

STROKE IN USERS OF LOW-DOSE ORAL CONTRACEPTIVES

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ABSTRACT

Background Previous studies have linked the use of oral contraceptive agents to an increased risk of stroke, but those studies have been limited to oral contraceptives containing more estrogen than is now generally used.

Methods In a population-based, case-control study, we identified fatal and nonfatal strokes in female members of the California Kaiser Permanente Medical Care Program who were 15 through 44 years of age. Matched controls were randomly selected from female members who had not had strokes. Information about the use of oral contraceptives (essentially limited to low-estrogen preparations) was obtained in interviews.

Results A total of 408 confirmed strokes occurred in a total of 1.1 million women during 3.6 million woman-years of observation. The incidence of stroke was thus 11.3 per 100,000 woman-years. On the basis of data from 295 women with stroke who were interviewed and their controls, the odds ratio for ischemic stroke among current users of oral contraceptives, as compared with former users and women who had never used such drugs, was 1.18 (95 percent confidence interval, 0.54 to 2.59) after adjustment for other risk factors for stroke. The adjusted odds ratio for hemorrhagic stroke was 1.14 (95 percent confidence interval, 0.60 to 2.16). With respect to the risk of hemorrhagic stroke, there was a positive interaction between the current use of oral contraceptives and smoking (odds ratio for women with both these factors, 3.64; 95 percent confidence interval, 0.95 to 13.87).

Conclusions Stroke is rare among women of childbearing age. Low-estrogen oral-contraceptive preparations do not appear to increase the risk of stroke. (N Engl J Med 1996;335:8-15.)

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SOON after oral contraceptives were first marketed, case reports appeared of pulmonary embolism¹ and ischemic stroke² in women using these drugs. By the early 1970s, epidemiologic studies had confirmed a link between the current use of oral contraceptive agents and an increased risk of thrombotic stroke and venous thromboembolic disease.³⁻⁸ Studies published in the 1970s also showed an increased risk of acute myocardial infarction among current users of oral contraceptive agents⁹⁻¹¹ and suggested a link between the use of these drugs and hemorrhagic stroke.^{8,12,13} Studies of stroke in current users of oral contraceptives published thereafter have had inconsistent results.¹⁴⁻²³

The first oral contraceptive agents marketed in the

United States contained 150 μg of estrogen. Studies in the 1960s and early 1970s were based on the use of oral-contraceptive formulations that typically contained 80 or 100 μg of estrogen. Oral contraceptives now in widespread use in the United States contain 30 or 35 μg of estrogen. Previous large studies of stroke among users of oral contraceptives failed to provide information on the incidence of stroke. Moreover, the risk of stroke may be higher among users of oral contraceptives who are already at high risk of having a stroke for other reasons.^{23,24} In the United States, oral-contraceptive use has been largely restricted to women who are free of risk factors for cardiovascular disease.

We conducted a study of the relation of stroke to the use of oral contraceptives in a large health maintenance organization (HMO) in which the use of high-estrogen oral contraceptives (those containing ≥ 50 μg) was rare and among whose members risk factors for cardiovascular disease are likely to be detected. The population-based design allowed us to estimate the incidence of stroke.

METHODS

This case-control study was conducted among the members of the Kaiser Permanente Medical Care Programs of Northern and Southern California. The study was approved by the relevant institutional review boards.

Ascertainment and Classification of Strokes

An attempt was made to identify all fatal and nonfatal strokes that occurred from May 1991 through August 1994 (for northern California) and from July 1991 through August 1994 (for southern California) in female members of the northern and southern California programs who were 15 through 44 years of age. Cases were identified through hospital admission and discharge records, emergency department logs, and records of payments for out-of-plan hospitalizations.

Stroke was defined as the new onset of rapidly developing symptoms and signs of loss of cerebral function that lasted at least 24 hours and had no apparent nonvascular cause. We excluded neurologic events due to subdural hematoma, brain tumor, infection, metabolic derangement, and multiple sclerosis.

Two physicians reviewed the records of potentially eligible patients and used defined criteria that included clinical symptoms and the results of computed tomography (CT) and magnetic resonance imaging (MRI) of the head, lumbar puncture, angiography, surgery, and autopsy to assess whether the event was a stroke

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and, if so, its type and subtype. A project neurologist adjudicated discrepancies between the assessments of these two physicians. All but two women with possible strokes that were not immediately fatal underwent CT or MRI (or both) of the head. Strokes were classified as venous, hemorrhagic, resulting from ischemic infarction, "other," or "unknown." Hemorrhagic strokes were subclassified as intraparenchymal, subarachnoid, or of mixed or uncertain subtype on the basis of the results of tests and procedures. Ischemic infarctions were subclassified as cardioembolic if the embolism had a cardiac source, as resulting from arterial dissection if angiography showed a dissection, or as "other ischemic infarction."

Controls

For each woman with stroke, three controls, matched for year of birth and location of the facility where care was received, were randomly selected from among female members of the program. Controls who could not be located, declined to be interviewed, or spoke neither English nor Spanish were replaced with other randomly selected controls until three controls had been enrolled for each woman with stroke or two replacement controls had been selected.

Sources of Information

Eligible women with stroke and controls were interviewed in person by trained interviewers who used a standardized questionnaire. The mean (\pm SD) interval between enrollment and the date of the interview was 80 ± 56 days for women with stroke and 86 ± 59 days for controls.

If a woman with stroke had died or was unable to communicate orally, an attempt was made to interview a family member or other proxy in her place. The first-choice respondent was the woman's husband or other live-in companion. If the woman had no husband or live-in companion or if the husband or companion could not provide accurate information, a daughter, mother, sister, or close friend of the woman was interviewed (with preference assigned in the order stated); proxy respondents were interviewed for 20.5 percent of the women with stroke.

Each study subject was assigned an "index date," which was the date of onset of symptoms for a woman with stroke and the same date for her matched controls. We used a calendar method that structures questions in relation to important life events to obtain information on contraceptive methods. A book with pictures of oral-contraceptive formulations marketed in the United States was used to help the subjects identify the drugs they had taken.

A woman was classified as having hypertension if she or the proxy respondent answered yes to a question about the use of medication for high blood pressure. A yes answer to a question about the use of insulin or pills for diabetes was used to classify women as having diabetes. The height and weight values were reported by the women or their proxies.

Statistical Analysis

Odds ratios were used to estimate relative risk. For the multivariate analyses, conditional logistic regression was used to estimate the odds ratio. In multivariate analyses, we adjusted for major risk factors for stroke: cigarette smoking, hypertension, and diabetes. We also adjusted for variables that affected the odds ratio for oral-contraceptive users as compared with nonusers if the adjustment altered the unadjusted estimate by 10 percent or more. Variables that directly or indirectly measured socioeconomic status (education, race or ethnic group, and income) were highly correlated. In the final models, we adjusted for race or ethnic group because the proportion of subjects for whom data on income were missing was high and because there is an established association between race or ethnic group and the risk of stroke.²⁵ The incidence of stroke was estimated with the total number of girls and women 15 to 44 years of age who were members of the HMO as the denominator.

RESULTS

A total of 408 confirmed strokes occurred in 1.1 million girls and women 15 through 44 years of age during 3.6 million woman-years of observation (Table 1). The incidence of stroke was thus 11.3 per 100,000 woman-years of observation.

Of 408 women with confirmed cases of stroke, 13 were not eligible for interview because they were less than 18 years of age ($n=5$), did not speak English or Spanish ($n=2$), lived more than 200 miles from the study centers ($n=5$), or had an incorrect medical-record number that could not be matched accurately with the patient's name ($n=1$). Girls less than 18 years of age were not interviewed because of concern about privacy and confidentiality.

Interviews were completed for 357 of the 395 eligible women or their proxies (90.4 percent). This analysis is based on the 295 women with ischemic infarction or hemorrhagic stroke who were interviewed; we excluded women with venous strokes ($n=6$) and strokes of unknown type ($n=3$), women who were pregnant at the time of the stroke ($n=11$), those who had undergone a hysterectomy, bilateral oophorectomy, or both ($n=35$), women for whom there were no controls ($n=2$), and women for whom proxy respondents were interviewed and information on oral-contraceptive use was incomplete ($n=5$). We excluded women with venous strokes in

TABLE 1. TYPES AND SUBTYPES OF STROKES AMONG GIRLS AND WOMEN 15 THROUGH 44 YEARS OF AGE IN THE NORTHERN AND SOUTHERN CALIFORNIA KAISER PERMANENTE MEDICAL CARE PROGRAMS.*

| TYPE | ALL STROKES | STROKES INCLUDED IN OUR ANALYSIS† |
|-------------------------------|-------------|-----------------------------------|
| | no. (%) | |
| Hemorrhagic stroke | | |
| Intraparenchymal | 65 (15.9) | 44 (14.9) |
| Subarachnoid‡ | 110 (27.0) | 91 (30.8) |
| Mixed or uncertain | 26 (6.4) | 16 (5.4) |
| Venous stroke | 6 (1.5) | 0 |
| Ischemic infarction | | |
| Cardioembolic | 16 (3.9) | 13 (4.4) |
| Caused by arterial dissection | 8 (2.0) | 6 (2.0) |
| Other | 171 (41.9) | 125 (42.4) |
| Other or unknown | 6 (1.5)§ | 0 |
| Total | 408 | 295 |

*Because of rounding, percentages may not total 100.

†Strokes included in our analysis were those that occurred in women who were not pregnant, had not undergone hysterectomy, had at least one ovary, were interviewed, and had at least one matched control and for whom we had complete data on current oral-contraceptive use.

‡Includes "pure" intraventricular hemorrhage (8 cases, of which 7 were included in the analysis).

§Three women were eligible and interviewed but not included in the analysis.

order to focus on arterial vascular disease. One of the five women with venous strokes for whom information on oral-contraceptive use was available was a current user. We excluded women who had undergone hysterectomy or oophorectomy because none were current users of oral contraceptives and they therefore contributed no information about the relation of stroke to the current use of such agents. Furthermore, because hysterectomy and oophorectomy are related to the risk of disease, the statistical model would have been even more complex had these women been included. Controls who had undergone hysterectomy or bilateral oophorectomy were also excluded.

We compared information on the use of oral contraceptives from the medical records of eligible women who were interviewed (or whose proxies were interviewed) and those who were not in order to assess whether response bias was present. In the two years before the index date, 12.5 percent of the nonrespondents and 12.9 percent of the respondents had received a prescription for oral contraceptives. We could not determine with certainty whether oral contraceptives had been used within one month of the index date for about 50 percent of the subjects. Medical records were not useful for determining the extent of oral-contraceptive use, if any, in the distant past. The medical records did not contain reliable and complete information on smoking, race or ethnic group, or income. Because there was no evidence of response bias with respect to oral-contraceptive use within two years of the index date, because medical records were not useful for determining the extent of past use of oral contraceptives, if any, and because information on important confounding variables was not available for nonrespondents, we based our main analysis on the information gathered in the interviews.

We compared the information obtained from the women with stroke with that from proxy respondents and found no statistically significant differences in the distribution of any variables except past use of oral contraceptives and no lifetime use of such agents. The proportion of proxy respondents who reported that the women with stroke had never used oral contraceptives was higher and the proportion reporting past use was lower than the corresponding proportions of the women with stroke who were interviewed directly (data not shown). A review of the medical records showed that 13.2 percent of the women with stroke whom we interviewed and 13.1 percent of those interviewed by proxy had received a prescription for oral contraceptives in the two years before the index date. On the basis of this analysis, data from proxy respondents were excluded from the main analyses of past oral-contraceptive use and any oral-contraceptive use but were included in the analyses of current as compared with former use of oral contraceptives or no use of such agents.

Table 2 shows the characteristics of the women with ischemic infarction and hemorrhagic stroke, along with the distribution of oral-contraceptive use among all the controls. Among controls, factors associated with current use or nonuse of oral contraceptives were age, cigarette smoking, body-mass index (the weight in kilograms divided by the square of the height in meters), income, race or ethnic group, alcohol use, and marital status. Among the controls, only a small percentage of current users of oral contraceptives had hypertension, and none had diabetes.

The crude odds ratios for ischemic stroke were elevated among the women who smoked; had hypertension, diabetes, a higher body-mass index, a relatively low annual income, or a low educational level; or were black (Table 3). The crude odds ratio for ischemic infarction among current oral-contraceptive users as compared with the combined group of former users and those who had never used oral contraceptives was 0.96 (95 percent confidence interval, 0.49 to 1.90). Odds ratios for hemorrhagic stroke were elevated among women with the characteristics listed above, except higher body-mass index and lower educational attainment. The odds ratio for hemorrhagic stroke was also elevated in relatively heavy users of alcohol. The crude odds ratio for hemorrhagic stroke among current oral-contraceptive users as compared with former users and those who had never used oral contraceptives combined was 1.18 (95 percent confidence interval, 0.65 to 2.16).

The adjusted odds ratio for ischemic infarction among current oral-contraceptive users as compared with former users and those who had never used oral contraceptives combined was 1.18 (95 percent confidence interval, 0.54 to 2.59) (Table 4). For hemorrhagic stroke, the adjusted odds ratio for current oral-contraceptive users as compared with former users and those who had never used oral contraceptives was 1.14 (95 percent confidence interval, 0.60 to 2.16). When current users were compared with women who had never used oral contraceptives, the adjusted odds ratio for ischemic infarction with oral-contraceptive use was 0.65 (95 percent confidence interval, 0.25 to 1.70). The adjusted odds ratio for hemorrhagic stroke among current users as compared with women who had never used these agents (1.02; 95 percent confidence interval, 0.37 to 2.82) was essentially the same as the odds ratio among current users as compared with former users and those who had never used oral contraceptives combined. The adjusted odds ratios for ischemic infarction and hemorrhagic stroke among former users of oral contraceptives as compared with women who had never used them were less than 1 (Table 4).

The odds ratio for subarachnoid hemorrhage only, adjusted for smoking, hypertension, diabetes, and

race or ethnic group, was 1.49 (95 percent confidence interval, 0.62 to 3.55) among current users as compared with the combined group of former users and those who had never used oral contraceptives, a calculation based on 86 case-control pairs with complete information on these covariates.

After the exclusion of women for whom proxy respondents were interviewed, the adjusted odds ratio among current users of oral contraceptives as compared with former users and those who had never used oral contraceptives was 1.07 (95 percent confidence interval, 0.46 to 2.49) for ischemic stroke and 1.13 (95 percent confidence interval, 0.50 to 2.51) for hemorrhagic stroke. When we conducted an analysis based on medical records, the odds ratios for oral-contraceptive use within the past two years were 1.45 (95 percent confidence interval, 0.65 to 3.27) for ischemic stroke and 1.07 (0.58 to 1.97) for hemorrhagic stroke.

Table 5 shows the odds ratios among current users as compared with former users and those who had never used oral contraceptives according to smoking status, age, and progestogen type and for women who did not have hypertension. The small number

of current users with hypertension precluded the examination of the odds ratio in women with this condition. For hemorrhagic stroke, but not ischemic stroke, there was statistical evidence of a positive interaction between current oral-contraceptive use and smoking ($P=0.04$). The odds ratios for ischemic or hemorrhagic stroke associated with current oral-contraceptive use were not substantially higher for older women than for younger women. There was no statistical evidence of an interaction between current oral-contraceptive use and age ($P>0.05$ for both types of stroke). The adjusted odds ratio for all types of stroke among current oral-contraceptive users was 1.16 (95 percent confidence interval, 0.72 to 1.88; data not shown).

DISCUSSION

Several studies have found a relation between the use of oral contraceptive agents with relatively high estrogen content and a higher risk of ischemic stroke and venous thromboembolism.^{23,26-28} Women already at high risk for vascular disease may be at even greater risk for vascular disease when they use oral contraceptives.^{9-13,23,24} In the population we studied, 96

TABLE 2. CHARACTERISTICS OF WOMEN WITH ISCHEMIC OR HEMORRHAGIC STROKE AND CONTROLS, ACCORDING TO ORAL-CONTRACEPTIVE USE.*

| VARIABLE | WOMEN WITH ISCHEMIC INFARCTION (N=144) | WOMEN WITH HEMORRHAGIC STROKE (N=151) | CONTROLS | | | |
|---|--|---------------------------------------|----------------|--------------------|--------------------|-------------|
| | | | NO USE (N=138) | FORMER USE (N=543) | CURRENT USE (N=93) | ALL (N=774) |
| Age (yr) | 37.5±6.6 | 36.1±6.2 | 35.4±6.9† | 38.1±5.5† | 30.6±6.4† | 36.7±6.3 |
| Body-mass index‡ | 29.3±7.8 | 26.3±6.9 | 24.9±6.0† | 26.1±6.0† | 24.7±5.6† | 25.7±6.0 |
| Months of oral-contraceptive use | 61.7±59.0§ | 48.2±52.5§ | 0.0† | 48.8±47.0† | 82.2±58.0† | 53.7±50.1 |
| Parity | 2.0±1.6 | 2.0±1.2 | 2.0±1.2 | 2.0±1.2 | 1.8±1.2 | 2.0±1.2 |
| Current smoking (%) | 34.0 | 33.8 | 8.7† | 19.3† | 14.0† | 16.8 |
| Occasional use of alcohol or none (%) | 69.2 | 56.7 | 75.2† | 61.2† | 60.2† | 63.6 |
| Treated hypertension (%) | 18.1 | 13.5 | 0.7 | 3.9 | 1.1 | 3.0 |
| Treated diabetes (%) | 15.4 | 3.3 | 2.9 | 2.0 | 0.0 | 1.9 |
| Current use of oral contraceptives (%)¶ | 12.0 | 14.2 | — | — | — | 12.0 |
| Any use of oral contraceptives (%) | 77.4§ | 87.2§ | — | — | — | 82.2 |
| College education (%) | 16.1 | 20.5 | 35.5 | 28.4 | 29.0 | 29.7 |
| Annual income ≥\$35,000 (%) | 42.0 | 49.7 | 59.5 | 67.2 | 54.4 | 64.3 |
| Race or ethnic group (%) | | | | | | |
| Asian | 6.3 | 5.3 | 32.6 | 10.1 | 7.5 | 13.8 |
| Non-Hispanic white | 43.1 | 36.4 | 40.6 | 52.7 | 55.9 | 50.9 |
| Black | 30.6 | 27.8 | 5.8 | 14.4 | 10.8 | 12.4 |
| Hispanic | 16.0 | 26.5 | 18.1† | 19.2† | 20.4† | 19.1 |
| Married or living as married (%) | 57.6 | 59.6 | 58.0† | 68.0† | 64.5† | 65.8 |

*Plus-minus values are means ±SD.

† $P<0.05$ for the comparisons of nonusers, former users, and current users among the controls.

‡The weight in kilograms divided by the square of the height in meters.

§Excludes women for whom proxies were interviewed.

¶Use in the month before the index date.

||At least some college.

percent of current users of oral contraceptives used formulations containing less than 50 µg of estrogen. There were no users of formulations containing more than 50 µg of estrogen. Fewer than 5 percent of controls with treated hypertension were current oral-contraceptive users, no controls who had diabetes were current users, and fewer than 10 percent of current users were 40 years of age or older.

The virtually exclusive use of oral contraceptives containing less than 50 µg of estrogen and the selective use of oral contraceptives in young women without hypertension or diabetes is a plausible explanation for the lack of elevation in the risk of stroke in our study population. However, there are some limitations to our study. The analysis relied on information reported by the respondents. The adjusted odds ratios for oral-contraceptive use within two years, based on data from the medical records, were 1.45 (95 percent confidence interval, 0.65 to 3.27) for ischemic stroke and 1.07 (95 percent confidence interval, 0.58 to 1.97) for hemorrhagic stroke. Thus, we cannot entirely rule out recall or response bias as an explanation for our results. Furthermore, the confidence intervals for our estimates of the risk of stroke among current users of oral contraceptives were wide, and in this study we cannot reliably differentiate between a true null effect and a true small or moderate increase in risk.

A Danish case-control study of "thromboembolic attack" found an odds ratio of 1.8 (95 percent confidence interval, 1.1 to 2.9) among current users of low-estrogen oral contraceptives (those containing less than 50 µg),²¹ as compared with the combined group of former users and those who had never used oral contraceptives. This figure is compatible with our estimates. Taken together, our study and the Danish study suggest that the true relative risk of ischemic stroke among users of low-estrogen oral contraceptives, as compared with nonusers, is not more than 2.5.

Three other recent case-control studies determined odds ratios for subarachnoid hemorrhage among current oral-contraceptive users as compared with former users and those who had never used oral contraceptives.^{20,22,23} In a study of fatal subarachnoid hemorrhage by Thorogood et al.,²⁰ the odds ratio in current oral-contraceptive users was 1.1 (95 percent confidence interval, 0.7 to 1.9). Longstreth et al.²² reported an odds ratio for subarachnoid hemorrhage of 0.89 (95 percent confidence interval, 0.22 to 3.61). In an analysis from the Royal College of General Practitioners' Oral Contraception Study, which encompassed cases of stroke occurring from 1968 through 1990,²³ the relative risk of subarachnoid hemorrhage among current oral-contraceptive users was 1.5 (95 percent confidence interval, 0.6 to 3.7); for intraparenchymal hemorrhage, the relative risk was 1.1 (95 percent confidence interval, 0.2 to 7.1).

TABLE 3. UNADJUSTED ODDS RATIOS FOR ISCHEMIC INFARCTION AND HEMORRHAGIC STROKE, ACCORDING TO SELECTED VARIABLES.

| VARIABLE | ISCHEMIC INFARCTION | HEMORRHAGIC STROKE |
|-------------------------------------|----------------------|--------------------|
| | odds ratio (95% CI)* | |
| Cigarette smoking | | |
| Never† | 1.00 | 1.00 |
| Past | 0.94 (0.55–1.59) | 1.01 (0.59–1.75) |
| Occasional | 1.38 (0.42–4.56) | 1.65 (0.40–6.87) |
| Current regular | 2.66 (1.65–4.30) | 2.70 (1.71–4.27) |
| Treated for hypertension | 7.79 (3.51–17.31) | 4.64 (2.14–10.06) |
| Treated for diabetes | 7.15 (3.17–16.13) | 2.50 (0.62–10.08) |
| Current use of oral contraceptives‡ | 0.96 (0.49–1.90) | 1.18 (0.65–2.16) |
| Alcohol use | | |
| Never or occasional† | 1.00 | 1.00 |
| 1–3 drinks/mo | 0.80 (0.46–1.39) | 0.85 (0.49–1.48) |
| 1–3 drinks/wk | 0.69 (0.34–1.40) | 1.13 (0.65–1.97) |
| >3 drinks/wk | 1.93 (0.87–4.29) | 2.02 (1.06–3.85) |
| Body-mass index (quartile)§ | | |
| 1† | 1.00 | 1.00 |
| 2 | 1.60 (0.81–3.16) | 0.56 (0.31–1.00) |
| 3 | 2.07 (1.10–3.92) | 0.82 (0.47–1.44) |
| 4 | 4.87 (2.59–9.14) | 0.99 (0.57–1.71) |
| Parity | | |
| 0† | 1.00 | 1.00 |
| 1–2 | 0.79 (0.48–1.28) | 1.24 (0.77–2.02) |
| ≥3 | 0.79 (0.44–1.39) | 1.24 (0.70–2.18) |
| Income | | |
| <\$20,000† | 1.00 | 1.00 |
| \$20,000–34,999 | 0.48 (0.17–1.33) | 1.15 (0.41–3.24) |
| ≥\$35,000 | 0.19 (0.08–0.44) | 0.38 (0.17–0.86) |
| Marital status | | |
| Never married† | 1.00 | 1.00 |
| Married or living as married | 0.66 (0.38–1.17) | 0.80 (0.45–1.42) |
| Separated, divorced, or widowed | 0.96 (0.50–1.85) | 0.99 (0.51–1.93) |
| Educational level | | |
| Less than high-school graduate† | 1.00 | 1.00 |
| High-school graduation | 0.50 (0.25–1.00) | 0.87 (0.41–1.85) |
| Some college or business school | 0.45 (0.23–0.86) | 0.62 (0.30–1.27) |
| College graduation | 0.21 (0.10–0.44) | 0.48 (0.22–1.04) |
| Race or ethnic group | | |
| Non-Hispanic white† | 1.00 | 1.00 |
| Hispanic | 1.21 (0.66–2.19) | 1.90 (1.12–3.22) |
| Black | 4.74 (2.53–8.88) | 3.18 (1.78–5.68) |
| Asian | 0.60 (0.27–1.32) | 0.48 (0.21–1.11) |
| Other or unknown | 1.67 (0.58–4.83) | 0.97 (0.35–2.69) |

*CI denotes confidence interval.

†Reference category.

‡In the month before the index date.

§The weight in kilograms divided by the square of the height in meters. Quartile 1 had the lowest values, and quartile 4 the highest.

Our findings support the conclusion that current oral-contraceptive use does not increase the risk of hemorrhagic stroke overall.

In the Collaborative Study of Stroke in Young Women,²⁴ the odds ratio for hemorrhagic stroke among current oral-contraceptive users, as compared with the combined group of former users and those who had never used oral contraceptives, was 1.8 for

TABLE 4. ADJUSTED ODDS RATIOS FOR ISCHEMIC INFARCTION AND HEMORRHAGIC STROKE, ACCORDING TO ORAL-CONTRACEPTIVE USE.*

| VARIABLE | ISCHEMIC INFARCTION† | | | HEMORRHAGIC STROKE‡ | | |
|---|--------------------------|-------------------------|------------------|--------------------------|-------------------------|------------------|
| | NO. OF WOMEN WITH STROKE | NO. OF MATCHED CONTROLS | OR (95% CI) | NO. OF WOMEN WITH STROKE | NO. OF MATCHED CONTROLS | OR (95% CI) |
| Current use vs. non-current use | | | | | | |
| Current use | 17 | 43 | 1.18 (0.54–2.59) | 21 | 50 | 1.14 (0.60–2.16) |
| Noncurrent use§ | 125 | 335 | 1.00 | 127 | 346 | 1.00 |
| Current use vs. past use and no use¶ | | | | | | |
| Current use | 14 | 43 | 0.65 (0.25–1.70) | 14 | 50 | 1.02 (0.37–2.82) |
| Past use | 82 | 271 | 0.49 (0.25–0.98) | 81 | 272 | 0.89 (0.41–1.91) |
| No use§ | 28 | 64 | 1.00 | 14 | 74 | 1.00 |
| Any use vs. no use¶ | | | | | | |
| Any use | 96 | 314 | 0.52 (0.27–1.00) | 95 | 322 | 0.91 (0.43–1.93) |
| No use§ | 28 | 64 | 1.00 | 14 | 74 | 1.00 |

*The numbers of subjects in the adjusted analyses do not total the numbers shown in Table 2 because women with missing values were not included. OR denotes odds ratio, and CI confidence interval. Current use denotes use in the month before the index date. Noncurrent use includes past use and no use.

†Odds ratios have been adjusted for the presence or absence of treated hypertension, the presence or absence of treated diabetes, smoking status, race or ethnic group, and body-mass index.

‡Odds ratios have been adjusted for the presence or absence of treated hypertension, the presence or absence of treated diabetes, smoking status, and race or ethnic group.

§Reference category.

¶Women for whom proxy respondents were interviewed have been excluded.

women with normal blood pressure, 2.8 for women with borderline hypertension, 8.4 for those with moderate hypertension, and 25.7 for those with severe hypertension. The Royal College of General Practitioners' study also reported an interaction between hypertension and current oral-contraceptive use with respect to hemorrhagic stroke.²³ Our study included so few current users of oral contraceptives who had hypertension that the odds ratio for hemorrhagic stroke among current oral-contraceptive users in the subgroup of women with hypertension could not be estimated. Given all the evidence, hypertension should be considered a contraindication to the use of oral contraceptives.

Studies of myocardial infarction have reported interactions of current oral-contraceptive use with current smoking and age over 35 years.^{9–11} We found a positive interaction of smoking with current oral-contraceptive use with respect to hemorrhagic stroke. Our data on a possible interaction of oral contraceptive use with age are difficult to interpret. Our results neither establish nor rule out an interaction of age and current oral-contraceptive use with respect to the risk of stroke. The 95 percent confidence intervals for our odds ratios were wide for all subgroup analyses.

Studies in Great Britain in the late 1970s and early 1980s suggested that the risk of arterial vascular

disease may be related to the type of progestogen contained in oral contraceptives.^{29,30} The World Health Organization Collaborative Study reported an increased risk of venous thromboembolism among current users of oral contraceptive formulations containing desogestrel or gestodene.³¹ In our study, there were no known users of formulations containing these progestogens. The small number of current oral-contraceptive users limits the power of our study to detect differences in risk between formulations containing norethindrone-type progestogens and those containing norgestrel.

In our study, during 3.6 million woman-years of observation, there were 195 ischemic and 201 hemorrhagic strokes in girls and women 15 through 44 years of age. The incidence of ischemic infarction was 5.4 per 100,000 woman-years of observation, and the incidence of hemorrhagic stroke was 5.6 per 100,000 woman-years. Our study documents the low incidence of stroke among young women and provides a basis for interpreting the small increases in the risk of stroke that our results do not rule out.

A drug is deemed safe when the magnitude of its benefits appears to outweigh that of its risks.³² The use of oral contraceptives has a number of established beneficial effects, including most prominently the prevention of pregnancy. This study establishes

TABLE 5. ADJUSTED ODDS RATIOS FOR ISCHEMIC INFARCTION AND HEMORRHAGIC STROKE AMONG CURRENT USERS OF ORAL CONTRACEPTIVES, ACCORDING TO SMOKING STATUS, AGE, AND TYPE OF PROGESTOGEN AND AMONG WOMEN WITHOUT HYPERTENSION.*

| VARIABLE | ISCHEMIC INFARCTION | | | HEMORRHAGIC STROKE | | |
|---------------------|------------------------------------|-----------------|-------------------|------------------------------------|-----------------|-------------------|
| | NO. OF WOMEN WITH STROKE | NO. OF CONTROLS | OR (95% CI) | NO. OF WOMEN WITH STROKE | NO. OF CONTROLS | OR (95% CI) |
| | current users/ noncurrent users | | | current users/ noncurrent users | | |
| Smoking status† | | | | | | |
| Current smoker | 4/43 | 9/55 | 0.74 (0.17-3.25) | 8/42 | 4/62 | 3.64 (0.95-13.87) |
| Not current smoker | 13/82 | 34/280 | 1.32 (0.56-3.13) | 13/85 | 46/284 | 0.80 (0.38-1.70) |
| Age‡ | | | | | | |
| ≥35 yr | 2/99 | 12/256 | 0.35 (0.05-2.65) | 7/93 | 13/252 | 1.44 (0.54-3.83) |
| <35 yr | 15/26 | 31/79 | 1.66 (0.67-4.11) | 14/34 | 37/94 | 0.97 (0.43-2.21) |
| No hypertension§ | 16/100 | 43/324 | 1.24 (0.55-2.80) | 20/108 | 49/331 | 1.38 (0.69-2.76) |
| | current users | | | current users | | |
| Progestogen‡ | | | | | | |
| Norethindrone type¶ | 8 | 28 | 1.04 (0.40-2.69) | 7 | 30 | 0.59 (0.23-1.56) |
| Norgestrel type | 3 | 11 | 0.64 (0.12-3.55) | 6 | 15 | 0.87 (0.29-2.58) |
| Other or unknown | 6 | 4 | 3.12 (0.61-15.86) | 8 | 5 | 4.64 (1.42-15.11) |

*The numbers of subjects in the adjusted analyses do not total the numbers shown in Table 2 because women with missing values were not included. OR denotes odds ratio, and CI confidence interval. Odds ratios are for current users, defined as women who used oral contraceptives in the month before the index date, as compared with the combined group of former users and those who had never used oral contraceptives (noncurrent users).

†Odds ratios have been adjusted for treated hypertension, treated diabetes, and race or ethnic group; those for ischemic infarction have also been adjusted for body-mass index.

‡Odds ratios have been adjusted for treated hypertension, treated diabetes, smoking status, and race or ethnic group; those for ischemic infarction have also been adjusted for body-mass index.

§Odds ratios have been adjusted for treated diabetes, smoking status, and race or ethnic group; that for ischemic infarction has also been adjusted for body-mass index.

¶Includes norethindrone, norethindrone acetate, and ethynodiol diacetate.

||Includes norgestrel, *dl*-norgestrel, levonorgestrel, and unknown types of norgestrel.

the low incidence of stroke among women of child-bearing age. Even if the small increase we observed was due directly to the use of oral contraceptives, the number of excess cases of stroke in healthy women would be small. We found no association between the past use of oral contraceptives and an increased risk of stroke. We conclude that, as used by the women in this study, currently available low-estrogen oral contraceptives are generally safe with respect to the risk of stroke.

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REFERENCES

1. Jordan WM. Pulmonary embolism. *Lancet* 1961;2:1146-7.
2. Lorentz IT. Parietal lesion and "Enovid." *BMJ* 1962;2:1191.
3. Inman WHW, Vessey MP. Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. *BMJ* 1968;2:193-9.
4. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease: a further report. *BMJ* 1969;2:651-7.

5. Sartwell PE, Masi AT, Arthes FG, Greene GR, Smith HE. Thromboembolism and oral contraceptives: an epidemiologic case-control study. *Am J Epidemiol* 1969;90:365-80.
6. Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumours: report from the Boston Collaborative Drug Surveillance Programme. *Lancet* 1973;1:399-404.
7. Sartwell PE. Oral contraceptives and thromboembolism: a further report. *Am J Epidemiol* 1971;94:192-201.
8. Collaborative Group for the Study of Stroke in Young Women. Oral contraception and increased risk of cerebral ischemia or thrombosis. *N Engl J Med* 1973;288:871-8.
9. Mann JI, Vessey MP, Thorogood M, Doll SR. Myocardial infarction in young women with special reference to oral contraceptive practice. *BMJ* 1975;2:241-5.
10. Mann JI, Inman WHW. Oral contraceptives and death from myocardial infarction. *BMJ* 1975;2:245-8.
11. Ory HW. Association between oral contraceptives and myocardial infarction: a review. *JAMA* 1977;237:2619-22.
12. Petitti DB, Wingerd J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid haemorrhage. *Lancet* 1978;2:234-5.
13. Beral V. Mortality among oral-contraceptive users. *Lancet* 1977;2:727-31.
14. Jick H, Porter J, Rothman KJ. Oral contraceptives and nonfatal stroke in healthy young women. *Ann Intern Med* 1978;89:58-60.
15. Inman WHW. Oral contraceptives and fatal subarachnoid haemorrhage. *BMJ* 1979;2:1468-70.
16. Thorogood M, Adam SA, Mann JI. Fatal subarachnoid haemorrhage in young women: role of oral contraceptives. *BMJ* 1981;283:762.
17. Royal College of General Practitioners' Oral Contraception Study. Further analyses of mortality in oral contraceptive users. *Lancet* 1981;1:541-6.

18. Vessey MP, Lawless M, Yeates D. Oral contraceptives and stroke: findings in a large prospective study. *BMJ* 1984;289:530-1.
19. Porter JB, Hunter JR, Jick H, Stergachis A. Oral contraceptives and nonfatal vascular disease. *Obstet Gynecol* 1985;66:1-4.
20. Thorogood M, Mann J, Murphy M, Vessey M. Fatal stroke and use of oral contraceptives: findings from a case-control study. *Am J Epidemiol* 1992;136:35-45.
21. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ* 1993;306:956-63.
22. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrhage and hormonal factors in women: a population-based case-control study. *Ann Intern Med* 1994;121:168-73.
23. Hannaford PC, Croft PR, Kay CR. Oral contraception and stroke: evidence from the Royal College of General Practitioners' Oral Contraception Study. *Stroke* 1994;25:935-42.
24. Collaborative Group for the Study of Stroke in Young Women. Oral contraceptives and stroke in young women: associated risk factors. *JAMA* 1975;231:718-22.
25. Dyken ML, Wolf PA, Barnett HJM, et al. Risk factors in stroke: a statement for physicians by the Subcommittee on Risk Factors and Stroke of the Stroke Council. *Stroke* 1984;15:1105-11.
26. Inman WHW, Vessey MP, Westerholm B, Englund A. Thromboembolic disease and the steroidal content of oral contraceptives: a report to the Committee on Safety of Drugs. *BMJ* 1970;2:203-9.
27. Stolley PD, Tonascia JA, Tockman MS, Sartwell PE, Rutledge AH, Jacobs MP. Thrombosis with low-estrogen oral contraceptives. *Am J Epidemiol* 1975;102:197-208.
28. Gerstman BB, Piper JM, Tomita DK, Ferguson WJ, Stadel BV, Lundin FE. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. *Am J Epidemiol* 1991;133:32-7.
29. Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 30-microgram oestrogen preparations. *BMJ* 1980;280:1157-61.
30. Kay CR. Progestogens and arterial disease — evidence from the Royal College of General Practitioners' study. *Am J Obstet Gynecol* 1982;142:762-5.
31. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995;346:1575-82.
32. Ory HW, Forrest JD, Lincoln R. Making choices: evaluating the health risks and benefits of birth control methods. New York: Alan Guttmacher Institute, 1983.