Original Paper

History of Gestational Hypertension Is Associated With the Metabolic Syndrome and Masked Hypertension But Not Arterial Stiffness in Women With Essential Hypertension

Azra Mahmud, MD, PhD; Mehnaz Jatoi, MD; Yei Roi Chee, MD; John Feely, MD

The underlying mechanisms of subsequent increased risk of cardiovascular disease with a history of gestational hypertension (GH) are not known. Untreated hypertensive women (n=155, age 43±1 years) underwent ambulatory blood pressure (BP) monitoring and assessment of aortic pulse wave velocity (PWV) and augmentation index (AIx). Despite identical clinic BP readings, the group of women with GH (n=54) had higher (P=.002) ambulatory daytime systolic BP levels and a greater number of extreme nocturnal dippers (P=.005) than the group without GH. Women with GH had higher body mass index (P=.003), greater waist circumference (P=.02), higher levels of triglycerides (P=.002), lower levels of high-density lipoprotein cholesterol (P=.004), a higher prevalence of the metabolic syndrome (P<.05) and microalbuminuria (P=.004), higher plasma renin activity (P=.03), and higher aldosterone levels (P=.01). There was no significant difference in PWV and AIx between the 2 groups. The higher prevalence of the metabolic syndrome, microalbuminuria, masked hypertension, and activation of the renin-angiotensin-aldosterone system but not arterial stiffness may explain the subsequent propensity to high BP and cardiovascular disease in women with GH. (J Clin Hypertens (Greenwich). 2008;10:21–26) ©2008 Le Jacq

From the Department of Pharmacology and Therapeutics, Trinity College, Dublin, Ireland; and Hypertension Clinic, St James's Hospital, Dublin, Ireland
Address for correspondence:
Azra Mahmud, MD, PhD, Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James's Hospital, Dublin 8, Ireland
E-mail: mahmuda@tcd.ie
Manuscript received June 22, 2007;
revised August 29, 2007;
accepted September 4, 2007

www.lejacq.com ID: 7400

Some 10% to 12% of all pregnancies are thought to be complicated by high blood pressure (BP).[1,2] In a cohort study of 1 million Canadian women, 7% were diagnosed with a maternal placental syndrome, gestational hypertension (GH), preeclampsia, placental abruption, or infarction.[3] Until recently, GH and preeclampsia were considered to be conditions with no long-term sequelae; however, Chesley[4] concluded that women with eclampsia in any pregnancy, but particularly in the first one, had increased numbers of cardiovascular events. More recently, confirmatory evidence showed that such women are at increased risk for the development of hypertension and other cardiovascular disorders.[3]

Despite extensive research, the etiology of GH, occurring de novo after the 20th week of pregnancy and settling within 6 weeks of delivery, with about 40% of women developing proteinuria (preeclampsia), remains elusive.[2] One theory suggests that such women are predisposed to develop gestational and essential hypertension in later life because of weight gain and insulin resistance.[2,5] Endothelial dysfunction is also implicated.[5,6] Of note in women with prior preeclampsia, endothelial dysfunction is commonly found subsequent to the pregnancy,[6,7] and mildly elevated BP levels are also seen.[6] More recently, stiffening of the larger arteries has been

noted in preeclampsia.[8,9] Whether, like endothelial dysfunction, there is increased arterial stiffness in women with a history of GH and whether this contributes to the increased predisposition to hypertension in later life is not clear. One study[10] compared 30 women with prior preeclampsia with 21 women with a history of normal pregnancy to show that both endothelium-dependent and -independent vasodilatation were attenuated in women with previous preeclampsia with no evidence of ongoing increased arterial stiffness. Unfortunately, a confounding factor in the study group was a significantly higher BP level in those with a history of preeclampsia. The aim of our study was to compare the metabolic profile and arterial stiffness in age- and BP-matched women with a history of GH to those without.

METHODS

Patient Population

We performed a cross-sectional study to compare hypertensive women (n=54) aged 42±11 years with a history of GH with an age-matched group (n=101) aged 43±8.6 years with similar clinic BP readings but no history of GH. The diagnosis of hypertension was confirmed on the basis of 3 separate clinic BP measurements (≥140/90 mm Hg) and daytime ambulatory BP ≥135/85 mm Hg. None of the women had secondary forms of hypertension, coronary heart disease, valvular heart disorders, arrhythmias, heart failure, or any other significant illnesses including renal impairment or diabetes. None were receiving antihypertensive medication, hormonal preparations, or any other vasoactive drugs. The patients gave informed consent and the study had Institutional Ethics Committee permission.

Measurements

Body weight, height, waist, and hip measurements were recorded in each patient and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the midpoint between the bottom of the rib cage and the top of the iliac crest at minimal respiration. Hip circumference was measured at the level of the widest diameter around the buttocks. The metabolic syndrome (MS) was evaluated according to the currently used Third Report of the Adult Treatment Panel (ATP III)[11] definition criteria, that is, the presence of 3 or more of the following 5 criteria: abdominal obesity (waist circumference >88 cm), elevated blood pressure level (≥135/85 mm Hg), abnormal fasting glucose level (≥6.1 mmol/L), elevated serum triglyceride level (≥1.70 mmol/L), and low high-density lipoprotein (HDL) cholesterol level (<1.29 mmol/L). Fasting venous blood samples were drawn and total cholesterol, HDL cholesterol, triglyceride, fasting glucose, and serum creatinine levels were measured by routine laboratory methods. Plasma aldosterone levels and renin activity were measured by radioimmunoassay. Early morning samples of urine were collected for the quantification of microalbuminuria and calculation of the albumin/creatinine ratio.

Hemodynamic Measurements

Participants rested in the supine position for 15 minutes in a quiet room with a temperature of 22°C, and brachial BP was then measured using an automated oscillometric device in the right arm (Omron Model HEM 705-CP; Omron Corporation, Tokyo, Japan) by a trained observer. Three BP readings were taken at 1-minute intervals, and the mean was used for data analysis. Pulse pressure was calculated as the difference between systolic and diastolic BP. Ambulatory BP was measured using oscillometric Spacelabs 90207/10 monitors (Spacelabs Inc, Issaquah, WA) to obtain BP readings at intervals of 30 minutes from 6 AM until 12 PM and intervals of 60 minutes from 12 PM to 6 AM, as previously described.[12] Dippers were defined as those individuals with a 10% to 20% fall in either systolic or diastolic nocturnal BP levels relative to daytime values. Extreme dipping was defined as a >20% fall in nocturnal BP. Nondipping was defined as a <10% nocturnal fall; those with no fall (≤0%) in BP were defined as reverse-dippers. A patient diary marking the awake and sleeping periods was used to determine the time of onset and duration of sleep.

Assessment of Arterial Stiffness

Carotid-femoral pulse wave velocity (PWV) was measured with an automatic device (Complior; Artech Medical, Pantin, France), as previously described,[13] with the foot-to-foot method. The carotid and femoral waveforms were acquired simultaneously with 2 pressure-sensitive transducers, and the transit time of the pulse was calculated by the system software. The distance between the 2 arterial sites was measured on the body using a tape measure, and PWV was calculated as the distance divided by time (m/s). At least 12 successive readings were used for analysis to cover a complete respiratory cycle. Applanation tonometry was used to continuously record the pressure waveform at the radial artery, and a validated generalized transfer function was then applied to derive the

Table I. Clinical Characteristics of the Patient Population According to History of Gestational Hypertension (N=155)

Variables	History of Gestational Hypertension		
	Yes (n=54)	No (n=101)	*P* Value
Age, y	42±11	43±8.6	.45
Body mass index, kg/m^2	31±6	28±5	.003
Waist, cm	92±15	87±13	.02
Hip, cm	107±12.5	101±13.2	.006
Smoker/nonsmoker/ex-smoker	14.8/53.7/31.4	29.7/54.4/15.8	.02
Maternal hypertension, %	46	12	.01
Alcohol intake, units/wk	7±6	10±10	.03
Total cholesterol, mmol/L	5.16±0.9	4.99±0.9	.29
Fasting glucose, mmol/L	5.07±0.5	5.03±0.5	.7
Triglycerides, mmol/L	1.61±1	1.21±1	.002
HDL cholesterol, mmol/L	1.28±0	1.44±0	.004
Patients with the metabolic syndrome, %	45	28	.03
Microalbuminuria, mg/L	31.47±42	14.17±11	.004
Albumin/creatinine ratio	2.61±2.5	1.69±1.3	.08
Patients with microalbumin/creatinine ratio >3.5 mg, %	29	11	.05
Creatinine, µmol/L	78.53±9.3	78.94±8.7	.79
Aldosterone, pmol/L	570±293	467±251	.01
Plasma renin activity, ng/mL/h	2.2±2.9	1.93±4.4	.03

Abbreviation: HDL, high-density lipoprotein. Values are mean ± SD.

corresponding aortic pressure waveform within the system software of the SphygmoCor apparatus (SphygmoCor version 8.0; AtCor Medical, West Ryde, Australia). The aortic pressure waveform was used to generate the augmentation index (AIx)—the difference between the height of the first and second systolic peaks expressed as a percentage of aortic pulse pressure. We have previously shown that the interclass correlation coefficients between the first and second measurements are 0.94 for AIx and 0.84 for PWV and the coefficient of variation for both AIx and PWV is <5%.[14]

Statistical Analysis

Data were analyzed by JMP version 5.0 (SAS for Windows; SAS Institute, Inc, Cary, NC). The differences between means were analyzed using the Wilcoxon rank sum test for continuous variables and chi-square test for categorical data. Results are expressed as mean ± SD and $P<.05$ was considered significant.

RESULTS

The clinical and hemodynamic characteristics of the patient population are summarized in Table I and Table II. Groups were well matched in terms of age and BP levels. Women with GH were significantly heavier than the control group and had a stronger maternal family history of hypertension (Table I). There was a significant difference in smoking habits between the 2 groups (Table I), with a greater number of smokers in the group of women with no history of GH, while those with a positive history were more likely to be ex-smokers.

Compared with the women with no GH history, women with a history of GH had significantly higher triglyceride levels, lower HDL cholesterol levels, and similar plasma glucose levels (Table I). According to the ATP III definition of MS,[11] 45% of the study group had features of MS, compared with 28% in the control group. Urinary excretion of microalbuminuria was higher in the study group, and the number of patients with a microalbumin/creatinine ratio >3.5 mg was significantly higher in the study group than in the controls (Table I). In addition, women with GH had higher plasma aldosterone levels and plasma renin activity than did women in the control group (Table I).

Despite having similar clinic BP readings as the controls, women with GH had higher ambulatory daytime systolic and diastolic BP levels and similar nighttime systolic and diastolic BP readings (Table II). There was no statistical difference in the number of dippers between the group with a history of GH and the control group (Table II). However, a significantly higher number of women with GH exhibited the extreme dipping pattern than did the control population (Table II). No significant difference was noted in measures of arterial stiffness; AIx, and PWV, between the 2 groups (Table II).

Table II. Hemodynamic Data of the Patient Population According to History of Pregnancy-Related Hypertension (N=155)

Variables	History of Gestational Hypertension		*P* Value
	Yes (n=54)	No (n=101)	
Clinic systolic BP, mm Hg	154.2±2.7	152.8±2.0	.51
Clinic diastolic BP, mm Hg	91.2±0.93	92.5±0.9	.31
Heart rate, bpm	71±11	72.2±12	.57
Ambulatory daytime systolic BP, mm Hg	141±15	134±13	.002
Ambulatory daytime diastolic BP, mm Hg	89±9	85±9	.008
Ambulatory nighttime systolic BP, mm Hg	123.6±17	119.3±19	.17
Ambulatory nighttime diastolic BP, mm Hg	74.4±11	73±11	.50
Nocturnal dipping, %	39	40	.42
Nocturnal extreme dipping, %	22	6	.005
Augmentation index, %	30.4±14	33.1±12	.22
Pulse wave velocity, m/sec	9.5±1	9.6±2	.59

Abbreviations: BP, blood pressure; bpm, beats per minute. Values are mean ± SD.

DISCUSSION

Emerging data from Canada,[3] Scotland,[1] and a number of other countries including Iceland, Norway, and Israel[5] indicate that women who had pregnancy-related high BP readings or preeclampsia have increased prevalence of cardiovascular disease in later life. In the Canadian Cardiovascular Health After Maternal Placental Syndromes (CHAMPS) study,[3] there is a suggestion of a graded increase in the hazard ratios of cardiovascular disease: 1.8 for GH, 2.1 for preeclampsia, 3.1 for maternal placental syndrome and poor fetal growth, and 4.4 for maternal placental syndrome and intrauterine fetal death. This marker of premature vascular disease is now established even if it occurs other than in the first pregnancy. An unanswered question, however, is whether GH causes later-life cardiovascular disease or whether the same constitutional factors associated with this disease also increase the risk of GH. Alternatively, a normal pregnancy may protect against cardiovascular disease in later life[4]; nulliparous women have been shown to be much less likely to suffer from hypertension and ischemic and degenerative cardiovascular and cerebrovascular disease.[15]

The suggestion that a widespread disorder of vascular dysfunction such as endothelial dysfunction or arterial stiffness may be implicated is attractive as both are seen in preeclampsia and are intimately involved in the pathogenesis of hypertension and cardiovascular disease.[5,6] However, our data show that in age- and BP-matched groups, there was no evidence of increased arterial stiffness in women who had a history of GH. On the other hand, despite similar clinic BP readings, women in the study group had higher daytime systolic and diastolic BP levels, with similar nighttime BP readings as the controls. Interestingly, although there was no difference in the number of dippers between the 2 groups, there was a significantly higher number of extreme dippers (nocturnal reduction of ≥20% of daytime systolic BP level) in the group with a history of GH. Kario and coworkers[16] suggested that extreme dippers are at increased risk for cerebrovascular events and silent cerebrovascular damage. This may imply that women with a history of GH and extreme dipping may be at higher risk for developing cerebrovascular events in the future as compared with the controls.

There is increasing evidence linking similar risk factors for GH, essential hypertension, and cardiovascular disease. Obesity, insulin resistance, endothelial dysfunction, and prior hypertension are risk factors for the development of preeclampsia, as is dyslipidemia.[3,7] In favor of shared risk factors, we found that women with pregnancy-related hypertension/preeclampsia were more likely than those in the control group to have higher BMIs, greater waist circumference, lower HDL cholesterol levels, and higher triglyceride levels, resulting in a prevalence of MS some 60% greater. Forest and coworkers[17] have recently drawn attention to the early occurrence of MS after hypertension in pregnancy in a nonhypertensive population. In a longitudinal follow-up of 5889 women born in Finland in 1966, women who had either GH or preeclampsia during their first pregnancy had increased BP levels at age 31 years, along with a higher BMI, greater waist circumference, and higher levels of insulin and glucose.[18] Interestingly, women who had been born before gestational week 36/37 had a 2-fold greater risk of GH in their own first pregnancy.

It is also possible that mothers who themselves had been the offspring of preeclamptic pregnancies

are more likely to develop preeclampsia, which may be familial.[2] We found that women with a history of GH were 2 times more likely to have a strong maternal family history of hypertension (46% vs 12%; *P*=.01), which supports the theory that familial factors increase a woman's susceptibility to developing hypertension in pregnancy.

Women with a history of preeclampsia have persistent insulin resistance after pregnancy associated with increased sympathetic activity of the cardiovascular system and coronary artery disease later in life.[19] The increase in renal sympathetic activity could play an important role in mediating hypertension by stimulating the renin-angiotensin system,[20] which may be the mechanism for the increased plasma renin activity and aldosterone levels observed in the women with history of GH in the present study.

An additional finding in our study is the greater renal albumin excretion in the urine and increased prevalence of microalbuminuria. The number of patients with a microalbumin/creatinine ratio >3.5 mg/mmol was significantly higher in the study group than in the controls. Albumin excretion in urine correlates significantly to the albumin/creatinine ratio during pregnancy. This is strongly related to endothelial dysfunction[21] and may suggest that ongoing endothelial dysfunction could be a causative factor.

Because of the cross-sectional nature of the study design, while we can observe an association between clinical parameters, we cannot infer causality. Lower socioeconomic status and education level have been shown to be associated with increased incidence of cardiovascular disease and could have been confounding factors in the present study. However, alcohol intake and smoking prevalence, both more common in lower socioeconomic groups, were actually lower in women with a history of GH in the present study, suggesting that inequalities in socioeconomic factors are an unlikely mechanism. This is supported by an earlier study by Lawlor and colleagues,[22] who did not find any association between GH and either childhood or adult socioeconomic status.

CONCLUSIONS

We did not find evidence to implicate increased arterial stiffness as a mechanism of high BP in women with a history of GH. However, the increased prevalence of MS and activation of the renin-angiotensin-aldosterone system, both associated with risk of cardiovascular disease, may in part explain why such patients subsequently experience increased numbers of cardiovascular events. In addition, the finding that clinic BP measurements underestimate the extent of hypertension in these patients, revealed by ambulatory BP monitoring, a better prognosticator than clinic BP,[23] may be an additional factor. Patients with GH should therefore be considered as a group at additional cardiovascular risk.

REFERENCES

1 Smith WC, Kenicer MB, Tunstall-Pedoe H, et al. Prevalence of coronary heart disease in Scotland: Scottish heart health study. *Br Heart J*. 1990;64:295–298.
2 Walker JJ. Pre-eclampsia. *Lancet*. 2000;356:1260–1265.
3 Ray JG, Vermeulen MJ, Schull MJ, et al. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797–1803.
4 Chesley LC. Recognition of the long-term sequelae of eclampsia. *Am J Obstet Gynecol*. 2000;182:249–250.
5 Sibai B, Dekker G, Kupfeminc M. Pre-eclampsia. *Lancet*. 2005;365:785–799.
6 Agatisa PK, Ness RB, Roberts JM, et al. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. *Am J Physiol Heart Circ Physiol*. 2004;286:H1389–H1393.
7 Mangos GJ. Cardiovascular disease following preeclampsia: understanding the mechanism. *J Hypertens*. 2006;24:639–641.
8 Ronnback M, Lampinen K, Groop PH, et al. Pulse wave reflection in currently and previously preeclamptic women. *Hypertens Pregnancy*. 2005;24:171–180.
9 Elvan-Taspinar A, Franx A, Bots ML, et al. Central hemodynamics of hypertensive disorders in pregnancy. *Am J Hypertens*. 2004;17:941–946.
10 Lampinen KH, Ronnback M, Kaaja RJ, et al. Impaired vascular dilatation in women with a history of pre-eclampsia. *J Hypertens*. 2006;24:751–756.
11 National Heart, Lung and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). Bethesda, MD: National Institutes of Health; 2003. http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf. Accessed June 1, 2007.
12 Jerrard-Dunne P, Mahmud A, Feely J. Circadian blood pressure variation: relationship between dipper status and measures of arterial stiffness. *J Hypertens*. 2007;25:1233–1239.
13 Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension*. 2005;46:1118–1122.
14 Jatoi NA, Jerrard-Dunne P, Feely J, et al. The impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension*. 2007;49:981–985.
15 Wilson BJ, Watson MS, Prescott GJ, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003;326:845–849.
16 Kario K, Matsuo T, Kobayashi H, et al. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension*. 1996;27:130–135.
17 Forest JC, Girouard J, Masse J, et al. Early occurrence of metabolic syndrome after hypertension in pregnancy. *Obstet Gynecol*. 2005;105:1373–1380.
18 Pouta A, Hartikainen AL, Sovio U, et al. Manifestation

of metabolic syndrome after hypertensive pregnancy. *Hypertension*. 2004;43:825–831.
19 Kaaja RJ, Pöyhönen-Alho MK. Insulin resistance and sympathetic overactivity in women. *J Hypertens*. 2006;24:131–141.
20 Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25:932–943.
21 Stehouwer CD, Smulders YM. Microalbuminuria and risk of cardiovascular disease: analysis of potential mechanisms. *J Am Soc Nephrol*. 2006;17:2106–2111.
22 Lawlor DA, Morton SM, Nitsch D, et al. Association between childhood and adulthood socioeconomic position and pregnancy induced hypertension; results from the Aberdeen children of the 1950s cohort study. *J Epidemiol Community Health*. 2005;59:49–55.
23 Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurements in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.