

## Review: current oral contraceptive use increases the risk for ischaemic 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 ischaemic 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 ischaemic stroke or cerebral venous sinus thrombosis, a clear differentiation of ischaemic 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 non-use, 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; oestrogen 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 ischaemic 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 ischaemic stroke than 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 oestrogen were associated with an risk for ischaemic stroke; however, smaller doses were associated with a less increased risk ( $p = 0.01$  for trend). Low dose oestrogen oral contraceptive use was associated with a higher risk for ischaemic stroke than was non-use (weighted RR 1.93, CI 1.35 to 2.74); this finding translates into an additional 4.1 ischaemic strokes/100 000 women using oral contraceptives.

### Conclusion

People who are currently using oral contraceptives have a slightly higher risk for ischaemic stroke than those who are not currently using oral contraceptives.

### COMMENTARY

Determining whether a causal link exists between oral contraceptive use and ischaemic 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 *et al* is limited to 7 studies of low oestrogen 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 ischaemic 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 oestrogen 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,<sup>1</sup> the association between oral contraceptive use and cerebral venous sinus thrombosis is strong and consistent across studies,<sup>2,3</sup> and a patent foramen ovale occurs in 15% of young adults.<sup>4</sup> Therefore, one can postulate that many oral contraceptive associated ischaemic strokes are venous in origin.

In summary, a causal link between oral contraceptive use and ischaemic 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 ischaemic stroke in women without stroke risk factors and the health benefits of oral contraceptives.

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- 2 de Bruijn SF, Stam J, Koopman MM, *et al*. 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, *et al*. 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.

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