

RISK FACTORS FOR PREECLAMPSIA, ABRUPTIO PLACENTAE, AND ADVERSE NEONATAL OUTCOMES AMONG WOMEN WITH CHRONIC HYPERTENSION

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ABSTRACT

Background Women with chronic hypertension who become pregnant have an increased risk of preeclampsia and adverse neonatal outcomes. However, within this group, the risk factors for these adverse events are not known.

Methods We analyzed data on outcomes for 763 women with chronic hypertension enrolled in a multicenter trial of low-dose aspirin for the prevention of preeclampsia. Preeclampsia was defined as new-onset proteinuria (urinary protein excretion, ≥ 300 mg per 24 hours) in the 682 women without proteinuria at base line. It was defined according to strict clinical criteria in the 81 women who had proteinuria at base line. The end points were maternal and neonatal outcomes.

Results Among the 763 women, 193 (25 percent) had preeclampsia. The frequency of preeclampsia was not affected by the presence of proteinuria at base line (27 percent among women with proteinuria, vs. 25 percent among those without it), but it was greater in women who had had hypertension for at least four years (31 percent vs. 22 percent; odds ratio, 1.6; 95 percent confidence interval, 1.1 to 2.2) and in those with preeclampsia during a previous pregnancy (32 percent vs. 23 percent; odds ratio, 1.6; 95 percent confidence interval, 1.1 to 2.3). Women with proteinuria at base line were significantly more likely to deliver their babies at less than 35 weeks of gestation (36 percent vs. 16 percent; odds ratio, 3.1; 95 percent confidence interval, 1.8 to 5.3) and to have infants that were small for gestational age (23 percent vs. 10 percent; odds ratio, 2.8; 95 percent confidence interval, 1.6 to 5.0).

Conclusions In women with chronic hypertension, the presence of proteinuria early in pregnancy is associated with adverse neonatal outcomes independently of the development of preeclampsia. (N Engl J Med 1998;339:667-71.)

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FROM 1 to 5 percent of pregnant women have chronic hypertension, defined as sustained hypertension that is present before conception or during the first 20 weeks of gestation.¹ The rates are higher in older women, obese women, and black women.²⁻⁴ Chronic hypertension is associated with increased risks of preeclampsia and abruptio placentae, as well as increases in neonatal mortality and morbidity.³⁻⁷ The poor neonatal out-

come among women with chronic hypertension may be due to superimposed preeclampsia,⁴⁻⁸ but data regarding risk factors for preeclampsia and for adverse outcomes of pregnancy in women with chronic hypertension are sparse.³ We therefore examined the data on outcomes among a large number of women with chronic hypertension who were followed prospectively at 13 medical centers in the United States.⁹

METHODS

Study Group

The study group consisted of women with chronic hypertension and singleton pregnancies who were enrolled in a multicenter, randomized trial comparing low-dose aspirin with placebo for the prevention of preeclampsia.⁹ The trial was designed and carried out by members of the Network of Maternal-Fetal Medicine Units of the National Institute of Child Health and Human Development. The subjects had chronic hypertension, were pregnant with more than one fetus, had type 1 diabetes mellitus, or had had preeclampsia during a previous pregnancy. They were randomly assigned to receive aspirin or placebo after stratification according to diagnosis. In this study we evaluated the 774 women in the chronic-hypertension group whose clinical course was followed prospectively from randomization at 13 to 26 weeks of gestation (mean, 20 weeks) to the end of the pregnancy. Complete outcome data were available for 763 of these women, 381 of whom were assigned to receive aspirin and 382 to receive placebo.

Diagnostic Criteria

The diagnosis of chronic hypertension was based on a well-documented diagnosis of hypertension before pregnancy in association with antihypertensive-drug therapy either before or early in pregnancy, or sustained hypertension, defined as either systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg on at least two occasions at least four hours

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*The members of the network are listed in the Appendix.

apart before entry into the study or 20 weeks of gestation, whichever was earlier. Women with hypertension and type 1 diabetes mellitus were not assigned to this group.

At the initial visit, a personal history was obtained and demographic data were collected. Prenatal care then followed the routine schedule used for such high-risk women at each center. When the result of a dipstick test for urinary protein was at least +1 at base line, a 24-hour urine sample was collected and protein excretion was measured. The women were treated for hypertension according to the clinical practice at each center. The women were then divided into two groups, those who had proteinuria at base line (≥ 300 mg of urinary protein in 24 hours) and those who did not. At each visit, blood pressure, weight, and urinary protein excretion (assessed by dipstick) were measured. Blood pressure was measured with a sphygmomanometer, with the woman seated; the fifth Korotkoff sound was used to determine the diastolic blood pressure.

Preeclampsia was defined as new-onset proteinuria (as defined above) in women with no proteinuria at base line. In women who had proteinuria at base line, the diagnosis of preeclampsia required an elevated serum alanine aminotransferase concentration (>70 U per liter) or worsening hypertension (either two diastolic blood pressure measurements of at least 110 mm Hg four hours apart no more than one week before delivery, or one diastolic measurement of at least 110 mm Hg no more than one week before delivery if the woman had been treated with an antihypertensive drug), plus one of the following: increasing proteinuria, persistent severe headaches, or epigastric pain. Women who had thrombocytopenia (platelet count, $<100,000$ per cubic millimeter) and hemolysis (the HELLP syndrome) or who had eclampsia (defined by the development of convulsions) were considered to have preeclampsia. To ensure consistency of diagnosis, the medical records of all women suspected of having preeclampsia, worsening severe hypertension, or proteinuria were reviewed independently by three physicians, and unanimous agreement was required for the diagnosis of preeclampsia. In addition, the records of all women with suspected abruptio placentae were reviewed by two physicians. The diagnosis then was confirmed on the basis of clinical findings (vaginal bleeding and uterine tenderness) and placental examination or was rejected.

The risk factors for preeclampsia were derived from data obtained before randomization. Neonatal outcome data included gestational age, preterm birth (<37 weeks of gestation), small size for gestational age (birth weight below the 10th percentile for gestational age, according to the criteria of Brenner et al.¹⁰), admission to a neonatal intensive care unit, and neonatal complications.

Statistical Analysis

Comparisons between groups were performed with the chi-square, Wilcoxon rank-sum, or Mantel-Haenszel test. Because preeclampsia was defined differently in the women who had proteinuria at base line and those who did not, the results in the two groups were analyzed separately. Multivariate logistic-regression analysis was used to adjust for potentially confounding factors affecting adverse outcomes. All statistical tests were two-sided.

RESULTS

The base-line characteristics of the women are shown in Table 1. Eighty-one women had proteinuria at base line (Table 2). The mean (\pm SD) serum creatinine concentration at that time was significantly higher in those who had proteinuria (0.85 ± 0.26 mg per deciliter [75 ± 23 μ mol per liter], vs. 0.75 ± 0.17 mg per deciliter [66 ± 15 μ mol per liter]; $P < 0.001$ in the women without proteinuria). At randomization, 51 percent were receiving antihypertensive-drug therapy, and 102 women (13 percent) started it during the

TABLE 1. BASE-LINE CHARACTERISTICS OF PREGNANT WOMEN WITH CHRONIC HYPERTENSION.

CHARACTERISTIC	VALUE*
Maternal age — %	
<25 yr	26.8
26–30 yr	27.9
>30 yr	45.2
Primigravida — %	18.2
Smoked during pregnancy — %	16.9
Antihypertensive-drug therapy before pregnancy — %	65.5
Antihypertensive-drug therapy at randomization — %	50.9
Week of gestation at first prenatal visit	10.9 \pm 4.3
Week of gestation at time of randomization	19.9 \pm 3.8
Preeclampsia — no./total no. (%)	193/763 (25)
Abruptio placentae — no./total no. (%)	11/756 (1.5)

*Plus-minus values are means \pm SD.

TABLE 2. INCIDENCE OF PREECLAMPSIA ACCORDING TO BASE-LINE CHARACTERISTICS OF WOMEN WITH CHRONIC HYPERTENSION.

CHARACTERISTIC	PROPORTION WITH PREECLAMPSIA no./total no. (%)	OR (95% CI)*	P VALUE
Maternal age			
≥ 35 yr	51/194 (26)	1.1 (0.7–1.6)	0.69
< 35 yr	142/569 (25)	1.0	
Race			
Black	117/465 (25)	1.0 (0.7–1.3)	0.91
White†	76/298 (26)	1.0	
Previous preeclampsia			
Yes	58/181 (32)	1.6 (1.1–2.3)	0.02
No	135/582 (23)	1.0	
Duration of hypertension‡			
≥ 4 yr	94/308 (31)	1.6 (1.1–2.2)	0.007
< 4 yr	99/452 (22)	1.0	
Diastolic blood pressure			
100–110 mm Hg	18/43 (42)	2.2 (1.3–5.0)	0.01
< 100 mm Hg	175/720 (24)	1.0	
Proteinuria			
No	171/682 (25)	1.1 (0.7–1.6)	0.68
Yes	22/81 (27)	1.0	

*OR denotes odds ratio, and CI confidence interval.

†30 percent of whites were Hispanic.

‡Data were not available for three patients.

current pregnancy. The use of therapy was not standardized for women with mild hypertension (diastolic pressure, < 110 mm Hg); however, it was considered indicated for severe hypertension (diastolic pressure, ≥ 110 mm Hg). The overall incidence of preeclampsia was 25 percent, and the incidence was similar in the women in the low-dose aspirin and placebo groups (26 percent and 25 percent, respectively). The inci-

dence of preeclampsia was not affected by maternal age, race, or urinary protein excretion at base line (Table 2). However, it was significantly increased in those with a history of preeclampsia, in those who had had hypertension for at least four years, and in those whose diastolic blood pressure was 100 to 110 mm Hg early in pregnancy.

Eleven women (1.5 percent) had abruptio placentae. The frequency of abruptio was similar in the women in the low-dose aspirin and placebo groups, those with and without proteinuria at base line, those less than 35 years old and those 35 years or older, those with and without a history of preeclampsia, those who had had hypertension for at least four years and those with hypertension for less than four years, those with diastolic blood pressure of at least 100 mm Hg and those with diastolic blood pressure of less than 100 mm Hg before randomization, and white (including Hispanic) and black women (data not shown). However, the frequency of abruptio placentae was significantly higher in women with superimposed preeclampsia than in those without this condition (3 percent vs. 1 percent, $P=0.04$).

The neonatal outcomes among women with and without preeclampsia are shown in Table 3. The women with preeclampsia had a significantly higher incidence of preterm delivery, more infants admitted to neonatal intensive care units, a higher incidence of intraventricular hemorrhage, and more neonatal deaths. These differences remained significant when multivariate logistic-regression analysis was used to adjust for maternal age and race, presence or absence of preeclampsia during a previous pregnancy, duration of hypertension, and use or nonuse of antihypertensive-drug therapy.

Women with proteinuria at base line had a significantly higher incidence of preterm delivery, more small-for-gestational-age infants, more frequent admission of infants to neonatal intensive care units, and a higher incidence of intraventricular hemorrhage (Table 4). These differences remained significant when multivariate logistic-regression analysis was used to adjust for superimposed preeclampsia, maternal age and race, duration of hypertension, preeclampsia during previous pregnancy, and antihypertensive-drug therapy.

DISCUSSION

Evaluating a large number of pregnant women and using detailed diagnostic criteria to define hypertension, proteinuria, and preeclampsia, we found that the presence of preeclampsia in a previous pregnancy, hypertension lasting at least four years, and diastolic blood pressure of at least 100 mm Hg early in pregnancy were significantly associated with a higher rate of preeclampsia. These findings are consistent with those of two other studies in which the incidence of preeclampsia was found to be increased among women with diastolic blood pressure of at least 100 mm Hg early in pregnancy.^{6,7} In addition, our findings support the results of a longitudinal study that found an increased risk of superimposed preeclampsia in women with chronic hypertension and a history of preeclampsia.¹¹

We found that neither advanced maternal age (35 years or older) nor black race was a risk factor for superimposed preeclampsia, although others have reported a higher incidence of superimposed preeclampsia in black women with chronic hypertension.⁶ The rate of superimposed preeclampsia was not affected

TABLE 3. NEONATAL OUTCOME ACCORDING TO PRESENCE OR ABSENCE OF SUPERIMPOSED PREECLAMPSIA IN WOMEN WITH CHRONIC HYPERTENSION.*

OUTCOME	PREECLAMPSIA		ADJUSTED OR (95% CI)†	P VALUE
	PRESENT (N=193)	ABSENT (N=570)		
	no./total no. (%)			
Delivery				
<37 wk	109/193 (56)	145/570 (25)	3.9 (2.7–5.4)	<0.001
<35 wk	69/193 (36)	69/570 (12)	4.1 (2.7–6.0)	<0.001
Infant small for gestational age (<10th percentile)	24/186 (13)	58/552 (11)	1.3 (0.7–2.2)	0.42
Admission to NICU‡	73/183 (40)	105/549 (19)	2.9 (2.0–4.2)	<0.001
Intraventricular hemorrhage‡	5/182 (3)	5/545 (1)	4.5 (1.5–14.2)	0.003
Perinatal death	15/193 (8)	20/570 (4)	2.3 (1.1–4.8)	0.02

*OR denotes odds ratio, CI confidence interval, and NICU neonatal intensive care unit.

†The odds ratios have been adjusted for the presence or absence of proteinuria at base line.

‡Numbers are for live-born infants only.

TABLE 4. NEONATAL OUTCOME ACCORDING TO URINARY PROTEIN EXCRETION AT BASE LINE IN WOMEN WITH CHRONIC HYPERTENSION.*

OUTCOME	PROTEINURIA		ADJUSTED OR (95% CI)†	P VALUE
	PRESENT (N=81)	ABSENT (N=682)		
	no./total no. (%)			
Delivery				
<37 wk	43/81 (53)	211/682 (31)	2.7 (1.6–4.3)	<0.001
<35 wk	29/81 (36)	109/682 (16)	3.1 (1.8–5.3)	<0.001
Infant small for gestational age (<10th percentile)	18/78 (23)	64/660 (10)	2.8 (1.6–5.0)	<0.001
Admission to NICU‡	34/75 (45)	144/657 (22)	3.1 (1.9–5.2)	<0.001
Intraventricular hemorrhage‡	3/75 (4)	7/652 (1)	3.9 (1.3–11.6)§	0.01
Perinatal death	7/81 (9)	28/682 (4)	2.2 (0.9–5.2)	0.08

*OR denotes odds ratio, CI confidence interval, and NICU neonatal intensive care unit.

†The odds ratios have been adjusted for the presence or absence of preeclampsia at delivery.

‡Numbers are for live-born infants only.

§The odds ratio as adjusted for gestational age is 2.09 (0.64–6.79).

by low-dose aspirin treatment, confirming the results of previous studies.^{12,13}

The presence of proteinuria before 20 weeks of gestation in women with hypertension is consistent with the presence of known or undetected renal disease. In many of these women, renal dysfunction may be minimal, and the presence of underlying renal diseases may not be suspected until proteinuria is detected during pregnancy. With longer gestation, an exacerbation of maternal hypertension or an increase in urinary-protein excretion may signify the development of preeclampsia or may be due to exacerbation of the underlying renal disease. In this study, we used strict criteria to diagnose superimposed preeclampsia in women with proteinuria and hypertension at base line. Using these criteria, we found that the presence of proteinuria early in pregnancy in such women was not a risk factor for preeclampsia.

In pregnant women, chronic hypertension has been suggested to be a risk factor for abruptio placentae,^{4,6,7} and there is general agreement that the frequency of abruptio placentae is increased in women with hypertension and superimposed preeclampsia.^{4,7} In addition, in some studies the frequency of abruptio placentae was higher among women who had severe hypertension in the first trimester.¹⁴ In our study, the frequency of abruptio placentae was 1.5 percent, and it was significantly higher among women with superimposed preeclampsia (3 percent). However, the frequency of abruptio placentae was not affected by the duration of hypertension, the presence or absence of proteinuria at base line, the diastolic blood pressure early in pregnancy, or the use or nonuse of low-dose aspirin therapy.

The frequency of adverse neonatal outcomes was higher in women with preeclampsia than in those without this complication. Moreover, the presence of preeclampsia was associated with an increased rate of perinatal death. These findings support the results of several other longitudinal studies.^{3,4,6,7,14}

In our study, women who had proteinuria early in pregnancy had more preterm deliveries, more infants who were small for gestational age, higher rates of admission of infants to neonatal intensive care units, and worse neonatal outcomes for their infants than women without proteinuria early in pregnancy. Those adverse neonatal outcomes occurred despite the facts that the rates of superimposed preeclampsia were similar in the two groups and that none of the women with proteinuria at base line had abruptio placentae. These findings suggest that proteinuria early in pregnancy is an important risk factor for adverse neonatal outcomes among the infants of women with chronic hypertension. In this respect, studies of women with known kidney disease have revealed that severe proteinuria in early pregnancy is a major risk factor for adverse neonatal outcomes, whether or not blood pressure is controlled.^{15,16} These findings underscore the importance of preconception counseling regarding the adverse effects of proteinuria in women with hypertension.¹

In summary, we found that diastolic blood pressure of at least 100 mm Hg, hypertension of at least four years' duration, and a history of preeclampsia are risk factors for preeclampsia in women with chronic hypertension. In addition, the presence of proteinuria early in pregnancy and the development of preeclampsia in these women are associated with adverse neonatal outcomes.

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APPENDIX

The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units was established in 1986. In addition to the authors, the participants in the network were as follows: Magee-Women's Hospital, Pittsburgh: J. Harger, M. Cotroneo, and T. Kamon; University of Tennessee, Memphis: B. Mercer and R. Ramsey; University of Southern California, Los Angeles: Y. Rabello, D. McCart, and E. Mueller; University of Alabama, Birmingham: R. Goldenberg and R. Copper; Wayne State University, Detroit: G. Norman and A. Millinder; Medical College of Virginia, Richmond: J. Christmas, S. McCoy, and S. Elder; University of Cincinnati, Cincinnati: N. Elder, B. Carter, and V. Schneider; University of Oklahoma, Oklahoma City: A. Meier and V. Minton; Bowman Gray School of Medicine, Winston-Salem, N.C.: M. Swain and J. MacErnest; University of Chicago, Chicago: A. Moawad and P. Jones; Ohio State University, Columbus: J. Iams, S. Meadows, and S. Brenner; Medical University of South Carolina, Charleston: B. Collins, R. Newman, and S. Carter; Yale University School of Medicine, New Haven, Conn.: R. Romero and V. Sabo; George Washington University Biostatistics Center, Bethesda, Md.: R. Bain, E. Thom, D. Johnson, and M. Fischer; and the National Institute of Child Health and Human Development, Bethesda, Md.: C. Catz and S. Yaffe.

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