Oral contraceptives use and the risk of myocardial infarction: a meta-analysis
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CRD summary
This review assessed oral contraceptive (OC) use and the risk of myocardial infarction. The authors concluded that current OC use appears to increase the risk of myocardial infarction, but that past use does not. The authors’ conclusions are likely to be reliable, but it must be recognised that the use of observational studies and a limited search for studies limits the strength of the evidence.

Authors’ objectives
To assess the relationship between oral contraceptive (OC) use and the risk of myocardial infarction (MI).

Searching
MEDLINE was searched from January 1966 to October 2002 for studies published in English; the MeSH terms were stated. Only full-length publications were included; abstracts and unpublished data were not included. The reference lists in identified studies were reviewed.

Study selection
Study designs of evaluations included in the review
Cohort and case-control studies were eligible for inclusion if they contained at least 20 cases of MI. The studies had to control for age in the study design or the analysis (criteria for defining control were stated in the paper).

Specific interventions included in the review
Studies of current or past use of OC were eligible for inclusion. The review compared the effects of OC use with never use, current use with never use, and current use with noncurrent use. Definitions for current, past and never use of OC were those used in the primary studies. The included studies defined past and ever use consistently, while the definitions of current use varied from last used one week to one year before the MI. The studies used first-, second- and third-generation OC, but the definitions of first- and second-generation OCs varied. The studies were conducted in the USA, Europe, Asia and Africa.

Participants included in the review
The studies had to define cases as women with fatal or nonfatal MI. Most of the studies diagnosed MI using symptoms, cardiac enzymes and electrocardiogram. The women in the included studies were aged from 15 to 55 years.

Outcomes assessed in the review
Studies that presented the risk of MI (fatal or nonfatal), or provided sufficient data to allow the risk to be calculated, were eligible for inclusion. Studies with inadequate definitions of MI were excluded. The review assessed the risk of MI according to OC use.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and resolved any disagreements through discussion with a third reviewer.

Assessment of study quality
The authors specifically stated that validity was not assessed.

Data extraction
Three reviewers independently extracted the data onto a standardised form and resolved any disagreements through
discussion, or through recourse to a fourth reviewer. The extracted data included characteristics of the population, study design and potential confounding factors adjusted for (or matched). For each study, the odds ratios (ORs) or relative risks were extracted or calculated from raw data, then transformed logarithmically. Where variances of log OR were not reported, they were calculated from statistics presented or from standard formulae.

Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis. The pooled OR and 95% confidence intervals (CIs) were calculated using random-effects and fixed-effect models, with weighting by the inverse of the variance of log OR. In view of the heterogeneity among the studies, the authors only presented results for the random-effects model. Publication bias was assessed by potting the log ORs against the variance, and by calculating the rank correlation between variance and log OR using Kendall's tau statistic.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. A sensitivity analysis was conducted based on different exclusion criteria (further details were not provided). The influence of the following predefined factors on the results was explored in subgroup analyses: study location (USA versus Europe); generation of OC (first, second or third); estrogen dose; age (younger than 35 years versus 35 years and older); cigarette smoking status; and combination of OC with other risk factors for cardiovascular disease (smoking, hypertension, hypercholesterolaemia and factor V Leiden or a G20210A mutation in the prothrombin gene).

Results of the review
Nineteen case-control studies (4,599 cases and 18,838 controls) and four cohort studies (7,076 women) were included.

The number of cases per study ranged from 26 to 910 and the number of controls ranged from 63 to 3,120. Most of the studies used matching or adjustment to account for potential confounders. The most common confounders were age, diabetes, hypertension, smoking, body mass index and abnormal lipids.

The symmetry of the funnel plot and the lack of significant correlation between the variance and log OR (P=0.146) provided no evidence for publication bias.

Current OC use (13 studies).
The meta-analysis showed that current OC users had a significantly higher risk of MI than never users after adjusting for confounders (OR 2.48, 95% CI: 1.91, 3.22, P<0.0005). Significant heterogeneity was detected (P=0.035). The sensitivity analysis showed that the adjusted ORs ranged from 2.30 to 2.75 and the lower limits of the 95% CI were greater than 1. A meta-analysis (6 studies) showed that current users had a significantly higher risk of MI than noncurrent users (past or never users) (OR 3.00, 95% CI: 1.70, 5.28, P<0.0005).

Past OC use (12 studies).
The meta-analysis showed that there were no significant differences in the risk of MI between past OC users and never users (OR 1.15, 95% CI: 0.98, 1.35, P=0.096).

Results from the subgroup analyses were reported in the paper.

Authors' conclusions
The findings suggested that current OC use increases the risk of MI, but that past use does not.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Only one database was searched for studies published in English and this might have resulted in the omission of other relevant studies. The
potential for publication bias was assessed. At least two reviewers independently selected the studies and extracted the data, thus reducing the potential for bias and errors. The authors discussed their reasons for not assessing study validity. However, a discussion of the methods used to select the cases and controls would have allowed an evaluation of some potential sources of bias.

The data were combined in a meta-analysis and statistical heterogeneity was assessed. Appropriate subgroup analyses were conducted (although heterogeneity was not assessed). The authors did note other potential sources of heterogeneity, but these could not be assessed. The authors’ conclusions are likely to be reliable but it must be recognised that the use of observational studies, the restricted search for studies, and the unexplained heterogeneity limit the strength of the evidence.

**Implications of the review for practice and research**

Practice: The authors stated that clinicians making decisions about prescribing OCs should consider that the absolute risk of MI is very low among women of the age to be taking OCs, even when there are other risk factors.

Research: The authors stated that, in future, meta-analyses should be conducted using individual patient data.

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