patient records/information was anonymized prior to analysis.

## Statistical Analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean±standard deviation or as median and interquartile range (IQR). When comparing prepartum and postpartum data, the paired t-test was used for continuous variables. Correlation analysis for cardiac diastolic function (e' and E/e') was conducted with Pearson's product-moment. A P-value <0.05 was considered statistically significant in all analyses. Statistical analyses were performed using JMP version 14 (SAS Corp., Cary, NC, USA).

## Results

### Baseline Characteristics

The baseline data of the 397 pregnant women are presented in **Table 1**. Their mean age was 33.7±5.0 years and 46% of the women had advanced maternal age (≥35 years). The mean parity was 1.41±0.70 and 64% were primipara. The prevalence of hypertensive disorders in pregnancy (HDP) was 4.0%. Cesarean section accounted for 17% of deliveries and approximately 34% of women underwent induction of labor, which predominantly involved usage of oxytocin. The median duration of delivery was 7.2 (IQR: 4.2–12.2) h. There were no maternal deaths during the peripartum

**Table 2. Echocardiographic Findings During Pregnancy and After Delivery**

	During pregnancy (n=397)	After delivery (n=397)	P value
LVEF (%)	62.8±3.6	62.9±3.4	0.54
LVDd (mm)	47.1±3.5	48.4±3.5	<0.0001
LVDs (mm)	31.2±2.6	31.9±2.5	<0.0001
IVST (mm)	6.51±0.91	6.74±0.10	<0.0001
PWT (mm)	6.65±0.88	6.96±0.90	<0.0001
LAD (mm)	31.9±3.5	32.7±3.9	<0.0001
LAVI (mL/m <sup>2</sup> )	17.1±3.9	19.0±4.5	<0.0001
E [median (IQR), cm/s]	0.81 (0.71–0.93)	0.85 (0.73–0.95)	0.0074
A [median (IQR), cm/s]	0.52 (0.45–0.62)	0.58 (0.49–0.67)	<0.0001
E/A ratio [median (IQR)]	1.50 (1.28–1.83)	1.40 (1.21–1.70)	<0.0001
E DT [median (IQR), ms]	187.0 (163.0–208.0)	179.0 (157.5–201.5)	0.0008
e' (cm/s)	12.5±2.4	11.6±2.4	<0.0001
e' <8 cm/s [n (%)]	11 (2.8)	18 (4.5)	
e' <7 cm/s [n (%)]	4 (1.0)	5 (1.3)	
E/e' [median (IQR)]	6.4 (5.6–8.0)	7.3 (6.1–8.9)	<0.0001
E/e' >15 [n (%)]	0 (0)	1 (0.3)	
SBP (mmHg)	109.7±11.2	115.0±13.1	<0.0001
DBP (mmHg)	66.4±7.5	69.9±10.9	<0.0001
HR (beats/min)	72.9±10.4	72.4±10.3	0.59

A, mitral peak A-wave velocity; DBP, diastolic blood pressure; DT, deceleration time; E, mitral peak E-wave velocity; e', velocity of mitral annulus early diastolic motion; HR, heart rate; IQR, interquartile range; IVST, interventricular septal thickness; LAD, left atrial dimension; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness; SBP, systolic blood pressure.

**Table 3. Cardiac Geometry During Pregnancy and After Delivery**

	During pregnancy (n=302)	After delivery (n=302)	P value
RWT	0.28±0.04	0.28±0.04	0.59
LVM (g)	95.8±18.6	105.7±23.1	<0.0001
LVMI (g/m <sup>2</sup> )	59.9±10.1	66.0±12.6	<0.0001
LV geometry [n (%)]			
Normal geometry	300 (99.4)	297 (98.3)	
Concentric remodeling	1 (0.3)	0 (0)	
Concentric hypertrophy	0 (0)	0 (0)	
Eccentric hypertrophy	1 (0.3)	5 (1.7)	

LVM, left ventricular mass; LVMI, left ventricular mass index; RWT, relative wall thickness.

period.

### Echocardiographic Findings During the Peripartum Period

The results of echocardiography during the 3rd trimester and within 4 days of delivery are summarized in **Table 2**. In all pregnant women, LVEF was maintained at more than 50% during the peripartum period. The cardiac chamber size and wall thickness were significantly enlarged after delivery (LVDd: 47.1±3.5 vs. 48.4±3.5 mm;  $P<0.0001$ ; LAVI: 17.1±3.9 vs. 19.0±4.5 mL/m<sup>2</sup>;  $P<0.0001$ ; and PWT: 6.65±0.88 vs. 6.96±0.90 mm;  $P<0.0001$ ).

### Cardiac Geometry

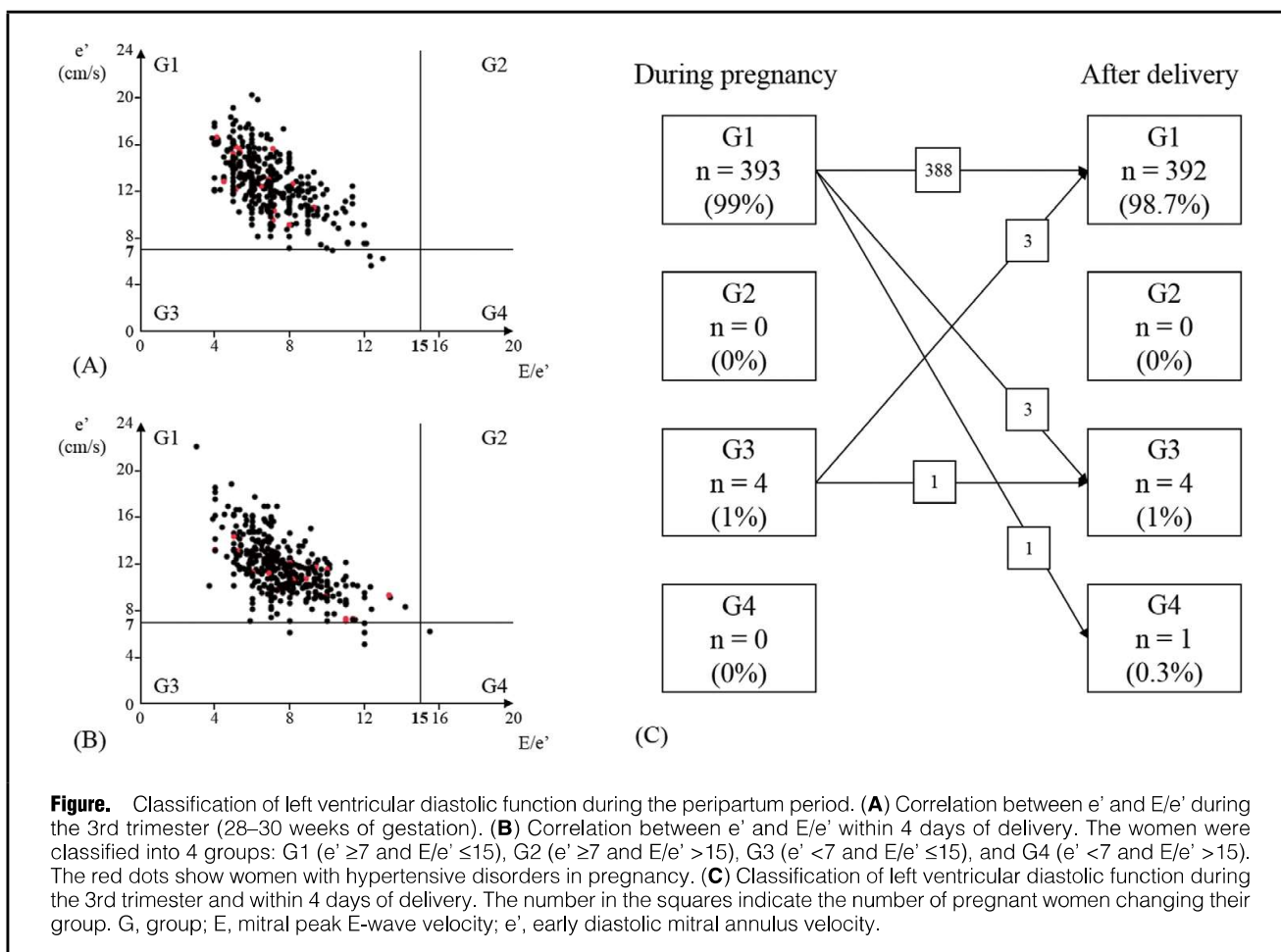
**Table 3** shows the LV geometry during the 3rd trimester and within 4 days of delivery. LVMI was significantly increased after delivery (59.9±10.1 vs. 66.0±12.6 g/m<sup>2</sup>;  $P<0.0001$ ), but RWT did not significantly change (0.28±0.04 vs. 0.28±0.04;  $P=0.59$ ). Regarding the pattern of LV

geometry, 1.7% of the pregnant women exhibited eccentric hypertrophy after delivery; however, the rest mostly exhibited normal geometry during pregnancy and after delivery.

There was no significant difference in the echocardiographic findings and LV geometry (RWT and LVMI) during the 3rd trimester between women with or without HDP. However, LV wall thickness, RWT, and LVMI after delivery were higher in women with HDP compared with those without HDP (IVST: 7.63±0.96 vs. 6.70±0.97 mm;  $P=0.0002$ ; PWT: 7.75±0.93 vs. 6.93±0.89 mm;  $P=0.0003$ ; RWT: 0.32±0.04 vs. 0.28±0.04;  $P=0.0015$ ; and LVMI: 75.7±13.6 vs. 65.6±12.4 g/m<sup>2</sup>;  $P=0.0062$ ).

### Cardiac Diastolic Function

LV diastolic function significantly decreased after delivery [mean e': 12.6±2.4 vs. 11.6±2.4 cm/s;  $P<0.0001$ ; and median E/e' ratio: 6.4 (IQR: 5.6–8.0) vs. 7.3 (IQR: 6.1–8.9);



$P < 0.0001$ ] (Table 2). Additionally, cardiac diastolic function during the 3rd trimester correlated with age ( $e'$ :  $R = -0.26$ ,  $P < 0.0001$ ; and  $E/e'$ :  $R = 0.18$ ,  $P = 0.0003$ ) and LVMI ( $e'$ :  $R = -0.24$ ,  $P < 0.0001$ ; and  $E/e'$ :  $R = 0.14$ ,  $P = 0.007$ ). Cardiac diastolic function after delivery was associated with the prevalence of HDP ( $e'$ :  $P = 0.035$ ; and  $E/e'$ :  $P = 0.032$ ) and correlated with age ( $e'$ :  $R = -0.17$ ,  $P = 0.0009$ ; and  $E/e'$ :  $R = 0.13$ ,  $P = 0.009$ ) and LVMI ( $e'$ :  $R = -0.30$ ,  $P < 0.0001$ ; and  $E/e'$ :  $R = 0.25$ ,  $P < 0.0001$ ). However, almost all these changes in diastolic function remained within the normal range (Figure, Group 1) and only 1 woman had LV diastolic dysfunction after delivery (1/397, 0.3%) (Figure, Group 4). In total 1% of the study population had a low  $e'$  ( $< 7$  cm/s) and normal  $E/e'$  ( $\leq 15$ ) (Figure, Group 3).

## Discussion

The main findings of this study were as follows: (1) cardiac diastolic function in pregnant women slightly decreased after delivery and was associated with the prevalence of HDP, and correlated with age and LVMI; and (2) cardiac diastolic function was preserved during normal pregnancy and the prevalence of diastolic dysfunction after delivery was only 0.3% in women with a normal pregnancy.

Generally, LV function with preserved LVEF is assessed by a combination of  $e'$ ,  $E/e'$ , peak velocity of tricuspid regurgitation (TR velocity), and LAVI.<sup>11</sup> TR velocity is affected by ventricular loading conditions,<sup>11</sup> so this param-

eter may not be useful in pregnant women with increased blood volume.<sup>16</sup> LAVI reflects the cumulative effects of increased LV filling pressure over time<sup>11</sup> and is difficult to use to assess short-term changes in diastolic function during pregnancy. However, in the current study LAVI was elevated after delivery. Therefore, the increased volume status might have affected the increase in LAVI, in addition to the cumulative effects of increased LV filling pressure. On the other hand, tissue Doppler imaging is less load-dependent than conventional blood-pool Doppler parameters and is a more accurate method for evaluating cardiac diastolic function during pregnancy.<sup>11,17</sup> Considering these, we selected  $e'$  and  $E/e'$  for evaluation of cardiac diastolic function during the peripartum period.

In general, women with a normal pregnancy demonstrate normal cardiac geometry during pregnancy.<sup>18–20</sup> However, the change in cardiac geometry in pregnant women from the 3rd trimester to early after delivery is not well known. In the current study, almost all the pregnant women exhibited normal cardiac geometry, but some exhibited an eccentric hypertrophy after delivery. RWT did not significantly change after delivery but LVMI was significantly increased, because LV wall thickness increases with enlarged LV dimensions.<sup>21</sup> Kim et al reported eccentric hypertrophy in 24% of women with a normal pregnancy at 33 weeks of gestation.<sup>12</sup> Cardiac geometry with eccentric hypertrophy shows a spherical left ventricle, which is best adapted to efficient diastolic filling and increased stroke volume.<sup>13</sup>

This change in geometry may occur late in the 3rd trimester in order to adapt to the increase in blood plasma and LV filling pressure. In pregnant women with HDP, the prevalence of eccentric hypertrophy increases up to 40%.<sup>20</sup> Additionally, approximately 20% of pregnant women with HDP demonstrate cardiac geometry with concentric remodeling.<sup>19,20</sup> The mechanism of concentric remodeling is considered to be the increase in peripheral resistance with a decrease in preload caused by a contraction of the intravascular volume, as in preeclampsia.<sup>22</sup>

In the current study, the blood pressure at echocardiography was significantly higher after delivery than during the 3rd trimester. The value of  $e'$  is less affected by afterload, whereas, transmitral flow is affected by LV volume and afterload.<sup>11</sup> However, the change in blood pressure after delivery was within the normal range, which may be associated with the mechanism of the change in systemic vascular resistance (SVR) during pregnancy. SVR decreased over the course of pregnancy, with the lowest value being 30% below the non-pregnant value during the early 3rd trimester.<sup>1</sup> After delivery, the SVR gradually returned to the non-pregnant value.<sup>1</sup> The changes in blood pressure after delivery were caused by the decrease in SVR during pregnancy. Additionally, the values of  $e'$  and  $E/e'$  after delivery in the current study were slightly low compared with those in normal non-pregnant women in a previously reported study ( $e'$ :  $13.1 \pm 2.4$  cm/s in the 20s age group,  $12.8 \pm 2.4$  cm/s in the 30s; and  $E/e'$ :  $7.1 \pm 1.6$  in the 20s,  $6.8 \pm 1.5$  in the 30s).<sup>23</sup> The blood pressure at echocardiography in the normal non-pregnant women is similar to that observed in the current study (systolic blood pressure:  $109 \pm 13$  mmHg in the 20s,  $112 \pm 9$  mmHg in the 30s and diastolic blood pressure:  $68 \pm 10$  mmHg in the 20s,  $69 \pm 7$  mmHg in the 30s).<sup>23</sup> Based on these results, the effect of blood pressure on the changes in diastolic function is considered to be small.

Cardiac diastolic function is reported to decrease during the 3rd trimester and to recover 6 months after delivery in women with a normal pregnancy.<sup>5,24</sup> The present study additionally showed that diastolic function further decreases early after delivery compared with during the 3rd trimester. These changes in diastolic function were within the normal ranges but the cutoff values of  $e'$  and  $E/e'$ , which were used for the evaluation of diastolic dysfunction in the current study, did not consider age and sex. Therefore, we evaluated the prevalence of diastolic dysfunction using the cutoff values of  $e'$  and  $E/e'$  at the 2SD limit of the age- and sex-adjusted values for normal people.<sup>23,25</sup> These yielded a prevalence of diastolic dysfunction during the 3rd trimester of 0.7% (3/397), which increased after delivery up to 2.0% (8/397). Considering these results, some women with a normal pregnancy might develop diastolic dysfunction early after delivery. Additionally, the decreased diastolic function may accumulate during each pregnancy and delivery. Aggarwal et al reported that high parity ( $\geq 5$  live births) was associated with the presence of LV diastolic dysfunction.<sup>9</sup> According to the present study's results, pregnant women with advanced age, HDP, or elevated LVMI have a propensity for reduced diastolic function. LV diastolic dysfunction during the peripartum period can cause heart failure despite preserved LVEF;<sup>26</sup> therefore, not only cardiac systolic function but also diastolic function should be evaluated in order to predict heart failure with preserved LVEF during the peripartum period.

## Study Limitations

First, there may have been variability in the echocardiographic data because 2 cardiac sonographers performed the examinations. Second, the pregnant women in this study were slightly older than is found in the general population in Japan<sup>27</sup> because they were attending a general hospital. Therefore, selection bias in participant enrollment cannot be excluded. Third, we did not perform strain analysis during echocardiography for the evaluation of systolic and diastolic function. Fourth, we followed up the patients for only 4 days after delivery and evaluated the diastolic function early after delivery. Finally, prospective studies are needed to investigate the relationship between changes in the diastolic function and peripartum cardiomyopathy.

In conclusion, cardiac diastolic function in pregnant women significantly decreased after delivery, and was associated with the prevalence of HDP, and correlated with age and LVMI. However, these changes in diastolic function remained within the normal range, and diastolic function was preserved during the normal peripartum period.

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## Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

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