OBSTETRICS

The combined association of psychosocial stress and chronic hypertension with preeclampsia

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OBJECTIVE: This study aims to evaluate perceived lifetime stress, perceived stress during pregnancy, chronic hypertension, and their joint association with preeclampsia risk.

STUDY DESIGN: This study includes 4314 women who delivered a singleton live birth at the Boston Medical Center from October 1998 through February 2008. Chronic hypertension was defined as hypertension diagnosed before pregnancy. Information regarding lifetime stress and perceived stress during pregnancy was collected by questionnaire. Preeclampsia was diagnosed by clinical criteria.

RESULTS: Lifetime stress (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.6—2.9), perceived stress during pregnancy (OR, 1.7; 95% CI, 1.3—2.2), and chronic hypertension (OR, 10.4; 95% CI, 7.5—14.4) were each associated with an increased risk of preeclampsia. Compared to normotensive pregnancy with low lifetime stress, both normotensive pregnancy with high lifetime stress (OR, 2.1; 95% CI, 1.6—2.9) and pregnancy with chronic hypertension and low lifetime stress (OR, 10.2; 95% CI, 7.0—14.9) showed an increased risk of preeclampsia, while pregnancy with high lifetime stress and chronic hypertension yielded the highest risk of preeclampsia (OR, 21.3; 95% CI, 10.2—44.3). The joint association of perceived stress during pregnancy and chronic hypertension with preeclampsia was very similar to that of the joint association of lifetime stress and chronic hypertension with preeclampsia.

CONCLUSION: This finding indicates that high psychosocial stress and chronic hypertension can act in combination to increase the risk of preeclampsia up to 20-fold. This finding underscores the importance of efforts to prevent, screen, and manage chronic hypertension, along with those to reduce psychosocial stress, particularly among women with chronic hypertension.

Key words: chronic hypertension, combined effect, preeclampsia, psychosocial stress

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Preeclampsia occurs in 5-7% of pregnancies, and is a major cause of maternal and fetal mortality and morbidity in both developed and developing countries. Onset early in pregnancy is associated with a poorer prognosis. For the fetus, preeclampsia may result in growth restriction, preterm birth, hypoxia, and death. For the mother, it may induce placental abruption with possible disseminated intravascular coagulation, end organ damage as a result of accelerated hypertension, stroke, and death.[1] Women who have preeclampsia as a multipara, have it as a recurrent event, or develop it in the second trimester have been found to be at higher risk for hypertension and diabetes later in life.[2] Worldwide, 10-15% of the half million maternal deaths that occur every year are associated with hypertensive disorders of pregnancy, mainly preeclampsia/eclampsia (PE/E).[3] In Canada, PE/E was one of the leading causes of maternal death from 1997 through 2000, directly accounting for 21% of maternal deaths.[4]

Previous studies have found that women with certain conditions, including nulliparity, a family history or self-history of preeclampsia, increased body mass index (BMI), multiple pregnancies, increased age, chronic hypertension, diabetes mellitus, renal and connective tissue diseases, work-related psychosocial strain during pregnancy, poor social status, coagulation abnormalities, and dyslipidemia are at increased risk for preeclampsia.[2,5] Of note, chronic hypertension is a well-known risk factor for preeclampsia. Its prevalence in

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pregnant women varies from 1-5%; and the rates are higher in older, obese, and black women.[6] It is estimated that 25% of women with preexisting hypertension will have PE/E during pregnancy.[7] In Thailand, pregnant women with chronic hypertension had a 19.5-fold (95% confidence interval [CI], 2.4−155.7) increased risk of preeclampsia, compared with those without chronic hypertension.[5] Previously, our study group found that chronic hypertension was associated with preeclampsia among black and white pregnant women.[8] In short, data from different studies have consistently shown that chronic hypertension is a leading risk factor of PE/E.[5-8]

In contrast, findings to date on psychosocial stress and PE/E have been inconsistent. Some studies found depression, anxiety, and other psychopathologies during pregnancy to be risk factors for adverse fetal and neonatal outcomes including preterm delivery,[9-11] fetal growth restriction,[12] and low Apgar scores.[13] In addition, the mother's anxiety during pregnancy is associated with an increased risk of asthma in the child.[14] Indeed, accumulating evidence indicates that psychiatric disorders during pregnancy are related to an increased risk of preeclampsia. One prospective study indicated that women with depression, anxiety, or both had a 3.1-fold increased risk for preeclampsia, compared to those without.[15] Another recent study by Qiu et al[16] found that a positive history of maternal mood or anxiety disorder was associated with a 2.12-fold increased risk of preeclampsia. Four further studies observed an association of preeclampsia/gestational hypertension with job stress in working women,[17-20] and another demonstrated that anxiety during early pregnancy increased the risk of preeclampsia >3-fold among 652 Finnish nulliparous women (odds ratio [OR], 3.2; 95% CI, 1.4−7.4).[15] Likewise, both depression and perceived stress during pregnancy were associated with increased rates of preeclampsia.[15,21]

Data from animal studies have indicated that in 14-day pregnant rats, chronic stress leads to increased adrenal weight and lower endothelium-derived relaxing factor release; likewise, in 20-day pregnant rats, chronic stress caused higher blood pressure, increased vasomotility and proteinuria, and lower endothelium-derived relaxing factor release.[22] The animal data also imply that mental stress during pregnancy may increase the risk of hypertension-associated disorders. In contrast with these animal findings, there was no association between work stress, anxiety, depression, or pregnancy-related anxiety early in pregnancy and the development of gestational hypertension or preeclampsia later in pregnancy among a cohort of 3679 pregnant women in Amsterdam, The Netherlands.[23] Two other prospective studies did not observe an association between depression or anxiety and hypertensive complications,[24,25] and moreover, these studies also did not find a significant association between maternal psychopathology and preeclampsia.[23-25]

To date, no study has examined the combined association of psychosocial stress and chronic hypertension with PE/E in a US urban minority population, in which both psychosocial risk factors and chronic hypertension are prevalent. The objectives of this study were to examine the individual and joint association of psychosocial stress and chronic hypertension with preeclampsia in an urban US population, and to explore whether the associations differ between black and nonblack women.

MATERIALS AND METHODS

Study population and data collection

This study is part of an ongoing National Institutes of Health−funded case-control study on preterm birth, and includes women enrolled at the Boston Medical Center (BMC) from October 1998 through February 2008. The parent study (1998 through present) is also being conducted at the BMC, a large urban hospital with a predominantly minority, inner-city patient population. Case mothers were those who delivered singleton, live births occurring at <37 weeks of gestation, and controls were defined as mothers delivering at ≥37 weeks of gestation with birthweight appropriate for gestational age as defined by the National Center for Health Statistics/Centers for Disease Control and Prevention guidelines (birthweight 2500-4000 g).[26] Pregnancies resulting in multiple births and newborns with major birth defects were excluded; a detailed description of the study population is available elsewhere.[27] For this study, we collected epidemiologic data, clinical data, and maternal venous blood samples. In addition, placenta samples were sent for histopathology based on routine indications, including preterm birth. The institutional review boards of BMC; the Massachusetts Department of Public Health; Children's Memorial Hospital in Chicago (now Ann and Robert H. Lurie Children's Hospital of Chicago); and the Bloomberg School of Public Health, Johns Hopkins University approved the study protocol, and all participants gave written informed consent.

Definition of preeclampsia and other key variables

Preeclampsia and chronic hypertension

All of the following key outcomes were defined by physician diagnosis and confirmed by a review of prenatal care records in accordance with published clinical studies.[28] Preeclampsia was defined according to the report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy,[29] as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on at least 2 occasions, and proteinuria of at least 1+ by urine dipstick testing on ≥2 occasions, >20 weeks of gestation. In the present report, the preeclampsia group also included women with eclampsia. Women with gestational hypertension, defined as elevated blood pressure occurring >20 weeks of gestation without preexisting hypertension, and not associated with proteinuria or other systemic manifestations, were excluded from the analysis. Chronic hypertension was defined as persistent hypertension that is present before conception or during the first 20 weeks of gestation.

Variables of psychological stress

We examined the following variables: women's perceived amount of general

TABLE 1
Study population characteristics

Variable	Preeclampsia	No preeclampsia	*P* value
n	424	3890	
Maternal age, y (mean ± SD)	29.3 ± 6.9	27.8 ± 6.4	< .001
Prepregnancy BMI, kg/m^2 (mean ± SD)	28.2 ± 7.1	25.6 ± 6.0	< .001
Gestational age, wk (mean ± SD)	35.3 ± 3.7	38.2 ± 3.2	< .001
Birthweight, g (mean ± SD)	2332.3 ± 898.4	3015.9 ± 743.9	< .001
Maternal age distribution, n (%)			
<20 y	41 (9.7)	453 (11.6)	< .001
20-29 y	178 (42.0)	2027 (52.1)	
30-34 y	109 (25.7)	820 (21.1)	
≥35 y	96 (22.6)	590 (15.2)	
Highest education completed, n (%)			
Primary school	28 (6.7)	245 (6.4)	.022
Middle school	83 (19.9)	1020 (26.5)	
High school	168 (40.3)	1317 (34.2)	
Some college	88 (21.1)	861 (22.4)	
≥College degree	50 (12.0)	403 (10.5)	
Marital status, n (%)			
Married	270 (63.8)	2549 (65.7)	.447
Unmarried	153 (36.2)	1332 (34.3)	
Maternal ethnicity, n (%)			
Black	259 (61.1)	1998 (51.4)	.002
White	39 (9.2)	444 (11.4)	
Hispanic	84 (19.8)	968 (24.9)	
Other	42 (9.9)	480 (12.3)	
Parity, n (%)			
0	204 (48.1)	1559 (40.1)	.001
≥1	220 (51.9)	2331 (59.9)	
Maternal smoking, n (%)			
Never	361 (85.1)	3061 (78.7)	< .001
Intermittent	34 (8.0)	264 (6.8)	
Persistent	29 (6.8)	565 (14.5)	
Passive smoking, n (%)			
No	337 (79.5)	2961 (76.1)	.121
Yes	87 (20.5)	929 (23.9)	
Maternal illicit drug use, n (%)			
No	379 (89.4)	3356 (86.3)	.074
Yes	45 (10.6)	534 (13.7)	

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TABLE 1
Study population characteristics *(continued)*

Variable	Preeclampsia	No preeclampsia	*P* value
Maternal alcohol use, n (%)			
No	415 (97.9)	3736 (96.0)	.060
Yes	9 (2.1)	154 (4.0)	
Preterm birth, n (%)			
No	167 (39.4)	2964 (76.2)	< .001
Yes	257 (60.6)	926 (23.8)	
Low birthweight delivery, n (%)			
No	208 (49.1)	2506 (64.4)	< .001
Yes	216 (50.9)	1384 (35.6)	
Chronic hypertension, n (%)			
No	318 (75.0)	3787 (97.4)	< .001
Yes	106 (25.0)	103 (2.6)	

BMI, body mass index.

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life stress, perceived stress during pregnancy, major stressful life events within 1 year prior to pregnancy, major stressful life events during pregnancy, any violence witnessed during pregnancy, father of baby involved in index pregnancy, father of baby supportiveness, family and friend supportiveness, whether pregnancy was desired, annual household income, and food supply. Information about psychological stress was collected by questionnaire. Lifetime stress and stress during pregnancy were defined, respectively, by responses to the following 2 questions: "How would you characterize the amount of stress in your life in general?" and "How would you characterize the amount of stress in your life during pregnancy?" Three options for response to these questions were provided: "not stressful," "average stressful," and "very stressful." For the analyses, "not stressful" and "average stressful" were considered to be low stress, and "very stressful" was regarded as high stress; missing data indicate that the pregnant woman was not employed.

Statistical analysis

All analyses were conducted using software (SAS, version 8.0; SAS Institute Inc, Cary, NC). First, the sociodemographic and clinical variables were described, stratified by nonpreeclampsia and preeclampsia. The continuous and categorical variables were analyzed by *t* test and χ^2 test, respectively. Second, the distributions of variables related to psychological stress were presented, stratified by the nonpreeclampsia and preeclampsia groups. Third, the separate association of life stress, pregnancy stress, and either life or pregnancy stress combined with chronic hypertension relative to the risk of preeclampsia was analyzed before and after the adjustment of covariates using logistic regression models. Finally, the adjusted joint effects of life stress, pregnancy stress, and chronic hypertension on the risk of preeclampsia were evaluated for the entire study samples as well as for the population subgroups (black and nonblack mothers) using logistic regression models.

In the logistic regression models, the following covariates were included: marital status, maternal ethnicity, maternal education level, maternal active and passive smoking during pregnancy, maternal age, prepregnancy BMI, parity, drug use, and alcohol use.

RESULTS

Altogether, 4314 mothers were included in the final analysis, including 3890 mothers without preeclampsia and 424 mothers with preeclampsia. The prevalence of preeclampsia was 9.9% in the study population. Table 1 shows the demographic and clinical characteristics of the study sample. As compared to those without preeclampsia, mothers with preeclampsia were older, had higher prepregnancy BMI, and had delivered babies with lower gestational age and/or lower birthweight (all $P < .001$). Mothers with preeclampsia were more likely to be black and primiparous, have a lower prevalence of active smoking, a higher prevalence of chronic hypertension, and a different distribution for education status than mothers without preeclampsia (all $P < .01$). Marital status and prevalence of passive smoking, illicit drug use, and alcohol drinking during pregnancy were similar between the 2 groups (all $P > .05$).

Table 2 presents the distribution of stress-related variables in the 2 groups. Women with preeclampsia had higher perceived levels of general stress in their lives, and higher perceived stress during pregnancy. They also had higher job-related stress during the first and second trimester compared to those without preeclampsia, and experienced more major stressful events within 1 year prior to pregnancy. The distributions of the other stress variables were similar in the 2 groups.

The associations of chronic hypertension, life stress, pregnancy stress, and either general life stress or pregnancy stress with the risk of preeclampsia were evaluated for the entire study population (Table 3). After adjusting for potential confounding variables, the risk of preeclampsia was increased by life stress (OR, 2.1; 95% CI, 1.6−2.9; $P < .0001$), stress during pregnancy (OR, 1.7; 95% CI, 1.3−2.2; $P < .0001$), and chronic hypertension (OR, 10.4; 95% CI, 7.5−14.4; $P < .0001$). Additionally, having either general life stress or pregnancy stress also increased the risk of preeclampsia (OR, 1.7; 95% CI, 1.3−2.1; $P < .0001$). Meanwhile, in the subanalyses based on maternal ethnicity (Appendix; Supplemental Table 1), the strength of the association between chronic hypertension, life stress, pregnancy stress, and either general life stress or pregnancy stress with the risk of preeclampsia among black mothers and nonblack mothers was highly similar to that of the entire study sample.

Table 4 and Supplemental Table 2 present the joint association between stress and chronic hypertension in the entire study population, and in the black and nonblack subgroups. Mothers with both chronic hypertension and high stress had a high risk of preeclampsia. Normotensive mothers with high life stress, and chronic hypertensive mothers with either low or high life stress, had an increased risk of preeclampsia as compared with normotensive mothers with low life stress. Notably, the combination of high life stress and chronic hypertension yielded the highest risk of preeclampsia (OR, 21.3; 95% CI, 10.2−44.3; $P < .0001$). Hypertensive mothers with both life stress and pregnancy stress also had a markedly high increased risk of preeclampsia (OR, 21.5; 95% CI, 9.6−48.0; $P < .0001$). The joint effect of stress during pregnancy with chronic hypertension or having either general life stress or pregnancy stress with chronic hypertension on preeclampsia was very similar (Table 4). The mothers with chronic hypertension and high stress during pregnancy had 18.5-fold (95% CI, 10.0−34.4) increased risk of preeclampsia, compared with normotensive mothers with low stress during pregnancy. Additionally, the joint effects of psychological stress and chronic hypertension on preeclampsia were also observed among black mothers and nonblack mothers, respectively, though there was no association of chronic hypertension and stress during pregnancy on preeclampsia among black mothers (Appendix; Supplemental Table 2).

TABLE 2
Stress-related variables in study population

Variable	Level	Preeclampsia, n (%)	No preeclampsia, n (%)	*P* value
n		424	3890	
Life stress[a]	Low	345 (81.4)	3460 (88.9)	< .001
	High	79 (18.6)	430 (11.1)	
Pregnancy stress[b]	Low	310 (73.1)	3126 (80.4)	< .001
	High	114 (26.9)	764 (19.6)	
Job stress during first and second trimester	Low	2925 (75.2)	295 (69.6)	.009
	High	816 (21.0)	116 (27.4)	
	Missing	149 (3.8)	13 (3.1)	
Job stress during third trimester	Low	3190 (82.0)	338 (79.7)	.507
	High	533 (13.7)	65 (15.3)	
	Missing	167 (4.3)	21 (5.0)	
Event within 1 y[c]	No	349 (82.3)	3381 (86.9)	.009
	Yes	75 (17.7)	509 (13.1)	
Event during pregnancy[d]	No	325 (76.7)	3026 (77.8)	.593
	Yes	99 (23.3)	864 (22.2)	
Violence[e]	No	410 (96.7)	3695 (95.0)	.119
	Yes	14 (3.3)	195 (5.0)	
Father involved[f]	Low	101 (23.8)	976 (25.1)	.566
	High	323 (76.2)	2914 (74.9)	
Father supportive[g]	Low	96 (22.6)	967 (24.9)	.314
	High	328 (77.4)	2923 (75.1)	
Family supportive[h]	Low	27 (6.4)	349 (9.0)	.071
	High	397 (93.6)	3541 (91.0)	
Planned pregnancy[i]	Yes	227 (53.5)	2059 (52.9)	.812
	No	197 (46.5)	1831 (47.1)	
Annual household income	<$15,000	132 (42.0)	1216 (43.9)	.308
	$15,000-29,999	75 (23.9)	726 (26.2)	
	≥$30,000	107 (34.1)	831 (30.0)	
Food supply	Sufficient	386 (91.0)	3557 (91.4)	.779
	Insufficient	38 (9.0)	333 (8.6)	

[a] Amount of stress in mother's life in general; [b] Amount of stress in mother's life during pregnancy; [c] Major stressful events within 1 y prior to pregnancy; [d] Major stressful events during pregnancy; [e] Any violence witnessed during pregnancy; [f] Father of baby involved in index pregnancy; [g] Support from father of baby; [h] Support from family and friends; [i] Mother wanted to become pregnant at this time.

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COMMENT

This study found that perceived general lifetime stress, stress during pregnancy, and chronic hypertension were associated

TABLE 3
Adjusted associations of chronic hypertension and stress with risk of preeclampsia

Variable	Preeclampsia, n (%)	No preeclampsia, n (%)	OR (95% CI)	*P* value
Life stress				
Low	345 (9.1)	3460 (90.9)	1.0	—
High	79 (15.5)	430 (84.5)	2.1 (1.6–2.9)	< .0001
Pregnancy stress				
Low	310 (9)	3126 (91)	1.0	—
High	114 (13)	764 (87)	1.7 (1.3–2.2)	< .0001
Either life or pregnancy stress				
Low	301 (8.9)	3063 (91.1)	1.0	—
High	123 (12.9)	827 (87.1)	1.7 (1.3–2.1)	< .0001
Chronic hypertension				
No	318 (7.7)	3787 (92.3)	1.0	—
Yes	106 (50.7)	103 (49.3)	10.4 (7.5–14.4)	< .0001

Covariates included marital status, maternal ethnicity and education level, maternal active and passive smoking during pregnancy, maternal age, prepregnancy body mass index, parity, drug use, and alcohol use. Additionally, chronic hypertension was included as covariate when associations of life stress, pregnancy stress, and either one with preeclampsia were analyzed; life stress and pregnancy stress were included as covariates when associations of chronic hypertension with preeclampsia were analyzed.

CI, confidence interval; *OR*, odds ratio.

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with an increased risk of preeclampsia. A critical finding was that chronic hypertension, in combination with high stress before or during pregnancy, was associated with a dramatically increased risk of preeclampsia. Compared with normotensive women with low life stress and low stress during pregnancy, the adjusted OR of hypertensive mothers with high life stress or high stress during pregnancy reached up to 21.3 and 18.5, respectively. Furthermore, in the subanalyses of black mothers and nonblack mothers, the joint association of chronic hypertension and perceived stress on the risk of preeclampsia was basically consistent with that of the entire study sample.

Chronic hypertension is a relatively common and increasingly prevalent comorbidity of pregnancy. Recent US data have shown that the age-adjusted prevalence of all-cause chronic hypertension increased significantly throughout the seven 2-year intervals, from 1.01% in 1995 through 1996 to 1.76% in 2007 through 2008.[30] Our results revealed that chronic hypertension is associated with an elevated risk of preeclampsia (OR, 10.4; 95% CI, 7.5–14.4), a finding that is consistent with the results of other investigators.[5,31] Whereas the OR of chronic hypertension relative to the development of preeclampsia from different studies have varied from 2.21-19.5,[5,30,31] all human epidemiological studies have consistently shown that chronic hypertension increases the risk of preeclampsia.[5,30,31] Moreover, separate analyses of black and nonblack mothers showed results similar to those from the entire study population, which indicates that the association of chronic hypertension with preeclampsia was very stable. As well, the present data infer that controlling blood pressure can decrease the risk of preeclampsia among pregnant women with chronic hypertension.

Thus far, our understanding of whether psychological stress is related to an increased risk for preeclampsia is quite limited. It has been hypothesized that preeclampsia is, in part, a stress-related disease, and epidemiologic studies have shown that the relative risk for preeclampsia increases in relation to the number of stressful situations experienced.[32] Our findings suggest that psychological stress, in general or during pregnancy, is moderately associated with an increased risk of preeclampsia—findings that are similar to those of previous studies.[15,16,31] For example, a prospective cohort study found that anxiety in early pregnancy was associated with a 3.2-fold increased risk for subsequent preeclampsia among mothers in the Helsinki, Finland, metropolitan area.[15] Another study found that a history of maternal mood or anxiety disorder was associated with a 2.12-fold increased risk of preeclampsia.[16] Stressful work or home environments were also found to be associated with an increased risk of preeclampsia,[31] and pregnant women with worsening or severe preeclampsia/severe gestational hypertension were found to have higher psychological stress than those with mild preeclampsia/mild gestational hypertension.[33] Conversely, in a study conducted in Amsterdam, The Netherlands, there was no significant association between work stress, anxiety, depression, or early pregnancy-related anxiety and the development of gestational hypertension or preeclampsia later in pregnancy.[23] Similarly, 2 other prospective studies did not find an association between depression or anxiety and hypertensive complications of pregnancy.[24,25] A further case-control study conducted in Canada also found no association between job stress and preeclampsia.[34]

Known neuropsychoimmunological mechanisms may begin to account for a causal relationship between stress and preeclampsia. Psychological stress activates the hypothalamus-pituitary–adrenal (HPA) axis, which in turn increases blood levels of corticosteroids and catecholamines, hormones that are produced in the adrenal glands in the case of psychological or physiological stress. Stress also activates the sympathetic nervous system and has been found to influence immune system function.[35,36] In accordance with these findings, increased blood levels of corticotropin-releasing hormone and increased sympathetic activity have

been observed in women with preeclampsia.[37]

Our most compelling finding was that the combination of stress and chronic hypertension was associated with a 20-fold increase in the risk of preeclampsia among our study population. The hypertensive mother with either high general life stress and pregnancy stress or the combination of both had up to a 50.0-fold (95% CI, 13.4–187.0) increased risk of preeclampsia. Importantly, the findings from the entire study sample were confirmed by analyses performed on individual population subgroups.

This is the first study to examine the combined effects of psychological stress and chronic hypertension on the incidence of preeclampsia. With that stated, there is mounting evidence that chronic hypertension and psychological stress are individually associated with an increased risk of preeclampsia—almost all previous studies suggest that chronic hypertension is positively related to the risk of preeclampsia. There are plausible mechanisms by which the synergistic influences of psychological stress and chronic hypertension could contribute to the development of preeclampsia. For example, psychological stress can lead to sympathetic overactivity in the HPA-axis, and the resulting increase in sympathetic activity may contribute to vasoconstriction, the key abnormality in preeclampsia. Understanding the effects of stress during human pregnancy is complicated by the development of the placenta as a significant endocrine organ that may be highly "stress-sensitive."[38,39] All HPA-axis peptides increase during human gestation, but the dramatic elevations of placental corticotropin-releasing hormone in maternal plasma during pregnancy reach levels observed only in the hypothalamic portal system during physiological stress.[40] Stress is also indicated in the pathogenesis of chronic hypertension.[41]

Pregnant black women have a greater risk of preeclampsia and chronic hypertension, particularly Americans of West African origin.[42] The high prevalence of chronic hypertension in blacks can be partly explained by the individual social and racial status of living in the United States; such psychosocial stress may evoke neuroendocrine responses favoring an increase in arterial pressure.[43] Moreover, depression and anxiety during pregnancy could prove harmful through the altered excretion of vasoactive hormones or other neuroendocrine transmitters,[44-47] which in turn may increase the risk for hypertension.

Relative to the sympathetic nervous system, Schobel et al[48] observed a greater increase in activity in pregnant women with preeclampsia than in normotensive pregnant and nonpregnant women. Because sympathetic nervous system activity has been found to revert to normal in some pregnant women with preeclampsia, it has been hypothesized that preeclampsia is a state of increased sympathetic activity. As well, stress can exert its effects on individuals via an increase in sympathetic vasoconstrictor activity. For example, women experiencing high levels of stress during pregnancy have increased circulating levels of proinflammatory cytokines relative to women who do not report high levels of prenatal stress.[49] This is a potentially critical observation, since increased levels of proinflammatory cytokines and decreased amounts of antiinflammatory cytokines have been associated with the occurrence of preeclampsia.[50] Moreover, an increase in proinflammatory cytokines

TABLE 4
Joint associations of stress vs chronic hypertension with risk of preeclampsia

Variable			Preeclampsia, n (%)	No preeclampsia, n (%)	OR (95% CI)	*P* value
Hypertension						
Life stress						
	No	Low	262 (7.2)	3370 (92.8)	1.0	—
		High	56 (11.8)	417 (88.2)	2.1 (1.6–2.9)	< .0001
	Yes	Low	83 (48.0)	90 (52.0)	10.4 (7.3–14.9)	< .0001
		High	23 (63.9)	13 (36.1)	21.3 (10.2–44.3)	< .0001
Stress during pregnancy						
	No	Low	235 (7.2)	3044 (92.8)	1.0	—
		High	83 (10.0)	743 (90.0)	1.7 (1.3–2.2)	< .0001
	Yes	Low	75 (47.8)	82 (52.2)	10.2 (7.0–14.9)	< .0001
		High	31 (59.6)	21 (40.4)	18.5 (10.0–34.4)	< .0001
Any one of life and pregnancy stress						
	No	Low	230 (7.2)	2983 (92.8)	1.0	—
		High	88 (9.9)	804 (90.1)	1.6 (1.3–2.2)	< .0001
	Yes	Low	71 (47.0)	80 (53.0)	10.0 (6.8–14.6)	< .0001
		High	35 (60.3)	23 (39.7)	18.8 (10.4–33.7)	< .0001
Both life and pregnancy stress						
	No	Low	230 (7.2)	2983 (92.8)	1.0	—
		High	51 (12.5)	356 (87.5)	2.3 (1.7–3.3)	< .0001
	Yes	Low	71 (47.0)	80 (53.0)	10.0 (6.8–14.6)	< .0001
		High	19 (63.3)	11 (36.7)	21.5 (9.6–48.0)	< .0001

Covariates included marital status, maternal ethnicity and education level, maternal active and passive smoking during pregnancy, maternal age, prepregnancy body mass index, parity, drug use, and alcohol use.

CI, confidence interval; *OR*, odds ratio.

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is associated with the general occurrence of hypertension in human beings.[51] Hence, psychological stress combined with chronic hypertension via the inflammatory cytokine pathway may also drive the occurrence of preeclampsia during pregnancy. Our study reveals a synergistic effect between perceived stress and chronic hypertension, resulting in a strongly increased risk of preeclampsia. These key data can be harnessed to inform clinical practice. Currently, prevention of preeclampsia focuses primarily on lowering blood pressure, and does not generally address the reduction of psychological stress. We suggest that efforts to control stress during pregnancy could decrease the risk of preeclampsia.

Our study has the following limitations. First, levels of general life stress and pregnancy stress were recalled by the mothers in our study after delivery and could be subject to recall bias. Second, both the duration and period of psychological stress may have different effects on preeclampsia; however, information about both the duration and period of psychological stress were not obtained in this study; thus, we could not further explore the effects of different degrees of psychological stress on preeclampsia during different pregnancy trimesters. Third, other psychological disorders (eg, neurosis), which were not identified in our study, might distort the joint association of psychological stress and chronic hypertension with preeclampsia. Fourth, while each type of psychological stress was determined by only a single question in the questionnaire, it is possible that this may better reflect stress than more comprehensive measures of stress load (eg, life event scales). Moreover, it is possible that a single question may make interpretation of the results more distinct than a conglomerate of combined items and questions. Our question on stress has been used in several previous studies and was found to be related to an indicated increased risk for dementia,[52] hypertension,[53] cancer,[54] and psychosomatic diseases.[55]

In summary, we studied an urban, predominantly minority population and found that high perceived stress and chronic hypertension interact synergistically to increase the risk of preeclampsia up to 40-fold. Given the high prevalence of these risk factors in the general population, we propose that an obvious reduction in the incidence of preeclampsia might be gained through effective control of maternal stress and hypertension, both prepregnancy and throughout the gestational period. While further research to validate the efficacy of such interventions is needed, this research holds great promise and tremendous potential to yield substantial human and economic benefits. ■

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REFERENCES

1. Curtin WM, Weinstein L. A review of HELLP syndrome. J Perinatol 1999;19:138-43.
2. Ness RB, Roberts JM. Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications. Am J Obstet Gynecol 1996;175:1365-70.
3. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066-74.
4. Health Canada. Special report on maternal mortality and severe morbidity in Canada enhanced surveillance: the path to prevention. Ottawa, Ontario (Canada): Minister of Public Works and Government Services; 2004.
5. Luealon P, Phupong V. Risk factors of preeclampsia in Thai women. J Med Assoc Thai 2010;93:661-6.
6. Sibai BM. Treatment of hypertension in pregnant women. N Engl J Med 1996;335:257-65.
7. Sibai BM, Lindheimer M, Hauth J, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension: National Institute of Child Health and Human Development network of maternal-fetal medicine units. N Engl J Med 1998;339:667-71.
8. Wang L, Feng Y, Zhang Y, et al. Prolylcarboxypeptidase gene, chronic hypertension, and risk of preeclampsia. Am J Obstet Gynecol 2006;195:162-71.
9. Orr ST, Reiter JP, Blazer DG, James SA. Maternal prenatal pregnancy-related anxiety and spontaneous preterm birth in Baltimore, Maryland. Psychosom Med 2007;69:566-70.
10. Catov JM, Abatemarco DJ, Markovic N, Roberts JM. Anxiety and optimism associated with gestational age at birth and fetal growth. Matern Child Health J 2010;14:758-64.
11. Orr ST, James SA, Blackmore Prince C. Maternal prenatal depressive symptoms and spontaneous preterm births among African-American women in Baltimore, Maryland. Am J Epidemiol 2002;156:797-802.
12. Hoffman S, Hatch MC. Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. Health Psychol 2000;19:535-43.
13. Berle JO, Mykletun A, Daltveit AK, Rasmussen S, Holsten F, Dahl AA. Neonatal outcomes in offspring of women with anxiety and depression during pregnancy: a linkage study from the Nord-Trondelag health study (HUNT) and medical birth registry of Norway. Arch Womens Ment Health 2005;8:181-9.
14. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. J Allergy Clin Immunol 2009;123. 847-53.e11.
15. Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 2000;95:487-90.
16. Qiu C, Williams MA, Calderon-Margalit R, Cripe SM, Sorensen TK. Preeclampsia risk in relation to maternal mood and anxiety disorders diagnosed before or during early pregnancy. Am J Hypertens 2009;22:397-402.
17. Klonoff-Cohen HS, Cross JL, Pieper CF. Job stress and preeclampsia. Epidemiology 1996;7:245-9.
18. Marcoux S, Berube S, Brisson C, Mondor M. Job strain and pregnancy-induced hypertension. Epidemiology 1999;10:376-82.
19. Landsbergis PA, Hatch MC. Psychosocial work stress and pregnancy-induced hypertension. Epidemiology 1996;7:346-51.
20. Wergeland E, Strand K. Working conditions and prevalence of pre-eclampsia, Norway 1989. Int J Gynaecol Obstet 1997;58:189-96.
21. Shamsi U, Hatcher J, Shamsi A, Zuberi N, Qadri Z, Saleem S. A multicenter matched case control study of risk factors for preeclampsia in healthy women in Pakistan. BMC Womens Health 2010;10:14-6.
22. Takiuti NH, Kahhale S, Zugaib M. Stress in pregnancy: a new Wistar rat model for human preeclampsia. Am J Obstet Gynecol 2002;186: 544-50.
23. Vollebregt KC, van der Wal MF, Wolf H, Vrijkotte TG, Boer K, Bonsel GJ. Is psychosocial stress in first ongoing pregnancies associated with pre-eclampsia and gestational hypertension? BJOG 2008;115:607-15.
24. Andersson L, Sundstrom-Poromaa I, Wulff M, Astrom M, Bixo M. Implications of antenatal depression and anxiety for obstetric outcome. Obstet Gynecol 2004;104:467-76.
25. Sikkema JM, Robles de Medina PG, Schaad RR, et al. Salivary cortisol levels and

anxiety are not increased in women destined to develop preeclampsia. J Psychosom Res 2001;50:45-9.
26. Hamill PV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. Am J Clin Nutr 1979;32:607-29.
27. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. JAMA 2002;287:195-202.
28. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350:672-83.
29. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. Am J Obstet Gynecol 2000;183:S1-22.
30. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol 2012;206:134.e1-8.
31. Anorlu RI, Iwuala NC, Odum CU. Risk factors for pre-eclampsia in Lagos, Nigeria. Aust N Z J Obstet Gynaecol 2005;45:278-82.
32. Takiuti NH, Kahhale S, Zugaib M. Stress-related preeclampsia: an evolutionary maladaptation in exaggerated stress during pregnancy? Med Hypotheses 2003;60:328-31.
33. Black KD. Stress, symptoms, self-monitoring confidence, well-being, and social support in the progression of preeclampsia/gestational hypertension. J Obstet Gynecol Neonatal Nurs 2007;36:419-29.
34. Haelterman E, Marcoux S, Croteau A, Dramaix M. Population-based study on occupational risk factors for preeclampsia and gestational hypertension. Scand J Work Environ Health 2007;33:304-17.
35. Mulder EJ, Robles de Medina PG, Huizink AC, Van den Bergh BR, Buitelaar JK, Visser GH. Prenatal maternal stress: effects on pregnancy and the (unborn) child. Early Hum Dev 2002;70:3-14.
36. Coussons-Read ME, Okun ML, Nettles CD. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain Behav Immun 2007;21:343-50.
37. Perkins AV, Linton EA, Eben F, Simpson J, Wolfe CD, Redman CW. Corticotrophin-releasing hormone and corticotrophin-releasing hormone binding protein in normal and pre-eclamptic human pregnancies. Br J Obstet Gynaecol 1995;102:118-22.
38. Jones SA, Brooks AN, Challis JR. Steroids modulate corticotropin-releasing hormone production in human fetal membranes and placenta. J Clin Endocrinol Metab 1989;68:825-30.
39. Petraglia F, Aguzzoli L, Florio P, et al. Maternal plasma and placental immunoreactive corticotrophin-releasing factor concentrations in infection-associated term and pre-term delivery. Placenta 1995;16:157-64.
40. Duclow DF. Perspective and therapy in Boethius's consolation of philosophy. J Med Philos 1979;4:334-43.
41. Kaplan NM. Heart disease: a textbook of cardiovascular medicine, 4th ed. Philadelphia: WB Saunders Co; 1992.
42. Wilson TW, Hollifield LR, Grim CE. Systolic blood pressure levels in black populations in sub-Sahara Africa, the West Indies, and the United States: a meta-analysis. Hypertension 1991;18(Suppl):I87-91.
43. Grim CE, Henry JP, Laragh BH, Brenner BM. Hypertension—pathophysiology, diagnosis and management, 2nd ed. New York: Raven Press; 1995.
44. Lewinsky RM, Riskin-Mashiah S. Autonomic imbalance in preeclampsia: evidence for increased sympathetic tone in response to the supine-pressor test. Obstet Gynecol 1998;91:935-9.
45. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Van Geijn HP. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. J Psychosom Res 1995;39:563-95.
46. Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Porto M, Sandman CA. Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. Psychosom Med 1996;58:432-46.
47. Sandman CA, Wadhwa PD, Chicz-DeMet A, Dunkel-Schetter C, Porto M. Maternal stress, HPA activity, and fetal/infant outcome. Ann N Y Acad Sci 1997;814:266-75.
48. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia—a state of sympathetic overactivity. N Engl J Med 1996;335:1480-5.
49. Coussons-Read ME, Okun ML, Schmitt MP, Giese S. Prenatal stress alters cytokine levels in a manner that may endanger human pregnancy. Psychosom Med 2005;67:625-31.
50. Piccinni MP, Maggi E, Romagnani S. Role of hormone-controlled T-cell cytokines in the maintenance of pregnancy. Biochem Soc Trans 2000;28:212-5.
51. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Hum Hypertens 2005;19:149-54.
52. Johansson L, Guo X, Waern M, et al. Midlife psychological stress and risk of dementia: a 35-year longitudinal population study. Brain 2010;133:2217-24.
53. Eriksson H, Svardsudd K, Larsson B, et al. Risk factors for heart failure in the general population: the study of men born in 1913. Eur Heart J 1989;10:647-56.
54. Helgesson O, Cabrera C, Lapidus L, Bengtsson C, Lissner L. Self-reported stress levels predict subsequent breast cancer in a cohort of Swedish women. Eur J Cancer Prev 2003;12:377-81.
55. Hange D, Bengtsson C, Sundh V, Bjorkelund C. The natural history of psychosomatic symptoms and their association with psychological symptoms: observations from the population study of women in Gothenburg. Eur J Gen Pract 2007;13:60-6.

Appendix

SUPPLEMENTAL TABLE 1

Adjusted associations of chronic hypertension and stress with risk of preeclampsia among black and nonblack mothers

Variable	Preeclampsia, n (%)	No preeclampsia, n (%)	OR (95% CI)	*P* value
BLACK MOTHERS				
Life stress				
Low	210 (10.7)	1761 (89.3)	1.0	—
High	49 (17.1)	237 (82.9)	2.0 (1.4–3.0)	.0003
Pregnancy stress				
Low	189 (10.7)	1583 (89.3)	1.0	—
High	70 (14.4)	415 (85.6)	1.4 (1.1–2.0)	.0297
Either life or pregnancy stress				
Low	184 (10.6)	1546 (89.4)	1.0	—
High	75 (14.2)	452 (85.8)	1.4 (1.1–2.0)	.0278
Chronic hypertension				
No	183 (8.7)	1927 (91.3)	1.0	—
Yes	76 (51.7)	71 (48.3)	11.2 (7.5–16.7)	< .0001
NONBLACK MOTHERS				
Life stress				
Low	135 (7.4)	1699 (92.6)	1.0	—
High	30 (13.5)	193 (86.5)	2.2 (1.3–3.5)	.0018
Pregnancy stress				
Low	121 (7.3)	1543 (92.7)	1.0	—
High	44 (11.2)	349 (88.8)	2.0 (1.3–3.0)	.0010
Either life or pregnancy stress				
Low	117 (7.2)	1517 (92.8)	1.0	—
High	48 (11.3)	375 (88.7)	2.0 (1.3–3.0)	.0009
Chronic hypertension				
No	135 (6.8)	1860 (93.2)	1.0	—
Yes	30 (48.4)	32 (51.6)	9.7 (5.4–17.6)	< .0001

Covariates included marital status, maternal education level, maternal active and passive smoking during pregnancy, maternal age, prepregnancy body mass index, parity, drug use, and alcohol use. Chronic hypertension was included as covariate when associations of life stress, pregnancy stress, and either one with preeclampsia were analyzed. Life stress and pregnancy stress were included as covariates when associations of chronic hypertension with preeclampsia were analyzed.

CI, confidence interval; *OR*, odds ratio.

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SUPPLEMENTAL TABLE 2

Joint associations of stress vs chronic hypertension with risk of preeclampsia among black and nonblack mothers

Variable		Preeclampsia, n (%)	No preeclampsia, n (%)	OR (95% CI)	*P* value
BLACK MOTHERS					
Hypertension					
Life stress					
No	Low	148 (8)	1699 (92)	1.0	—
	High	35 (13.3)	228 (86.7)	2.1 (1.4–3.2)	.0003
Yes	Low	62 (50.0)	62 (50.0)	11.8 (7.7–18.3)	< .0001
	High	14 (60.9)	9 (39.1)	18.0 (7.4–43.7)	< .0001
Stress during pregnancy					
No	Low	133 (8.0)	1528 (92.0)	1.0	—
	High	50 (11.1)	399 (88.9)	1.5 (1.1–2.2)	.0182
Yes	Low	56 (50.5)	55 (49.5)	12.2 (7.8–19.3)	< .0001
	High	20 (55.6)	16 (44.4)	12.9 (6.3–26.1)	< .0001
Any one of life and pregnancy stress					
No	Low	130 (8.0)	1492 (92.0)	1.0	—
	High	53 (10.9)	435 (89.1)	1.5 (1.1–2.1)	.0215
Yes	Low	54 (50.0)	54 (50.0)	12.0 (7.6–19.0)	< .0001
	High	22 (56.4)	17 (43.6)	13.6 (6.8–27.1)	< .0001
Both life and pregnancy stress					
No	Low	130 (8.0)	1492 (92.0)	1.0	—
	High	32 (14.3)	192 (85.7)	2.3 (1.5–3.5)	.0002
Yes	Low	54 (50.0)	54 (50.0)	11.9 (7.5–19.0)	< .0001
	High	12 (60.0)	8 (40.0)	16.3 (6.3–41.9)	< .0001
NONBLACK MOTHERS					
Life stress					
No	Low	114 (6.4)	1671 (93.6)	1.0	—
	High	21 (10.0)	189 (90.0)	2.1 (1.2–3.5)	.0072
Yes	Low	21 (42.9)	28 (57.1)	8.6 (4.5–16.7)	< .0001
	High	9 (69.2)	4 (30.8)	39.2 (7.8–109.3)	< .0001
Stress during pregnancy					
No	Low	102 (6.3)	1516 (93.7)	1.0	—
	High	33 (8.8)	344 (91.2)	1.8 (1.2–2.8)	.0091
Yes	Low	19 (41.3)	27 (58.7)	7.4 (3.7–14.7)	< .0001
	High	11 (68.8)	5 (31.2)	50.0 (13.4–187.0)	< .0001
Any one of life and pregnancy stress					
No	Low	100 (6.3)	1491 (93.7)	1.0	—
	High	35 (8.7)	369 (91.3)	1.8 (1.2–2.7)	.0087
Yes	Low	17 (39.5)	26 (60.5)	7.0 (3.4–14.2)	< .0001
	High	13 (68.4)	6 (31.6)	41.1 (12.6–133.7)	< .0001

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(continued)

SUPPLEMENTAL TABLE 2

Joint associations of stress vs chronic hypertension with risk of preeclampsia among black and nonblack mothers *(continued)*

Variable		Preeclampsia, n (%)	No preeclampsia, n (%)	OR (95% CI)	*P* value
Both life and pregnancy stress					
No	Low	100 (6.3)	1491 (93.7)	1.0	—
	High	19 (10.4)	164 (89.6)	2.3 (1.3—4.1)	.00429
Yes	Low	17 (39.5)	26 (60.5)	7.2 (3.5—14.7)	< .0001
	High	7 (70.0)	3 (30.0)	38.6 (8.3—179.7)	< .0001

Covariates include marital status, maternal education level, maternal active and passive smoking during pregnancy, maternal age, prepregnancy body mass index, parity, drug use, and alcohol use.

CI, confidence interval; *OR*, odds ratio.

Yu. Psychosocial stress and chronic hypertension associated with preeclampsia. Am J Obstet Gynecol 2013.