Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis

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CRD summary
This review concluded that oral contraceptive exposure could decrease the risk of endometriosis in current users, but increase the risk in previous users. The evidence was insufficient to recommend oral contraceptives to prevent endometriosis. The methodological limitations in the included studies and in the review mean that these conclusions may not be reliable.

Authors' objectives
To determine whether combined oral contraceptives change the risk of endometriosis.

Searching
MEDLINE was searched for publications, in English, from 1970 to January, 2010. Search terms were reported. Reference lists of included articles were handsearched to locate further studies. Review articles, books, monographs, and their reference lists were searched.

Study selection
Eligible studies compared the incidence of a diagnosis of endometriosis in women who had taken oral contraceptives in the past, at present, or at any time (ever user), versus women who had never taken them. Studies were excluded if they reported interim results before publication of a full report.

The included studies were published between 1974 and 2008. Half were conducted in North America, and half were conducted in Europe (three in the UK). Participant eligibility criteria varied across the studies. Where reported, their age ranged from 15 years to over 90 years; most participants were post-adolescent and pre-menopausal. The diagnosis of endometriosis was surgical, or by visualisation at laparotomy or laparoscopy, or confirmed by histology.

Two reviewers selected studies for inclusion.

Assessment of study quality
Study quality was assessed for participant selection, comparability of groups, and assessment of exposure, using the Newcastle-Ottawa Scale. The authors did not state the number of reviewers who performed the quality assessments.

Data extraction
The incidence of endometriosis diagnosis in participants by group was extracted to calculate adjusted odds ratios for cross-sectional and case-control studies, or relative risks for cohort studies, and their corresponding 95% confidence intervals.

Two reviewers independently extracted the data; any discrepancies were resolved through consensus.

Methods of synthesis
Effect estimates and their 95% confidence intervals were pooled using random-effects models. Heterogeneity was assessed using Cochran’s Q and I². A priori subgroup analyses were conducted by study design. Where deemed appropriate, sensitivity analyses were conducted by removing one outlier study at a time. Publication bias was assessed using funnel plots and Egger's test.

Results of the review
Eighteen studies were included (5,031 cases of endometriosis): five were cohort studies (2,235 cases), seven were case-control studies (1,231 cases), and six were cross-sectional studies (1,565 cases). Cases were selected carefully in all studies, participant groups at the start were comparable in 14 of the 18 studies, and the method of confirmation of exposure was clearly defined in 10 of the 18 studies. Overall quality scores ranged from 4 to 9.

Compared with never users, the risk of endometriosis was statistically significantly reduced for current users of oral
contraceptives (RR 0.63, 95% CI 0.47 to 0.85; 11 studies; $I^2=63\%$). Small, statistically non-significant increases in risk were observed for past users (RR 1.21, 95% CI 0.94 to 1.56; 11 studies; $I^2=81\%$) and for ever users (RR 1.19, 95% CI 0.89 to 1.60; nine comparisons, eight studies; $I^2=73\%$).

In subgroup analyses by study design, the risk of endometriosis was statistically significantly reduced for current users in case-control studies (RR 0.49, 95% CI 0.27 to 0.88; three studies; $I^2=61\%$) and cohort studies (RR 0.57, 95% CI 0.40 to 0.80; five studies; $I^2=45\%$). The risk was statistically significantly increased for past users in cohort studies (RR 1.60, 95% CI 1.40 to 1.82; five studies; $I^2=2\%$), and for ever users in cross-sectional studies (RR 1.42, 95% CI 1.12 to 1.80; two studies; $I^2=0\%$). Some asymmetry was indicated in the funnel plot for past users of oral contraceptives; this was linked to one study with a large sample. Further results were reported in the review.

**Authors' conclusions**

Oral contraceptive exposure appeared to decrease the risk of endometriosis in current users, but increase the risk in previous users. The evidence was insufficient to recommend oral contraceptives to prevent endometriosis.

**CRD commentary**

The review question and inclusion criteria were clearly defined. Relevant studies may have been missed because only one database was searched, studies had to be in English, and no attempts were made find unpublished or grey literature. Study selection and data extraction were performed by two people, but this was not reported for quality assessment, so reviewer error and bias cannot be ruled out.

There was a discrepancy for the total cases of endometriosis between the table (5,031) and the text (4,802). A suitable quality assessment tool was used; there were some limitations to the studies, such as information on the modality of exposure ascertainment. The methods of synthesis seem to have been appropriate; attempts were made to explore heterogeneity due to study design. The authors acknowledged several limitations to the study designs, including uncertain temporal relationships between exposure and outcome in cross-sectional studies, and sub-optimal selection of controls in case-control studies. Another limitation with all the studies was the difficulty in knowing the exact time of the onset of endometriosis. The authors' conclusions generally reflect the evidence, but methodological limitations in the included studies and in the review itself mean that these conclusions may not be reliable.

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

**Practice:** The authors did not state any implications for clinical practice.

**Research:** The authors stated that cohort studies should describe the indications for the prescription of an oral contraceptive, and the gynaecological symptoms preceding their use. Studies should enrol younger women, and menstrual pain and the symptoms of endometriosis should be assessed as primary outcomes.

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