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Preeclampsia and the Risk of Ischemic Stroke Among Young Women

Results From the Stroke Prevention in Young Women Study

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Background and Purpose—Preeclampsia is a pregnancy-specific systemic syndrome of unknown cause that affects 3% to 8% of pregnancies in the United States. Although preeclampsia is known to be an important risk factor for pregnancy-associated stroke, few data exist with regard to its association with stroke not occurring during pregnancy or the postpartum period.

Methods—Using data from the Stroke Prevention in Young Women Study (SPYW), a population-based case-control study of risk factors for ischemic stroke in women aged 15 to 44 years (recruitment period: 1992 to 1996, SPYW-1; 2001 to 2003, SPYW-2), we examined the independent association between a history of preeclampsia and the likelihood of ischemic stroke. Odds ratios (ORs) and 95% CIs were estimated using logistic regression. Cases (n=261) were women with stroke in the greater Baltimore-Washington area, and controls (n=421) were women free of a history of stroke identified by random digit dialing. Women who were pregnant at the time of stroke, those whose stroke occurred within 42 days postpartum, and nulligravida women were excluded from the analysis.

Results—The prevalence of preeclampsia among cases and controls was 15% (SPYW-1: 16%; SPYW-2: 15%) and 10% (SPYW-1: 10%; SPYW-2: 11%), respectively. Preeclampsia was associated with an increased likelihood of ischemic stroke (crude OR: 1.59; 95% CI: 1.00 to 2.52). After multivariable adjustment for age, race, education, and number of pregnancies, women with a history of preeclampsia were 60% more likely to have a nonpregnancy-related ischemic stroke than those without a history of preeclampsia (OR: 1.63; 95% CI: 1.02 to 2.62). Similar patterns were observed for women who reported symptoms of preeclampsia (elevated blood pressure and proteinuria).

Conclusion—These results suggest an association between a history of preeclampsia and ischemic stroke remote from pregnancy. If these results are confirmed in other studies, evaluation of the importance of targeting women with preeclampsia for close risk factor monitoring and control beyond the postpartum period may be warranted. (***Stroke.* 2006;37:000-000.**)

Key Words: case control studies ■ cerebrovascular accident ■ preeclampsia ■ women's health

Preeclampsia, a pregnancy-specific systemic syndrome of unknown cause, is a leading cause of maternal and perinatal mortality.[1] Also known as toxemia, preeclampsia is characterized by widespread physiological changes (ie, vasospasm, activation of the coagulation system) that result in pathologic changes (often ischemic changes) in the placenta, kidney, liver, and brain.[1] The pathogenesis of preeclampsia, which affects 3% to 8% of pregnancies in the United States,[1–3] is complex. Determined by elevated gestational blood pressure (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) accompanied by proteinuria (urinary excretion ≥0.3 g protein in a 24-hour specimen), preeclampsia tends to resolve with the removal of the placenta.[1,2] Factors associated with an increased risk of preeclampsia include black race; preexisting hypertension, diabetes, or obesity; family history of hypertension, myocardial infarction, or stroke; multifetal gestation; antiphospholipid antibody syndrome; vascular and connective tissue disease; increased testosterone; increased homocysteine concentration; family history of preeclampsia; and preeclampsia in prior pregnancies.[2,4,5–7]

Although several studies have observed an increased risk of stroke associated with preeclampsia,[3,5,8,9] few data exist with regard to associations between preeclampsia and stroke occurring after pregnancy and the postpartum period. Irgens and associates[8] and Wilson and colleagues[9] examined the risk

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of stroke associated with preeclampsia during extended periods of follow-up, but neither study excluded strokes occurring during pregnancy or the puerperium (periods associated with an increased risk of stroke).[5,10,11] Moreover, the outcome for each of these studies was all-stroke, and associations may differ among subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke. Therefore, in this study of young women aged 15 to 44 years, we present data on associations between history of preeclampsia and the likelihood of ischemic stroke occurring after pregnancy and the postpartum period.

Methods and Materials

The Stroke Prevention in Young Women Study (SPYW) is a population-based case-control study initiated to examine risk factors for ischemic stroke in young women. Study recruitment and data collection occurred in 2 waves: SPYW-1 was conducted between 1992 and1996 and SPYW-2 was conducted between 2001 and 2003. Case patients were women hospitalized with a first cerebral infarction identified by discharge surveillance from one of 59 hospitals in the greater Baltimore-Washington area and direct referral from regional neurologists. The methods for discharge surveillance, chart abstraction, case adjudication, and assignment of probable and possible underlying causes have been described elsewhere.[11–13] Control subjects were women free of a history of stroke identified by random-digit dialing and were frequency-matched to the cases by age and geographic region of residence. For SPYW-1, recruitment within 1 year of stroke was required for participation, whereas recruitment within 3 years of stroke was required for SPYW-2.

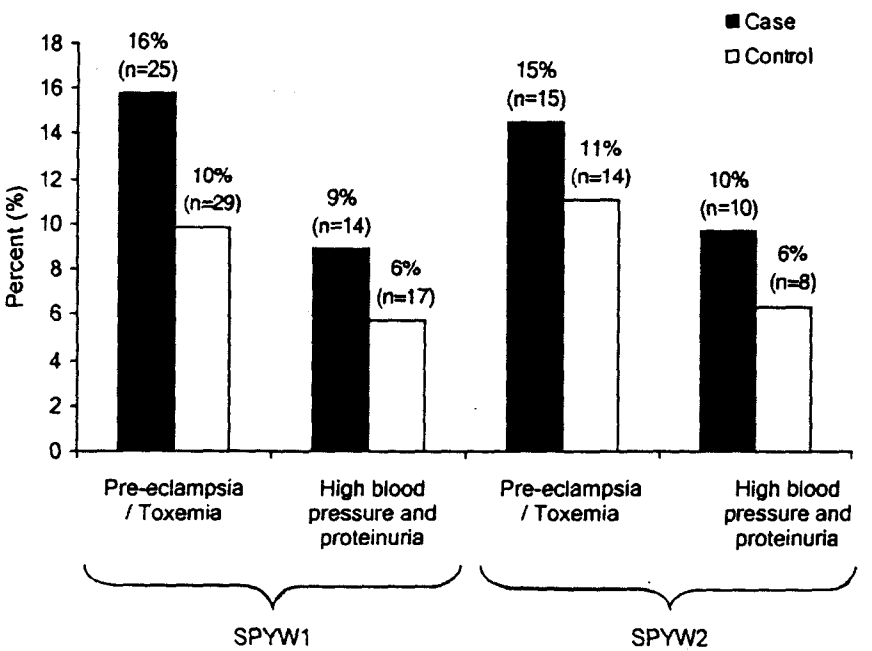
We conducted interviews with both case patients and controls to assess demographic (age, race, and educational level), medical (history of hypertension, diabetes, elevated total cholesterol, angina, and myocardial infarction [MI]), and lifestyle (smoking status) characteristics. Women were considered to have hypertension, diabetes mellitus, elevated cholesterol, angina/MI if they responded affirmatively to whether they had ever been told by a physician that she had the condition. Body mass index (BMI) was based on self-report and calculated as the weight in kilograms (kg) divided by the square of the height in meters (m^2).

As part of the interview, we asked women questions about pregnancy history up to the period before the index stroke. In particular, women were asked, "Were you ever told by a doctor that you had toxemia or preeclampsia with any pregnancy?" Women who responded affirmatively were considered to have preeclampsia. Women were also asked the following questions: (1) "Did you have elevated blood pressure with any pregnancy?" and (2) "Did you have protein in your urine with any pregnancy?" Women who responded affirmatively to both questions were considered to have a history of preeclampsia symptoms.

We restricted analyses to women aged 15 to 44 years with complete information for analysis variables. We excluded women who were pregnant at the time of stroke, those whose stroke occurred within 42 days postpartum, and nulligravida women leaving an analysis sample consisting of 261 cases and 421 controls. We completed statistical analyses using SAS v9 (SAS Institute). Distributions of demographic, medical, and lifestyle characteristics were compared using χ^2 tests. We used logistic regression to estimate the relative odds (OR) of ischemic stroke comparing women with preeclampsia to those without. Three models were fit to the data: Model A adjusted for age, race, educational attainment, and number of pregnancies; Model B adjusted for Model A variables and smoking, BMI, diabetes, elevated cholesterol, and angina/MI; and Model C adjusted for Model B variables and hypertension. Because respondent answers regarding preeclampsia were not specific to the last pregnancy before the index stroke, we repeated Model A analyses among women with only one pregnancy. Model parameter estimates were computed using maximum-likelihood techniques, and 95% CIs were based on the standard error of the model coefficients. All statistical inferences were based on a significance level of P (2-sided) ≤ 0.05.

Results

Among the 261 case patients, 15% (n=40) reported preeclampsia before the index stroke compared with 10% (n=43) of control subjects, whereas the prevalence of preeclampsia symptoms was nearly 10% (n=24) for case patients and 6% (n=25) for control subjects (Figure). Among women who reported a history of preeclampsia, 41% (n=34) also reported a history of symptoms, whereas <3% (n=15) of those without a history of preeclampsia reported symptoms. Women with a history of preeclampsia were more likely than those without to be obese (BMI ≥30; 49% versus 29%; $P \leq 0.01$) or to have a history of hypertension (46% versus



Crude prevalence of preeclampsia and symptoms of preeclampsia (high blood pressure and proteinuria) during pregnancy among cases and controls

TABLE 1. Characteristics of Women Age 15 to 44 Years With at Least 1 Pregnancy: Stroke Prevention in Young Women Study

	SPYW1			SPYW2		
	Cases (n=158)	Controls (n=295)	P	Cases (n=103)	Controls (n=126)	P
Age, y			0.944			0.151
15–19	3 (1.90)	9 (3.05)		1 (0.97)	1 (0.79)	
20–24	6 (3.80)	13 (4.41)		0 (0.00)	2 (1.59)	
25–29	13 (8.23)	26 (8.81)		5 (4.85)	12 (9.52)	
30–34	21 (13.29)	35 (11.86)		21 (20.39)	16 (12.70)	
35–39	48 (30.38)	96 (32.54)		22 (21.36)	39 (30.95)	
40–44	67 (42.41)	116 (39.32)		54 (52.43)	56 (44.44)	
Black	81 (51.27)	114 (38.64)	0.010	49 (47.57)	55 (43.65)	0.553
<High school education	19 (12.03)	34 (11.53)	0.875	12 (11.65)	8 (6.35)	0.157
Current smoker	84 (53.16)	97 (32.88)	<0.001	57 (55.34)	34 (26.98)	<0.001
Body mass index			0.138			0.647
<18	2 (1.27)	2 (0.68)		1 (0.97)	1 (0.79)	
18–<25	58 (36.71)	132 (44.75)		40 (38.83)	47 (37.30)	
25–<30	45 (28.48)	87 (29.49)		23 (22.33)	29 (23.02)	
30–<35	21 (13.29)	41 (13.90)		21 (20.39)	27 (21.43)	
35–<40	19 (12.03)	22 (7.46)		10 (9.71)	18 (14.29)	
≥40	13 (8.23)	11 (3.73)		8 (7.77)	4 (3.17)	
Hypertension	51 (32.28)	40 (13.56)	<0.001	33 (32.04)	23 (18.25)	0.016
Diabetes	20 (12.66)	8 (2.71)	<0.001	13 (12.62)	4 (3.17)	0.007
Elevated cholesterol	34 (21.52)	51 (17.29)	0.272	16 (15.53)	19 (15.08)	0.924
Angina or heart attack	29 (18.35)	9 (3.05)	<0.001	11 (10.68)	4 (3.17)	0.022
No. of pregnancies, mean (SD)	2.77 (1.55)	2.88 (1.70)	0.515	3.01 (1.73)	3.19 (2.14)	0.489

Data reported as n (%) unless otherwise noted.

18%; $P \leq 0.01$), diabetes (13% versus 6%; $P \leq 0.01$), or elevated cholesterol (30% versus 16%; $P \leq 0.01$). Compared with controls, stroke patients were more likely to be current smokers or to have a history of hypertension, diabetes, or angina/MI (Table 1).

Overall, women with a history of preeclampsia were more likely to have an ischemic stroke than women without such a history after adjustment for age, race, education, and number of pregnancies (Table 2). Further adjustment for smoking, BMI, diabetes, elevated cholesterol, angina/MI, and hypertension (Models B and C) attenuated the association and rendered it statistically nonsignificant (OR: 1.38; 95% CI: 0.81 to 2.33; $P=0.24$). We repeated Model A among 535 women without a history of nonpregnancy-related hypertension and observed similar results (OR: 1.64; 95% CI: 0.87 to 3.08). We also repeated Model A analyses among 128 women with only 1 pregnancy and observed a positive association between preeclampsia and ischemic stroke, though the association was not statistically significant with a wide 95% CI (OR: 1.35; 95% CI: 0.15 to 11.99).

We examined associations between symptoms of preeclampsia and the likelihood of ischemic stroke and observed results similar to those in Table 2. After multivariable adjustment (Model A), the relative odds of ischemic stroke associated with symptoms was 1.65, though the estimate did not attain statistical significance (95% CI: 0.91 to 2.99).

Discussion

In this population-based case-control study of young women, we observed an increased likelihood of ischemic stroke after pregnancy and the puerperium among women with a history of preeclampsia compared with women without a history of preeclampsia. We observed some attenuation of the association after adjustment for a history of nonpregnancy-related hypertension, which was strongly associated with both preeclampsia and ischemic stroke.

Relationships between preeclampsia and the risk of stroke have been examined previously, but the relationship with ischemic stroke after pregnancy and postpartum periods has not been fully described. Irgens and associates observed an increased risk of death from stroke associated with severe preeclampsia (hazard ratio: 5.08; 95% CI: 2.09 to 12.35) over a 25-year period (median follow-up, 13 years) among a retrospective cohort of Norwegian mothers whose first delivery was between 1967 and 1992.[8] Using data from a retrospective cohort study of 3593 women living in Aberdeen at the time of their first delivery between 1951 to 1970, Wilson and colleagues observed that women with a history of preeclampsia or eclampsia were at increased risk of self-reported physician-diagnosed stroke (OR: 3.41; 95% CI: 0.95 to 12.2), admission to hospital for stroke (relative risk: 2.10; 95% CI: 1.02 to 4.32), and stroke mortality (relative risk: 3.59; 95% CI: 1.04 to 12.4) after multivariable adjustment.[9] As noted

TABLE 2. Association Between Preeclampsia During Pregnancy and Ischemic Stroke Among Women Aged 15–44 Years With at Least One Pregnancy

			Case	Control
SPYW-1	Preeclampsia	+	25	29
		−	133	266
	Crude OR (95% CI)		1.72 (0.97–3.06)	
	Model A: Adjusted OR (95% CI)		1.85 (1.02–3.34)	
	Model B: Adjusted OR (95% CI)		1.87 (0.99–3.53)	
	Model C: Adjusted OR (95% CI)		1.66 (0.87–3.18)	
			Case	Control
SPYW-2	Preeclampsia	+	15	14
		−	88	112
	Crude OR (95% CI)		1.36 (0.63–2.98)	
	Model A: Adjusted OR (95% CI)		1.42 (0.63–3.17)	
	Model B: Adjusted OR (95% CI)		1.32 (0.53–3.32)	
	Model C: Adjusted OR (95% CI)		1.12 (0.43–2.90)	
			Case	Control
Overall	Preeclampsia	+	40	43
		−	221	378
	Crude OR (95% CI)		1.59 (1.00–2.52)	
	Model A: Adjusted OR (95% CI)		1.63 (1.02–2.62)	
	Model B: Adjusted OR (95% CI)		1.58 (0.95–2.64)	
	Model C: Adjusted OR (95% CI)		1.38 (0.81–2.33)	

The referent for estimated odds ratios is women without preeclampsia.

Model A adjusts for age, race, education, and No. of pregnancies. Model B adjusts for Model A variables as well as smoking, BMI, diabetes, elevated cholesterol, angina-MI. Model C adjusts for Model B variables as well as hypertension.

earlier, however, neither study excluded strokes occurring during pregnancy or the puerperium; thus, it is difficult to assess the risk of stroke later in life associated with preeclampsia.

Our results are subject to several limitations. The exposure was based on self-reported physician-diagnosed preeclampsia and therefore subject to issues of recall. Women were asked questions about the occurrence of preeclampsia during any pregnancy. For women with multiple pregnancies, the response to the preeclampsia question may not have reflected the most recent pregnancy or relevant exposure period. We attempted to address this by repeating analyses among women who had only 1 pregnancy in the first wave of the study and observed similar associations though CIs were wide (OR: 1.68; 95% CI: 0.17 to 16.25) attributable to small numbers in this subanalysis. In addition, we observed measures of association that were slightly greater in the first (SPYW-1) than in the second (SPYW-2) wave of the study. SPYW-1 included detailed questions about oral contraception use that were not included in SPYW-2. Thus, it is possible that the detailed questions on oral contraceptives for each pregnancy in SPYW-1 may have prompted women to remember whether they had preeclampsia moreso than in SPYW-2. Also, the time since stroke at study interview differed between SPYW-1 (within 1 year) and SPYW-2 (within 3 years), which may influence observed relationships attributable to differences in recall. Finally, we observed an attenuation of the odds ratio after the addition of nonpregnancy-related hypertension to the multivariable adjusted model (Model C), suggesting that the association between history of preeclampsia and ischemic stroke may be partially mediated by hypertension. It should be noted, however, that we cannot be certain whether the history of nonpregnancy-related hypertension occurred before pregnancy or between pregnancy and the index stroke, limiting our ability to speak to the possibility of mediation. In addition, the power of this study to detect an association may be limited by the small number of events.

In summary, women with preeclampsia may be at increased risk of ischemic stroke later in life. Although there are no widely accepted measures for preventing preeclampsia,[4] morbidity and mortality related to the condition can be prevented. If our results are confirmed in other studies, evaluation of the importance of targeting women with preeclampsia for close risk factor monitoring and control beyond the postpartum period may be warranted.

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