Oral Contraceptives and Stroke

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In 1962 Lorentz described a 41-year-old woman who had an ischemic stroke while taking oral contraceptives. By 1970, 93 cases of ischemic strokes in young women using oral contraceptives had been reported. Establishing that a common exposure, oral contraceptives, causes a rare outcome, stroke, is methodologically challenging. Experimental studies with random allocation of subjects are not possible. Instead, epidemiological, observational studies are needed to distinguish coincidence from causation. In evaluating whether oral contraceptives cause stroke, two major types of observational studies have been undertaken: case-control and cohort.

The case-control study is well suited for the investigation of rare diseases. Investigators begin by identifying cases with the disease (stroke), finding appropriate controls without the disease, and then proceeding retrospectively to determine exposure (oral contraceptives) in the cases and controls. Although these studies yield no information concerning the absolute risk of developing disease, an estimate can be made of the relative risk in the exposed individual compared with the unexposed. For example, a relative risk of one would indicate equal risk. Greater than one, the larger the estimated relative risk, the greater the risk of disease in the exposed, and the stronger the association between exposure and outcome. Case-control studies can be done swiftly and inexpensively, but because of their retrospective nature, they are particularly susceptible to bias.

In cohort studies, investigators begin with an exposed and unexposed population that is followed until the outcomes of interest occur. Since incidence of disease is measured, both the absolute risk and the relative risk of disease can be determined. The difference between the incidence of disease in the exposed and unexposed is the risk difference. Because the outcomes are rare, huge numbers of exposed and unexposed persons need to be followed for years. These studies are expensive and difficult to conduct.

Case-Control Studies

In all case-control studies relating oral contraceptives and stroke, the focus has been on stroke survivors because of the need to determine retrospectively the use of oral contraceptives (Table 1). In 1969 two case-control studies appeared that had similar designs and results. Vessey and Doll identified 19 young women with ischemic strokes from several British hospitals, and Sartwell and associates reported 13 from several United States hospitals. In both studies investigators excluded from cases and controls any patients with conditions that might predispose to stroke, such as hypertension and diabetes mellitus. In the British study the estimated relative risk was 6, and in the United States study it was 19. Despite small numbers both of these risks were statistically significant.

The Collaborative Group for the Study of Stroke in Young Women followed with a large case-control study. Cases were women aged 15 to 44 years admitted to a hospital with a diagnosis of cerebrovascular disease. This was the first study to consider both ischemic and hemorrhagic strokes; over 50% of the latter group were subarachnoid hemorrhages. Matched controls came both from the cases' hospitals and neighborhoods. Information on use of oral contraceptives was obtained by interview and was available in only about 70% of cases and controls. Because death was more common after a hemorrhagic than an ischemic stroke, fewer patients with hemorrhagic strokes were interviewed. The investigators estimated that the risk of thrombotic stroke was nine times greater for oral contraceptive users than for nonusers, and the risk of hemorrhagic stroke was two times greater. The Group also studied other risk factors for stroke and concluded that oral contraceptives increased the risk of stroke even after considering the effects of smoking, hypertension, and migraine. Smoking increased the risk of hemorrhage but not thrombotic strokes. At each level of cigarette consumption, pill users were at greater risk for hemorrhagic stroke than were nonusers.

The Boston Collaborative Drug Surveillance Program considered both ischemic and hemorrhagic strokes. After including women discharged alive after all types of stroke and excluding those with conditions that might predispose to stroke or contraindicate oral contraceptive use, only 14 cases remained; only one had a subarachnoid hemorrhage. Eleven of the 14 cases used oral contraceptives compared to seven of 56 controls. They estimated the relative risk of stroke associated with oral contraceptive use to be 26, again significant.

The last two case-control studies which had similar designs and results dealt exclusively with subarachnoid hemorrhage. Inman identified 286 women aged 15 to 44 years who were certified as dying from subar-
earlier in the 1960's. The four studies that we shall review are listed in Table 2.

### Cohort Studies

Several cohort studies were begun in 1968 to settle the issue of whether oral contraceptives had serious adverse effects. Unlike the case-control design the cohort design does not have the problems of determining exposure to oral contraceptives. Most of the experience in these studies is with contraceptive preparations containing lower doses of estrogens than had been used earlier in the 1960's. The four studies that we shall review are listed in Table 2.

The largest and longest running study was initiated by the Royal College of General Practitioners in 1968. Over a 14-month period 23,000 users of oral contraceptives and 23,000 nonusers matched for age and marital status were enrolled. The cohort has been followed for over a decade to determine deleterious outcomes. As of 1981, users were four times more likely to die from vascular disease than were nonusers. The excess was due to deaths from ischemic heart disease and subarachnoid hemorrhage. Unlike the case-control studies that examined mostly survivors, this study examined only fatalities. The risk of strokes not due to subarachnoid hemorrhage was elevated but not significantly. The results is not unexpected because, unlike subarachnoid hemorrhage, these strokes are rarely fatal in this young population. Patients who had ever used oral contraceptives were four times more likely than never users to have a fatal subarachnoid hemorrhage. Interestingly, both current and former users were at increased risk.

Despite over 300,000 woman-years of observation, these findings were based on only 34 stroke-related deaths, 20 due to subarachnoid hemorrhages. Only three of the 20 patients with subarachnoid hemorrhage, mean age 42 years, had never used the pill; six were current users and 11 former users. The relative risk for current users was 3.2 and for former users 4.5. Fourteen of the patients with subarachnoid hemorrhage were smokers. The authors concluded that the use of oral contraceptives significantly increases the risk for fatal subarachnoid hemorrhage but that the risk is confined to women over 35 years, especially if they smoke. Younger, healthy women who did not smoke did not significantly increase their risk of fatal stroke by using oral contraceptives. Future analyses will include disease-related morbidity as well as mortality.

The Oxford/Family Planning Association Contraceptive Study also began in 1968 and enrolled 17,032 women from family planning clinics; 56% were using oral contraceptives. In an interim report from 1976, Vessey and associates described the 13 strokes, both fatal and nonfatal, that had occurred; 10 of these patients had used oral contraceptives. There were four subarachnoid hemorrhages, two in users and two in nonusers, and only two fatal strokes, one thrombotic and one hemorrhagic. The relative risk of all types of

### Table 1: Case-control Studies of Oral Contraceptives and Stroke

<table>
<thead>
<tr>
<th>Studies</th>
<th>Types of strokes (N)</th>
<th>Estimated relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey and Doll 1969</td>
<td>Ischemic (19)</td>
<td>6</td>
</tr>
<tr>
<td>Sartwell et al 1969</td>
<td>Ischemic (13)</td>
<td>19</td>
</tr>
<tr>
<td>Collaborative 1973</td>
<td>Ischemic (140)</td>
<td>9</td>
</tr>
<tr>
<td>Collaborative 1975</td>
<td>Hemorrhagic (195)</td>
<td>2</td>
</tr>
<tr>
<td>Jick et al 1978</td>
<td>Ischemic (13)</td>
<td>26</td>
</tr>
<tr>
<td>Inman 1979</td>
<td>Subarachnoid hemorrhage (134)</td>
<td>1.5</td>
</tr>
<tr>
<td>Thorogood et al 1981</td>
<td>Subarachnoid hemorrhage (168)</td>
<td>1.4</td>
</tr>
</tbody>
</table>

### Table 2: Cohort Studies of Oral Contraceptives and Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Type of stroke (N)</th>
<th>Type of oral contraceptive use</th>
<th>Relative risk</th>
<th>Risk differences (per 100,000 woman-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal College of General Practitioners 1968</td>
<td>46,000</td>
<td>Fatal strokes, not SAH (14)</td>
<td>Ever</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Oxford/Family Practice Association 1968</td>
<td>17,032</td>
<td>Fatal and nonfatal strokes (13)</td>
<td>Current</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Walnut Creek 1968</td>
<td>16,638</td>
<td>Fatal and nonfatal SAH (11)</td>
<td>Current</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Boston Collaborative 1977</td>
<td>40,000</td>
<td>Fatal and nonfatal strokes (7)</td>
<td>Current</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

SAH = subarachnoid hemorrhage.
stroke was five. The number for subarachnoid hemorrhage was too small to analyze separately. In 1981, when they next reviewed their data on vascular deaths, only one additional stroke had occurred, a subarachnoid hemorrhage. Although the over-all risk for stroke, fatal and nonfatal, was significantly elevated at five, the findings for fatal strokes were not significant due to small numbers. In both reports, these authors emphasize that their population was healthier with substantially lower death rates than an age and sex adjusted population from England and Wales. The good health in this cohort and the relatively small number of total woman-years of observation (142,210 woman-years compared to 322,438 woman-years in Royal College of General Practitioners’ Study) may explain why only one death from subarachnoid hemorrhage was seen instead of 6.7 as predicted using the Royal College of General Practitioners’ data.

A third study involved a cohort of women using a comprehensive medical care program at the Kaiser-Permanente Medical Center in Walnut Creek, California. The Walnut Creek Contraceptive Drug Study enrolled and followed 16,638 women and is the smallest of the cohort studies. Despite 127,490 total woman-years of observation, investigators, did not find a significant excess of hospitalization or deaths due to ischemic strokes in users compared to nonusers. From this group of women, Pettiti and Wingred chose to analyze the data from patients with subarachnoid hemorrhage using a case-control method. They identified 11 cases in the cohort with subarachnoid hemorrhages from ruptured aneurysms. Each case had from 197 to 516 matched controls that were drawn from the remainder of the cohort. Nine of the 11 cases had used the pill; four were current users, and five were past users. Eight of the 11 cases were smokers. The relative risk associated with oral contraceptive use or with smoking was six, but for smoking and oral contraceptive use combined the relative risk was 22. As in the Royal College of General Practitioners’ study, past users also had a significantly elevated risk for subarachnoid hemorrhage. Most of these cases were in women over 50 years old, and only four were under 44 years, a cutoff age used in many of the case-control studies. In a subsequent study, cigarette smoking was found to be the major risk factor in this cohort for all types of vascular disease that led to hospitalization or death.

The final cohort study suffers from the same problems as the previous two studies. It has relatively small numbers and a population that is healthier than an age and sex adjusted population. Porter and associates from the Boston Collaborative Drug Surveillance Program defined oral contraceptive use and adverse outcomes in over 40,000 healthy women aged 20 to 44 at the Group Health Cooperative of Puget Sound. They used computerized records of prescriptions filled and hospital discharge diagnoses covering three years beginning in 1977. Based on 141,717 woman-years experience, 21 women with stroke were identified, and 14 were excluded because of predisposing conditions. Of the remaining seven strokes in previously healthy young women, none was a current user of oral contraceptives. Among the 14 patients excluded, three were on oral contraceptives: two developed hemorrhagic strokes, and one developed thrombotic stroke.

Discussion
The first step in establishing whether oral contraceptives cause strokes is to evaluate the validity of the epidemiological studies. Do bias, chance, and confounding explain away the association? These issues have been addressed by several authors, and the consensus is that oral contraceptives are associated with strokes, both ischemic and hemorrhagic. We believe that study design can explain some of the apparent inconsistencies among studies. Ischemic strokes are infrequently fatal in this age group so studies examining mortality of ischemic strokes have shown less effect of oral contraceptives than studies examining morbidity or both mortality and morbidity. From these latter studies, the estimates of relative risk for ischemic stroke associated with oral contraceptive use has varied from 5 to 26.

The association between the pill and subarachnoid hemorrhage was not initially suspected. Case reports dealt only with ischemic strokes, and the early case-control studies excluded patients with hemorrhagic strokes. Because of difficulty determining exposure in the case-control studies, the cohort studies are the best for evaluating the relation between the pill and subarachnoid hemorrhage. Whether considering fatal or fatal and nonfatal subarachnoid hemorrhages in the cohort studies, the risk associated with oral contraceptive use is significantly elevated with relative risks between 3.2 and 6.5. The association between the pill and subarachnoid hemorrhage is substantially modified by cigarette smoking which by itself seems to be an independent risk. Sturtevant has questioned this independence. He has argued that cigarette smoking confounds the relation between oral contraceptives and subarachnoid hemorrhages and may be the sole factor responsible for the increased risk.

From these studies has come a clearer picture of the woman at increased risk of stroke from oral contraceptives. Most strokes have occurred in women who are older, who smoke cigarettes, and who have other risk factors such as hypertension. Both practitioners and patients have become increasingly aware of these factors. As healthier populations with a lower incidence of stroke were studied, it becomes more difficult to demonstrate an increased risk of stroke in pill users.

So far, we have considered consistency among epidemiological studies. How about consistency with other medical knowledge? Is it biologically plausible that oral contraceptives cause stroke? Tooke and McNicol and others have reviewed data indicating that oral contraceptives bring about thrombotic strokes by changes in the clotting system, fibrinolytic systems, and platelets. Changes in glucose metabolism, in lipid metabolism, and of hematocrit have also been noted. Hypertension is a major risk factor for ischemic and hemorrhagic stroke. Dalen and Hickler have reviewed the convincing evidence that the pill is associated with a rise in systolic and diastolic blood pressure.
Investigators\textsuperscript{11, 15} have also hypothesized that oral contraceptives somehow make cerebral vasculature more prone to aneurysm formation and rupture.

Distinguishing thrombotic from embolic strokes can be difficult, and none of these epidemiological studies analyzed embolic strokes separately. One of the early case reports\textsuperscript{23} described a patient on oral contraceptives whose stroke occurred while on the toilet. A postmortem the foramen ovale was patent. In their review of paradoxical emboli, Jones and associates\textsuperscript{24} propose that some of the strokes in oral contraceptive users might be due to paradoxical emboli, especially given users' increased risk for venous thromboembolic disease.

Evidence for causation can be strengthened by showing a dose-related gradient of risks. Early studies of oral contraceptives and vascular complications suggested that complications were more common with high doses of estrogens. Although not conclusive, the evidence was deemed strong enough that policy makers encouraged the use of oral contraceptives containing as little estrogen as possible.\textsuperscript{16} The trend to use agents with lower contents of estrogens has been accompanied by a similar trend for progestogens because of evidence linking them, as well as estrogens, to vascular complications.\textsuperscript{25} The changes in the composition of the oral contraceptives may also have contributed to the reduced risk of vascular complications found in recent studies.\textsuperscript{17}

The evidence from all these epidemiological studies supports the contention that oral contraceptives are \textit{associated} with stroke. The question of whether they \textit{cause} stroke is less settled and may be less important if more selective use of oral contraceptives can reduce the occurrence of stroke in young women. These studies have also identified other risk factors such as hypertension and smoking whose control could prevent more deaths due to vascular disease than could be prevented by limiting the use of oral contraceptives.

\textbf{Conclusions}

1. Use of oral contraceptives increases the risk of ischemic strokes.

2. Use also increases the risk of subarachnoid hemorrhage, but especially in women who smoke cigarettes.

3. Most strokes occur in women older than 35 years with other risk factors.

\textbf{Table 3} Recommendations for Use of Oral Contraceptives

<table>
<thead>
<tr>
<th>Age</th>
<th>Stroke risk factor*</th>
<th>Smoking</th>
<th>Advice for contraception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 35</td>
<td>+ or -</td>
<td>+ or -</td>
<td>Not oral</td>
</tr>
<tr>
<td>35 to 44</td>
<td>+ or -</td>
<td>+ or -</td>
<td>Oral</td>
</tr>
<tr>
<td>Greater than 44</td>
<td>+ or -</td>
<td>+ or -</td>
<td>Not oral</td>
</tr>
</tbody>
</table>

| *Risk factors include especially hypertension, but also diabetes mellitus, lipid abnormalities, atherosclerotic cardiovascular disease + = present; - = absent. |

4. The use of oral contraceptives containing low doses of estrogens and progestogens in healthy young women is associated with little or no increase of absolute risk for stroke.

5. Recommendations for use of oral contraceptives are given in Table 3.

\textbf{References}

3. Fletcher RH, Fletcher SW, Wagner EH: Clinical Epidemiology — The Essentials, Baltimore, Williams and Wilkins, 1982
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http://stroke.ahajournals.org/content/15/4/747.citation