

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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