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Research Article

Onset of hypertension during pregnancy is associated with long-term worse blood pressure control and adverse cardiac remodeling

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Abstract

Up to 20% of women with hypertensive pregnancy disorders might persist with chronic hypertension. This study compared clinical and echocardiographic features between women whose hypertension began as hypertensive pregnancy disorders (PH group) and women whose diagnosis of hypertension did not occur during pregnancy (NPH group). Fifty PH and 100 NPH women were cross–sectionally evaluated by clinical, laboratory, and echocardiography analysis, and the groups were matched by duration of hypertension. PH exhibited lower age (46.6 ± 1.4 vs. 65.3 ± 1.1 years; $P < .001$), but higher systolic (159.8 ± 3.9 vs. 148.0 ± 2.5 mm Hg; $P = .009$) and diastolic (97.1 ± 2.4 vs. 80.9 ± 1.3 mm Hg; $P < .001$) blood pressure than NPH, although used more antihypertensive classes (3.4 ± 0.2 vs. 2.6 ± 0.1; $P < .001$). Furthermore, PH showed higher left ventricular wall thickness and increased prevalence of concentric hypertrophy than NPH after adjusting for age and blood pressure. In conclusion, this study showed that PH may exhibit worse blood pressure control and adverse left ventricular remodeling compared with NPH. J Am Soc Hypertens 2014;8(11):827–831. © 2014 American Society of Hypertension. All rights reserved.

Keywords: Echocardiography; concentric hypertrophy; hypertensive pregnancy disorders; left ventricular.

Introduction

Hypertensive pregnancy disorders, namely gestational hypertension and pre–eclampsia, occur in 5%–7% of all pregnancies and are recognized causes of maternal and fetal complications.[1] Gestational hypertension is defined as the development of hypertension after 20 weeks of gestation, while women with the same pattern of elevated blood pressure (BP) and proteinuria (>300 mg protein/24-hour urine collection) are considered to present pre–eclampsia.[2]

Epidemiologic data have shown that women with a history of pregnancy–induced hypertension are at increased risk of developing hypertension and metabolic alterations later in life in comparison with women without a history of pregnancy–induced hypertension.[3–5] However, up to 20% of women with hypertensive pregnancy disorders might persist with high BP levels after 6 weeks postpartum, thus developing chronic hypertension.[6–8] Hitherto it remains unknown whether women who developed chronic hypertension starting as hypertensive pregnancy disorders present adverse long–term cardiovascular features among hypertensive women. In this study, we enrolled a sample

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of women with chronic hypertension referred to a university hospital outpatient clinic and evaluated whether those whose hypertension began as hypertensive pregnancy disorders and persisted afterwards (PH group) exhibited clinical and echocardiographic differences in comparison with those whose diagnosis of hypertension did not occur during pregnancy (NPH group).

Methods

Study Population

Between 2005 and 2011, we evaluated a total of 638 hypertensive women who were referred to the hypertension unit of the University Hospital of the State University of Campinas, which is an outpatient clinic aimed to evaluate and treat subjects with end–organ damage and uncontrolled hypertension. All subjects were systematically asked about the onset of hypertension using questionnaires and were cross–sectionally evaluated by clinical, laboratory, and echocardiography analysis. Inclusion criteria in the study were age >18 years and no evidence of moderate or severe cardiac valve disease, hypertrophic cardiomyopathy, previous myocardial infarction, neoplastic disease, and secondary cause of hypertension. Fifty women stated that hypertension began after 20 weeks of pregnancy and persisted afterwards (PH group). Seven other women reported that hypertension onset took place before 20 weeks of pregnancy and therefore were not included in the study. Among PH women, 14 declared that hypertension began with the diagnosis of pre–eclampsia/eclampsia, 30 stated that hypertension did not begin with pre–eclampsia/eclampsia, and 6 did not know whether the onset of hypertension was associated with pre–eclampsia/eclampsia. The NPH group comprised hypertensive women who stated that hypertension onset did not occur during pregnancy or within 1 year after the delivery. Each PH woman was compared with two NPH women, and the PH and NPH groups were matched by duration of hypertension. Among NPH women, 93% stated that they had at least one pregnancy. Written informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved by the Human Research Ethics Committee of the University of Campinas.

BP was measured using a validated digital oscillometric device (Omron HEM-705CP, Omron Healthcare, Kyoto, Japan) with appropriate cuff sizes. Two readings were averaged, and, if they differed by more than 5 mm Hg, one additional measurement was performed and then averaged. Body mass index was calculated as body weight divided by height squared. Blood samples were obtained in the morning after 12 hours of fasting for analysis of cholesterol fractions, triglycerides, glucose, C-reactive protein, and creatinine levels. Albuminuria was evaluated in patients by measuring the albumin–creatinine ratio in morning urine samples. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or current antihypertensive medication use. Diabetes mellitus was diagnosed if fasting blood glucose was ≥126 mg/dL or when participants were taking hypoglycemic medications.

Echocardiography

Echocardiography studies were conducted on each subject at rest in the left lateral decubitus position using a Vivid 3 Pro (General Electric, Milwaukee, WI, USA) apparatus equipped with a 2.5–MHz transducer as previously described.[9,10] Aortic root and left atrial diameter as well as left ventricular (LV) dimensions were measured in accordance with the American Society of Echocardiography guidelines.[11] All recordings were made by the same physician, who was unaware of other data relating to the subjects. LV mass index was calculated as LV mass divided by body surface area. Body surface area was estimated by the DuBois formula. LV hypertrophy was defined with the use of cutoff point LV mass index >110 g/m^2,[12] whereas concentric geometry was considered if the relative wall thickness was ≥0.45.[13] The reproducibility of both acquiring and measuring LV mass was determined in recordings obtained from 10 subjects. Intraobserver LV mass variability was <8%.

Statistical Analysis

Data were analyzed using SPSS 15.0. Continuous normal and non–normal variables are presented as mean ± standard error and median (25th–75th percentile), respectively. The Kolmogorov–Smirnov test was used to test for normal distribution of the variables. Chi–squared test was used to compare categorical variables, whereas the unpaired *t*–test and Mann–Whitney test compared normal and non–normal continuous variables, respectively. Two–way analysis of covariance was used to assess intergroup difference in low–density lipoprotein cholesterol levels adjusted for statins use. Linear and logistic multivariate analyses were used to assess intergroup differences in echocardiographic parameters adjusted for age and diastolic blood pressure. A *P*–value <.05 was considered significant.

Results

Clinical and laboratory features of PH and NPH groups are presented in Table 1. In comparison with the NPH group, PH women exhibited lower age, but presented higher systolic and diastolic BP levels, although they used a higher number of antihypertensive classes. The PH group also exhibited higher low–density lipoprotein cholesterol levels than the NPH one, although this difference did not remain statistically significant after adjustment for statin use.

Echocardiographic features of the studied women are presented in Table 2. Unadjusted comparisons showed

Table 1
Clinical features of hypertensive women

Characteristics	PH (n = 50)	NPH (n = 100)	*P*
Age, y	46.6 ± 1.4	65.3 ± 1.1	<.001
Body mass index, kg/m^2	32.9 ± 1.2	31.8 ± 0.7	.352
Waist circumference, cm	100.4 ± 2.5	100.4 ± 1.4	.991
Duration of hypertension, y	17 (15)	15 (12)	.141
Systolic blood pressure, mm Hg	159.8 ± 3.9	148.0 ± 2.5	.009
Diastolic blood pressure, mm Hg	97.1 ± 2.4	80.9 ± 1.3	<.001
Smoking, n (%)	3 (6)	8 (8)	.658
Diabetes mellitus, n (%)	18 (36)	32 (32)	.624
Glycemia, mg/dL	98 (51)	97 (29)	.470
Triglycerides, mg/dL	135 (76)	134 (94)	.926
HDL-cholesterol, mg/dL	52.8 ± 1.8	55.6 ± 1.6	.270
LDL-cholesterol, mg/dL	126.9 ± 4.8	112.7 ± 3.9	.026*
Log C-reactive protein, mg/dL	−0.36 ± 0.06	−0.49 ± 0.05	.128
Creatinine, mg/dL	0.82 ± 0.03	0.85 ± 0.04	.541
Log urinary albumin/creatinine ratio, mg/g	1.39 ± 0.09	1.23 ± 0.06	.160
Diuretics, n (%)	43 (86)	80 (80)	.367
Beta–blockers, n (%)	28 (56)	40 (40)	.064
Calcium channel blockers, n (%)	29 (58)	44 (44)	.106
ACEI or ARB, n (%)	43 (86)	75 (75)	.121
Vasodilators, n (%)	9 (18)	5 (5)	.009
Alpha–central agonists, n (%)	16 (32)	16 (16)	.024
Number of antihypertensive classes	3.4 ± 0.2	2.6 ± 0.1	<.001
Statins, n (%)	12 (24)	37 (37)	.110

ACEI, angiotensin–converting enzyme inhibitors; ARB, angiotensin receptor blockers; HDL, high–density lipoprotein; LDL, low–density-lipoprotein; NPH, onset of chronic hypertension not at pregnancy; PH, onset of chronic hypertension at pregnancy.
* $P > .05$ adjusted for statins use.

that the PH and NPH groups presented similar echocardiographic features, except for higher LV wall thickness and relative wall thickness and increased prevalence of concentric LV geometry in the PH group. After adjusting for age and diastolic blood pressure, the PH group showed higher LV wall thickness, relative wall thickness, and LV mass index as well as increased prevalence of concentric LV geometry and concentric LV hypertrophy in comparison with the NPH group.

Discussion

Several reports have suggested that up to 20% of women who develop hypertension during pregnancy remain with chronic hypertension.[6–8] In the present report, we evaluated a sample of women with chronic hypertension and found that those whose hypertension began after 20 weeks of pregnancy and persisted afterwards (PH group) had worse BP control and adverse LV remodeling compared with those whose diagnosis of hypertension was not made during pregnancy (NPH group). These novel findings suggest that PH women might comprise a subgroup of hypertensive patients at increased cardiovascular risk, and therefore, could be potential candidates for more individualized preventive and treatment strategies.

Several findings of the present report suggest that the PH group had worse BP control than the NPH one. First, higher systolic and diastolic BP levels were detected in PH women compared with NPH ones. Second, despite the higher BP levels, the PH group used a significantly higher number of anti–hypertensive medications than the NPH group. Third, although exhibiting similar duration of hypertension, the NPH sample showed a remarkable higher age than the PH sample. Since age is considered a strong determinant of resistant and uncontrolled hypertension,[14] it would be expected that NPH rather than PH subjects presented higher BP levels.

Results of multivariate analysis adjusted for age and blood pressure revealed that PH women also exhibited higher LV relative wall thickness, LV mass index, and increased prevalence of concentric LV hypertrophy than NPH women, which are markers of adverse hypertensive LV remodeling.[15] These findings suggest that PH women may be predisposed to LV remodeling independent of variation in blood pressure. In accordance with this assumption, data from other groups showed that women with hypertensive pregnancy disorders may exhibit persistent abnormalities in LV structure independent of blood pressure levels,[7,8] which could contribute to explain the higher prevalence of adverse LV structural features seen in the PH group.

The mechanisms underlying the higher BP levels in PH women were not apparent in our study. However, some

Table 2
Echocardiographic features of hypertensive women

Features	PH (n = 50)	NPH (n = 100)	Mean Difference or Exp(B) (95% CI)		
			Unadjusted	Adjusted for Age	Adjusted for Age and DBP
Aortic root, mm	30.6 ± 0.6	31.9 ± 0.4	−1.3 (−2.7 to 0.2)	−0.7 (−2.6 to 1.1)	−1.0 (−2.9 to 0.9)
Left atrial diameter, mm	38.8 ± 0.7	39.1 ± 0.5	−0.3 (−2.1 to 1.2)	1.1 (−1.1 to 3.5)	0.8 (−1.6 to 3.1)
LV end-diastolic diameter, mm	48.0 ± 0.8	49.7 ± 0.6	−1.7 (−3.6 to 0.3)	−1.1 (−3.7 to 1.5)	−0.9 (−3.6 to 1.8)
Interventricular septum, mm	11.2 ± 0.3	10.4 ± 0.2	0.8 (0.2–1.4)*	1.4 (0.6–2.3)**	1.3 (0.5–2.2)**
Posterior wall thickness, mm	10.9 ± 0.3	10.3 ± 0.1	0.6 (0.3–1.1)*	1.2 (0.4–1.9)**	1.0 (0.3–1.7)**
Relative wall thickness, mm	0.46 ± 0.01	0.42 ± 0.01	0.04 (0.01–0.06)**	0.05 (0.02–0.09)**	0.05 (0.01–0.08)**
LV mass index, g/m^2	138 ± 7	138 ± 4	0 (−16 to 16)	25 (6–45)*	24 (4–44)*
LV ejection fraction, %	66.5 ± 0.9	67.3 ± 0.8	−0.8 (−3.2 to 2.2)	−0.4 (−3.8 to 3.0)	−0.2 (−3.6 to 3.3)
Concentric LV geometry, n (%)	25 (50)	33 (33)	2.0 (1.0–4.0)*	4.2 (1.6–11.0)**	4.3 (1.6–11.7)**
LV hypertrophy, n (%)	34 (68)	72 (72)	0.8 (0.4–1.6)	1.9 (0.7–5.1)	2.2 (0.8–6.0)
Concentric LV hypertrophy, n (%)	20 (40)	29 (29)	1.6 (0.8–3.3)	2.5 (1.0–6.5)*	2.7 (1.0–7.3)*

CI, confidence interval; DBP, diastolic blood pressure; LV, left ventricular; NPH, onset of chronic hypertension not at pregnancy; PH, onset of chronic hypertension at pregnancy.

Mean difference (95% CI) is shown for continuous variables while Exp(B) (95% CI) is shown for categorical variables. Adjusting for systolic blood pressure instead of DBP did not significantly change the results. In logistic regression analysis, age ≥60 years and DBP ≥90 mmHg were included as confounding variables.

* $P < .05$.

** $P < .01$.

potential explanations can be proposed. It can be argued that pregnancy exerted direct effects on the cardiovascular system of PH women. In this context, PH women might have not adapted adequately to pregnancy–induced hemodynamic overload, possibly due to genetic, environmental, inflammatory, and placental factors,[6,16,17] thus triggering the development of a more severe form of hypertension. On the other hand, since earlier onset of hypertension is associated with worse cardiovascular prognosis,[18] the adverse cardiac features and worse blood pressure profile seen in PH women could be a consequence of their earlier hypertension onset rather than to pregnancy–related mechanisms. Another potential explanation could be that the PH group had a higher prevalence of hypertensive risk factors. This hypothesis is based on previous data showing that the association between hypertensive pregnancy disorders and long–term development of hypertension was largely caused by shared risk factors rather than a direct influence of pregnancy on the heart or vasculature.[16] In the present study, we were unable to assess the features of the studied women before and during pregnancy, but at the time of our evaluation PH and NPH women showed similar clinical and metabolic characteristics. These results suggest that discrepancies in hypertensive risk factors may not explain the differences in BP levels between the studied groups. At last, it might be argued that PH group exhibited a higher prevalence of secondary causes of hypertension. Nevertheless, all enrolled subjects in our protocol were systematically investigated in order to discard common secondary causes of hypertension, namely renal parenchymal disease, renovascular disease, pheochromocytoma, hyperaldosteronism, and aortic coarctation, and all women in the PH group stated that BP levels were normal before pregnancy, thus turning the diagnosis of secondary hypertension less probable.

Despite the lack of a precise mechanistic explanation, we believe that the worse BP control and adverse LV remodeling among PH women may be clinically relevant. Previous reports have consistently shown that increased BP levels and concentric hypertrophy are independent predictors of cardiovascular events in hypertensive subjects.[15,19,20] Therefore, the results of our study may serve to identify a subgroup of hypertensive patients who might be at increased cardiovascular risk and therefore should be managed more closely.

Some limitations of this study should be acknowledged. First, all patients were enrolled from an outpatient clinic of a tertiary university hospital, which is a reference unit for subjects with complicated hypertension. Thus, the results cannot yet be applied to all hypertensive patients, and further studies in other hypertensive populations are necessary to confirm the present results. Second, the NPH group exhibited a significantly higher age than the PH group, which could be a confounding factor in the analysis. Third, the classification of women as PH and NPH was based on information gathered from questionnaires and not from medical records, which might limit the accuracy of such categorization.

Conclusions

In summary, this report showed that PH women may exhibit long–term worse BP control and adverse LV remodeling compared with NPH women. These findings

support the need for studies to evaluate the long–term cardiovascular outcome of hypertensive women whose onset of hypertension was during pregnancy.

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