Ischemic stroke risk with oral contraceptives: a meta-analysis
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Authors' objectives
To determine whether oral contraceptive use is associated with increased stroke risk.

Searching
Index Medicus (before 1966), MEDLINE (after 1966), BIOSIS Previews (after 1985) and Dissertation Abstracts Online (North American Universities) were searched using the following keywords: oral contraceptives (side-effects, complications), stroke, estrogen, cerebral, ischemia, thrombosis, and venous sinus. All languages and publication types were included. Bibliographies of pertinent articles and reviews were searched for additional references. Relevant textbooks and foreign-language articles were also reviewed. An expert in the field was contacted for additional sources.

Study selection
Study designs of evaluations included in the review
Studies that evaluated stroke risk with OC and fulfilled the following criteria were included: greater than ten cases of ischemic stroke or CVST were included; clear differentiation of ischemic and haemorrhagic stroke; cohort design or case control design with controls gathered within 2 years of cases; sufficient data provided to determine the odds ratio (OR) or relative risk (RR) and confidence intervals (CI) comparing OC users to nonusers; controlled for age in study design or analysis; and no later study fully reported the same data. Cohort and case control studies were included with controls taken from hospital, outpatients or the general population.

Specific interventions included in the review
Oral contraceptives (OC) including those containing estrogen in high (> 50 micrograms), medium (50 micrograms) and low (< 50 micrograms) doses and progesterone (first second and third generation) were studied.

Participants included in the review
Women who were current, noncurrent or never users of OC were included. Limits of last use varied from 2 weeks to 12 months prior to stroke. Participants included smokers, non smokers, those with a history of migraine, or hypertension and those with combinations of these factors.

Outcomes assessed in the review
The incidence of ischemic stroke (including those confirmed by firm diagnosis using computed tomography, magnetic resonance imaging or angiography) and cerebral venous sinus thrombosis (CVST) were assessed.

How were decisions on the relevance of primary studies made?
Two investigators independently applied the inclusion criteria. A third investigator adjudicated disagreements.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
Two investigators independently abstracted data with disagreements resolved through discussion. The following data appear to have been extracted: author; date of publication; region of study; years of study; person years of current/noncurrent OC use; estrogen dose; losses to follow-up; firm diagnosis of stroke; study design; source of controls; number of cases and controls and factors controlled for. Results for stroke incidence were chosen where provided. Otherwise, mortality results were included.
Methods of synthesis

How were the studies combined?
Summary risk estimates were calculated using a general variance-based random-effects method, weighting individual study results by the inverse of their variance. Results were reported as relative risk (RR). Publication bias was assessed using a funnel plot and Kendall’s tau statistic.

How were differences between studies investigated?
Homogeneity was assessed using a general variance-based method. Results were considered heterogeneous when $P < 0.10$. Sensitivity analysis was performed by iteratively eliminating each study and calculating the RR. A two-tailed $z$ test was used to detect differences across dichotomous sub-groups. The non-parametric test of Cuzick was used to assess trend in risk by estrogen dosage. Multivariate meta-regression was used to assess OC stroke risk controlling for a series of covariables. The influence of the following factors on RR was evaluated: estrogen dose (high, medium and low); progesterone type (first, second or third generation); control for risk factors in the study design (smoking, hypertension, smoking and hypertension, alcohol use); study design type (cohort or case control); type of control (population control or hospital control); exposure classification; and the independent effect of OC among various groups including non smokers, history with or without hypertension, with and without migraine; and age ($< 35$ years and $\geq 35$ years).

Results of the review

Sixteen studies including three cohort studies and thirteen case-control studies were included.

Current OC use was associated with increased risk of ischemic stroke. $RR = 2.75$ (95% CI: 2.24, 3.38; $P < 0.001$). Heterogeneity was present ($P = 0.01$). After eliminating each study in turn RR ranged from 2.63 to 3.00 with the lower 95% CI never crossing 1. Stroke risk was not associated with past use of OC (9 studies). RR (past vs never use) = 0.86 (95% CI: 0.69, 1.08). No evidence of heterogeneity. Stroke risk appeared to decrease with time ($P = 0.006$).

Smaller estrogen doses were associated with lower risk ($P = 0.01$ for trend) but risk was significantly elevated for all doses. RR for low dose estrogen (7 studies) 2.08 (95% CI: 1.55, 2.80). Heterogeneity was present among the low dose studies.

Newer generation progesterones tended to be associated with less elevated risk. RR (3 first generation studies) = 3.21 (95% CI: 2.16, 4.77) compared to 3 third generation studies RR = 2.11 (95% CI: 0.96, 4.64). Trend across generations was non significant. Within progesterone generations there was a non significant trend for higher estrogen doses to be associated with higher risk of stroke.

No differences were seen between generations at equivalent estrogen doses.

Cohort studies tended to produce higher summary RR than case-control studies.

Studies that did not control for smoking and those using hospital based controls found higher RR but no other patient characteristics or elements of study design were important.

Stratification by potential confounders: no evidence of heterogeneity in studies controlling for alcohol use, for smoking, hypertension or both smoking and hypertension. The risk of stroke was minimally affected by the presence of other risk factors. Similar RR were found for smokers vs non smokers, in those with and without a history of migraine or hypertension and for those $< 35$ years of age vs those $\geq 35$ years of age.

Risk of stroke with low dose estrogen after adjustment for smoking and hypertension (6 studies): $RR = 2.04$ (95% CI: 1.51, 2.76).

Risk of stroke with low dose estrogen in population based studies after adjustment for smoking and hypertension (5 studies): $RR = 1.93$ (95% CI: 1.35, 2.74).

Risk of CVST with OC use (2 studies): increased risk in current users of OC. $RR = 15.9$ (95% CI: 6.98, 36.2).

Neither the funnel plot nor Kendall tau demonstrated evidence of publication bias.
Authors' conclusions
The risk of ischemic stroke is increased in current oral contraceptive users, even with the newer low-estrogen preparations. However, the absolute increase in stroke risk is expected to be small since the incidence is very low in this population.

CRD commentary
The aims were stated. However, the definition of the type of oral contraceptive under study (whether limited to the combined estrogen/progesterone contraceptive or inclusion of progesterone only types) was not clear. Attempts were made to locate published material from several sources as well as unpublished dissertations. No language restrictions were applied and publication bias was assessed. Methods used to select primary studies and extract data were described. Validity was not assessed. Heterogeneity was assessed statistically and investigated. Results were clearly presented.

The authors correctly advise caution in considering the magnitude of the estimates in view of the heterogeneity among studies incorporated into the summary estimates.

The evidence supports the author's conclusion, although it must be recognised that the results were based on observational studies.

Implications of the review for practice and research
Clinical practice: the authors' consider that the additional risk of stroke appears to be outweighed by the health benefits of OC use in improved birth control.

Research: the authors' state that further research is required to clarify the relationship between CVST and OC use.

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Other publications of related interest
This additional published commentary may also be of interest. Douketis JD. Review: current oral contraceptive use increases the risk for ischaemic stroke. Evid Based Med 2001;6:60.

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Brain Ischemia /epidemiology /etiology; Contraceptives, Oral /adverse effects; Estrogens /administration & dosage; Female; Humans; Progesterone /administration & dosage; Risk; Stroke /epidemiology /etiology

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.