Annals of Internal Medicine
Established in 1927 by the American College of Physicians

ARTICLE

Use of Low-Dose Oral Contraceptives and Stroke in Young Women

Stephen M. Schwartz, PhD, MPH; David S. Siscovick, MD, MPH; W.T. Longstreth Jr., MD, MPH; Bruce M. Psaty, MD, PhD, MPH; R. Kevin Beverly, MS; T.E. Raghunathan, PhD; Danyu Lin, PhD; and Thomas D. Koepsell, MD, MPH

15 October 1997 | Volume 127 Issue 8 (Part 1) | Pages 596-603

Background: Low-dose oral contraceptives are widely used, but there are limited data on the cerebrovascular risks associated with these medications.

Objective: To determine whether use of low-dose oral contraceptives influences the risk for stroke.

Design: Population-based case–control study.

Setting: Women 18 to 44 years of age who resided in western Washington State between 1991 and 1995.

Participants: Patients with ischemic stroke (*n* = 60), hemorrhagic stroke (*n* = 102), and other types of stroke (*n* = 11) and controls identified through random-digit dialing (*n* = 485).

Measurements: Details about oral contraceptive use and other risk factors for stroke were obtained through in-person interviews.

Results: The estimated incidences of hemorrhagic stroke and ischemic stroke were 6.4 and 4.3 per 100 000 women-years, respectively. Compared with women who had never used oral contraceptives (after adjustment for risk factors for stroke), current users of low-dose oral contraceptives had estimated odds ratios of 0.93 (95% CI, 0.37 to 2.31) for hemorrhagic stroke and 0.89 (CI, 0.27 to 2.94) for ischemic stroke. Compared with past users of oral contraceptives, current users had odds ratios of 1.41 (CI, 0.67 to 2.96) for hemorrhagic stroke and 1.37 (CI, 0.49 to 3.81) for ischemic stroke. For past users compared with never users, the odds ratios were 0.59 (CI, 0.30 to 1.18) for hemorrhagic stroke and 0.57 (CI, 0.25 to 1.32) for ischemic stroke. The odds ratio for hemorrhagic stroke in current users of low-dose oral contraceptives containing norgestrel or levonorgestrel was elevated (3.23 [CI, 1.24 to 8.41]). Among patients with hemorrhagic stroke, the odds ratio for aneurysmal bleeding associated with current use of low-dose oral contraceptives containing norgestrel or levonorgestrel was 4.46 (CI, 1.58 to 12.53).

Conclusions: The overall risk for stroke and type of stroke was not increased among current users of low-dose oral contraceptives in the study population. Larger studies are needed to clarify both the relation of risk for stroke to past use of oral contraceptives and the possible association between current use of norgestrel-containing oral contraceptives and hemorrhagic stroke.

■ Article
- Table of Contents
- Abstract of this article
- Figures/Tables List
- Articles citing this article

■ Services
- Send comment/rapid response letter
- Notify a friend about this article
- Alert me when this article is cited
- Add to Personal Archive
- Download to Citation Manager
- ACP Search

■ PubMed
Articles in PubMed by Author:
- Schwartz, S. M.
- Koepsell, T. D.
- Related Articles in PubMed
- PubMed Citation
- PubMed

Epidemiologic studies conducted in the 1960s and 1970s [1-4] showed an increased risk for stroke as well as myocardial infarction and venoocclusive disease in women who used oral contraceptives containing more than 50 µg of ethinyl estradiol. These reports spurred the development of oral contraceptive pills containing less than 50 µg of ethinyl estradiol. Initial studies of cerebrovascular

risk in users of low-dose oral contraceptives produced conflicting results: Some investigators found increased risks [5, 6], and others found no increased risk [7]. In addition, few data are available on whether the risk for stroke associated with use of low-dose oral contraceptives is influenced by the type of progestin present in these medications. In the United States, most currently available low-dose oral contraceptives contain either norethindrone-type progestins (norethindrone, norethindrone acetate, ethynodiol diacetate, or norethynodrel) or norgestrel-type progestins (norgestrel or levonorgestrel). It has been proposed that the levonorgestrel component of oral contraceptives may offset the cardiovascular benefits that arise from the use of low doses of estrogen [8, 9], but little empirical research has addressed this hypothesis.

A recent study [10] conducted among the members of the Northern and Southern California Kaiser Permanente medical care programs reported that the use of low-dose oral contraceptives available in the United States was not associated with an increased risk for either hemorrhagic or ischemic stroke, regardless of progestin type. In that study, past users of oral contraceptives were at reduced risk for ischemic stroke but not hemorrhagic stroke; this finding was consistent with findings from an earlier study of cerebral thromboembolic attack [5] but differed from those in a previous study of subarachnoid hemorrhage [7]. To provide information on the occurrence of stroke among oral contraceptive users in a U.S. community, we report the results of a population-based case–control study done in a defined geographic region of western Washington State.

Methods

Top
Methods
Results
Discussion
Author & Article Info
References

The source population for our study was women 18 to 44 years of age residing in King, Pierce, or Snohomish counties, Washington, between 1 July 1991 and 28 February 1995. This represented approximately 2.2 million women-years at risk, according to population estimates provided by the State of Washington Office of Financial Management.

Definition and Ascertainment of Case-Patients and Controls

Eligible case-patients were women in the source population with a first diagnosis of fatal or nonfatal stroke and without a history of major coronary heart disease, such as myocardial infarction, angina, or congestive heart failure. We identified potential case-patients through regular review and abstraction of 1) medical records containing cerebrovascular disease discharge diagnoses at all 34 acute care hospitals within the study region and 2) death certificates filed at county health departments. These sources were supplemented with monthly letters sent to all neurologists, neurosurgeons, and physiatrists in the region.

We defined stroke as the new, rapid onset of symptoms and signs consistent with loss of cerebral function that lasted at least 24 hours and could not be ascribed to subdural hematoma; brain tumor; infection; seizure; or other neurologic disease, such as multiple sclerosis. A neurologist reviewed the records to confirm the diagnosis of stroke and to classify confirmed strokes as either arterial or venous in origin. Arterial strokes were further classified as hemorrhages, ischemic events, or "other" [a category that included arterial dissections]. Aneurysmal bleeding was defined as a hemorrhagic stroke in which the diagnostic workup or autopsy showed 1) blood in the subarachnoid space with or without a demonstrated aneurysm and no evidence of arteriovenous malformation or 2) an aneurysm with blood in other locations, such as the parenchyma or ventricles, and no evidence of arteriovenous malformation.

Eligible controls were women 18 to 44 years of age who were residents of King, Pierce, or Snohomish counties during the case-diagnosis period and had no history of major coronary or cerebrovascular disease. We identified a sample of these women by using random-digit dialing [11].

Data Collection

Participating case-patients and controls were interviewed in person by trained female interviewers who used a structured questionnaire that elicited information about cardiovascular risk factors. We used the reproductive calendar method and color photographs of all oral contraceptive pills marketed in the United States to help women recall dates and specific brands of oral contraceptives used. All interview questions elicited information about the time period before each participant's reference date, which was the date of stroke for a case-patient and a date assigned at random from among the potential stroke occurrence dates

for a control. We also sought in-person interviews with proxy respondents for case-patients who had died or were mentally impaired. To evaluate the quality of information received from proxy respondents, we did in-person interviews with proxy respondents for case-patients who had not died and who were not mentally impaired and for a random one third of controls [12]. The interviews with proxy respondents contained the same questions asked of the case-patients and controls. Proxy respondents and participants were not interviewed in each other's presence.

Statistical Analysis

A woman was considered to be a current user of oral contraceptives if she or her proxy reported that she had been taking these pills within a month of her reference date. She was considered to be a past user if she had used oral contraceptives but was not using them at that time. The remaining women were classified as having never used oral contraceptives. We classified current users of oral contraceptives according to whether the pill was a low-dose (<50 µg of ethinyl estradiol) or a high-dose (50 µg of ethinyl estradiol) formulation. No women reported current use of pills containing more than 50 µg of ethinyl estradiol.

We used unconditional logistic regression models to compute estimated odds ratios and 95% CIs [13]. We excluded from all analyses women who were pregnant at the reference date (5 case-patients, 14 controls) and women for whom information on use of oral contraceptives was missing (6 case-patients, 24 controls). Thus, 173 case-patients and 485 controls were included in the analysis. Of the case-patients, 102 were classified as having had hemorrhagic stroke, 60 were classified as having had ischemic stroke, and 11 were classified as having had other types of stroke. Sixty-nine of the hemorrhagic strokes were classified as cases of aneurysmal bleeding.

In all analyses, we examined the potential confounding effect of known or suspected cerebrovascular risk factors. We initially adjusted all odds ratios for age (in years), race, treated hypertension, and cigarette smoking; we then examined whether further adjustment for other characteristics changed the estimates of association. We also conducted subanalyses in which case-patients who did not have residential telephones were excluded. To determine whether the risk for total stroke associated with oral contraceptive use varied according to other cardiovascular risk factors, we estimated odds ratios separately by age, cigarette smoking status, obesity (body mass index $\geq$ 27.3 kg/m^2 or <27.3 kg/m^2), and among women not receiving treatment for hypertension.

Results

▲ Top
▲ Methods
▪ Results
▼ Discussion
▼ Author & Article Info
▼ References

Case-Patients and Controls

We identified 249 women who met the eligibility criteria for stroke: One hundred forty-one were classified as having had hemorrhagic stroke, 95 as having had ischemic stroke, 10 as having had arterial dissection, and 3 as having had venous stroke. The results of computed tomography, magnetic resonance imaging, or both were available for 92% of patients with stroke diagnoses. Ninety-one of the 141 patients with hemorrhagic strokes were further classified as having had strokes as a result of aneurysms. Of the 198 patients who were alive and not mentally impaired as a result of their strokes, 149 (75.3%) participated in the study. Most nonparticipation was due to patient refusal (n = 30) or inability to locate the patient (n = 13). For the 51 eligible patients with stroke who died or were mentally impaired as a result of the stroke, we attempted to identify and recruit proxy respondents.

Through random-digit dialing, we completed a household census for 94.9% of the residences contacted. Among the eligible women identified, we attempted to recruit 691 who were similar in age to the patients with stroke. Six of the potential controls were excluded because of a history of major coronary heart disease or stroke, and one was excluded because she was unable to communicate in English. Of the remaining 684 women, 526 were recruited into the study, for an estimated overall response rate of 73.0% (526 ÷ 684 x 0.949).

Proxy Respondents

We recruited proxy respondents for 34 of the 51 patients with stroke who had died or were mentally impaired, 106 of the 149

patients with stroke who had not died and were not mentally impaired, and 160 of the 273 controls whom we had selected at random. Approximately 80% of the proxy respondents for both case-patients and controls were spouses or sexual partners (54.3% of proxy respondents for case-patients; 64.4% of proxy respondents for controls), mothers (15.7% of proxy respondents for case-patients; 10.0% of proxy respondents for controls), or roommates or close friends (10.7% of proxy respondents for case-patients; 8.1% of proxy respondents for controls) of the participants.

Because data for approximately 18% of the case-patients were obtained through proxy respondents, we used proxy respondent data rather than control respondent data for 93 of the controls selected. The distribution of proxy types (spouse or sexual partner versus another person) for these 93 controls was similar to the distribution of proxy types for the 34 deceased or mentally impaired case-patients. On the basis of data for the 79 case-patients and 120 controls for whom we had conducted interviews with both the participant and her proxy respondent, the sensitivity and specificity of proxy reporting of current use of oral contraceptives among case-patients were 90.9% and 100%, respectively. The corresponding figures for controls were 100% and 99.0%, respectively. There were too few current users to allow us to examine the sensitivity and specificity of proxy reporting specifically for oral contraceptives containing norgestrel-type and norethindrone-type progestin. Past use of oral contraceptives was underestimated by proxy respondents, but the underestimation was similar for case-patients and controls. Sensitivity and specificity were 67.9% and 100%, respectively, for case-patients and 76.7% and 92.3%, respectively, for controls.

Incidence of Stroke

The incidence of total stroke among 18- to 44-year-old women in our population was 11.3 per 100 000 women-years, and the rate of hemorrhagic stroke was higher than the rate of ischemic stroke (6.4 per 100 000 women-years compared with 4.3 per 100 000 women-years).

Cardiovascular Risk Factors

Compared with controls, patients with stroke were more likely to be African American, to have received less formal education, to be receiving current treatment for hypertension or diabetes, to be current cigarette smokers, and to be postmenopausal, and they were less likely to exercise three or more times per week (Table 1). For the most part, these differences were statistically significant and were consistent across types of stroke; exceptions were that diabetes was not more common among case-patients with hemorrhagic stroke than among controls and patients with aneurysmal bleeding were not more likely than controls to be postmenopausal. Body mass index was similar for all patients with stroke combined compared with controls, but patients with ischemic stroke had a higher body mass index than controls.

View this table:
[in this window]
[in a new window]

Table 1. **Distribution of Demographic and Cardiovascular Risk Factors for Case-Patients by Type of Stroke and Controls by Oral Contraceptive Use***

Correlates of Oral Contraceptive Use among Controls

Current users of oral contraceptives tended to be younger, were more likely to be of non-Hispanic white ethnicity, and tended to have lower body mass indices compared with past users or never users (Table 1). Past users were more likely to be current smokers (23.6%) than were either current users (14.8%) or never users (9.8%). Treated hypertension and diabetes were uncommon among controls, but the prevalence of treated hypertension was lowest among current users and highest among never users. Past users were less likely than current users or never users to have treated diabetes. Use of oral contraceptives was not associated with level of education or vigorous exercise, but women who had never used these medications consumed alcohol less frequently than did either current users or past users. Except as indicated in Table 1, all differences between current, past, and never users of oral contraceptives were consistent with chance ($P > 0.2$).

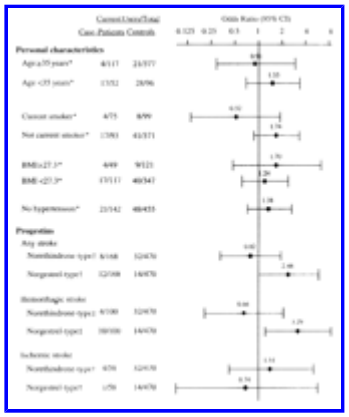
Oral Contraceptive Use and Stroke

Current users of low-dose oral contraceptives had a risk for stroke similar to that of women who had never used these medications (odds ratio, 0.89 [95% CI, 0.42 to 1.90]) (Table 2). The results did not differ appreciably between hemorrhagic stroke and ischemic stroke. Compared with women who were not current users of oral contraceptives, the odds ratios for current users were 1.51 (CI, 0.71 to 3.19) for hemorrhagic stroke and 1.30 (CI, 0.61 to 2.79) for ischemic stroke. The odds ratios for current users compared with past users were generally higher than those for current users compared with women who were not current users. For past users compared with never users, the odds ratios were about 0.5 to 0.6 (CI including 1.0) for both hemorrhagic and ischemic stroke. The odds ratios for aneurysmal bleeding were similar to or slightly greater than the odds ratios for all hemorrhagic strokes, but none of the CIs excluded 1.0. We did not calculate odds ratios for stroke for the few women who were current users of oral contraceptives containing 50 µg of ethinyl estradiol (two case-patients with hemorrhagic stroke, one case-patient with ischemic stroke, and three controls).

View this table:
[in this window]
[in a new window]

Table 2. **Adjusted Odds Ratios for Stroke and Type of Stroke in Relation to Current Use of Low-Dose Contraceptives and Past Use of Oral Contraceptives***

The odds ratios for current use of low-dose oral contraceptives and total stroke were not clearly elevated among older women, cigarette smokers, or obese women (Figure 1), and they were essentially the same among women without treated hypertension as among all women; there were too few women with treated hypertension to allow us to compute odds ratios for this group. These analyses were based on small numbers of current users of low-dose oral contraceptives among older women, current smokers, and obese women. Odds ratios greater than 2 were found for total stroke and hemorrhagic stroke in relation to current use of pills containing norgestrel-type progestins (levonorgestrel or norgestrel) but not pills containing norethindrone-type progestins (norethindrone, norethindrone acetate, ethynodiol diacetate, or norethynodrel) (Figure 1). For aneurysmal bleeding, the odds ratio for norgestrel-type progestins was 4.46 (CI, 1.58 to 12.53) and the odds ratio for norethindrone-type progestins was 0.86 (CI, 0.23 to 3.20). In relation to ischemic stroke, the odds ratios for current use of norgestrel-type pills and norethindrone-type pills differed little and were imprecisely estimated. The odds ratios calculated according to progestin type in the currently used pill were similar when current users were compared with past users, but they generally were decreased when current users were compared with never users. For example, for use of norgestrel-type pills compared with never use of oral contraceptives, the odds ratio for hemorrhagic stroke was 2.13 (CI, 0.71 to 6.38) and the odds ratio for aneurysmal bleeding was 3.03 (CI, 0.89 to 10.35). All analyses in relation to the progestin type of the currently used oral contraceptive were based on small numbers of current users, particularly for ischemic stroke. Exclusion of case-patients who did not have residential telephones from these and other analyses produced minor increases in the odds ratios that did not alter the direction or strength of our findings.



View larger version (25K):
[in this window]
[in a new window]

Figure 1. **Odds ratios and 95% CIs for stroke in current users of low-dose oral contraceptives. Top.** For total stroke by personal characteristics. **Bottom.** According to progestin type, by type of stroke. * Compared with women who were not current users, adjusted for age (continuous), treated diabetes (yes, no), ethnicity (African American, other), and other risk factors for stroke listed. For example, odds ratios according to smoking are adjusted for age (continuous), treated diabetes (yes, no), ethnicity (African American, other), body mass index (BMI) (continuous), and treated hypertension (yes, no). † Compared with women who were not current users, adjusted for age (continuous), cigarette smoking (current, not current), ethnicity (African American, other), treated hypertension (yes, no), treated diabetes (yes, no), and body mass index (continuous). ‡ Compared with women who were not current users, adjusted for age (years), treated hypertension (yes, no), smoking (current, past, never), race (white non-Hispanic, African American, other), and average frequency of alcohol use in the year before the reference date (≥1

time per week, 1 to 3 times per month, < 1 time per month).

Discussion

Top
Methods
Results
Discussion
Author & Article Info
References

Like another recent U.S. population-based study [10], we found that stroke is a very rare event in women 18 to 44 years of age. We did not find that current users of low-dose oral contraceptive pills in our population were at increased risk for either hemorrhagic or ischemic stroke compared with women who had never used these medications. At most, we found weak, nonsignificant elevations in odds ratios for current users compared with women who were not current users or women who were past users. We found no strong evidence that the odds ratios for oral contraceptive use and total stroke were elevated in women who were at increased risk for stroke because of age, smoking, or obesity. We also found a suggestion of inverse associations between past oral contraceptive use and both hemorrhagic and ischemic stroke, although the CIs overlapped 1. Odds ratios for hemorrhagic stroke, especially aneurysmal bleeding, were significantly elevated for current use of low-dose oral contraceptive pills containing norgestrel-type progestins but not of those containing norethindrone-type progestins.

Our findings for current users of low-dose oral contraceptives in relation to hemorrhagic and ischemic strokes are similar to those reported recently from European sites in a large multinational study [14, 15], and they are probably statistically compatible with the odds ratios of 1.1 to 1.2 reported from the Kaiser Permanente study [10]. The odds ratios of less than 1.0 for ischemic stroke in past users in our population are similar to those reported elsewhere [5, 10], but they contrast with the absence of an association found in the European centers of the World Health Organization Multinational Study [15]. Our suggestion of a reduced odds ratio with hemorrhagic stroke is consistent with the results of a previous study of subarachnoid hemorrhage conducted earlier in our area [7], but it differs from the results of others [6, 10, 14]. Results of analyses of past oral contraceptive use are difficult to interpret because of variation in the ethinyl estradiol and progestin doses over time and across populations. Past use reported by women who are of mid-to-late childbearing age in the 1990s is likely to have consisted of a mixture of low-dose and high-dose formulations; thus, one interpretation of the inverse associations in recent studies would be a favorable long-term impact of low-dose ethinyl estradiol on the development of stroke. Alternatively, past use of oral contraceptives among women who are currently of childbearing age may reflect the selection of women at very low risk for stroke for reasons that we could not adequately measure, and thus control for, in our study.

Our results for hemorrhagic and ischemic stroke in relation to the progestin component of current low-dose oral contraceptives are similar to those reported from the Kaiser Permanente study [10], with one exception. For hemorrhagic stroke, we found an odds ratio of 3.28 (CI, 1.27 to 8.57) for current use of norgestrel-type progestin pills compared with no current use of oral contraceptives, whereas the corresponding odds ratio was 0.82 in the Kaiser Permanente Study [CI, 0.29 to 2.58]. The relatively few current users of low-dose oral contraceptives in both reports and the overlapping CIs suggest that chance may account for the apparently different results. Characteristics of the two studies that may also contribute to the discrepant results include 1) variation in ethnic composition [our population almost entirely comprised non-Hispanic white persons, in contrast to the Kaiser Permanente study] and 2) different levels of missing information on progestin type (the progestin type of the pill used by one third of the case-patients and one tenth of the controls who were current users in the Kaiser Permanente study could not be classified; the corresponding figures for our study were 4% and 15%, respectively).

Compared with norethindrone-type or newer progestins (desogestrel or norgestimate), levonorgestrel may produce greater elevations in blood pressure [16, 17] and may have stronger antiestrogenic actions [18]. If low-dose ethinyl estradiol mimics the observed effects of natural estrogens on blood pressure reduction, prevention of collagen and elastin wasting [19, 20], and reduced susceptibility to arterial stiffening [21], the antiestrogenic effects of levonorgestrel might increase the chances that an aneurysm will develop, rupture, or both. The few case-patients on which our progestin type results are based do not allow us to draw firm conclusions. Rather, given the results of previous studies suggesting associations between levonorgestrel and risk for arterial vascular disease [8, 9], they support the need for additional studies to clarify whether the progestin component of low-dose oral contraceptive pills has any influence on the risk for stroke.

Our population-based study design and standardized case review incorporating original diagnostic reports strengthen the validity and generalizability of our results. In addition, by including proxy respondents for case-patients who had died or were impaired

because of stroke, as well as for a similar proportion of controls, we reduced the chances that our findings were influenced by associations between use of oral contraceptives and severity of stroke. Proxy respondents provided highly accurate information about whether a case-patient or control was a current user of oral contraceptives, but they underestimated past use. This misclassification would tend to attenuate associations with past use of oral contraceptives.

The most important limitation of our study is that all odds ratios for current use (particularly those estimated according to risk factors for stroke and progestin type) were based on small numbers of case-patients. As a result, most of the small differences that we observed were consistent with chance, and the absence of statistically discernible differences in some analyses could be a consequence of low statistical power. For example, we cannot exclude the possibility that for total stroke, the true odds ratio associated with current use of low-dose oral contraceptives is as high as 2.4 or as low as 0.7. Diagnostic bias [22] is an unlikely explanation for our results because the only odds ratios that were elevated were those for specific formulations of low-dose oral contraceptives in relation to the more severe hemorrhagic strokes. Reliance on participant memory for information on oral contraceptive use could have led to recall bias, and nonparticipation could have caused response bias. These potential errors may account for some or all of the small elevations in the odds ratios for current users of low-dose oral contraceptives compared with women not currently using these medications.

The incidence of stroke is very low among young women, and our data suggest that in the general population, there is little or no increased risk for stroke associated with the use of currently available low-dose oral contraceptive pills. Even if the risk is elevated by as much as 30% to 40%, less than one additional stroke will occur annually per 100 000 women 18 to 44 years of age. This rate is very low considering that oral contraceptive pills are highly effective, reversible methods of contraception and have well-established health benefits [23]. Our results are therefore consistent with those of other recent reports [10, 14, 15] indicating that, in the aggregate, reduction in the estrogen content of oral contraceptives has greatly enhanced the cerebrovascular safety of these commonly prescribed medications. Although we did not observe increased risks for stroke associated with low-dose oral contraceptive use among cigarette smokers or persons with hypertension, other recent studies [10, 14, 15] have found strong associations among women who are at increased risk for stroke because of these characteristics. Physicians should therefore continue to follow existing contraindications when prescribing low-dose oral contraceptives.

Dr. Longstreth: Harborview Medical Center, Department of Neurology, Box 359775, Seattle, WA 98195.

Dr. Raghunathan: Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI 48106-1248.

Author and Article Information

Top
Methods
Results
Discussion
Author & Article Info
References

From University of Washington, Seattle, Washington.
Acknowledgments: The authors thank the hospital record administrators and physicians who assisted in identifying patients for this study; Fran Chard, Karen Graham, and Carol Handley-Dahl for abstracting medical records; Judy Kaiser, Marlene Bengeult, Carol Ostergard, Denise Horlander, and Barb Twaddell for recruiting and interviewing case-patients and controls; Sandy Tronsdal and Jill Ashman for coordinating these activities; and all of the women who participated in the study.
Grant Support: By contract HD-1-3107 with the National Institute of Child Health and Human Development.
Requests for Reprints: Stephen M. Schwartz, PhD, Cardiovascular Health Research Unit, 1730 Minor Avenue, Suite 1360, Seattle, WA 98101.
Current Author Addresses: Drs. Schwartz, Siscovick, Psaty, Lin, and Koepsell: Cardiovascular Health Research Unit, 1730 Minor Avenue, Suite 1360, Seattle, WA 98101.

References

1. Inman WH, Vessey MP. Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. Br Med J. 1968; 2:193-9.

2. Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumours. Report from the Boston Collaborative Drug Surveillance Programme. Lancet.

Top
Methods
Results
Discussion
Author & Article Info

1973; 1:1399-404.[Medline]

- **References**

3. Mortality among oral contraceptive users. Royal College of General Practitioners' Oral Contraceptive Study. Lancet. 1977; 2:727-31.

4. Mann JI, Inman WH. Oral contraceptives and death from myocardial infarction. Br Med J. 1975; 2:245-8.

5. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case–control study. BMJ. 1993; 306:956-63.

6. Thorogood M, Mann M, Murphy M, Vessey M. Fatal stroke and use of oral contraceptives: findings from a case–control study. Am J Epidemiol. 1992; 136:35-45.

7. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrage and hormonal factors in women. A population-based case–control study. Ann Intern Med. 1994; 121:168-73.

8. Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 30-µg oestrogen preparations. Br Med J. 1980; 280:1157-61.

9. Kay CR. Progestogens and arterial disease-evidence from the Royal College of General Practitioners' study. Am J Obstet Gynecol. 1982; 142(6 pt 2):762-5.

10. Petitti DB, Sidney S, Bernstein A, Wolf S, Quesenberry C, Ziel HK. Stroke in users of low-dose oral contraceptives. N Engl J Med. 1996; 335:8-15.

11. Hartge P, Brinton LA, Rosenthal JF, Cahill JI, Hoover RN, Waksberg J. Random digit dialing in selecting a population-based control group. Am J Epidemiol. 1984; 120:825-33.

12. Nelson LM, Longstreth WT Jr, Koepsell TD, van Belle G. Proxy respondents in epidemiologic research. Epidemiol Rev. 1990; 12:71-86.

13. Thompson WD Jr. Statistical analysis of case–control studies. Epidemiol Rev. 1994; 16:33-50.

14. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case–control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1996; 348:505-10.[Medline]

15. Ischemic stroke and combined oral contraceptives: results of an international, multicentre, case–control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1996; 348:498-505.

16. Meade TW, Haines AP, North WR, Chakrabarti R, Howarth DJ, Stirling Y. Haemostatic, lipid, and blood-pressure profiles of women on oral contraceptives containing 50 µg or 30 µg oestrogen. Lancet. 1977; 2:948-51.

17. Godsland IF, Crook D, Devenport M, Wynn V. Relationships between blood pressure, oral contraceptive use and metabolic risk markers for cardiovascular disease. Contraception. 1995; 52:143-9.

18. Phillips A, Hahn DW, Klimek S, McGuire JL. A comparison of the potencies and activities of progestogens used in contraceptives. Contraception. 1987; 36:181-92.

19. Brincat M, Moniz CF, Studd JW, Darby AJ, Magos A, Cooper D. Sex homones and skin collagen content in postmenopausal women. Br Med J (Clin Res Ed). 1983; 287:1337-8.

20. Bolognia JL, Braverman IM, Rousseau ME, Sarrel PM. Skin changes in menopause. Maturitas. 1989; 11:295-304.

21. Gangar KF, Vyas S, Whitehead M, Crook D, Meire H, Campbell S. Pulsatility index in internal carotid artery in relation to

transdermal oestradiol and time since menopause. Lancet. 1991; 338:839-42.

22. Realini JP, Goldzieher JW. Oral contraceptives and cardiovascular disease: a critique of the epidemiologic studies. Am J Obstet Gynecol. 1985; 152(6 pt 2):729-98.

23. Vessey MP. Benefits and risks of combined oral contraceptives. Methods Inf Med. 1993; 32:222-4.

This article has been cited by other articles:

ARCHIVES OF INTERNAL MEDICINE HOME

W.-S. Chan, J. Ray, E. K. Wai, S. Ginsburg, M. E. Hannah, P. N. Corey, and J. S. Ginsberg
Risk of Stroke in Women Exposed to Low-Dose Oral Contraceptives: A Critical Evaluation of the Evidence
Archives of Internal Medicine, April 12, 2004; 164(7): 741 - 747.
[Abstract] [Full Text] [PDF]

■ **Article**
- Table of Contents
- Abstract of this article
- Figures/Tables List
- Articles citing this article

■ **Services**
- Send comment/rapid response letter
- Notify a friend about this article
- Alert me when this article is cited
- Add to Personal Archive
- Download to Citation Manager
- ACP Search

■ **PubMed**

Articles in PubMed by Author:
- Schwartz, S. M.
- Koepsell, T. D.
- Related Articles in PubMed
- PubMed Citation
- PubMed

Home | Current Issue | Past Issues | Search | Collections | CME | PDA Services | Subscribe | Contact Us | Help | ACP Online