Review: Current oral contraceptive use increases the risk for ischemic stroke

Gillum LA, Mamidipudi SK, Johnston SC. **Ischemic stroke risk with oral contraceptives. A meta-analysis.** JAMA. 2000 Jul 5;284:72-8.

Question

Is oral contraceptive use associated with an increased risk for ischemic stroke?

Data sources

Studies published from January 1960 to November 1999 were identified by searching *Index Medicus*, MEDLINE, BIOSIS, and Dissertation Abstracts Online with the terms oral contraceptives, stroke, estrogen, cerebral, ischemia, thrombosis, and venous sinus. Textbooks, foreign-language articles, and bibliographies of relevant papers were reviewed, and content experts were contacted.

Study selection

Studies were included that had > 10 cases of ischemic stroke or cerebral venous sinus thrombosis, a clear differentiation of ischemic and hemorrhagic stroke, a cohort or case–control design with control patients gathered within 2 years of stroke, sufficient data to compare oral contraceptive use with nonuse, a design or analysis that controlled for age, and no later publication of identical data.

Data extraction

Data were extracted on study region; follow-up or refusal rate; current, past, and ever use of oral contraceptives; estrogen doses; confounding risk factors; and outcomes.

Main results

10 409 references were identified: 804 were potentially relevant, 73 examined oral contraceptive use and risk for ischemic stroke, and 16 (2 cohort and 14 case-control studies) met the selection criteria. Meta-analysis showed that women who were currently using oral contraceptives had a higher risk for ischemic stroke than did those who were not currently using oral contraceptives (weighted relative risk [RR] 2.75, 95% CI 2.24 to 3.38). Heterogeneity existed among the studies ($P = 0.01$). Higher RR estimates were seen in studies that did not control for smoking ($P = 0.01$) or that used hospital-based control patients ($P < 0.001$). All doses of estrogen were associated with an elevated risk for ischemic stroke; however, smaller doses were associated with a less elevated risk ($P = 0.01$ for trend). Low-dose estrogen oral contraceptive use was associated with a higher risk for ischemic stroke than was nonuse (weighted RR 1.93, CI 1.35 to 2.74); this finding translates into an additional 4.1 ischemic strokes/100 000 women using oral contraceptives.

Conclusion

Persons who are currently using oral contraceptives have a slightly higher risk for ischemic stroke than do those who are not currently using oral contraceptives.

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Commentary

Determining whether a causal link exists between oral contraceptive use and ischemic stroke is problematic given the potential that bias and confounding by concomitant stroke risk factors might produce a spurious association. If the carefully done meta-analysis by Gillum and colleagues is limited to 7 studies of low-estrogen oral contraceptives in which stroke is objectively confirmed and major stroke risk factors are controlled for (thereby reducing diagnostic suspicion bias), the association is weaker (RR 1.65, CI 1.49 to 1.82). In 3 of these studies, no association was found (RR 1.28, CI 0.85 to 1.89). Thus, the most rigorously designed studies do not show a strong and consistent association between oral contraceptive use and ischemic stroke, although a small risk increase cannot be ruled out.

In arguing for a causal association, it can be said that an appropriate temporal relation between oral contraceptive use and stroke and a dose-response effect relating to estrogen does exist. The weakness of the association, as measured by the magnitude of the RR; the lack of consistent results across studies; and the potential for bias and confounding argue against a causal association. However, oral contraceptive use is a risk factor for venous thrombosis (1), the association between oral contraceptive use and cerebral venous sinus thrombosis is strong and consistent across studies (2, 3), and a patent foramen ovale occurs in 15% of young adults (4). Therefore, one can postulate that many oral contraceptive-associated ischemic strokes are venous in origin.

In summary, a causal link between oral contraceptive use and ischemic stroke is possible, although the mechanism is unclear and the RR should be interpreted with caution. Should this study change a physician's practice? The answer is "no" because of the small absolute increased risk for ischemic stroke in women without stroke risk factors and the health benefits of oral contraceptives.

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References

1. **Douketis JD, Ginsberg JS, Holbrook A, et al.** A reevaluation of the risk for venous thromboembolism with the use of oral contraceptives and hormone replacement therapy. Arch Intern Med. 1997;157:1522-30.
2. **de Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP.** Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in [correction of who are] carriers of hereditary prothrombotic conditions. The Cerebral Venous Sinus Thrombosis Study Group. BMJ. 1998;316:589-92.
3. **Martinelli I, Taioli E, Palli D, Mannucci PM.** Risk of cerebral vein thrombosis and oral contraceptives. Lancet. 1998;352:326.
4. **Webster MW, Chancellor AM, Smith HJ, et al.** Patent foramen ovale in young stroke patients. Lancet. 1988;2:11-2.