ORIGINAL ARTICLE

Left ventricular hypertrophy in Japanese pregnant women with chronic hypertension predicts blood pressure elevation during pregnancy

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Key words:

chronic hypertension, echocardiography, left ventricular hypertrophy

Received: September 30, 2019

Revised: February 3, 2020

Accepted: March 19, 2020

J-STAGE Advance published date: April 25, 2020

DOI:10.14390/jssh.p.HRP2019-016

Aim: The influence of cardiovascular changes resulting from hypertension on the course of pregnancy is unclear. The purpose of this study was to evaluate the influence of cardiovascular changes as detected by echocardiography on the course of pregnancy with chronic hypertension.

Methods: This retrospective cohort study targeted women with a singleton pregnancy and chronic hypertension during the period between January 1, 2010 and December 31, 2018. We compared echocardiographic values between subjects with blood pressure (BP) elevation (BP elevation group) and normotensive subjects (control group) during pregnancy.

Results: Twenty-nine hypertensive pregnant women were eligible for this study (14 subjects in the BP elevation group and 15 subjects in the control group). Left ventricular posterior wall thickness (PWT) and left ventricular mass index (LVMI) tended to be greater in the BP elevation group compared to the control group, but the differences were not significant. In the sub-cohort of subjects aged ≥ 35 years, PWT and LVMI were significantly greater in the BP elevation group compared to the control group.

Conclusions: Left ventricular hypertrophy (LVH) in pregnant women with chronic hypertension may be a predictor of BP elevation during pregnancy.

Introduction

Chronic hypertension during pregnancy is defined as a systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, persisting beyond postpartum week 12. The prevalence of this pathology is thought to be 1–5% and may be gradually increasing.^{1,2)} This increasing prevalence has been attributed to advancing maternal age and obesity.^{1,2)} Chronic hypertension during pregnancy increases the risks of developing superimposed preeclampsia, fetal growth restriction, placental abruption, preterm birth, Cesarean section, and more. Even if superimposed preeclampsia does not develop, maternal, fetal, and neonatal adverse events appear more frequently in women with chronic hypertension during pregnancy. Worsening BP control without new onset of proteinuria

and without development of superimposed preeclampsia is reportedly experienced by 7–20% of women with chronic hypertension during pregnancy.^{1–3)}

Drastic hemodynamic alterations occur during pregnancy. Although circulation volume during pregnancy increases to about 1.5-fold of the pre-pregnancy baseline, BP usually drops and remains lower than that pre-pregnancy because systemic vascular resistance decreases until gestational weeks 32–34.^{4–8)} BP then shows a slight elevation and is maintained around normal with the elevation of systemic vascular resistance in normotensive pregnant women. Moreover, wall thickness of the left ventricle and left ventricular mass (LVM) usually increase during pregnancy compared with pre-pregnancy.^{5,7,9–11)} Mabie et al. reported that wall thickness of the left ventricle and LVM increase

throughout pregnancy, becoming significantly greater by gestational weeks 24–27 and gestational weeks 20–23, respectively.⁵⁾ In chronic hypertension, cardiovascular changes such as arteriosclerotic vascular changes followed by left ventricular hypertrophy (LVH) can arise depending on the duration and severity of hypertension. The Framingham study showed that the relative risk of cardiovascular disease was 1.57 for each 50-g/m increment in LVM, which is corrected by height in women.¹²⁾ We hypothesized that such cardiovascular changes would affect BP and prognosis for chronically hypertensive pregnant women. Such cardiovascular changes would also be detectable on echocardiography. Accordingly, the purpose of this study was to evaluate the influence of cardiovascular changes as detected by echocardiography during the course of pregnancy, particularly in terms of changes in BP during pregnancy, among chronically hypertensive pregnant women.

Methods

Subjects in this retrospective cohort study were women with a singleton pregnancy and chronic hypertension who were managed in our institution between January 1, 2010 and December 31, 2018. Although the classification of hypertensive disorder of pregnancy was revised in April 2018 in Japan, we applied the previous classification because the present study comprised subjects treated before the revision. Chronic hypertension was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg before gestational week 20. Exclusion criteria included a pregnancy complicated by cardiac disease, superimposed preeclampsia, or preterm delivery before gestational week 34 not due to BP, or absence of echocardiographic data. Superimposed preeclampsia was diagnosed when significant proteinuria (≥ 300 mg/24 h) emerged after gestational week 20 with preexisting hypertension. We defined the BP elevation group as those subjects who required medication adjustment, hospital admission, and termination of pregnancy due to BP elevation after gestational week 20. Subjects who remained normotensive during pregnancy were defined as the control group.

We reviewed medical charts to collect information on height, body weight before pregnancy, parity, medication, smoking status, patient history, BP on the initial visit to our institute, proteinuria, and echocardiography. We routinely evaluated proteinuria through 24-h urine collection.

Transthoracic echocardiography was performed as soon as possible after the initial visit. Interventricular septum distance (IVSd) and left ventricular posterior wall thickness (PWT) were measured from M-mode. Left ventricular dimension was also

obtained from M-mode in end-diastole. LVM was calculated in grams using the Devereux formula¹³⁾: $0.8 \times (1.04(\text{LVDd} + \text{IVSd} + \text{PWT})^3 - \text{LVDd}^3) + 0.6$. LVM index (LVMI) (in grams/meter) was defined as LVM divided by height in meters, in order to correct for physique. We compared each value between the BP elevation and control groups.

We collected data on neonates from medical charts, including gestational age at delivery, birth weight, pH of blood in the umbilical artery, and Apgar score at 5 min after birth.

Continuous variables were analyzed using Student's *t*-test or the Welch *t*-test and expressed as mean $\pm$ standard deviation. Categorical variables were compared using Fisher's exact test. Receiver operating characteristic analysis was performed to predict blood pressure elevation during pregnancy. $P < 0.05$ was considered statistically significant. This study was approved by the ethics committee of the institution (M31–026).

Results

During the study period, 42 pregnancies with chronic hypertension were identified. Of these, 29 pregnancies were eligible for this study. We excluded 3 cases of pregnancy complicated by cardiac disease (angina pectoris, $n=1$; uncorrected atrial septum defect, $n=1$; bicuspid aortic valve, $n=1$), 5 cases of superimposed preeclampsia, 1 case of premature preterm rupture of membrane at gestational week 25, and 4 cases for which echocardiography was not performed. Fourteen cases were assigned to the BP elevation group and 15 cases to the control group.

Subject characteristics are shown in Table 1. Age, parity, and smoking status did not differ significantly between groups. BMI was 25.3 ± 6.4 kg/m² for the total cohort and did not differ significantly between groups. One case of diabetes mellitus and 1 case of gestational diabetes mellitus were identified in the BP elevation group. BP measured at initial visit did not differ significantly between groups. Antihypertensive medications were prescribed for 12 cases (85.7%) in the BP elevation group and 8 cases (53.3%) in the control group (Table 2). Methyldopa was the most frequently prescribed antihypertensive and was used for 15 cases (51.7%). Calcium channel blockers were prescribed for 7 cases. The prevalence of antihypertensive medication use did not differ significantly between groups.

Cardiac parameters for each group are shown in Table 3. Gestational age at the time of echocardiography did not differ significantly between groups. PWT and LVMI tended to be greater in the BP elevation group compared to the control group, but these differences were not significant.

Table 1. Characteristics of BP elevation and control groups

Variable	BP elevation group (n = 14)	Control group (n = 15)	P value
Age (years)	36.6 ± 3.8	36.3 ± 4.7	0.88
BW (kg) [†]	66.2 ± 18.0	62.2 ± 13.9	0.51
BMI (kg/m ²) [†]	26.5 ± 7.4	24.1 ± 5.4	0.32
Systolic BP (mm Hg) [‡]	145 ± 15	141 ± 24	0.68
Diastolic BP (mm Hg) [‡]	95 ± 13	91 ± 15	0.59
Smoking	1 (7.1)	3 (20.0)	0.60
Parity			
0	7 (50.0)	5 (33.3)	0.46
1	6 (42.9)	7 (46.7)	
> 1	1 (7.1)	3 (20.0)	

Data are presented as mean ± standard deviation, or n (%)

[†] measured before pregnancy

[‡] measured at initial visit

BW, body weight; BMI, body mass index; BP, blood pressure

Table 2. Antihypertensive medications in BP elevation and control groups

Variable	BP elevation group (n = 14)	Control group (n = 15)	P value
Number of medications			
0	2 (14.3)	7 (46.7)	0.11
1	9 (64.3)	6 (40.0)	
> 1	3 (21.4)	2 (13.3)	
Methyldopa	7 (50.0)	8 (53.3)	
Ca channel blocker	4 (28.6)	3 (20.0)	
Hydralazine	1 (7.1)	0 (0.0)	
Labetalol	1 (7.1)	0 (0.0)	
Spironolactone	1 (7.1)	0 (0.0)	

Data are presented as n (%)

Table 3. Cardiac parameters in BP elevation and control groups

Variable	BP elevation group (n = 14)	Control group (n = 15)	P value
Gestational age (weeks)	13.8 ± 6.5	15.4 ± 8.4	0.57
IVSd (mm)	9.4 ± 2.0	8.6 ± 1.0	0.17
PWT (mm)	9.4 ± 2.0	8.3 ± 0.9	0.07
LVDd (mm)	46.9 ± 4.2	46.4 ± 2.4	0.73
LVMI (g/m)	100.1 ± 34.7	82.0 ± 11.1	0.08
LADs (mm)	35.9 ± 8.3	34.1 ± 3.5	0.46

Data are presented as mean ± standard deviation

IVSd, interventricular septum distance; PWT, left ventricular posterior wall thickness;

LVDd, left ventricular dimension in end-diastole; LADs, left atrial dimension in end-

systole; LVMI, left ventricular mass index.

Neonatal outcomes for each group are shown in Table 4. More preterm births occurred in the BP elevation group compared to the control group. In the BP elevation group, factors associated with preterm delivery included uncontrollable hypertension (4 cases; 66.7%), labor onset (1 case; 16.7%), and preterm premature rupture of membrane (1 case; 16.7%). Birth weight was significantly lower in the BP elevation group compared to the control group. Frequencies of pH in the umbilical artery at

birth < 7.2 and Apgar score at 5 min after birth < 7 did not differ significantly between groups.

A sub-cohort comprising subjects aged ≥ 35 years was also analyzed. Among the 22 pregnancies in this sub-cohort, 11 were assigned to the BP elevation group and 11 to the control group. Baseline characteristics did not differ significantly between groups (Table 5). Among echocardiographic parameters, PWT and LVMI were significantly greater in the BP elevation group compared

Table 4. Neonatal outcomes in BP elevation and control groups

Variable	BP elevation group (n = 14)	Control group (n = 15)	P value
Preterm delivery	6 (42.9%)	1 (6.7%)	0.04
Delivery weeks	37.3 (33.0–39.1)	38.1 (36.4–40.6)	0.005
Birth weight (g)	2,452 (1,598–3,486)	2,876 (2,280–3,298)	0.006
pH of UmA < 7.2	1 (7.1%)	1 (6.7%)	1.00
Apgar score < 7 [†]	0 (0.0%)	0 (0.0%)	1.00

Data are presented as median (range), or n (%)

[†]5 min after birth

UmA, umbilical artery

Table 5. Characteristics of BP elevation and control groups in sub-cohort of subjects aged ≥ 35 years

Variable	BP elevation group (n = 11)	Control group (n = 11)	P value
Age (years)	37.9 ± 2.9	38.5 ± 3.1	0.63
BW (kg) [†]	69.2 ± 19.3	60.6 ± 11.2	0.21
BMI (kg/m ²) [†]	27.7 ± 7.9	23.7 ± 4.2	0.15
Systolic BP (mm Hg) [‡]	144 ± 12	142 ± 26	0.84
Diastolic BP (mm Hg) [‡]	92 ± 9	95 ± 14	0.67
Smoking	1 (9.1)	3 (27.3)	0.59
Parity			
0	6 (54.5)	4 (36.4)	0.67
1	5 (45.5)	5 (45.5)	
> 1	0 (0.0)	2 (18.2)	

Data are presented as mean ± standard deviation, or n (%)

[†]measured before pregnancy

[‡]measured at initial visit

BW, body weight; BMI, body mass index; BP, blood pressure

Table 6. Cardiac parameters in BP elevation and control groups in sub-cohort of subjects aged ≥ 35 years

Variable	BP elevation group (n = 11)	Control group (n = 11)	P value
Gestational age (weeks)	14.5 ± 6.7	15.4 ± 8.9	0.81
IVSd (mm)	9.8 ± 2.0	8.6 ± 1.1	0.09
PWT (mm)	10.0 ± 1.9	8.4 ± 1.0	0.02
LVDd (mm)	47.2 ± 3.8	45.9 ± 1.9	0.32
LVMI (g/m)	108.4 ± 34.7	81.4 ± 11.1	0.03
LADs (mm)	38.3 ± 7.6	34.6 ± 3.8	0.17

Data are presented as mean ± standard deviation

IVSd, interventricular septum distance; PWT, left ventricular posterior wall thickness;

LVDd, left ventricular dimension in end-diastole; LADs, left atrial dimension in end-systole; LVMI, left ventricular mass index.

to the control group (Table 6). The receiver operating characteristic curve based on LVMI for predicting BP elevation during pregnancy (area under the ROC curve=0.72; Figure. 1) demonstrated an optimal cut-off of 95.5 g/m, with a sensitivity of 63.6% and specificity of 90.9%. We also compared obstetrical outcomes such

as delivery weeks and birth weight using this cut-off, and found that subjects with LVMI ≥ 95.5 g/m showed a higher frequency of premature birth compared to subjects with LVMI < 95.5 g/m in the sub-cohort of subjects aged ≥ 35 years (Table 7).

Table 7. Neonatal outcomes by LVMI in sub-cohort of subjects aged ≥ 35 years

Variable	LVMI ≥ 95.5 g/m ($n = 8$)	LVMI < 95.5 g/m ($n = 14$)	P value
Preterm delivery	4 (50.0%)	1 (7.1%)	0.04
Delivery weeks	37.1 (33.0–39.1)	38.1 (36.4–40.6)	0.009
Birth weight (g)	2,362 (1,598–3,486)	2,906 (2,280–3,298)	0.09

Data are presented as median (maximum–minimum), or n (%)

Figure 1. Receiver operator characteristic curve based on LVMI for predicting BP elevation during pregnancy in the sub-cohort of subjects aged ≥ 35 years. Area under the curve is 0.72. The optimal cut-off is 95.5 g/m, with a sensitivity of 63.6% and specificity of 90.9%. LVMI, left ventricular mass index; BP, blood pressure.

Discussion

The present study demonstrated that PWT and LVMI tended to be greater in the BP elevation group. In particular, when subjects were limited to those aged ≥ 35 years, PWT and LVMI were significantly greater in the BP elevation group compared to the control group. Increased PWT and LVMI suggested LVH; that is, chronically hypertensive pregnant women with LVH had a risk of BP elevation during pregnancy. In particular, age ≥ 35 years and LVMI ≥ 95.5 g/m were considered risk factors for not only BP elevation during pregnancy, but also premature birth.

Hypertension, which represents pressure load, induces left ventricular wall stress. According to Laplace's law, which states that wall stress is proportional to cavity pressure and inversely proportional to wall thickness, pressure load causes thickening of the left ventricular wall to compensate for wall stress. Wall stress promotes the replication of sarcomeres and consequently induces enlargement of cardiomyocytes. The amount of interstitial extracellular matrix, such as collagen fiber

and fibronectin produced by fibroblasts, then increases. Interstitial fibrosis is influenced by angiotensin II and endothelin-1, which are secreted in response to pressure load.^{14–18} LVH is not necessarily induced by hypertension,¹⁹ and whether LVH occurs depends on the duration and severity of hypertension. LVH is also associated with increases in peripheral vascular resistance^{20–22} and arteriosclerosis.^{23–25} We consider systemic vascular resistance to have been originally high in those chronically hypertensive pregnant women who had hypertension severe enough to result in LVH. The BP of chronically hypertensive pregnant women with LVH, unlike that during normal pregnancy, would tend to rise excessively in the latter period of pregnancy.

In the present study, LVMI was significantly increased in the sub-cohort aged ≥ 35 years, but not in the total cohort. These older subjects, who would likely have been affected by hypertension for a longer duration, might have experienced larger changes in cardiac parameters. Generally, pregnant women aged ≥ 35 years are categorized as having advanced maternal age in Japan. We therefore examined the subject cohort using a cut-off age of 35 years. Two potential reasons were considered regarding why LVH could predict BP elevation only in subjects aged ≥ 35 years. First, the sample size of subjects aged < 35 years was small and insufficient. Second, subjects at a more advanced age likely had hypertension for a longer duration, so changes in cardiac parameters would have been larger in those subjects.

Some studies have examined the relationship between the course of pregnancy complicated by hypertension and LVM.^{26–28} Ambia et al.²⁶ conducted a retrospective study of 253 chronically hypertensive pregnant women. Forty-eight (19%) subjects had LVH, defined as LVMI > 95 g/body surface area. Subjects with LVH were more likely to develop persistent severe hypertension requiring antihypertensive treatment and also to give birth before term compared to subjects without LVH. Although those results appear broadly consistent with the present findings, more than 85% of the population in that study had BMI > 30 kg/m², whereas only 16% of our study cohort had BMI > 30 kg/m².²⁶ Quitete et al.²⁷ conducted a prospective, cross-sectional study of 31 chronically hypertensive pregnant women and 31 normotensive pregnant women. Echocardiography

performed after gestational week 25 demonstrated that chronically hypertensive subjects had higher LVM than normotensive subjects.²⁷⁾ However, the correlation between the difference in LVM and course of pregnancy was not mentioned.

This study has some potential limitations. First, echocardiography was performed at various gestational ages (median, 12.0 weeks; range, 9–19.3 weeks). This was due to the variable timing of the initial visit to our department. Cardiac parameters may have been affected by gestational age, but gestational age at the time of echocardiography did not differ significantly between groups. Second, although possible confounders such as age and parity were identified, we did not conduct multivariate analyses due to the insufficient number of subjects. However, no differences in characteristics were evident between groups, and thus this study was considered valid.

In the present study, we found that LVH of chronically hypertensive pregnant women predicted worsening of BP control during the latter period of pregnancy. We also identified LVMI ≥ 95 g/m as a significant risk factor for BP elevation among chronically hypertensive pregnant women aged ≥ 35 years. We considered LVH to reflect high systemic vascular resistance in chronically hypertensive pregnant women and believe that the present study offers important insight that clarifies the utility of echocardiography for predicting BP elevation in these women. Our recommendation based on the present findings is to conduct echocardiography for chronically hypertensive pregnant women, and if LVH is detected, then carefully manage these pregnancies.

Conflict of interest

None to report.

References

- Seely EW, Ecker J. Chronic hypertension in pregnancy. *NEJM*. 2011; 365: 439–446.
- Sibai BM. Chronic hypertension in pregnancy. *Obstet Gynecol*. 2002; 100: 369–377.
- Seely EW, Ecker J. Chronic hypertension in pregnancy. *Circulation*. 2014; 129: 1254–1261.
- Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. *Am J Obstet Gynecol*. 1989; 161: 1439–1442.
- Mabie WC, DiSessa TG, Crocker LG, et al. A longitudinal study cardiac output in normal human pregnancy. *Am J Obstet Gynecol*. 1994; 170: 849–856.
- Poppas A, Shroff SG, Korcarz CE, et al. Serial assessment of the cardiovascular system in normal pregnancy. *Circulation*. 1997; 95: 2407–2415.
- Robson SC, Hunter S, Boys RJ, et al. Serial study of factors influencing changes in cardiac output during pregnancy. *Am J Physiol*. 1989; 156: 1060–1065.
- Van Oppen AC, Van Der Tweel I, Alsbach GPJ, Heethaar RM, Bruinse HW. A longitudinal study of maternal hemodynamics during normal pregnancy. *Obstet Gynecol*. 1996; 88: 40–46.
- Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state on left ventricular performance in normal human subjects. *Circulation*. 1978; 58: 434–441.
- Mesa A, Jessurun C, Hernandez A, et al. Left ventricular diastolic function in normal human pregnancy. *Circulation*. 1999; 99: 511–517.
- Melchiorre K, Sharma R, Khalil A, Thilaganathan B. Maternal cardiovascular function in normal pregnancy. *Hypertension*. 2016; 67: 754–762.
- Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham heart study. *NEJM*. 1990; 322: 1561–1566.
- Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986; 57: 50–458.
- Nadruz W. Myocardial remodeling in hypertension. *J Hum Hypertens*. 2015; 29: 1–6.
- Drazner MH. The progression of hypertensive heart disease. *Circulation*. 2011; 123: 327–334.
- Frohlich ED, Apstein C, Chobanian AV, et al. The heart in hypertension. *N Engl J Med*. 1992; 327: 998–1008.
- Cacciapuoti F. Molecular mechanisms of left ventricular hypertrophy in systemic hypertension—possible therapeutic perspectives. *J Am Soc Hypertens*. 2011; 5: 449–455.
- Santos M, Shah AM. Alterations in cardiac structure and function in hypertension. *Curr Hypertens Rep*. 2014; 16: 428–437.
- Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *JACC*. 1992; 19: 1550–1558.
- Levy D, Anderson KM, Plehn J, et al. Echocardiographically determined left ventricular structural and functional correlates of complex or frequent ventricular arrhythmias on one-hour ambulatory electrocardiographic monitoring. *Am J Cardiol*. 1987; 59: 836–840.
- Dunn FG, Chandraratna P, de Carvalho JG, et al. Pathophysiologic assessment of hypertensive heart disease with echocardiography. *Am J Cardiol*. 1977; 39: 789–795.
- Devereux RB, Savage DD, Sachs I, et al. Relation of hemodynamic load to left ventricular hypertrophy and performance in hypertension. *Am J Cardiol*. 1983; 51: 171–176.
- Mehta SK, Rame JE, Khera A, et al. Left ventricular hypertrophy, subclinical atherosclerosis, and inflammation. *Hypertens*. 2007; 49: 1385–1391.
- Devereux RB, Pickering TG, Harshfield GA, et al. Left ventricular hypertrophy in patients with hypertension: importance of blood pressure responses to regularly recurring stress. *Circulation*. 1983; 68: 470–476.
- Vensel LA, Devereux RB, Pickering TG, et al. Cardiac anatomy and function in renovascular hypertension produced by unilateral and bilateral renal artery stenosis. *Am J Cardiol*. 1986; 58: 575–582.
- Ambia AM, Morgan JL, Wilson KL, et al. Frequency and consequences of ventricular hypertrophy in pregnant women with treated chronic hypertension. *Am J Obstet Gynecol*. 2017; 467:

- e1–6.
27. Quitete CMM, Salvany AM, Martins WA, Mesquita ET. Left ventricular remodeling and diastolic function in chronic hypertensive pregnant women. *Int J Women's cardiovascular health*. 2015; 5: 187–192.
28. Sanchez RA, Glenn JE, Marco E, et al. Two-dimensional and m-mode echocardiographic findings in hypertensive pregnant women. *Am J Obstet Gynecol*. 1986; 154: 910–913.