PREGNANCY AND THE RISK OF STROKE

STEVEN J. KITTNER, M.D., M.P.H., BARNEY J. STERN, M.D., BARBARA R. FEESER, M.P.H., J. RICHARD HEBEL, PH.D., DAVID A. NAGEY, M.D., DAVID W. BUCHHOLZ, M.D., CHRISTOPHER J. EARLEY, M.D., PH.D., CONSTANCE J. JOHNSON, M.D., RICHARD F. MACKO, M.D., MICHAEL A. SLOAN, M.D., ROBERT J. WITYK, M.D., AND MARCELLA A. WOZNIAK, M.D., PH.D.

ABSTRACT

Background It is widely believed that pregnancy increases the risk of stroke, but there are few data available to quantify that risk.

Methods We identified all female patients 15 through 44 years of age in central Maryland and Washington, D.C., who were discharged from any of 46 hospitals in the study area in 1988 or 1991. Two neurologists reviewed each case, using data from the women's medical records. We determined whether the women had been pregnant at the time of the stroke or up to six weeks before it occurred. For purposes of this analysis, the six-week period after pregnancy could begin with an induced or spontaneous abortion or with the delivery of a live or stillborn child.

Results Seventeen cerebral infarctions and 14 intracerebral hemorrhages occurred in women who were or had recently been pregnant (pregnancy-related strokes), and there were 175 cerebral infarctions and 48 intracerebral hemorrhages that were not related to pregnancy. For cerebral infarction, the relative risk during pregnancy, adjusted for age and race, was 0.7 (95 percent confidence interval, 0.3 to 1.6), but it increased to 8.7 for the postpartum period (after a live birth or stillbirth) (95 percent confidence interval, 4.6 to 16.7). For intracerebral hemorrhage, the adjusted relative risk was 2.5 during pregnancy (95 percent confidence interval, 1.0 to 6.4) but 28.3 for the postpartum period (95 percent confidence interval, 13.0 to 61.4). Overall, for either type of stroke during or within six weeks after pregnancy, the adjusted relative risk was 2.4 (95 percent confidence interval, 1.6 to 3.6), and the attributable, or excess, risk was 8.1 strokes per 100,000 pregnancies (95 percent confidence interval, 6.4 to 9.7).

Conclusions The risks of both cerebral infarction and intracerebral hemorrhage are increased in the six weeks after delivery but not during pregnancy itself. (N Engl J Med 1996;335:768-74.)

ALTHOUGH it is widely believed that pregnancy and the period shortly after pregnancy are associated with an increased risk of stroke, quantitative data supporting this assumption are scant.[1] Most of the studies of stroke and pregnancy have been based on a series of pregnancies at a single hospital[2-4] or have not identified strokes among women of childbearing age who were not either pregnant or recently pregnant.[2-5] There are few data on the risk of stroke in relation to the full range of outcomes of pregnancy (spontaneous or induced abortion, stillbirth, and live birth). The one population-based study of this issue[6] had a limited sample size and found no evidence of an association between stroke and pregnancy. We undertook this study to assess the risk of cerebral infarction and intracerebral hemorrhage during pregnancy and the six weeks after pregnancy, as compared with the risk among nonpregnant women, in a large, well-defined population and to determine the timing and clinical characteristics of the strokes that occurred during or shortly after pregnancy.

METHODS

Identification of Women with Stroke

The Baltimore–Washington Cooperative Young Stroke Study[7] is a regional, hospital-based registry initiated to study the incidence and causes of stroke in young adults. The study region encompasses Baltimore, Washington, D.C., and five central Maryland counties (Anne Arundel, Baltimore, Howard, Montgomery, and Prince Georges). The total population of this region in 1990 was 3,935,910. The population of girls and women 15 through 44 years of age was 1,051,113; 57 percent of this group were white, 38 percent were black, 4 percent were Asian, and 1 percent were from other racial and ethnic groups.

All 44 acute care hospitals and both rehabilitation hospitals in this region participated in the study. Because of referral patterns, it was considered unlikely that persons who lived in the study region would be admitted to hospitals outside this area. During 1988 and 1991, there were 2470 hospital discharges of persons 15 to 44 years of age with a primary or secondary diagnosis reflecting a possible cerebral infarction or intracerebral hemorrhage (in terms of the coding system of the *International Classification of Diseases, 9th Revision* [ICD-9], codes 431.00 through 438.00, indicating cerebrovascular disease other than subarachnoid hemorrhage; 671.50 through 671.54, indicating cerebral venous

From the Departments of Neurology (S.J.K., B.R.F., R.F.M., M.A.S., M.A.W.), Epidemiology and Preventive Medicine (S.J.K., J.R.H., M.A.S.), and Obstetrics and Gynecology (D.A.N.), University of Maryland, Baltimore; the Department of Neurology, Johns Hopkins University, Baltimore (D.W.B., C.J.E., C.J.J., R.J.W.); the Division of Neurology, Sinai Hospital, Baltimore (R.J.W.); and the Department of Neurology, Emory University, Atlanta (B.J.S.). Address reprint requests to Dr. Kittner at Bressler Bldg., Rm. 12-013, University of Maryland, 655 W. Baltimore St., Baltimore, MD 21201.

Other contributing authors were Thomas R. Price, M.D., and Roger Sherwin, M.B., B.Chir., University of Maryland, Baltimore.

Investigators and institutions participating in the study are listed in the Appendix.

thrombosis; and 674.00 through 674.04, indicating cerebrovascular complications of the puerperium). Of these cases, medical records from 2309 (93 percent) were reviewed by a nurse who had experience in caring for patients with stroke and who had been trained in the study procedures.

The abstracting process yielded a narrative summary for each patient that described past strokes and episodes of transient ischemic attacks, the neurologic symptoms and signs at presentation, and their evolution. In addition, the data recorded included demographic characteristics; risk factors (for intracerebral hemorrhage, only the 1991 data included this information); laboratory data, including the results of neuroimaging; and autopsy data, if available. A history of preeclampsia or eclampsia diagnosed by a physician was noted if it appeared in the medical records. For pregnant women, the estimated number of weeks of gestation at the time of the stroke or the timing of the stroke during the six weeks after the end of a pregnancy was also recorded.

The abstracted information on each possible acute stroke was reviewed by two neurologists who classified the event as a cerebral infarction, intracerebral hemorrhage, or other medical condition. Stroke was defined according to the criteria of the World Health Organization.[9] The definitions of cerebral infarction and intracerebral hemorrhage were based on the criteria of the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke.[10] We chose to include strokes due to cerebral venous thrombosis in the category of cerebral infarction because central venous thrombosis is difficult to diagnose and because any unrecognized cases would be included as cerebral infarctions. Probable and possible causes were also assigned during the review process.[11] Disagreements between the neurologists were resolved by consensus in meetings with a third neurologist. Strokes that occurred as an immediate consequence of trauma were excluded. Cerebral infarction associated with subarachnoid hemorrhage was also excluded. Only first strokes occurring in women of the specified ages who lived in the study region were included in the present analyses.

Determination of Person-Time at Risk

The person-time at risk during pregnancy or the six-week period after pregnancy (exposure) was estimated as a weighted average from the numbers of spontaneous and induced abortions, stillbirths, and live births in the population and from the average duration of pregnancy for each type of outcome. The person-time during which women in the population were not exposed — that is, were not pregnant or within six weeks after pregnancy — was estimated by subtracting the person-time calculated for exposure from the total person-time in the study population.

We determined the distribution of the population according to age and race on the basis of estimates for 1988 and 1991 for the region of Maryland under study[12,13] and on the basis of the 1990 U.S. Census for Washington, D.C.[14] The women were categorized according to five-year age groups; two racial categories were used — "white" and "all other." The "all other" category was 88 percent black.

The duration of pregnancy was assumed to be 10 weeks for spontaneous and induced abortions (Tew S, Alan Guttmacher Institute: personal communication), 28 weeks for stillbirths (Hoyert D, National Center for Health Statistics: personal communication), and 38 weeks for live births. In accordance with current definitions of maternal mortality[15] and standard usage,[16] the post-pregnancy period was defined as six weeks for each pregnancy outcome and was further characterized as either post-abortion (following a spontaneous or induced abortion) or post partum (following a live birth or stillbirth). Spontaneous abortions were defined as spontaneous fetal deaths before 20 weeks' gestation; stillbirths were defined as spontaneous fetal deaths at 20 weeks of gestation or later.

The total number of pregnancies for each subgroup defined according to age and race in the study region was estimated by calculating the age- and race-specific ratio of live births in the study region to live births in the United States[12,13,17-19] and applying it to the total number of pregnancies in the United States for that subgroup.[19]

Statewide data, but not data for individual counties, for single, twin, and other multiple births were available for Maryland.[12,13] Therefore, the number of pregnancies resulting in live births for each group defined according to age and race in the Maryland study area was estimated from statewide data and the ratio of live births in the study area to live births in the state as a whole. We determined the number of pregnancies resulting in live births for subgroups defined by age and race in Washington, D.C., from the number of single, twin, and other multiple births.[17,18]

The number of stillbirths for groups defined by age and race in the Maryland study area was estimated from county-specific data on the number of stillbirths and the proportion of live births in each category defined by age and race.[12,13] Data were available on the number of stillbirths according to the mother's age and race in Washington, D.C.[20,21]

For each group defined by age and race, the number for the combined category of spontaneous and induced abortions was obtained by subtracting live births and stillbirths from total pregnancies.

Statistical Analysis

To assess the statistical significance of differences in demographic characteristics and risk factors between women who had strokes during pregnancy or in the six weeks after pregnancy and those whose strokes occurred at other times, we used Student's t-test for age and Fisher's exact test for all other factors. The incidence of stroke was determined by dividing the number of strokes by the number of weeks of person-time, with separate rates calculated for pregnancy, for the six weeks after a stillbirth or a live birth (postpartum period), for the six weeks after a spontaneous or an induced abortion (post-abortion period), and for strokes unrelated to pregnancy. Relative risks of stroke related to pregnancy were expressed as ratios of the incidence rates; the women whose strokes were not related to pregnancy served as the reference group. Attributable risks were calculated as differences in incidence between pregnancy-related strokes and strokes that were not related to pregnancy.

Relative risks, adjusted for age and race, and 95 percent confidence intervals were obtained by fitting Poisson regression models that predicted the incidence of stroke according to race, age, and whether or not the woman was pregnant or recently pregnant. Attributable risk, with adjustment for age and race, and confidence intervals were obtained from stratified incidence rates by the direct standardization method,[22] with the total population as the standard.

RESULTS

There were 17 cerebral infarctions and 14 intracerebral hemorrhages during 8,011,852 woman-weeks of exposure (i.e., weeks during which women were pregnant or had been pregnant within the previous six weeks). Of these strokes, three cerebral infarctions and one intracerebral hemorrhage occurred among women who were known to have undergone an induced abortion (one cerebral infarction and one intracerebral hemorrhage) or who had delivered a stillborn child (two cerebral infarctions). Both abortions took place before the stroke; thus, these strokes were considered to have occurred in the post-pregnancy period. In both cases of stillbirth, fetal death preceded or occurred at the time of the stroke and the stroke preceded the delivery of the fetus; thus, these cases were considered to have occurred during

TABLE 1. CEREBRAL INFARCTIONS IN GIRLS AND WOMEN 15 THROUGH 44 YEARS OF AGE, ACCORDING TO SELECTED RISK FACTORS AND THE TIMING OF STROKE.*

RISK FACTOR	RELATED TO PREGNANCY (N=17)	NOT RELATED TO PREGNANCY (N=175)	P VALUE
Mean age (yr)	27	36	<0.001
Nonwhite race (%)	71	73	0.78
Hypertension (%)	41	46	0.80
Diabetes mellitus (%)	18	24	0.77
Ischemic heart disease (%)	0	5	1.0
Current cigarette use (%)	29	43	0.31
Illicit-drug use (%)†	24	20	0.75

*Strokes related to pregnancy occurred during pregnancy or within six weeks after a spontaneous or induced abortion, stillbirth, or live birth.

†Illicit-drug use was defined as a history of drug use or positive results on toxicologic screening.

TABLE 2. INTRACEREBRAL HEMORRHAGES IN GIRLS AND WOMEN 15 THROUGH 44 YEARS OF AGE, ACCORDING TO SELECTED RISK FACTORS AND THE TIMING OF STROKE.*

RISK FACTOR	RELATED TO PREGNANCY (N=14)	NOT RELATED TO PREGNANCY (N=48)	P VALUE
Mean age (yr)	28	38	<0.001
Nonwhite race (%)	79	69	0.53
Hypertension (%)†	50	46	1.0
Diabetes mellitus (%)†	0	4	1.0
Ischemic heart disease (%)†	0	0	1.0
Current cigarette use (%)†	13	17	1.0
Illicit-drug use (%)†‡	38	25	0.65

*Strokes related to pregnancy occurred during pregnancy or within six weeks after a spontaneous or induced abortion, stillbirth, or live birth.

†Only strokes occurring in 1991 are included (8 related to pregnancy, and 24 not related to pregnancy).

‡Illicit-drug use was defined as a history of drug use or positive results on toxicologic screening.

pregnancy rather than during the period after pregnancy. There were 175 cerebral infarctions and 48 intracerebral hemorrhages during 101,303,016 nonexposed woman-weeks (i.e., when the women had not been pregnant in the past six weeks). During this period, there were 140,167 pregnancies resulting in live births and 1076 pregnancies resulting in stillbirths (for a rate of 11 cerebral infarctions and 9 intracerebral hemorrhages per 100,000 deliveries), as well as 92,780 spontaneous or induced abortions.

Table 1 shows the demographic characteristics and risk factors of the women with cerebral infarction according to their status with regard to pregnancy. Of the 192 cases of cerebral infarction, 17 occurred among women who were pregnant or had recently been pregnant, and 175 occurred in other women. The women who had cerebral infarction during or shortly after pregnancy were almost 10 years younger, less likely to have hypertension, diabetes mellitus, or ischemic heart disease, and less likely to be current cigarette smokers than the women in whom cerebral infarction was not related to pregnancy; only the age difference was statistically significant, however.

Table 2 shows the demographic characteristics and risk factors of the women with intracerebral hemorrhage according to their pregnancy status. Of the 62 cases of intracerebral hemorrhage, 14 occurred among women who were pregnant or had recently been pregnant, and 48 were not related to pregnancy. Women who had pregnancy-related intracerebral hemorrhages were younger than women whose intracerebral hemorrhages were not related to pregnancy; there were no statistically significant differences with respect to other risk factors.

Figure 1 shows the timing of each cerebral infarction during pregnancy or the postpartum period, according to cause. Ten of 16 cerebral infarctions (62 percent) occurred during the six weeks after delivery. Only one of these cases occurred within 24 hours after delivery, a cerebral infarction associated with eclampsia that occurred after a spontaneous vaginal delivery. The cases of stroke related to eclampsia and angiographically defined central nervous system vasculopathy, constituting 38 percent of the cerebral infarctions, tended to cluster tightly in the postpartum period. Neither of the women with angiographically defined vasculopathy underwent biopsy, and cerebrospinal fluid was examined for only one (the results were normal). Thus, it could not be determined whether these strokes resulted from an inflammatory process,[23] a vasospastic process,[24] or intimal proliferation.[25] Only one woman with stroke due to venous thrombosis was identified; the stroke occurred five days post partum and was confirmed by angiography. In addition, one cerebral infarction associated with mitral-valve prolapse (not shown in Fig. 1) occurred four weeks after an abortion at six weeks of gestation.

Figure 2 shows the timing of each intracerebral hemorrhage during pregnancy or the postpartum period, according to cause. Eight of 13 intracerebral hemorrhages (62 percent) occurred during the six weeks post partum. Only one of these strokes occurred within 24 hours after delivery, an intracerebral hemorrhage of indeterminate cause that occurred after a cesarean section. The intracerebral hemorrhages of indeterminate cause and those associated with preeclampsia or eclampsia or with angiographically defined vasculitis tended to cluster tightly in the postpartum period. An arteriovenous malformation was present in three cases; two of the three became symptomatic in the second trimester.

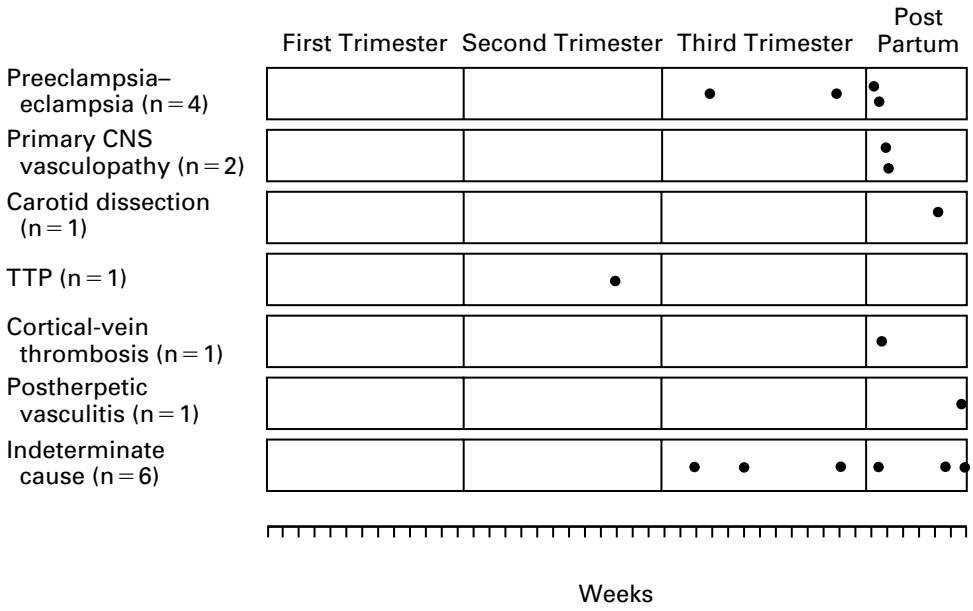

Figure 1. Timing of Cerebral Infarction during Pregnancy or after Delivery, According to Cause.
CNS denotes central nervous system, and TTP thrombotic thrombocytopenic purpura. One stroke that occurred after an abortion is not included.

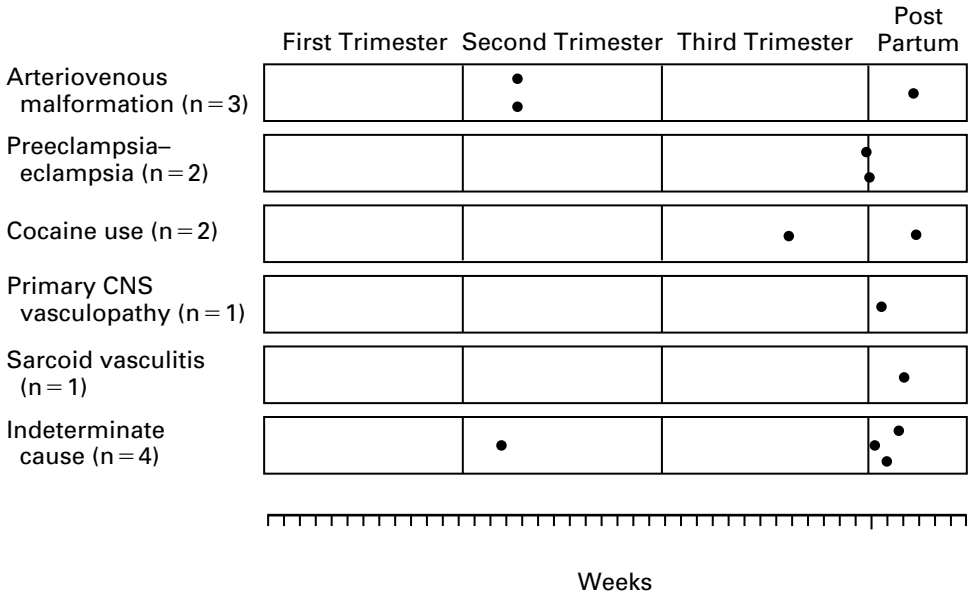

Figure 2. Timing of Intracerebral Hemorrhage during Pregnancy or after Delivery, According to Cause.
CNS denotes central nervous system. One stroke that occurred after an abortion is not included.

In addition, one intracerebral hemorrhage of indeterminate cause (not shown in Fig. 2) occurred 5 days after an abortion at 16 weeks' gestation.

With the possible exception of cocaine use in one woman, none of the predisposing causes of cerebral infarction or intracerebral hemorrhage were recognized before pregnancy. Furthermore, with the exception of preeclampsia or eclampsia that developed up to three days before the stroke occurred, the stroke itself was the presenting manifestation of the underlying disease in all cases.

Table 3 shows the age- and race-adjusted relative risks for cerebral infarction, intracerebral hemorrhage, and all strokes combined (except subarachnoid hemorrhage) during and shortly after pregnancy. The risk of stroke was highest in the postpartum period (relative risk, 8.7 [95 percent confidence interval, 4.6 to 16.7] for cerebral infarction and 28.3 [95 percent confidence interval, 13.0 to 61.4] for intracerebral hemorrhage).

The age- and race-adjusted attributable risk of either cerebral infarction or intracerebral hemorrhage during or within six weeks after pregnancy was 8.1 (95 percent confidence interval, 6.4 to 9.7) per 100,000 pregnancies.

DISCUSSION

Our main findings with respect to the association between pregnancy and stroke are in agreement with the results of several earlier studies. Through surveillance at the Neurosurgical Unit at Killearn Hospital of Glasgow from 1956 through 1967, Cross et al.[2] identified 31 cerebral infarctions in the distribution of the carotid artery in women who were pregnant or had recently delivered. On the assumption that the Neurosurgical Unit treated most such cases in the western region of Scotland, the authors estimated the incidence of such strokes as 5 per 100,000 deliveries. Sixteen such strokes occurred during pregnancy, whereas 15 occurred during the first 16 days after delivery. A total of 29 women underwent cerebral angiography, and only 1 case of cerebral venous thrombosis was identified.

Using the record-linkage system of the Mayo Clinic for the residents of Rochester, Minnesota, from 1955 through 1979, Wiebers and Whisnant[6] identified only 1 ischemic stroke and no intracerebral or subarachnoid hemorrhages among 26,099 women giving birth, for an incidence of 3.8 cerebral infarctions per 100,000 deliveries. Although this study provided no evidence that the risk of stroke during pregnancy was greater than the risk among nonpregnant women of childbearing age, its small sample was acknowledged as a limitation.

A recent population-based, case–control study of the risks of oral contraceptive agents[26] identified all 497 girls and women from 15 to 44 years of age in Denmark who had had cerebral thromboembolic attacks (13 of whom were pregnant) and 1370 randomly selected controls (31 of whom were pregnant). From Lidegaard's data, one can calculate an odds ratio of 1.2 (95 percent confidence interval, 0.6 to 2.3) for the association of cerebral infarction with pregnancy — a risk that is consistent with our odds ratio of 0.7 (95 percent confidence interval, 0.3 to 1.6). Lidegaard's study, however, did not address the risk of cerebral infarction during the six weeks after pregnancy.

The recent report by Sharshar et al. for the French Stroke in Pregnancy Study Group[5] also complements our study. Cerebral infarctions and intracerebral hemorrhages during pregnancy or the first two weeks post partum were identified through surveillance at 63 of the 65 public maternity clinics in and

TABLE 3. ADJUSTED RELATIVE RISK (RR) OF STROKE ACCORDING TO A WOMAN'S STATUS WITH RESPECT TO PREGNANCY.*

RISK PERIOD†	RR OF CEREBRAL INFARCTION (95% CI)	RR OF INTRACEREBRAL HEMORRHAGE (95% CI)	RR OF EITHER TYPE OF STROKE‡ (95% CI)
During pregnancy or 6 wk after pregnancy	1.6 (1.0–2.7)	5.6 (3.0–10.5)	2.4 (1.6–3.6)
During pregnancy	0.7 (0.3–1.6)	2.5 (1.0–6.4)	1.1 (0.6–2.0)
During 6 wk after pregnancy	5.4 (2.9–10.0)	18.2 (8.7–38.1)	7.9 (5.0–12.7)
After delivery	8.7 (4.6–16.7)	28.3 (13.0–61.4)	12.7 (7.8–20.7)
After abortion	1.1 (0.2–7.9)	4.5 (0.6–33.1)	1.8 (0.4–7.2)

*Relative risks have been adjusted for age and race. CI denotes confidence interval.

†The six-week period after pregnancy was defined as the six weeks after a spontaneous or induced abortion, stillbirth, or live birth.

‡Subarachnoid hemorrhages have been excluded.

around Paris and the neurology, neurosurgery, and intensive care units in the same geographic area. Strokes due to cerebral venous thrombosis were excluded. The incidence of cerebral infarction was 4.3 per 100,000 deliveries (95 percent confidence interval, 2.4 to 7.1), and that of intracerebral hemorrhage was 4.6 per 100,000 (95 percent confidence interval, 2.6 to 7.5). Both live births and stillbirths were considered in the calculation of these incidence rates; none of the 31 women included in the analysis had stroke associated with spontaneous or induced abortion (Mas J-L, Hôpital Sainte Anne: personal communication).

Sharshar et al. inferred an increased risk of intracerebral hemorrhage during pregnancy and the postpartum period from the similar rates of cerebral infarction and intracerebral hemorrhage in their study, a finding that contrasts with the preponderance of cerebral infarction over intracerebral hemorrhage in studies of the overall incidence of stroke among young women.[27] This inference is supported by the results of our study. Like us, the French group found that the risk of cerebral infarction or intracerebral hemorrhage per day was higher during the postpartum period than during any trimester of pregnancy.[5]

Although both our study and the French collaborative effort found eclampsia to be an important factor associated with stroke, we found preeclampsia or eclampsia in only 24 percent of the women with cerebral infarction (4 of 17), whereas the French investigators found it in 47 percent, and we found this factor in only 14 percent of women with intracerebral hemorrhage (2 of 14) as compared with 44 percent in the French study.[5] This difference may reflect differences in the study populations. Alternatively, because women with confusion and abnormal results on magnetic resonance imaging who are treated quickly with magnesium sulfate may not be assigned the ICD-9 codes reviewed in this study, we may have underestimated both the number of strokes caused by eclampsia and the risk of stroke during labor and delivery.

The extremely high relative risk of stroke during the postpartum period suggests a causal role for the large decrease in blood volume or the rapid changes in hormonal status that follow a live birth or stillbirth, perhaps by means of hemodynamic, coagulative, or vessel-wall changes. A causal role for preeclampsia and eclampsia does not fully explain the much stronger associations with stroke found for the postpartum state than for pregnancy itself.

With the possible exception of cocaine use in one patient, factors that strongly predispose patients to stroke were not apparent before pregnancy in our study. Thus, there is little to suggest that medical intervention could have prevented these strokes. The surprising absence of pregnancy-associated strokes in women previously recognized as having strong predisposing factors may be due to the relatively small numbers of women with these conditions, a low pregnancy rate among those at risk, or the use of effective measures to prevent stroke in those at risk. Our results demonstrate that stroke during pregnancy or shortly thereafter is etiologically heterogeneous and, as with stroke in any young patient, requires systematic evaluation.[28]

Our study has several potential limitations. Selection bias could have occurred if women who had strokes during or shortly after pregnancy were more likely to be hospitalized than other young women with stroke. This difference would have resulted in an overestimation of risk. However, selection bias seems unlikely, for several reasons. First, stroke in a young woman is always an unusual event that engenders a high degree of concern and leads to hospitalization in nearly all cases. In a separate, ongoing, case–control study of stroke in young women, we found that 145 of 151 cases of stroke (96 percent) reported directly by physicians were in women who had been hospitalized (unpublished data). Second, the specificity of the association between stroke and the postpartum period and the stronger association with intracerebral hemorrhage than with cerebral infarction would not be expected if selection bias had been at work.

Numerous assumptions were required to estimate the amount of person-time women were at risk for the different types of pregnancy outcome. We had direct information on the numbers of live births in Maryland and Washington, D.C., and the proportions of pregnancies resulting in spontaneous or induced abortion (39.6 percent), stillbirth (0.5 percent), and live birth (59.9 percent) are consistent with those in the available literature.[29,30] Since spontaneous or induced abortions may have been unrecognized or unreported among the women with stroke in our study, it is possible that we may have underestimated the risk in the six weeks after abortion.

Because of the design of our study, it was not possible to adjust relative risks for factors other than age and race. However, the prevalence of hypertension, diabetes mellitus, and current smoking was lower among pregnant women with stroke than among nonpregnant women with stroke or in the general population, according to data from the Maryland Behavioral Risk Factor Survey for the same region during the same years.[31] Thus, adjustment for these factors would have produced a stronger association between pregnancy and stroke.

In summary, this study focused on a defined population large enough to yield a useful estimate of the excess risk of stroke associated with pregnancy. Our results are conservative both because we considered the person-time contributed by women with all types of pregnancy outcomes and because we did not adjust for the lower frequency of risk factors for vascu-

lar disorders among the women whose strokes occurred during or shortly after pregnancy. We found that the postpartum state, but not pregnancy itself, was associated with an increased risk of cerebral infarction and, particularly, intracerebral hemorrhage.

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APPENDIX

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REFERENCES

1. Grosset DG, Ebrahim S, Bone I, Warlow C. Stroke in pregnancy and the puerperium: what magnitude of risk? J Neurol Neurosurg Psychiatry 1995;58:129-31.
2. Cross JN, Castro PO, Jennett WB. Cerebral strokes associated with pregnancy and the puerperium. BMJ 1968;3:214-8.
3. Amias AG. Cerebral vascular disease in pregnancy. I. Haemorrhage. J Obstet Gynaecol Br Commonw 1970;77:100-20.
4. Simolke GA, Cox SM, Cunningham FG. Cerebrovascular accidents complicating pregnancy and the puerperium. Obstet Gynecol 1991;78:37-42.
5. Sharshar T, Lamy C, Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium: a study in public hospitals of Ile de France. Stroke 1995;26:930-6.
6. Wiebers DO, Whisnant JP. The incidence of stroke among pregnant women in Rochester, Minn, 1955 through 1979. JAMA 1985;254:3055-7.
7. Kittner SJ, McCarter RJ, Sherwin RW, et al. Black-white differences in stroke risk among young adults. Stroke 1993;24:Suppl:I-13–I-15.
8. Bureau of the Census. 1990 Census of population and housing: summary tape file 3A. Washington, D.C.: Department of Commerce, Data User Services Division, 1992 (software).
9. Hatano S. Experience from a multicenter stroke register: a preliminary report. Bull World Health Organ 1976;54:541-53.
10. Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. Stroke 1988;19:547-54.
11. Johnson CJ, Kittner SJ, McCarter RJ, et al. Interrater reliability of an etiologic classification of ischemic stroke. Stroke 1995;26:46-51.
12. Center for Health Statistics. Maryland vital statistics annual report. Baltimore: Department of Health and Mental Hygiene, 1988.
13. Division of Health Statistics. Maryland vital statistics annual report. Baltimore: Department of Health and Mental Hygiene, 1991.
14. Bureau of the Census. 1990 Census of population: general population characteristics, District of Columbia. Washington, D.C.: Government Printing Office, 1992.
15. Atrash HK, Alexander S, Berg CJ. Maternal mortality in developed countries: not just a concern of the past. Obstet Gynecol 1995;86:700-5.
16. The puerperium. In: Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC III. Williams obstetrics. 19th ed. Norwalk, Conn.: Appleton & Lange, 1993:459-73.
17. National Center for Health Statistics. Vital statistics of the United States, 1988. Vol. 1. Natality. Washington, D.C.: Government Printing Office, 1991. (DHHS publication no. (PHS) 90–1100.)
18. *Idem.* Vital statistics of the United States, 1991. Vol. 1. Natality. Washington, D.C.: Government Printing Office, 1995. (DHHS publication no. (PHS) 95–1100.)
19. Centers for Disease Control, National Center for Health Statistics. Trends in pregnancies and pregnancy rates, United States, 1980-88. Vol. 41. No. 6. Washington, D.C.: Government Printing Office, 1992.
20. National Center for Health Statistics. Vital statistics of the United States, 1988. Vol. 2. Mortality. Part A. Washington, D.C.: Government Printing Office, 1991. (DHHS publication no. (PHS) 91–1101.)
21. *Idem.* Vital statistics of the United States, 1991. Vol. 2. Mortality. Part A. Washington, D.C.: Government Printing Office, 1995. (DHHS publication no. (PHS) 95–1101.)
22. Rothman KJ. Modern epidemiology. Boston: Little, Brown, 1986.
23. Calabrese LH, Furlan AJ, Gragg LA, Ropos TJ. Primary angiitis of the central nervous system: diagnostic criteria and clinical approach. Cleve Clin J Med 1992;59:293-306.
24. Garner BF, Burns P, Bunning RD, Laureno R. Acute blood pressure elevation can mimic arteriographic appearance of cerebral vasculitis — (a postpartum case with relative hypertension). J Rheumatol 1990;17:93-7.
25. Irey NS, Norris HJ. Intimal vascular lesions associated with female reproductive steroids. Arch Pathol 1973;96:227-34.
26. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. BMJ 1993;306:956-63.
27. Nencini P, Inzitari D, Baruffi MC, et al. Incidence of stroke in young adults in Florence, Italy. Stroke 1988;19:977-81.
28. Stern BJ, Kittner SJ, Sloan MA, et al. Stroke in the young. Md Med J 1991;40:453-62, 565-71.
29. Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC III. Williams obstetrics. 19th ed. Norwalk, Conn.: Appleton & Lange, 1993:3-6.
30. *Idem.* Williams obstetrics. 19th ed. Norwalk, Conn.: Appleton & Lange, 1993:662.
31. Rohr J, Kittner SJ, Feeser BR, et al. Traditional risk factors and stroke in young adults: the Baltimore-Washington Cooperative Young Stroke Study. Arch Neurol 1996;53:603-7.