Morphofunctional Cardiac Changes in Singleton and Twin Pregnancies

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Abstract

Objectives To compare heart echocardiographic changes between women with singleton and twin pregnancies

Methods We enrolled pregnant and postpartum women for this longitudinal cohort study in a tertiary center from 2014 through 2016. We analyzed 166 and 83 prospectively collected longitudinal data on simultaneously determined echocardiography parameters and blood variables in 44 and 22 normotensive women with either singleton or twin pregnancies, respectively. We tested mixed effect models for echocardiographic parameters and cardiac biomarkers.

Results The mean left atrial volume index and brain natriuretic peptide (BNP) level were significantly higher in women with twin pregnancies than in those with singleton pregnancies during the 3rd trimester and immediately postpartum (within 1 week after childbirth). The 2nd trimester inferior vena cava diameters were significantly smaller and the 3rd trimester creatinine levels were significantly higher in women with twin pregnancies than in those with singleton pregnancies. BNP was positively correlated with left atrial volume index (β=0.49, p<0.01) and with the ratio of early diastolic transmitral to mitral annular velocity (E/e') (β=0.41, p<0.01). BNP and N-terminal precursor protein BNP (NT-proBNP) fragments immediately postpartum were negatively correlated with the later E/e', at 1 month postpartum in women with singleton pregnancies (r=−0.33, p=0.02 and r=−0.36, p<0.01, respectively).

Conclusions The intravascular cardiac load at postpartum within 1 week after childbirth was greater in women with twin pregnancies than in those with singleton pregnancies. BNP/NT-proBNP was significantly positively correlated with LA volume index and E/e', BNP may be secreted to reduce the volume and pressure overload on the myocardial wall by diuretic action and may have improved the diastolic functions 1 month after childbirth. Our results provide evidence to deepen the understanding of the pathophysiological hemodynamic changes after delivery.

Introduction

Twin pregnancy differs from singleton pregnancy in many respects like the greater physiological increase in circulating blood volume [1], greater gestational weight gain and newborn weight (sum for twins) [2], shorter pregnancy length [3], persistent systolic dysfunction after delivery [4], and greater risk of peripartum cardiomyopathy in women with twin pregnancies than in those with singleton pregnancies [5, 6].

The blood volume increases physiologically in pregnancy [1], and this volume expansion is associated with cardiac morphofunctional changes during pregnancy [7–11]. In a classical study by Pritchard [1], the mean net increases in circulating blood volume in singleton and twin pregnancies were 1570 mL and 1960 mL, respectively. This causes significant differences between singleton and twin pregnancy women in echocardiographic findings [12–16] and in blood levels of cardiac biomarkers, such as B-type natriuretic peptide (BNP), N-terminal precursor protein BNP fragment (NT-proBNP), and high-sensitivity troponin I (hs-TnI) [17]. Kuleva et al. revealed a higher cardiac output in twin than in singleton pregnancies [15], and Ghi et al. showed changes in maternal systolic and diastolic function from the first to the third trimester and a persisting decreased systolic function after delivery [16]. The BNP levels increase with heart failure severity, and their measurements are used widely to assess the presence, severity, and prognosis of heart failure [18, 19]. Both BNP and atrial natriuretic peptide have beneficial effects in patients with heart failure [20, 21]. However, the echocardiographic parameters and cardiac biomarker levels in singleton and twin pregnancy have been studied independently, and any associations between them have not been assessed.

We designed this study to characterize the cardiac morphofunctional changes in normotensive women with twin or singleton pregnancies and to find associations with levels of BNP, NT-proBNP, and hs-TnI using longitudinal prospectively collected data.

Materials And Methods

This project began in April 2014 with a cohort of pregnant women scheduled to give birth at Hokkaido University Hospital. We invited them to participate in this study. All participants were asked to undergo echocardiographies at each of the trimesters of pregnancy, immediately postpartum within 1 week after childbirth (designated as “PP1”), 1 month after childbirth (postpartum day 23-39) (designated as “PP2”), and approximately at 3 months postpartum. In addition, we collected blood samples at the same time. Of 701 women with singleton and 61 with twin pregnancies who gave birth at the Hokkaido University Hospital during the 2-year study period, 151 and 41, respectively, participated in this project undergoing simultaneous echocardiographies and blood samplings (Fig.1). This study was conducted as an additional examination of our previous studies [11,22].

We conducted the study after receiving approval from the Institutional Review Board of Hokkaido University Hospital and participants provided voluntary written informed consent. This study abided by the Declaration of Helsinki.

Participants (Fig. 1) [11,22]

To compare longitudinal changes in echocardiographic findings between normotensive women with either singleton or twin pregnancy, we selected 22 twin pregnancies eligible participants meeting all of the following four criteria: (1) absence of preexisting hypertension or development of hypertension during the current pregnancy; (2) absence of preexisting diseases, including conditions involving hematological or endocrinological systems and connective tissue diseases; (3) uneventful clinical course during the current pregnancy; and (4) simultaneous echocardiography and blood sampling at least three times during the four stages of pregnancy/postpartum including the 2nd, 3rd, PP1, and PP2 timepoints. We selected two women with singleton pregnancies whose delivery date was closest to that of each woman with twin pregnancy meeting the above four criteria to serve as controls (44 women with singleton pregnancies in total).

Echocardiographic evaluations [11,22]

A single trained operator (TU) performed all the bedside transthoracic echocardiography with pregnant women in the left lateral decubitus position using the same machine (ProSound α7; Hitachi, Tokyo, Japan) according to the European Association of Cardiovascular Imaging guidelines [23]. We calculated the stroke volume as the product of the aortic valve area and the aortic flow velocity time integral. Only the inferior vena cava (IVC) diameter was evaluated in the dorsal position. To avoid any possible performance bias, the TU performed echocardiography blinded to the biochemical data.

Biochemical procedures [11,22]

Serum and plasma samples were stored at −20°C until assays of hs-TnI, NT-proBNP, BNP, and creatinine were ready to be performed. We used the following equation to obtain the estimated glomerular filtration rate (eGFR): $0.739 \times 194 \times \text{serum creatinine}^{-1.094} \times \text{age [years]}^{-0.287}$ [24]. The hs-TnI, BNP, and NT-proBNP concentrations were measured using CIA kits (ARCHITECT High-Sensitivity Troponin I™, ARCHITECT BNP-JP™; Abbott Japan, Chiba, Japan; and Elecsys proBNP II STAT Assay™; Roche Diagnostics K.K., Tokyo, Japan, respectively).

Statistical Methods [11,22]

We performed all statistical analyses using JMP Pro12© (SAS, Cary, NC, USA) and the SPSS Statistics 24.0 software (IBM, Armonk, NY). We compared changes in variables within a group using Student's t-test with Bonferroni's correction. We used the mixed effect model to consider correlations at each time point and assess associations between echocardiographic parameters and biomarker levels. We standardized dependent (echocardiographic parameters) and independent (biomarker levels) variables to interpret the regression coefficient as the correlation coefficient. We implemented a compound symmetry covariance structure at each time point. For all analyses, we considered $P<0.05$ as indicating statistical significance. However, we defined a significant finding regarding a linear correlation between two standardized variables as that meeting both a $P<0.05$ and a standardized regression coefficient (β)>0.3 or <−0.3.

Results

In 44 women with singleton pregnancies and 22 with twin pregnancies underwent 166 and 83 echocardiographic procedures with simultaneous blood sampling, respectively (Table 1). The percentage of gestational weight gains determined during 3rd trimester was significantly higher in women with twin pregnancies than in those with singleton pregnancies (Table 2).

Cardiac morphofunctional changes in women with singleton and twin pregnancies (Table 3, Fig. 2)

The left ventricular (LV) masses and LA volumes increased with advancing gestation, reaching their peak values 1 week after childbirth (at PP1). The ratio of early diastolic mitral flow velocity (E) to the average between early diastolic septal and lateral mitral annular velocities (e') (namely E/e') increased significantly at PP1 in women with singleton pregnancies compared to the initial 2nd trimester value. In women with twin pregnancy, E/e' values were higher during the 2nd trimester and the PP1 than the values in women with singleton pregnancies at the same timepoints (p=0.01 and 0.02, respectively). LA volume corrected by body surface area (BSA) were also significantly higher at PP1 in women with twin pregnancies than those in women with singleton pregnancies (p=0.04). The average of systolic septal and lateral mitral annular velocities (s') as indexes of long axis contractility were smaller at PP1 and PP2 in women with twin pregnancies than in those with singleton pregnancies (p<0.01 and <0.01, respectively); although the shortening fractions as an index of short axis contractility did not show significant differences between the groups of women during the postpartum periods (p=0.52 and 0.66, respectively). Heart rates and cardiac outputs (CO) were transiently significantly lower in women with twin pregnancies than in women with singleton pregnancies during the postnatal period.

Changes in biomarkers in women with singleton and those with twin pregnancies (Table 4, Fig. 3)

The maternal weights were maximum during the 3rd trimester, but the BNP and NT-proBNP levels reached their peak values during the PP1, and were significantly higher in women with twin pregnancies than in those with singleton pregnancies during the peripartum period. Hs-TnI did not show significant changes during this period. Serum creatinine concentrations were significantly higher and eGFR significantly lower in the 3rd trimester in women with twin pregnancies than in those with singleton pregnancies (p<0.01 and 0.01, respectively).

Associations between cardiac biomarker levels and echocardiographic parameters (Fig. 4)

We analyzed correlations between standardized cardiac biomarkers, namely BNP, NT-proBNP, and hs-TnI, and four echocardiography parameters, namely standardized s', e', E/e', and LA volume index. BNP and NT-proBNP were significantly positively correlated with E/e' and LA volume index. None of the four echocardiographic parameters was significantly correlated with hs-TnI.

Correlations between BNP/NT-proBNP and hs-TnI immediately postpartum (during PP1) and later systolic and diastolic functions at 1 month postpartum (PP2) (Fig. 5)

We analyzed standardized BNP, NT-proBNP and hs-TnI values at PP1 to detect correlations with later standardized s', e', E/e', and LA volume index values at PP2. We found the BNP/NT-proBNP values at PP1 were significantly negatively correlated with later E/e' values at PP2 in women with singleton pregnancies ($r = -0.34$, $p = 0.04$), but did not correlate in women with twin pregnancies ($r = -0.27$, $p = 0.23$) (Fig. 5). However, none of the four echocardiographic parameters was significantly correlated with hs-TnI.

Differences in echocardiographic parameters and cardiac biomarkers according to chorionicity (Table 5)

Echocardiographic parameters and cardiac biomarkers of monochorionic and dichorionic twins were compared at each time point. In the monochorionic twins, LA diameter in the 2nd trimester was larger ($p = 0.03$) and IVC diameter in the 2nd trimester was smaller ($p = 0.04$) than diamniotic twins, but there was no significant difference in LA volume (p=0.88). Other echocardiographic parameters and cardiac biomarkers did not show significant differences between the monochorionic and dichorionic twins.

Discussion

Our study resulted in the following findings: (1) the LA volume index, E/e', BNP/NT-proBNP reached a peak within 1 week postpartum and was higher in women with twin pregnancies than in those with singleton pregnancies; (2) the serum creatinine concentration was significantly higher and the eGFR significantly lower in the 3rd trimester in women with twin pregnancies than in those with singleton pregnancies; (3) the BNP/NT-proBNP was significantly positively correlated with the LA volume index and E/e', (4) the BNP/NT-proBNP within 1 week postpartum predicted the recovery of the diastolic function at 1 month postpartum with singleton pregnancy.

The LA volume index, E/e', and BNP/NT-proBNP variables exhibited their peak values within 1 week postpartum. This suggests that the maximal cardiac volume load occurred within 1 week postpartum, and not during the late stages of pregnancy regardless of the number of fetuses, consistent with our previous reports [11, 22] in which maximum cardiac volume load was suggested to occur within 1 week postpartum in normotensive as well as hypertensive singleton pregnancies. In addition, the LA volume index, E/e', and BNP/NT-proBNP within 1 week postpartum were higher in women with twin pregnancies than in those with singleton pregnancies in this study, explaining the reason why heart failure is most likely to occur within 1 week after childbirth among women with structural heart diseases [25], peripartum cardiomyopathy is often observed during the postpartum period [5], and twin pregnancy is a prominent risk factor for peripartum cardiomyopathy [5]. Interstitial fluid retention occurs physiologically even in normotensive singleton pregnancies; approximately 40% of normotensive women with singleton pregnancies exhibit pitting edema during the 3rd trimester [26]. The decrease in systemic vascular resistance [10] results in an increase in reserved blood at the splanchnic venous reservoir [27]. This process is thought to be reversed by parturition. The systemic vascular resistance increases during the postpartum period [10] can actively expel splanchnic blood into the systemic circulation [27], thus causing a maximal volume load in the early postpartum period.

To our knowledge, this is the first report of significantly higher 3rd trimester serum creatinine levels and lower eGFRs in women with twin than in those with singleton pregnancies (Table 4 and Fig. 3). Possible mechanisms for the lower eGFR in women with twin pregnancies are as follows: The central venous pressure may be higher in women with twin pregnancies than in those with singleton pregnancies based on the smaller IVC diameter (compressed by the enlarged uterus) in women with twin pregnancies (Fig. 2) despite their higher blood volume expansion [1]. In addition, the 3rd trimester CO were similar between both groups of women in the presence of similar heart rates (Fig. 2) despite the higher blood volume expansion in the women with twin than in those with singleton pregnancies [1], although some investigators have reported higher CO in women with twin than in those with singleton pregnancies [12–15]. These observations suggest slower blood flow velocities in twin than in singleton pregnancy resulting in lower eGFRs in women with twin than in those with singleton pregnancies.

BNP/NT-proBNP was significantly positively correlated both with the LA volume index and the E/e' (Fig. 4). The results imply that BNP is secreted by tension applied to the myocardium with volume and pressure overload [28]. On the other hand, BNP is synthesized by non-hemodynamic factors, such as catecholamines and other neuroendocrines [29]. In pregnant women, the mechanism of BNP secretion is not clear, but BNP may be secreted to reduce the volume and pressure overload on the myocardial wall by diuretic action [30, 31]. In this study, the women with singleton pregnancies had lower E/e' at 1 month postpartum with higher immediate postpartum BNP. The results suggest that BNP has a cardioprotective effect in healthy pregnant women with singleton pregnancies. We found a higher BNP immediately postpartum predicted recovery of the diastolic function at 1 month postpartum as evidenced by a decrease in E/e' as an index of the LV filling pressure (Fig. 5). This phenomenon may also be interpreted as active BNP secretions to protect the cardiac function from the cardiac volume load immediately postpartum.

Ghi et al. reported that monochorionic twin pregnancies recognized lower CO, higher systemic vascular resistance, and higher E/A compared to dichorionic twin pregnancies [32], but we found no differences in echocardiographic parameters and cardiac biomarkers between the monochorionic and dichorionic twin pregnancies in our study (Table 5). This result may also be associated with sample size issues, further investigation is warranted.

This study has limitations. First, we missed the first trimester twin pregnancy data. As our hospital is a regional core center, women with twin pregnancies are often referred to us after the 1st trimester. In another study, Ghi et al. revealed cardiac changes in women with twin pregnancies during their 1st trimester [16] and confirmed gradual changes in maternal systolic and diastolic functions from the first to the third trimesters. These cardiac changes were similar to those in women with singleton pregnancies in our previous study [11] and helped validate our current results. Second, the cesarean section rate for twin pregnancies was higher than for singleton pregnancies. Since cesarean delivery resulted in a greater intravascular burden after delivery compared with vaginal delivery [11], the postpartum course of twin pregnancies may be influenced by a higher cesarean section ratio. Third, our study population was limited, and our study was carried out at a single center, potentially limiting the generalizability of our findings.

In conclusion, we found considerable hemodynamic differences between women with singleton pregnancies and those with twin pregnancies. The greater cardiac load at peripartum in women with twin pregnancies may explain why twin pregnancy is a consistent and prominent risk factor for heart failure. In pregnant women, the mechanism of BNP secretion is not clear, but BNP/NT-proBNP was significantly positively correlated with the LA volume index and E/e'. BNP may be secreted to reduce the volume overload and pressure overload on the myocardial wall by diuretic action. Further studies following our approach may contribute to clarify the physiological role of BNP during pregnancy and to clarify the pathophysiology of hemodynamical changes after delivery.

Declarations

Contributorship Statement

All authors, TU, TY, IF, HI, MM, HW, and HM, participated in the design of the study and collected data on each pregnant woman that participated in this study. TU participated in design of the study, performed statistical analyses, and drafted the manuscript. HM conceived of the study, and participated in its design and coordination, and helped to draft the manuscript.

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Conflict of Interest

None declared.

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Tables

Due to technical limitations, table 1,2,3,4,5 is only available as a download in the Supplemental Files section.

Figures

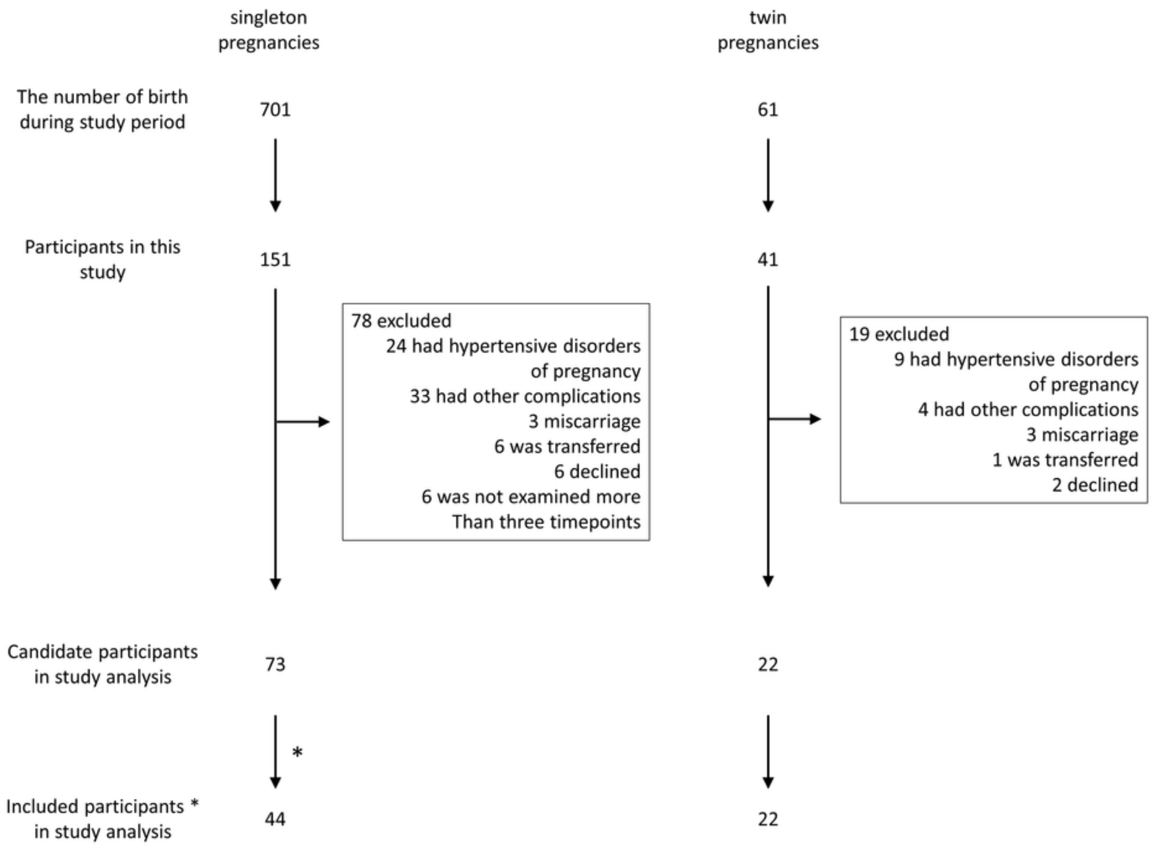

Figure 1

Study design *, We selected two women with singleton pregnancies whose delivery date was closest to that of each woman with twin pregnancy meeting the four criteria (see method) to serve as controls.

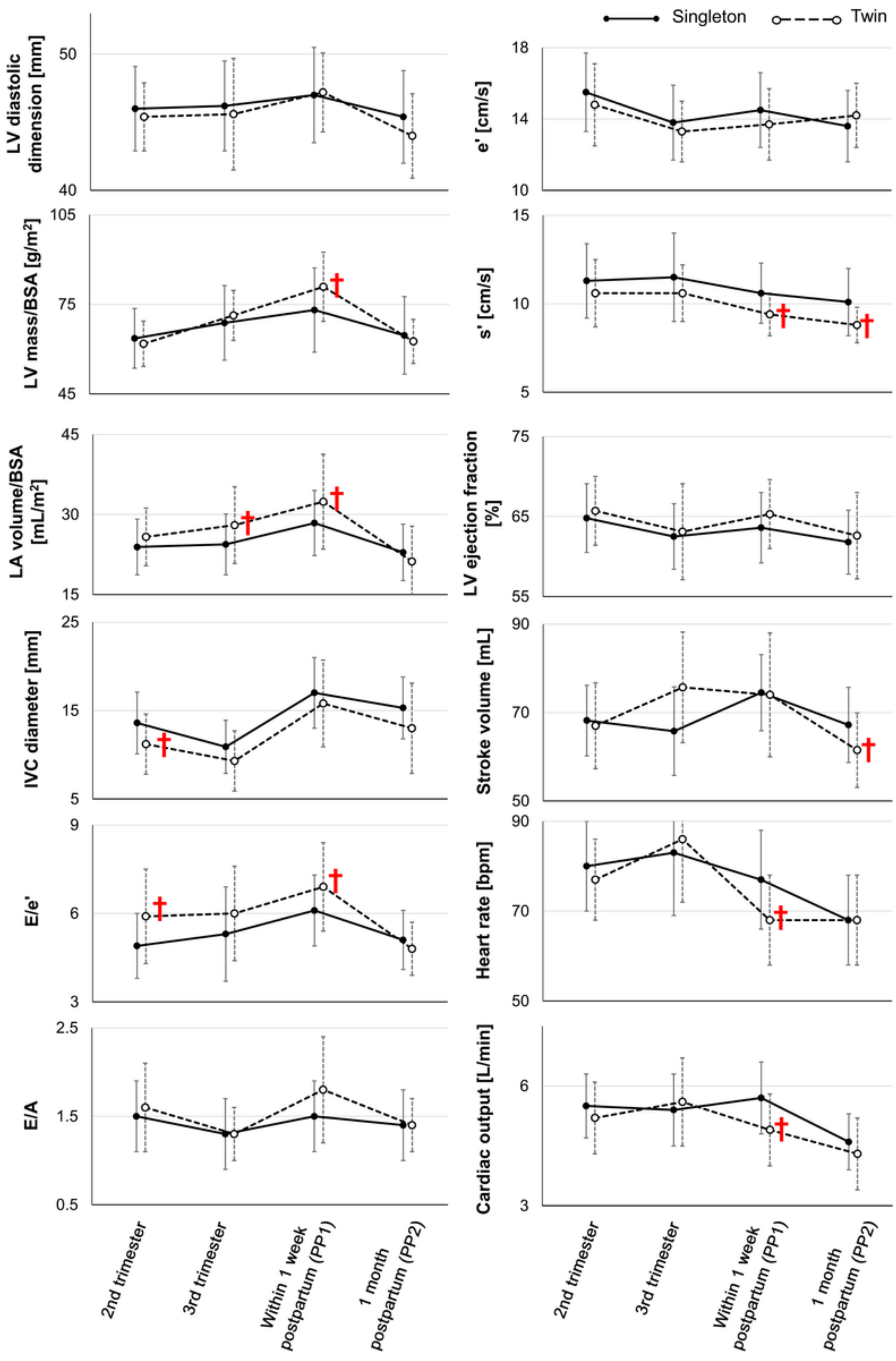

Figure 2

Cardiac morphofunctional changes in women with singleton and twin pregnancies †, P < 0.05 between two groups. A, late diastolic mitral flow velocity; BSA, body surface area; E, early diastolic mitral flow velocity; e', average of early diastolic septal and lateral mitral annular velocities; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; s', average of systolic septal and lateral mitral annular velocities. See Table 3 for detailed data on these and other variables.

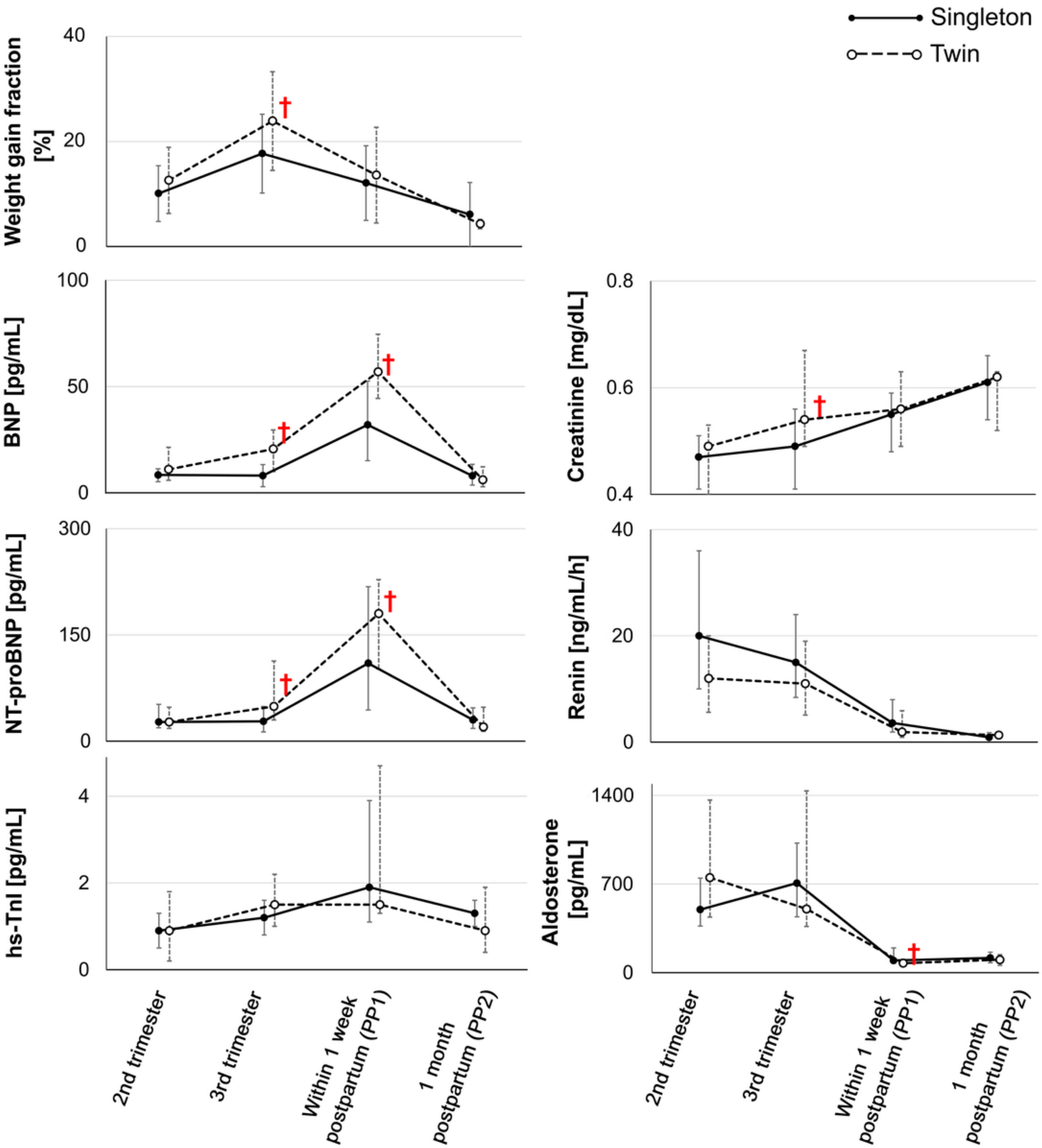

Figure 3

Changes in maternal body weight and biomarkers in women with singleton and twin pregnancies †, P < 0.05 between two groups. BNP, brain natriuretic peptide; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal fragment of precursor protein B-type natriuretic peptide. See Tables 2 and 4 for detailed data on these and other variables.

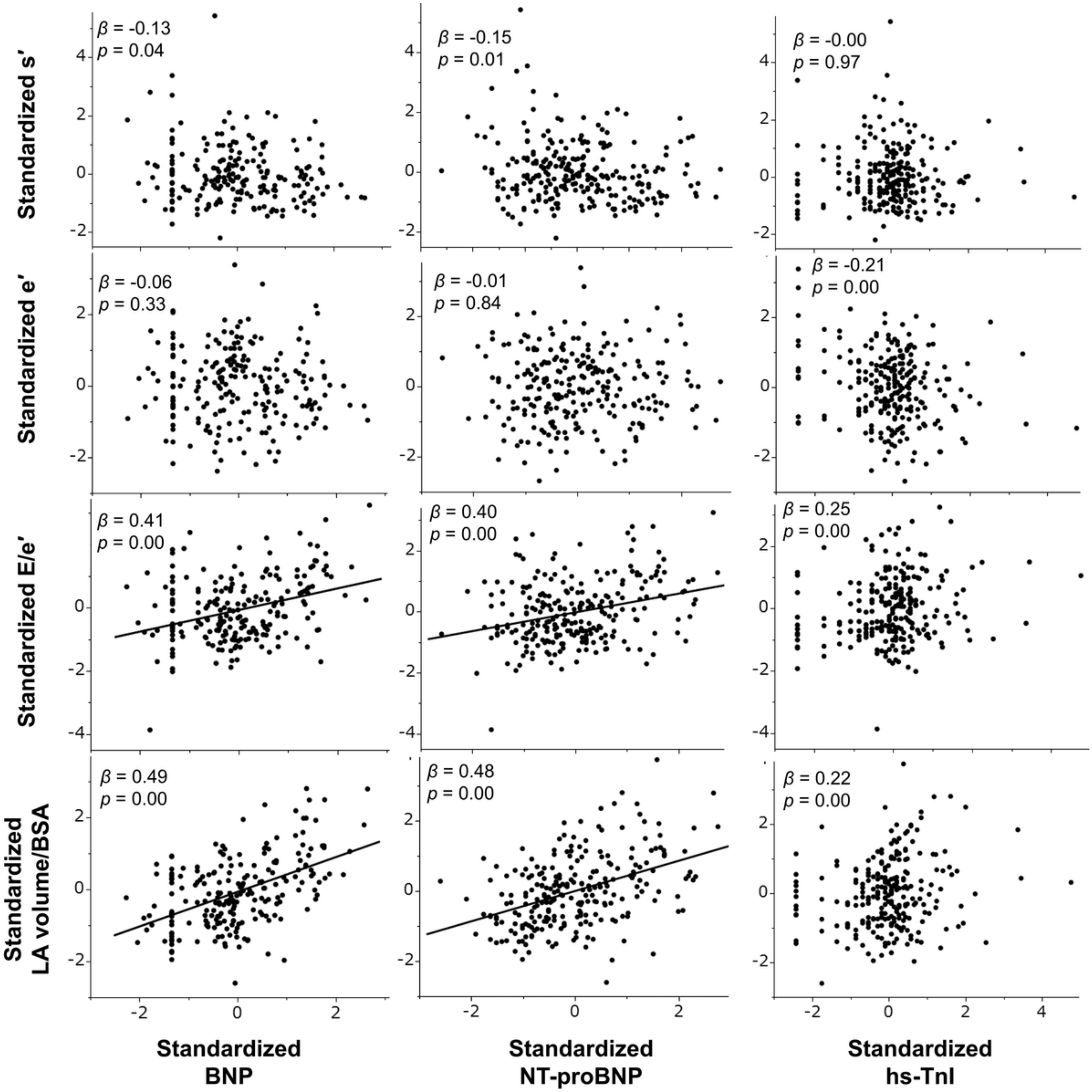

Figure 4

Standardized regression coefficients between blood variable levels and echocardiographic measurements β, Standardized regression coefficient. Regression line drawn for β >0.3. When the hs-TnI level was below the limit of detection (0.1 pg/mL), we assumed that hs-TnI was present at a serum concentration of 0.1 pg/mL. BSA, body surface area; BNP, brain natriuretic peptide; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal fragment of precursor protein B-type natriuretic peptide; E, early diastolic mitral flow velocity; e', average of early diastolic septal and lateral mitral annular velocities; LA, left atrium; s', average of systolic septal and lateral mitral annular velocities.

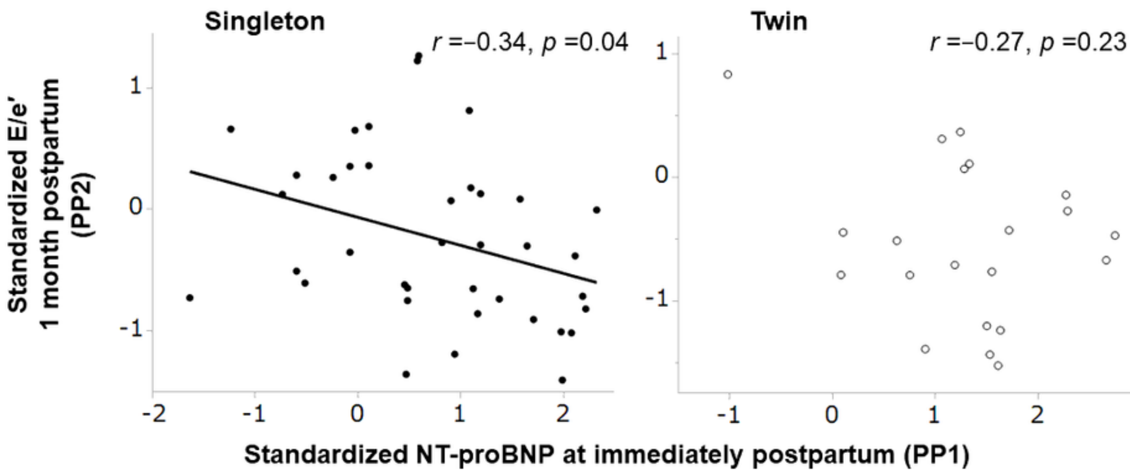

Figure 5

Correlations between NT-proBNP levels at immediate postpartum and later diastolic function at 1 month postpartum NT-proBNP, N-terminal precursor protein B-type natriuretic peptide fragment; E, early diastolic mitral flow velocities; e', average of early diastolic septal and lateral mitral annular velocities.

Supplementary Files

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