

Family History of Hypertension and Type 2 Diabetes in Relation to Preeclampsia Risk

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Abstract—In a case-control study of 190 preeclamptic patients and 373 control subjects, we assessed maternal family history of chronic hypertension and type 2 diabetes in relation to preeclampsia risk. Participants provided information on first-degree family history of the 2 conditions and other covariates during postpartum interviews. Logistic regression was used to estimate odds ratios and 95% confidence intervals adjusted for confounding by age, race, and obesity. Compared with women with no parental history of hypertension, women with maternal only (odds ratio=1.9), paternal only (odds ratio=1.8), or both maternal and paternal history of hypertension (odds ratio=2.6) had a statistically significant increased risk of preeclampsia. The odds ratio for women with at least one hypertensive parent and a hypertensive sibling was 4.7 (95% confidence interval, 1.9 to 11.6). Both maternal only (odds ratio=2.1; 95% confidence interval, 0.9 to 4.6) and paternal only (odds ratio=1.9; 95% confidence interval, 1.0 to 3.2) history of diabetes was associated with an increased risk of preeclampsia. Women with a diabetic sibling had a 4.7-fold increased risk of preeclampsia (95% confidence interval, 1.1 to 19.8). For women with at least one hypertensive parent and at least one diabetic parent, relative to those with parents with neither diagnosis, the odds ratio for preeclampsia was 3.2 (95% confidence interval, 1.6 to 6.2). Our results are consistent with the thesis that family history of hypertension and diabetes reflects genetic and behavioral factors whereby women may be predisposed to an increased preeclampsia risk. (*Hypertension*. 2003;41:408-413.)

Key Words: hypertension, chronic ■ diabetes mellitus ■ preeclampsia ■ pregnancy

Preeclampsia, one of the most common medical complications of pregnancy,¹ is the second leading cause of maternal death in the United States. Despite extensive research, the underlying cause of preeclampsia remains poorly understood, although numerous genetic, behavioral, and environmental characteristics are thought to be important risk factors of preeclampsia.^{2,3} Several recent studies offer compelling evidence supporting the notion that insulin resistance plays a role in the pathogenesis of preeclampsia.⁴⁻⁶ Furthermore, parallels between preeclampsia and the insulin resistance syndrome—a cluster of metabolic and hemostatic abnormalities strongly associated with diabetes mellitus and chronic hypertension^{7,8}—have been noted.

Several epidemiological studies indicate that a parental history of chronic hypertension is an independent risk factor for preeclampsia.⁹⁻¹³ However, few investigators have assessed the extent to which parental history of type 2 diabetes, alone or in association with chronic hypertension, is a risk factor for preeclampsia. Parental history of hypertension and type 2 diabetes, which are associated with dyslipidemia, chronic hypertension, and obesity in nonpregnant women and men,¹⁴⁻¹⁹ have

long been regarded as important risk factors of cardiovascular disorders. We used information from a case-control study to assess the extent to which parental history of chronic hypertension and type 2 diabetes are independently and jointly related with preeclampsia risk. We also completed analyses designed to evaluate the extent to which, if at all, sibling history of the 2 conditions is predictive of preeclampsia risk.

Methods

Study Design and Population

This case-control study was conducted at Swedish Medical Center and Tacoma General Hospital, Tacoma, Washington, from April 1998 through February 2001. During this study period, we identified 233 women with preeclampsia. We used the then-current American College of Obstetricians and Gynecologists (ACOG) guidelines¹ to create an operational clinical research definition for preeclampsia. These guidelines defined preeclampsia as sustained pregnancy-induced hypertension with proteinuria. Hypertension was defined as sustained blood pressure readings of $\geq 140/90$ mm Hg (with readings taking place ≥ 6 hours apart) and/or a sustained 15 mm Hg diastolic rise or a 30 mm Hg rise in systolic blood pressure above first-trimester blood pressure values. ACOG defined proteinuria as urine protein concentrations of ≥ 30 mg/dL (or 1+ on a urine dipstick) on

Received October 30, 2002; first decision December 18, 2002; revision accepted January 8, 2003.

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Hypertension is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000056996.25503.F5

≥ 2 random specimens collected ≥ 4 hours apart.¹ Nulliparity was not a criterion for diagnosis. Eighty-five percent of eligible preeclampsia cases were enrolled.

Normotensive women delivering on the same day as a case were potential control subjects. Control subjects were women with pregnancies uncomplicated by pregnancy-induced hypertension or proteinuria. We identified 772 women as eligible, and among them, 386 (50%) agreed to participate. Reasons for nonparticipation included (1) not having time to participate in the interview, (2) having no interest in the goals of the study, and (3) missed appointments. Given the low participation rate among control subjects in our study, we assessed data from Washington State computerized birth certificate files to evaluate the extent to which enrolled subjects were materially different from all women delivering at the 2 study hospitals. From this exercise, we noted that enrolled control subjects were largely similar for characteristics such as maternal race/ethnicity, marital status, gravidity, and smoking during pregnancy to members of the general population of women delivering at the 2 study hospitals. We did, however, note that enrolled control subjects tended to be slightly older and better educated than women from the larger population.

Data Collection and Assessment of Risk Factors

A structured interview questionnaire, administered during participants' postpartum hospital stay, was used to collect information on maternal sociodemographic, medical, reproductive, and lifestyle characteristics as well as family medical history. Maternal prepregnancy weight and height were also obtained by interview, and body mass index was calculated as weight (in kilograms) divided by height (in meters) squared.

Maternal history of essential hypertension was determined by response to the question: "Except during pregnancy, has your mother ever been diagnosed with chronic hypertension (high blood pressure)?" We determined maternal history of diabetes by response to the question: "Except during pregnancy, has your mother ever been diagnosed with type 2 diabetes (high blood sugar)?" Response to similar questions referring to the subject's biological father determined paternal history of chronic hypertension and type 2 diabetes. We classified subjects who reported having one or more full sibling as having a sibling history of hypertension and diabetes mellitus if they reported "yes" in response to similar questions.

Specification of Family History Patterns

We used family history of chronic hypertension and diabetes mellitus as a surrogate for hereditary factors and common environmental or behavioral exposures that may underlie preeclampsia risk. We categorized parental history of chronic hypertension as no history or any parental history. We subcategorized the latter group into maternal only, paternal only, and both maternal and paternal history of hypertension. We did the same for type 2 diabetes. Additionally, we evaluated the independent effect of parental history of chronic hypertension or type 2 diabetes by creating a "combination" variable, which allowed for the classification of study participants according to whether their parental medical history was characterized by hypertension only, type 2 diabetes only, or both conditions. Sibling history of these 2 chronic conditions was separately assessed. We also evaluated preeclampsia risk in relation to patterns of first-degree relative family history of these 2 conditions. First, we assessed risk associated with any positive family history of the disorder. Subsequently, we assessed risks after subdividing those with any positive family history into the following groups: parental history only, sibling history only, or both parental and sibling positive histories. In this study, first-degree relative refers to biological parents or biological siblings.

Statistical Analysis

From the 233 preeclampsia cases and 386 control subjects enrolled in our study, we excluded 8 subjects with preexisting diabetes mellitus (7 cases and 1 control) and 31 subjects with chronic hypertension (28 cases and 3 control subjects) from analysis. To minimize misclassification of our family medical history covariates,

we restricted the analysis to subjects who knew their biological first-degree relatives. We excluded subjects with missing or "don't know" responses to any of these 4 parental history questions (8 cases and 9 control subjects). Therefore, 190 preeclampsia cases and 373 control subjects were available for analyses of parental history in relation to preeclampsia risk. For analyses involving sibling medical history, we limited the study population to those 184 preeclampsia cases, and 359 control subjects who reported having at least one full sibling.

Using STATA version 7.0, we examined the frequency distributions of maternal sociodemographic characteristics and reproductive histories, according to case and control status. Initial univariate analyses were carried out to determine unadjusted odds ratios (ORs) and 95% CIs. Effect modification was evaluated by stratified analyses and by including appropriate interaction terms in logistic regression models. If there appeared to be no effect modification, logistic regression procedures were used to simultaneously control for confounding variables while estimating ORs and 95% CIs. Confounders were defined as those factors that altered unadjusted ORs by at least 10%. The following covariates did not appear to be confounders: maternal education, maternal marital status, smoking status, physical inactivity during pregnancy, employment during pregnancy, and prenatal vitamin use. Final logistic regression models included confounders as well as those covariates of a priori interest (ie, maternal age and parity). We included the number of siblings (expressed as a continuous variable) in models relating sibling medical histories to probands' preeclampsia risk. To estimate the OR for a parent and a sibling having a family history of diabetes (when a cell count was 0), we used LogXact statistical software to estimate the parameters of an exact logistic regression model (LogXact-4, Cytel Software Corp). All reported probability values are 2-tailed, and confidence intervals were calculated at the 95% level.

The procedures used in this study were in agreement with the protocols approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital, respectively. All participants provided written informed consent.

Results

Selected sociodemographic, medical, and lifestyle characteristics of cases and control subjects are presented in Table 1. The risk of preeclampsia was positively associated with parental history of chronic hypertension (Table 2). After adjusting for maternal age, race/ethnicity, parity, annual household income, and prepregnancy body mass index, we observed that women with any parental history of chronic hypertension, as compared with those women whose parents were normotensive, had a 2-fold increased risk of preeclampsia (OR=2.0; 95% CI, 1.3 to 3.0). Further evaluation of the pattern of preeclampsia risk in relation to parental history of chronic hypertension revealed that maternal only and paternal only history of the disorder conferred the same degree of increased preeclampsia risk. Notably, maternal and paternal history of chronic hypertension was associated with a 2.6-fold increased risk of preeclampsia (95% CI, 1.2 to 5.5).

Overall, we noted that parental history of type 2 diabetes was associated with an almost doubling in risk of preeclampsia (OR=1.8; 95% CI, 1.1 to 3.1). Again, it appeared that maternal only and paternal only history of the disorder conferred a similar degree of risk (OR=2.1 and 1.9, respectively). There were too few subjects with 2 diabetic parents to determine preeclampsia risk with any reasonable degree of precision for this population.

Next, we assessed the independent and joint contributions of parental history of chronic hypertension and type 2 diabetes to the risk of preeclampsia. Although inferences

TABLE 1. Distribution of Preeclampsia Cases and Control Subjects According to Selected Characteristics (Seattle, Washington, 1998–2001)

Characteristics	Preeclampsia Cases (n=190)		Control Subjects (n=373)	
	n	%	n	%
Maternal age, y				
≤19	7	3.7	22	5.9
20–34	138	72.6	242	64.9
≥35	45	23.7	109	29.2
≤High school education	48	25.3	75	20.1
Unmarried	52	27.4	76	20.4
Maternal race/ethnicity				
White	141	74.2	279	74.8
African American	20	10.5	30	8.0
Other	29	15.3	63	16.9
Unknown	0	0.0	1	0.3
Household income, annual \$				
<20 000	23	12.1	28	7.5
20 000–69 999	100	52.6	159	42.6
≥70 000	59	31.1	168	45.1
Unknown	8	4.2	18	4.8
Primigravid	84	44.2	135	36.2
Nulliparous	134	70.5	198	53.1
Prenatal vitamin use	186	97.9	366	98.1
Smoking during pregnancy	57	30.0	127	34.1
Physical inactivity during pregnancy	51	26.8	78	20.9
Prepregnancy body mass index*				
<20.2	13	6.8	96	25.7
20.2–21.9	30	15.8	95	25.5
22.0–24.8	38	20.0	93	24.9
>24.8	108	56.9	87	23.3
Unknown	1	0.5	2	0.5
Employed during pregnancy	164	86.3	319	85.5
Maternal history of preeclampsia	14	7.4	18	4.8

*Quartile of prepregnancy body mass index in control subjects (kg/m²).

from these analyses were hindered by our relatively small sample size, it appeared that parental history of hypertension was more strongly related with preeclampsia risk than was parental history of type 2 diabetes. Importantly, we observed that women with a positive parental history of both disorders, as compared with women whose parents were neither hypertensive nor diabetic, had a 3.2-fold increased risk of preeclampsia (95% CI, 1.6 to 6.2).

As shown in Table 3, women with at least one hypertensive sibling, when compared with those whose siblings were all normotensive, had a 2.7-fold increased risk of preeclampsia (95% CI, 1.3 to 5.8). Furthermore, a positive sibling history of type 2 diabetes was associated with an almost 5-fold increased risk of preeclampsia (OR=4.7; 95% CI, 1.1 to 19.8), though, again, inferences were limited by the relatively small sample size. In Table 4 we summarize results from analyses aimed at assessing the risk of preeclampsia in

relation to the pattern of first-degree family members' history of chronic hypertension and type 2 diabetes, respectively. The risk of preeclampsia appeared to be greatest for those women who reported having both a hypertensive parent and sibling (OR=4.7; 95% CI, 1.9 to 11.6). For women with any first-degree family history of type 2 diabetes, the risk of preeclampsia was increased 1.8-fold as compared with women with no such family history. Although based on a small number of cases and control subjects, it appeared that sibling only history of type 2 diabetes was associated with a 3-fold increased risk of preeclampsia. There were too few subjects with both a positive parental and sibling history of type 2 diabetes to assess preeclampsia risk using standard logistic regression procedures. However, using LogXact statistical software, we noted that parental and sibling history of type 2 diabetes was associated with an 8-fold increased risk of preeclampsia in probands (95% CI, 0.9 to ∞). This odds ratio was attenuated somewhat when confounding by maternal age and prepregnancy body mass index was accounted for (adjusted OR=6.0; 95% CI, 0.6 to ∞).

Discussion

Our results are consistent with the thesis that family history of hypertension and diabetes reflects genetic and behavioral factors whereby women may be predisposed to an increased risk of preeclampsia. Our observation of an association between parental history of chronic hypertension and risk of preeclampsia is consistent with several previous reports.^{9–13} For instance, Eskenazi and colleagues⁹ reported a 1.7-fold increase in risk of preeclampsia with positive parental history of chronic hypertension. In a case-control study including 152 patients with preeclampsia and 335 normotensive pregnant control subjects, Kobashi et al¹⁰ reported an odds ratio of 2.7 for parental history of chronic hypertension and risk of preeclampsia. To the best of our knowledge, we are the first to have conducted analyses to assess the separate effects of maternal and paternal history of chronic hypertension on preeclampsia risk. We noted that paternal history of chronic hypertension conferred a degree of risk similar to that of maternal history. Our findings suggest that parental history of type 2 diabetes, when occurring in conjunction with chronic hypertension, is associated with an increased risk of preeclampsia. However, parental history of type 2 diabetes in the absence of chronic hypertension does not appear to be an independent risk factor for preeclampsia. In addition, we observed an increased risk of preeclampsia in women with a positive sibling history of these 2 conditions. Additional assessments of independent or joint effects of sibling history (with or without parental history) were hindered by the limited sample size of our study. We did, however, observe that the risk of preeclampsia appeared to be greatest in women with both parental and sibling history of chronic hypertension or diabetes mellitus. We know of no previously published reports that have examined the risk of preeclampsia in relation to sibling history of these 2 medical conditions.

Several limitations must be considered when interpreting the results from our study. We cannot exclude the possibility that our results could be partially confounded by unidentified risk factors. Of particular concern was selection bias. In this

TABLE 2. Odds Ratios and 95% Confidence Intervals of Preeclampsia According to Parental History of Chronic Hypertension and Type 2 Diabetes (Seattle, Washington, 1998–2001)

Family History	Preeclampsia Cases (n=190)	Control Subjects (n=373)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Chronic hypertension				
No parental history	82	209	1.0 (referent)	1.0 (referent)
Any parental history	108	164	1.7 (1.2–2.4)	2.0 (1.3–3.0)
Mother only	47	69	1.7 (1.1–2.7)	1.9 (1.1–3.2)
Father only	41	75	1.4 (0.9–2.2)	1.8 (1.1–3.1)
Both parents	20	20	2.5 (1.3–5.0)	2.6 (1.2–5.5)
Diabetes mellitus				
No parental history	152	323	1.0 (referent)	1.0 (referent)
Any parental history	38	50	1.6 (1.0–2.6)	1.8 (1.1–3.1)
Mother only	18	16	2.4 (1.2–4.8)	2.1 (0.9–4.6)
Father only	19	30	1.3 (0.7–2.5)	1.9 (0.9–3.9)
Both parents	1	4	0.5 (0.1–4.8)	0.3 (0.1–3.4)
Combination (chronic hypertension and diabetes mellitus)				
No parental history	74	189	1.0 (referent)	1.0 (referent)
Any parental history	116	184	1.6 (1.1–2.3)	1.9 (1.3–2.9)
Hypertension only	78	134	1.5 (1.0–2.2)	1.7 (1.1–2.7)
Diabetes only	8	20	1.0 (0.4–2.4)	1.2 (0.4–3.2)
Both	30	30	2.6 (1.4–4.5)	3.2 (1.6–6.2)

*Adjusted for maternal age, parity, annual household income, race/ethnicity, and prepregnancy body mass index (quartile).

study, the participation rate for control subjects was 50% and 85% for cases. Although demographic and reproductive characteristics were largely similar for enrolled control subjects and members of the source population from which they were drawn, we cannot exclude the possibility that the observed associations are biased. However, our observation of an association between women’s parental history of chronic hypertension and preeclampsia is consistent with other published studies^{9–13} and thus suggests that the associations measured in this present study are not entirely due to bias.

Another concern relates to the likely misclassification of family history of the 2 medical conditions. We ascertained family history of hypertension and diabetes after delivery.

Thus, the pattern of associations seen in our study could result from bias if women’s reports of family history were influenced by events taking place during the labor and delivery period. However, the similarity of our observation with those of Eskenazi et al,⁹ who conducted a retrospective medical record study that was not subjected to participant recall, provides some reassurance that the results we observed are not entirely due to recall bias.

Like many family history studies, we cannot quantify the degree of genetic influence for the family history. In our study, we lacked data on the age of onset of hypertension and type 2 diabetes in first-degree relatives of preeclampsia cases and control subjects. Our inability to characterize “early” versus “late” onset hypertension and type 2 diabetes, respec-

TABLE 3. Odds Ratios (OR) and 95% Confidence Intervals of Preeclampsia According to Sibling History of Chronic Hypertension or Type 2 Diabetes (Seattle, Washington, 1998–2001)

Sibling History	Preeclampsia Cases (n=184)	Control Subjects (n=359)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Chronic hypertension				
No	165	339	1.0 (referent)	1.0 (referent)
Yes	19	20	2.0 (1.0–3.8)	2.7 (1.3–5.8)
Diabetes mellitus				
No	178	355	1.0 (referent)	1.0 (referent)
Yes	6	4	3.0 (0.8–10.7)	4.7 (1.1–19.8)

*Adjusted for maternal age, parity, annual household income, race/ethnicity, and prepregnancy body mass index (quartile) and sibling number.

TABLE 4. Odds Ratios and 95% Confidence Intervals of Preeclampsia According to First-Degree Relative History of Chronic Hypertension or Type 2 Diabetes (Seattle, Washington, 1998–2001)

First-Degree Relative History	Preeclampsia Cases (n=184)	Control Subjects (n=359)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Chronic hypertension				
No family history	80	191	1.0 (referent)	1.0 (referent)
Any family history	104	168	1.5 (1.0–2.1)	1.7 (1.2–2.6)
Parent only	85	148	1.4 (0.9–2.0)	1.6 (1.0–2.4)
Sibling only	2	7	0.7 (0.1–3.4)	0.9 (0.2–6.0)
Both	17	13	3.1 (1.5–6.7)	4.7 (1.9–11.6)
Diabetes mellitus				
No family history	145	306	1.0 (referent)	1.0 (referent)
Any family history	39	53	1.6 (0.9–2.5)	1.8 (1.1–3.1)
Parent only	33	49	1.4 (0.9–2.3)	1.6 (0.9–2.8)
Sibling only	3	4	1.6 (0.3–7.2)	3.0 (0.6–16.2)
Both	3	0	8.0 (0.9–∞)†	6.0 (0.6–∞)†

*Adjusted for maternal age, parity, annual household income, race/ethnicity, and prepregnancy body mass index (quartile) and sibling number.

†Unadjusted exact odds ratio and adjusted odds ratios (adjusted for maternal age and prepregnancy body mass index) were calculated using exact logistic regression model (LogXact).

tively, limited the specificity of our reported odds ratios. Further studies with genetic linkage methods and twin studies are needed to further quantify the genetic and nongenetic components of preeclampsia risk. Incidentally, in a twin study conducted in Sweden, Salonen and colleagues²⁰ reported that the genetic component of preeclampsia was ≈54%, with the remaining 46% attributable to nonshared environmental factors.

The findings from our study are biologically plausible for several reasons. First, epidemiological and clinical data document a close association between insulin resistance, type 2 diabetes, and hypertension.^{7,8,21–23} Furthermore, hyperinsulinemia has been shown to (1) stimulate the proliferation of vascular smooth muscle cells²⁴; (2) enhance acute asympathetic nervous system activity²⁵; and (3) modify transmembrane cation transport,²⁶ as well as renal sodium retention.²⁷ All of these alterations may contribute to blood pressure elevations.

Second, evidence from diverse settings suggests that family history of hypertension and diabetes is strongly and consistently related with biophysiological markers of vascular disorders. For instance, Pannaciuoli et al²⁸ reported that family history of type 2 diabetes was associated with increased plasma concentrations of C-reactive protein, an important biological marker of vascular disease in nonsmoking healthy adult women. Other investigators have noted alterations in the nitric oxide/cyclic-GMP pathway, in insulin sensitivity, and in glucose tolerance among individuals with a family history of hypertension or type 2 diabetes.^{29–33} These reports, when taken together with results from our study, suggest that women's family history of chronic hypertension and type 2 diabetes is an important risk factor for preeclampsia.

Perspectives

To the best of our knowledge, we are the first to have conducted analyses to assess the separate and joint effects of

maternal and paternal history of chronic hypertension on preeclampsia risk. We noted that paternal history of chronic hypertension conferred a degree of risk similar to that of maternal history. Our findings suggest that parental history of type 2 diabetes, when occurring in conjunction with chronic hypertension, is associated with an increased risk of preeclampsia. However, parental history of type 2 diabetes in the absence of chronic hypertension was not an independent risk factor for preeclampsia. In addition, we observed an increased risk of preeclampsia in women with a positive sibling history of these 2 conditions and that the risk of preeclampsia appeared to be greatest in women with both parental and sibling history of the conditions. We know of no previously published reports that have examined the risk of preeclampsia in relation to sibling history of these 2 medical conditions. Our results are consistent with the thesis that family history of hypertension and diabetes reflects genetic and behavioral factors whereby women may be predisposed to an increased risk of preeclampsia. Our data suggest that women's parental history of chronic hypertension and type 2 diabetes is an important and easy-to-acquire clinical risk marker of preeclampsia. Our results also suggest that information concerning sibling history of these conditions may be useful for identifying women at high risk of development of preeclampsia. These questions can be used as screening questions to identify pregnant women who need to be monitored more closely for the signs of preeclampsia during early pregnancy.

Acknowledgments

This research was supported by an award from the National Institutes of Health (R01 HD-34888). The authors thank Ray Miller and Kathy Ramsey for their expert technical assistance.

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Hypertension. 2003;41:408-413; originally published online February 17, 2003;

doi: 10.1161/01.HYP.0000056996.25503.F5

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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