Oral contraceptives and the risk of subarachnoid hemorrhage: a meta-analysis

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Authors' objectives
To estimate the risk of subarachnoid haemorrhage (SAH) produced by oral contraceptive (OC) use.

Searching
Electronic searches of MEDLINE (Jan 1966-Dec 1997) and Dissertation Abstracts On-line (Jan 1961-Nov 1997) were carried out using the keywords 'subarachnoid', 'cerebral', 'hemorrhage', 'aneurysm', 'risk factor' and 'oral contraceptive'. The Cumulated Index Medicus (Jan 1960-Dec 1965) was searched with the subject heading: contraceptives, oral. Additional references were retrieved from the bibliographies of reviews and other articles of interest. There were no restrictions on the language of publication.

Study selection
Study designs of evaluations included in the review
Cohorts and case-control studies where control individuals were gathered within 2 years of the patients. Studies were included only if at least five patients were reported with SAH; SAH was defined and distinguished from intraparenchymal haemorrhage; adequate information was given to determine the RR and CIs for SAH in OC users compared with nonusers; age was controlled either in the design or the analysis; and the data were not fully reported in a later study.

Specific interventions included in the review
Oral contraceptives (including high and low dose oestrogen formulations).

Participants included in the review
Women who were current or past users of oral contraceptives; women who had ever used oral contraceptives. Users were also compared to non-users.

Outcomes assessed in the review
Incident of, and mortality from, non-traumatic subarachnoid haemorrhage as defined by cerebral angiography, CT, MRI or autopsy.

How were decisions on the relevance of primary studies made?
All pertinent articles were reviewed independently by two investigators using six pre-determined inclusion criteria. Disagreements were discussed and full agreement reached in all cases.

Assessment of study quality
No formal assessment of validity was undertaken.

Data extraction
Data were extracted independently by two investigators. Disagreements were discussed and full agreement reached in all cases. If a potential confounding risk factor was restricted or matched in the study design or included in multivariate or stratified analysis, the factor was considered controlled in the study result. The most extensively controlled RR estimates from the individual studies were extracted as the primary outcome measures. If a study provided a RR for SAH incidence rather than for mortality the former category results were included to maximise the number of participants. Variances were extracted from the studies directly or calculated from confidence intervals (CIs) or two-by-two tables.
Methods of synthesis
How were the studies combined?
Overall summary RR estimates were calculated as an average of the individual study results weighted by the inverse of their variance using the random-effects method of DerSimonian and Laird. Subgroup analyses (study design; outcome measure, mortality vs incidence; exposure measure, current vs ever used; prevailing oestrogen dose used; and control for smoking and hypertension) were performed to examine potential sources of bias and heterogeneity. Summary estimates assuming unequal variances were compared using a z statistic.

How were differences between studies investigated?
Homogeneity was investigated using the Mantel-Haenszel method and the study results were considered heterogeneous if the resultant p value was less than 0.10. Based on published simulation studies, the authors estimated that the review had more than 75% power to identify heterogeneity in the overall estimate.

Results of the review
Eleven studies including 2 case-control (588,151 participants) and 9 cohort studies (8904 participants).

The overall summary RR of SAH due to OC was 1.42 (95% CI: 1.12, 1.80, p=0.004). When two study results failing to control for smoking were excluded from the analysis a slightly greater effect was seen, with an RR of 1.55 (95% CI: 1.26, 1.91, p<0.0001). In six studies controlling for smoking and hypertension the RR was 1.49 (95% CI: 1.20, 1.85, p=0.0003). High-oestrogen OC appeared to impart a greater risk than low-dose preparations in studies controlling for smoking, but the difference was not significant (high-dose RR=1.94, 95% CI: 1.06, 3.56; low-dose RR=1.51, 95% CI: 1.18, 1.92). The studies did not reveal evidence of heterogeneity.

Authors' conclusions
This meta-analysis of observational studies suggests that oral contraceptive use produces a small increase in the risk of subarachnoid haemorrhage.

CRD commentary
This review focuses on a well-defined review question with clearly stated inclusion and exclusion criteria. The review methods and analyses are described in detail. However, the review may be limited by its literature search, which focuses on only two databases and makes no attempt to locate unpublished research. The review only features cohort and case-control studies and there appears to be no formal consideration of study validity. Heterogeneity tests and subgroup analyses were performed in an attempt to avoid potential sources of bias from confounding factors. Considering these potential problems and the level of evidence on which the review is based, the author's conclusions should be interpreted with caution.

Implications of the review for practice and research
The authors state that: 'for women at high risk of SAH due to existing unruptured aneurysms, a strong positive family history, cigarette smoking, or hypertension, it may be advisable to consider alternative forms of contraception until more data are available'; 'heavy alcohol consumption, positive family history and lower socioeconomic status may also be risk factors for SAH. There were not enough studies controlling for these factors to determine whether they were confounding variables'.

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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.