Risk of stroke in women exposed to low-dose oral contraceptives

CRD summary
This review investigated the risk of stroke in women taking the oral contraceptive pill. The authors concluded that there is doubt over the association between low-dose oral contraceptive pills and stroke, and further good quality research is required. This conclusion seems reliable given the methodological limitations of the included studies.

Authors' objectives
To determine whether women taking the oral contraceptive pill (OCP) are at risk of stroke and, if so, the magnitude of the risk.

Searching
MEDLINE, EMBASE and the Science Citation Index were searched from 1970 to June 2000; the search terms were reported. Only articles published in English were included in the review.

Study selection
Study designs of evaluations included in the review
Case series and case reports were excluded from the review. The included studies were cohort and case-control studies. No randomised controlled trials were identified.

Specific interventions included in the review
Studies of oestrogen-containing OCPs were eligible for inclusion. Low-dose OCPs and second- and third-generation OCPs were defined as those containing less than 50 microg of ethinyl estradiol. Most of the included studies did not specify the type of OCP used.

Participants included in the review
There were no specific inclusion criteria relating to the women included in the review, such as age or duration of OCP use. Few details of the populations of the included studies were given.

Outcomes assessed in the review
Studies reporting the incidence of stroke were eligible for inclusion. Thrombotic stroke included thromboembolic and ischaemic strokes. Haemorrhagic stroke included strokes thought to be caused by subarachnoid, intracranial or intraparenchymal haemorrhage.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the studies for relevance.

Assessment of study quality
The authors did not state that they systematically assessed validity. However, they did report the numbers of studies where investigators were blinded to the status of OCP use and outcome status, diagnosis was independently verified, cases and controls were matched, and confounding factors were adjusted for.

Data extraction
Two reviewers, blinded to authorship, institution, journal of publication and funding source, independently extracted the data, with any disagreements resolved by consensus. Where multiple publications existed, the data were abstracted from the most relevant and recent study.
Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated (it was not specified whether a fixed-effect or random-effects model was used), weighted by within-study variance. A modified pooled OR, in which within- and between-study variances were taken into consideration, was also calculated (method not described). Publication bias was investigated using a funnel plot of the sample size against the natural logarithm of the reported OR.

How were differences between studies investigated?
Heterogeneity was investigated using the chi-squared statistic. Subgroup analyses were performed in relation to study design, stroke type, status of OCP use (current or ever-users), type of OCP and the number of events (more or less than 250 cases of stroke). Differences between the subgroups were calculated using the Z statistic.

Results of the review
Twenty studies were included in the review: 4 cohort studies (n=1,086,093) and 16 case-control studies (n=15,106).

Fourteen of the 20 studies used both clinical and objective diagnostic testing to define stroke cases, while in the remaining 6 studies the definition was not explicitly stated. Blinding of the investigators to status of OCP use was reported in 4 studies, and blinding to outcome status in 2 studies. Fifteen of the case-control studies matched for age; age adjustments were made in all 4 cohort studies. Fourteen studies adjusted for or stratified for smoking, four for diabetes, eight for body mass index, one for migraine and eleven for hypertension. Five studies excluded people with diabetes or hypertension.

There was a significant increase in the risk of stroke in women taking the OCP (modified OR 1.92, 95% CI 1.44, 2.57) when all studies were pooled. However, there was statistically significant heterogeneity between the studies (P<0.001).

Subgroup analyses showed that study design, type of stroke and status of OCP use altered this overall result. The risk of having a thrombotic stroke was increased in women taking the OCP (modified OR 2.74, 95% CI 2.24, 3.35). When the analysis was restricted to either cohort studies only, studies of haemorrhagic stroke or deaths, or women that were ever-users of OCP, there was no significant difference in the risk of stroke with OCP exposure compared with no exposure.

The authors reported that there was no evidence for publication bias.

Authors’ conclusions
There is doubt over the association between low-dose OCPs and stroke.

CRD commentary
The review question was clear in terms of the intervention, study design and outcomes, although inclusion criteria for the participants were not specified. The authors searched three relevant databases but restricted the review to studies published in English, thus increasing the risk of publication and language bias. The study selection and data extraction processes were carried out in duplicate, which reduces the possibility of error and bias. The overall pooled results were based on very statistically and clinically heterogeneous studies (with the results of cohort and case-control studies pooled together). However, the authors undertook several relevant subgroup analyses relating to study design, stroke type, OCP usage and number of events, to investigate these factors. It is likely that the conclusions of this review will be reliable.

Implications of the review for practice and research
Practice: The authors stated that, as the risk of stroke increases with OCP use in women with hypertension, older women and smokers, OCPs should be administered with caution to hypertensive women over 35 years of age who smoke.

Research: The authors suggested that future studies should minimise bias and confounding effects and address the
methodological limitations of previous studies.

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