

ECHOCARDIOGRAPHIC ASSESSMENT OF STRUCTURAL AND HEMODYNAMIC CHANGES IN HYPERTENSION-RELATED PREGNANCY

MI-JEONG KIM, MD¹, JONGGOO SEO, MD², KYOUNG-IM CHO, MD³, SE-JUNG YOON, MD⁴, JUNG-HYUN CHOI, MD⁵, AND MI-SEUNG SHIN, MD⁶

¹DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, INCHEON ST. MARY'S HOSPITAL, THE CATHOLIC UNIVERSITY OF KOREA, SEOUL, KOREA

²DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, HALLYM HOSPITAL, INCHEON, KOREA

³DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, KOSIN UNIVERSITY SCHOOL OF MEDICINE, BUSAN, KOREA

⁴DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, NHIC ILSAN HOSPITAL, GOYANG, KOREA

⁵DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, PUSAN NATIONAL UNIVERSITY SCHOOL OF MEDICINE, BUSAN, KOREA

⁶DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, GACHON UNIVERSITY, GIL MEDICAL CENTER, INCHEON, KOREA

BACKGROUND: Pregnancy induces dramatic cardiovascular changes in order to meet the increasing metabolic needs. Adaptive change of left ventricle (LV) might be modified in pregnancy complicated by hypertension.

METHODS: Data from 193 consecutive pregnant women were analyzed. Clinical and echocardiographic data were compared in normotensive and hypertensive women.

RESULTS: Significantly higher LV mass indexed by height was observed in hypertensive women compared with normotensive women (84 ± 21 g/m vs. 97 ± 20 g/m, $p = 0.001$). Diastolic function measured by the ratio of peak velocity of early diastolic transmitral blood flow to early diastolic mitral annular velocity was impaired in hypertensive women (11.0 ± 3.0 vs. 9.2 ± 2.5 , $p < 0.001$). Such change was more prominent in women with gestational hypertension (GH) than those with chronic hypertension (CH). Heavy maternal weight was an independent factor associated with LV hypertrophy (LVH) in both normotensive and hypertensive women. Overt eccentric LVH was more frequent than concentric remodeling/hypertrophy (24% vs. 8.4%) in GH, while the opposite result was observed in CH (14% vs. 23%).

CONCLUSION: Hypertensive pregnancy is associated with significant LVH and diastolic dysfunction. CH seems to induce different LV remodeling pattern from GH. Heavy maternal weight during pregnancy might intensify the unfavorable remodeling of LV, particularly in hypertensive pregnancy.

KEY WORDS: Echocardiography · Hypertension · Pregnancy.

INTRODUCTION

Pregnancy induces dramatic cardiovascular changes in order to meet the maternal and growing fetal metabolic needs.^{1,2)} Along with progressive placental growth, blood volume increases and peripheral vascular resistance decreases. Cardiac output and heart rate also increase during pregnancy. Such changes result in compensatory cardiac remodeling.³⁾ In pregnancy complicated by hypertension, abnormal pressure overloading would lead to different cardiac remodeling compared

to that of normal pregnancy. In the present study, we have performed comprehensive echocardiographic assessment for pregnancy-related hypertension in real world practice.

METHODS

STUDY DESIGN AND SUBJECTS

This was a retrospective study using medical record in a single tertiary care center from January 2008 to June 2012. Con-

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• Address for Correspondence: Mi-Seung Shin, Division of Cardiology, Department of Internal Medicine, Gachon University, Gil Medical Center, 783 Namdong-daero, Namdong-gu, Incheon 21556, Korea Tel: +82-32-460-3663, Fax: +82-32-469-1906, E-mail: msshin@gilhospital.com

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secutive pregnant women referred for echocardiography with a diagnosis of hypertension were assigned to hypertensive women. Non-hypertensive pregnant women with normal echocardiographic finding during the same period were assigned to a normotensive control group. Exclusion criteria were pregnancy other than singleton, significant non-cardiac comorbidities and any significant structural heart diseases including systolic left ventricular (LV) dysfunction of LV ejection fraction (EF) < 50%, hypertrophic or restrictive cardiomyopathy, more than moderate degree of valvular heart disease and congenital heart disease. Demographic, laboratory and echocardiographic data were reviewed. Height and body weight were measured just before echocardiography, and those values were used to calculate body mass index (BMI) and body surface area (BSA). Systolic and diastolic blood pressure (BP) obtained from the brachial artery in the sitting position immediately before echocardiography was recorded. Gestational hypertension (GH) was defined as hypertension diagnosed after the 20th gestational week and previously having normal BP. Chronic hypertension (CH) was defined as pre-existing hypertension diagnosed before pregnancy or the 20th gestational week. The Institutional Review Board of a university affiliated hospital approved the study protocol.

ECHOCARDIOGRAPHY

Standard two dimensional and Doppler echocardiography were performed in the left decubitus position using a 3.5-MHz transducer (Vivid 7 Dimension ultrasound equipment, General Electric, Horten, Norway) according to the current practice guidelines.⁴⁻⁶ LV wall thickness and LV end diastolic diameter (LVEDD) and LV end systolic diameter (LVESD) were measured from parasternal long and short axis views with M-mode recording under two-dimensional guidance. LV mass was calculated according to the formula of Devereux et al.⁷ Relative wall thickness (RWT) was calculated using the formula ($2 \times$ posterior wall thickness)/LVEDD.⁸ LV mass index (LVMI) was calculated by the normalization of LV mass by height and BSA.⁴ Value of LVMI calculated with BSA was used only for classification of LV geometry. Otherwise value of LVMI calculated with height was used throughout the study. LV geometry was classified according to LVMI normalized by BSA and RWT as follows: normal geometry if $LVMI \leq 95 \text{ g/m}^2$ and $RWT \leq 0.42$, concentric remodeling if $LVMI \leq 95 \text{ g/m}^2$ and $RWT > 0.42$, concentric hypertrophy if $LVMI > 95 \text{ g/m}^2$ and $RWT > 0.42$ and eccentric hypertrophy if $LVMI > 95 \text{ g/m}^2$ and $RWT \leq 0.42$.⁸ LV EF was derived from modified Simpson's method from apical 4-chamber and 2-chamber views. Left atrial volume was estimated using the biplane discs method using apical views. Peak velocity of early (E) and late (A) diastolic transmitral blood flow were measured with pulsed wave Doppler recording. Tissue Doppler indices of early diastolic mitral annular velocity (e') and peak systolic mitral annular velocity (s') were measured at the septal mitral annulus. LV and

right ventricular (RV) Tei indices were obtained with pulsed wave Doppler recording. RV systolic pressure was calculated by simplified Bernoulli equation using peak systolic tricuspid regurgitation velocity. Tricuspid annular plane systolic excursion was obtained from M-mode recording in four chamber view.

STATISTICAL ANALYSIS

Continuous data are presented as mean \pm SD or median with 25–75th interquartile range (IQR). Frequency data are presented as numbers and percentages. Student's t-test or Mann-Whitney U test was used for comparison of continuous variables of two different groups. Chi-square test was used for frequency variables. Linear regression analysis was used to determine the factors associated with LVMI. Variables with a $p < 0.1$ in univariate analysis were included in the multiple regression model according to collinearity test. Standardized regression coefficient (β) was used to present the degree of correlation. $p < 0.05$ was considered statistically significant. SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

BASELINE CHARACTERISTICS

A total of 193 women were included in the final analysis and the participants were categorized into two groups as normotensive and hypertensive; 63 women were normotensive and 130 women were hypertensive (Table 1). Among hypertensive women, 76 women had GH and 54 had CH. Median (IQR) gestational age was similar in the two groups, that is, 31 (22–37) weeks in normotensive group and 33 (28–36) weeks in hypertensive group. Compared to the normotensive group, the hypertensive group was older (31 ± 4 years vs. 33 ± 5 years, $p = 0.003$) with heavier weight (69 ± 13 kg vs. 76 ± 12 kg, $p < 0.001$) and higher BMI ($27 \pm 5 \text{ kg/m}^2$ vs. $30 \pm 5 \text{ kg/m}^2$, $p < 0.001$). Systolic and diastolic BP of the hypertensive group were 152 ± 15 mm Hg and 96 ± 10 mm Hg, which were significantly higher than those of the normotensive group with 118 ± 14 mm Hg ($p < 0.001$) and 71 ± 10 mm Hg ($p < 0.001$).

LV REMODELING IN HYPERTENSIVE PREGNANCY

Echocardiographic findings are listed in Table 2. Mean LVEDD normalized by BSA was $28 \pm 2 \text{ mm/m}^2$ in the normotensive group. LVEDD and LVESD did not differ between the normotensive and hypertensive group. However, significantly higher RWT (0.34 ± 0.05 vs. 0.37 ± 0.06 , $p = 0.001$) and LVMI ($84 \pm 21 \text{ g/m}^2$ vs. $97 \pm 20 \text{ g/m}^2$, $p = 0.001$) were observed in the hypertensive group compared with the normotensive group (Fig. 1A). LVMI showed correlation with gestational age ($r = 0.227$, $p = 0.002$), BMI ($r = 0.473$, $p < 0.001$), and systolic ($r = 0.330$, $p < 0.001$) and diastolic ($r = 0.334$, $p <$

0.001) BP (Table 3). In multivariate analysis, gestational age ($\beta = 0.161, p = 0.013$), BMI ($\beta = 0.370, p < 0.001$), and systolic BP ($\beta = 0.220, p = 0.001$) were significant factors for increased LVMI during pregnancy. For LV systolic function, the hypertensive group showed higher LV EF ($63 \pm 4\%$ vs. $65 \pm 6\%$, $p = 0.002$).

LV DIASTOLIC FUNCTION IN HYPERTENSIVE PREGNANCY

Diastolic functional parameters were significantly reduced in hypertensive women compared to normotensive women. Significantly low E/A ratio (1.4 ± 0.4 vs. $1.1 \pm 0.3, p < 0.001$) and e' velocity (9.2 ± 2.2 vs. $7.9 \pm 2.4, p = 0.001$) were observed in hypertensive women. Significantly high peak A wave

velocity (62 ± 15 vs. $75 \pm 16, p < 0.001$) and E/e' ratio (9.2 ± 2.5 vs. $11.0 \pm 3.0, p < 0.001$) were observed in hypertensive women (Table 2, Fig. 1B).

RV FUNCTION IN HYPERTENSIVE PREGNANCY

Higher estimated RV systolic pressure was observed in hypertensive women compared to normotensive women (25 ± 5 mm Hg vs. 23 ± 3 mm Hg, $p = 0.002$). RV contractility did not differ between the groups.

THE EFFECT OF HEAVY BODY WEIGHT ON LV REMODELING

BMI was a significant factor for increased LVMI. There was a positive correlation between BMI and LVMI both in the sec-

Table 1. Baseline characteristics according to hypertension status

	Normotensive (n = 63)	Hypertensive (n = 130)	p value
Age, years	31 ± 4	33 ± 5	0.003
Gestation, weeks	31 (22–37)	33 (28–36)	0.772
Height, cm	161 ± 6	160 ± 6	0.199
Weight, kg	69 ± 13	76 ± 12	< 0.001
Body mass index, kg/m ²	27 ± 5	30 ± 5	< 0.001
Systolic BP, mm Hg	118 ± 14	152 ± 15	< 0.001
Diastolic BP, mm Hg	71 ± 10	96 ± 10	< 0.001
Heart rate, beats/min	91 ± 17	87 ± 15	0.081
Hemoglobin, g/dL	12 ± 1	12 ± 1	0.486
eGFR, mL/min/1.73 m ²	130 ± 22	124 ± 37	0.423
Fasting blood glucose, mg/dL	89 ± 17	90 ± 28	0.843

BP: blood pressure, eGFR: estimated glomerular filtration rate

Table 2. Echocardiography according to hypertension status

	Normotensive (n = 63)	Hypertensive (n = 130)	p value
LVEDD, mm	48 ± 4	49 ± 3	0.111
LVESD, mm	32 ± 3	31 ± 3	0.433
LA volume index, mL/m ²	26 ± 5	27 ± 5	0.450
Relative wall thickness	0.34 ± 0.05	0.37 ± 0.06	0.001
LV mass/height, g/m	84 ± 21	97 ± 20	0.001
LV ejection fraction, %	63 ± 4	65 ± 6	0.002
s' velocity, cm/sec	8.3 ± 1.4	8.5 ± 1.5	0.406
LV Tei index	0.39 ± 0.15	0.40 ± 0.14	0.820
E velocity, cm/sec	80 ± 16	82 ± 16	0.453
A velocity, cm/sec	62 ± 15	75 ± 16	< 0.001
E/A ratio	1.4 ± 0.4	1.1 ± 0.3	< 0.001
e' velocity, cm/sec	9.2 ± 2.2	7.9 ± 2.4	0.001
E/e'	9.2 ± 2.5	11.0 ± 3.0	< 0.001
RV BMD, mm	23 ± 3	24 ± 3	0.022
RV free wall thickness, mm	4 ± 1	4 ± 1	0.165
RV systolic pressure, mm Hg	23 ± 3	25 ± 5	0.002
TAPSE, mm	27 ± 2	27 ± 5	0.665
RV Tei index	0.39 ± 0.07	0.24 ± 0.14	< 0.001

A: late diastolic transmitral blood flow velocity, BMD: basal minor diameter, E: early diastolic transmitral blood flow velocity, e': early diastolic mitral annular velocity, LA: left atrial, LV: left ventricular, LVEDD: LV end diastolic diameter, LVESD: LV end systolic diameter, RV: right ventricular, s': peak systolic mitral annular velocity, TAPSE: tricuspid annular plane systolic excursion

ond ($r = 0.536, p < 0.001$) and third trimester ($r = 0.415, p < 0.001$) (Fig. 2). The effect of BMI on LVMI was consistent in both normotensive and hypertensive women.

GESTATIONAL VS. CHRONIC HYPERTENSION

To determine the effect of hypertension subtype on cardiac remodeling, LVMI and E/e' ratios were compared in normotensive, GH and CH women. Women with GH tended to

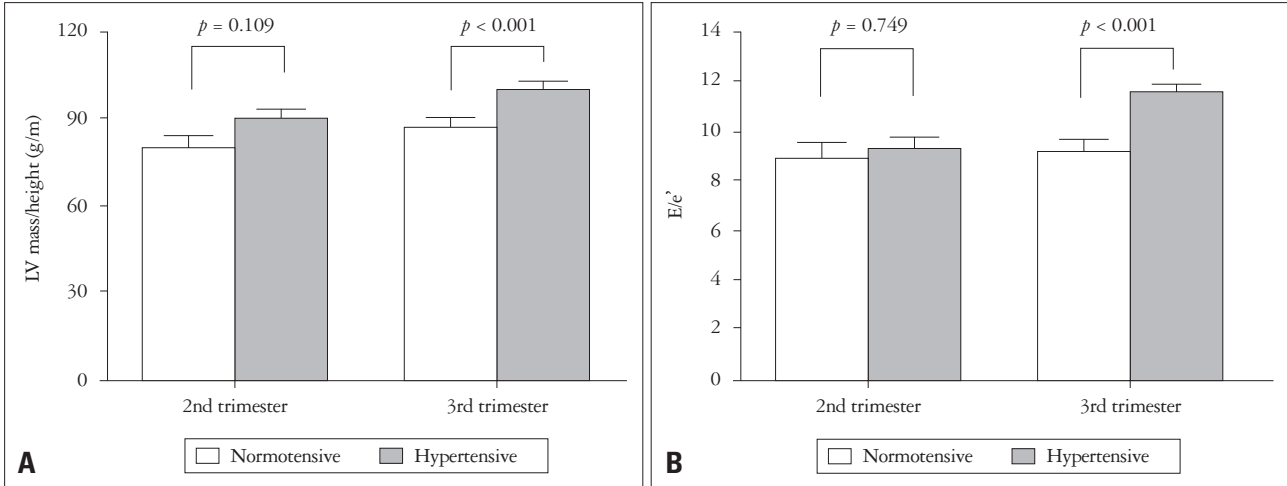


Fig. 1. Effects of hypertension on left ventricular (LV) mass and diastolic function. Hypertensive women show high LV mass index (A) and diastolic function index of E/e' ratio (B) compared with normotensive women in both middle and late trimester of pregnancy. Normotensive: normotensive women, Hypertensive: hypertensive women, E: early diastolic transmitral blood flow velocity, e': early diastolic mitral annular velocity.

Table 3. Factors influencing to left ventricular mass index in pregnant women

	Univariate		Multivariate	
	r	p value	β	p value
Age	0.158	0.030	0.093	0.144
Gestational age	0.227	0.002	0.161	0.013
Body mass index	0.473	< 0.001	0.370	< 0.001
Systolic BP	0.330	< 0.001	0.220	0.001
Diastolic BP	0.334	< 0.001	-	-
eGFR	-0.003	0.970	-	-
Fasting blood glucose	0.019	0.847	-	-

BP: blood pressure, eGFR: estimated glomerular filtration rate

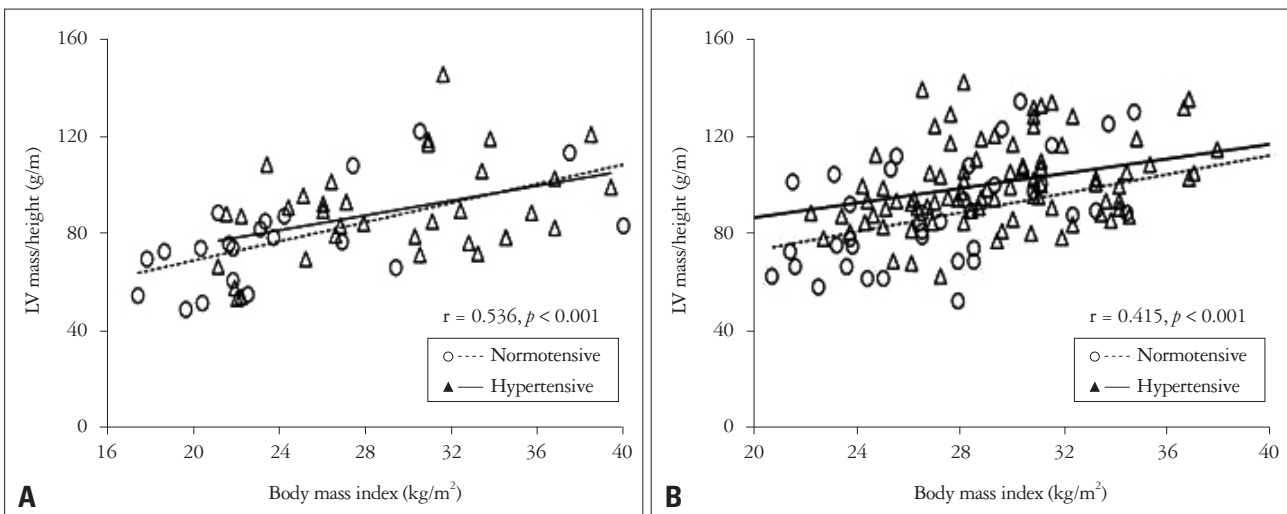


Fig. 2. Effects of body mass index on left ventricular (LV) mass in second (A) and third (B) trimester of pregnancy. Normotensive: normotensive women, Hypertensive: hypertensive women.

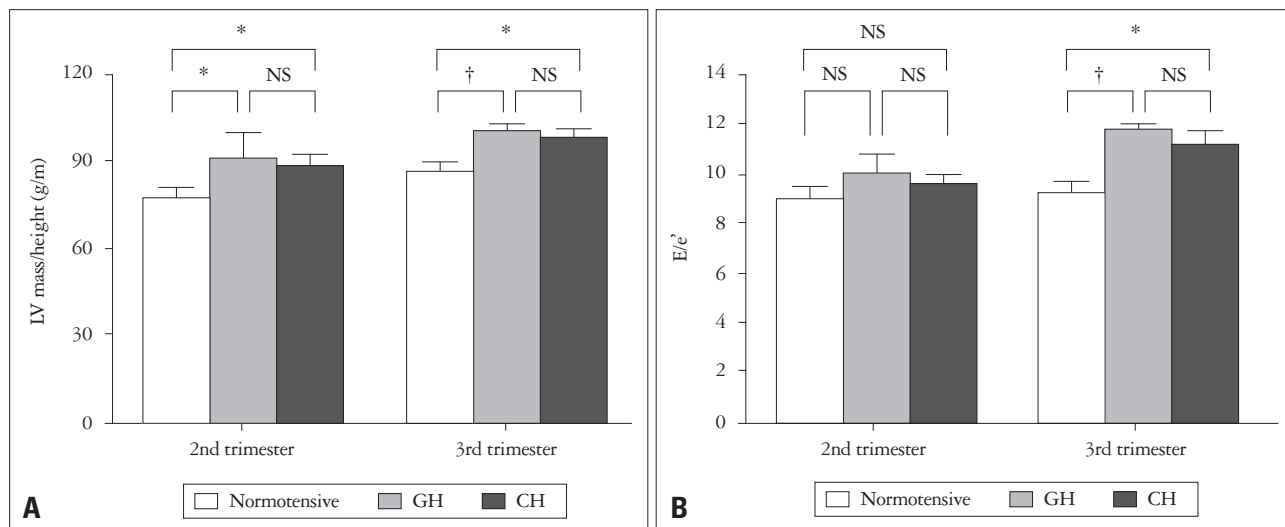


Fig. 3. Comparison of left ventricular (LV) mass (A) and diastolic function (B) in normotensive women, women with gestational hypertension (GH) and chronic hypertension (CH). * $p < 0.05$, † $p < 0.01$. E: early diastolic transmitral blood flow velocity, e': early diastolic mitral annular velocity, NS: not significant.

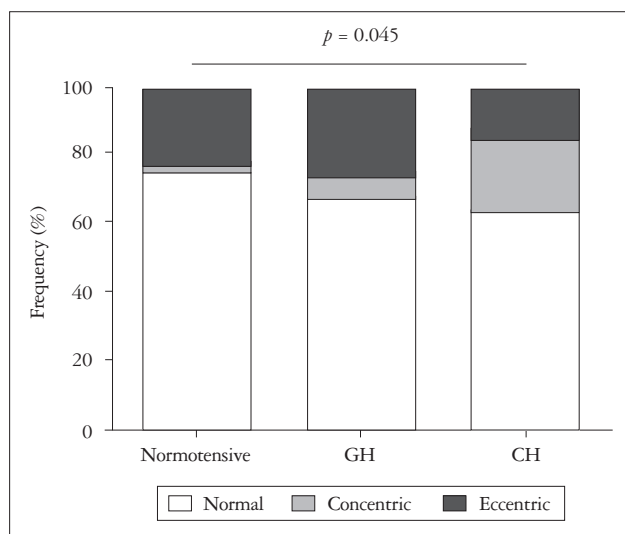


Fig. 4. Left ventricular geometry at the third trimester in normotensive women, women with gestational hypertension (GH) and women with chronic hypertension (CH). Eccentric left ventricular hypertrophy is more frequent in women with GH while concentric hypertrophy/remodeling is more frequent in those with CH.

have higher LVMI and E/e' ratio compared to those with CH although statistical significance was not reached (Fig. 3). LV geometry was analyzed for women in the third trimester (Fig. 4). In normotensive women, eccentric LV hypertrophy (LVH) was observed in 24%. In women with GH, eccentric LVH was observed in 24%. However, in women with CH, concentric remodeling/hypertrophy was more frequent (23%) than eccentric LVH (14%). The rate of concentric remodeling/hypertrophy was significantly higher in women with CH compared to those with GH ($p = 0.003$).

DISCUSSION

This study showed the recent echocardiographic data for

normal and hypertensive pregnant women. Hypertensive pregnancy was associated with significant LVH and diastolic dysfunction. Maternal excessive body weight was significantly associated with LVH in hypertensive pregnancy. In contrast to women with GH, concentric remodeling pattern was more prevalent in pregnant women with CH.

Profound cardiovascular adaptive changes occur during normal pregnancy. The noticeable change is the increase in cardiac output and blood volume, which starts as early as the sixth week of pregnancy. Progressive decreases in systemic vascular resistance and BP occur accordingly with gestational age.^{1,2} The primary stimulus to LV remodeling during normal pregnancy is volume overload, which leads to compensatory cardiac remodeling including progressive mild dilation of all cardiac chambers and increase in LV mass.⁹ During normal pregnancy, peripheral resistance keeps low despite elevated blood concentrations of renin and angiotensin II.¹⁰ Possible explanation for such vascular refractoriness to activated renin-angiotensin system is the role of humoral factors such as progesterone and prostaglandin.¹¹ Overall result of these modifications in a physiologic condition is the LV geometry of eccentric remodeling pattern.¹² Although data regarding diastolic function during pregnancy are limited, a progressive decrease in E-wave velocity has been reported during normal pregnancy in a small study.^{12,13}

In severe form of pregnancy-related hypertension, including severe preeclampsia and eclampsia, decreased circulatory volume and low central venous pressure in addition to elevated systemic vascular resistance result in hyperdynamic LV function, elevated LV filling pressure, decreased cardiac output, and decreased peripheral perfusion.¹⁴ Although the pathogenesis of GH is largely unknown, defects in uteroplacental vascular bed and endothelial dysfunction are thought to play critical roles.¹⁵ Aggressive LV remodeling, predominantly eccentric

LVH, was reported to be preceded pre-eclampsia.¹⁶⁾ There are few reports about LV geometry and function in pregnancy complicated with CH. In hypertensive pregnancy, effects to vascular resistance and heart might be more complicated. Previous study reported that degree of LVH was matched with the cardiac work load during pregnancy and was more prominent in pre-eclamptic pregnancy than normotensive pregnancy.¹²⁾ Concentric pattern of LV remodeling was frequently observed in pregnancy complicated by essential hypertension. Coexistence of pregnancy and hypertension tended to result in intensified LV hypertrophy and increased RWT.¹⁷⁾ In the current study, LVH was exaggerated in hypertensive pregnancy and LV geometry was quite different between the women with GH and CH, which were in agreement with the previous report. Whether such different patterns of LV remodeling in GH and CH induce different clinical outcome is needed to be confirmed in future study. In the current study, LV mass and diastolic dysfunction parameter of E/e' ratio was higher in women with GH than those with CH. Considering the short disease duration of GH, such findings might be due to inadequate cardiac adaptation or more severe vascular damaging process compared to CH.

RV change during hypertensive pregnancy was not prominent in the current study. Contrary to our expectation, RV Tei index was lower in hypertensive women than in normotensive women. RV might be hyperdynamic as LV in hypertensive women (Table 2).

Maternal obesity has known to have many negative impacts on mothers and fetuses, including spontaneous abortion, unexplained stillbirth, operative delivery, and future cardiovascular disease.¹⁸⁾ Risk of poor pregnancy outcomes associated with maternal obesity is proportional to the pre-gestational BMI. Pregnancy-related hypertensive disorders are thought to be the major mechanism of such dismal pregnancy outcomes.¹⁸⁾ In the current study, LVMI was proportional to BMI, which was shown in both normotensive and hypertensive women. Although BMI during pregnancy is very limited tool to assess maternal obesity, our result suggests that heavy maternal body weight might accentuate unfavorable LV remodeling in hypertensive pregnancy. Control of maternal obesity might reduce the cardiac risk of hypertensive pregnancy.

The current study was conducted retrospectively and data were obtained with a single measurement at different gestational ages. Serial examination might have provided more valuable information about progressive cardiac remodeling and postpartum resolution, particularly in patients with CH. The proportion of patients with severe preeclampsia was small. The result of GH might be intensified in a more severe form of pregnancy-related hypertension such as severe preeclampsia or eclampsia. Lack of data regarding peripheral resistance and pregnancy outcome may limit the interpretation of results. Small sample size was an additional limitation.

In conclusion, hypertensive pregnancy is associated with

significant LVH and diastolic dysfunction. CH seems to induce different LV remodeling pattern from GH. Excessive heavy maternal weight during pregnancy might intensify the unfavorable remodeling of LV, particularly in hypertensive pregnancy.

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