IUD use and the risk of ectopic pregnancy: a meta-analysis of case-control studies
Xiong X, Buekens P, Wollast E

Authors' objectives
To clarify some existing controversies about the relationship between intra-uterine contraceptive (IUD) use and the risk of ectopic pregnancy, and to determine the pooled risk of ectopic pregnancy caused by current and past IUD use, the influence of the selection of controls on the pooled risk and to investigate other factors that may explain the inconsistencies in study results.

Searching
MEDLINE was searched from 1980 to 1984, and Index Medicus from 1980 to 1994. Reference lists in selected articles were reviewed to find articles published before 1982 and those not included in MEDLINE.

Study selection
Study designs of evaluations included in the review
The studies were restricted to case-control studies which fulfilled the following criteria: controlled epidemiological study on ectopic pregnancy; presented original data; current or past IUD use, or both, were defined as exposures; presented as a full paper; odds ratio (OR), 95% confidence intervals (CI), standard errors or p values were reported, or could be derived from the data; and the study was published in English, French or Chinese. The data were obtained from 1935 to 1990.

Specific interventions included in the review
The following types of IUD were studied: Lippes Loop, TCu-200, Dakron Shield, Copper-T, Copper-T/7, steel-plastic and stainless steel.

Participants included in the review
The participants included women from Finland, USA, Australia, Sweden, Italy, China, France, Greece and Indonesia who were current users or past users of IUD. The women's ages ranged from 16 to 48 years.

Outcomes assessed in the review
The main outcome was the incidence of ectopic pregnancy.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of the primary studies was assessed on the following criteria: study design including study setting, representation of case and controls, definition of exposure, bias control (selection, information, confounding), and comparability of cases and controls.

Each assessed item received a score out of 30 points, which was divided by 30 to give scores ranging from 0 to 1. A form designed a priori was used to evaluate the quality of the included studies.

Data extraction
A uniform questionnaire designed a priori was used to extract information for further analysis.

The OR was extracted for both pregnant and non-pregnant controls, and potential confounders including pelvic inflammatory disease, prior ectopic pregnancy, smoking, sexually-transmitted diseases, prior abortion, chlamydia...
infection and age were noted.

**Methods of synthesis**

**How were the studies combined?**
The studies were combined using the pooled OR, weighted by the inverse variance. The effects of current and past IUD use were analysed separately.

**How were differences between studies investigated?**
The chi-squared test for homogeneity was used to assess differences across studies. Sensitivity analysis was performed by pooling the OR weighted by the quality score of the studies, and by taking into account whether the estimate of OR was adjusted for potential confounders.

Correlation analysis was used to test the correlation between OR and their corresponding quality scores.

Potential causes of heterogeneity were discussed.

**Results of the review**

Sixteen case-control studies involving 21,986 women (5,568 cases and 16,418 controls) were included.

**Current IUD use.**

Pregnant controls: OR 10.63 (95% CI: 7.66, 14.74), chi-squared homogeneity 23.37 (P < 0.01); adjusted for confounder, OR 6.29 (95% CI: 4.23, 9.34), chi-squared homogeneity 1.59 (P > 0.05).

Weighting by quality scores and inverse variance, and including confounding, OR 6.37 (95% CI: 4.09, 9.92).

Non-pregnant controls: OR 1.06 (95% CI: 0.91, 1.24), chi-squared homogeneity 133.29 (P < 0.01); adjusted for confounder, OR 1.06 (95% CI: 0.89, 1.28), chi-squared homogeneity 59.96 (P < 0.01).

Weighting by quality scores and inverse variance, and including confounding, OR 1.00 (95% CI: 0.83, 1.32).

**Past IUD use.**

Pregnant controls: OR 1.33 (95% CI: 1.08, 1.63), chi-squared homogeneity 13.55 (P > 0.05); adjusted for confounder, OR 1.38 (95% CI: 1.12, 1.70), chi-squared homogeneity 8.78 (P > 0.05).

Weighting by quality scores and inverse variance, and including confounding, OR 1.37 (95% CI: 1.08, 1.72).

Non-pregnant controls: OR 1.45 (95% CI: 1.23, 1.72), chi-squared homogeneity 5.99 (P > 0.05); adjusted for confounder, OR 1.45 (95% CI: 1.23, 1.72), chi-squared homogeneity 5.99 (P > 0.05).

Weighting by quality scores and inverse variance, and including confounding, OR 1.46 (95% CI: 1.12, 1.74).

Total pooled past IUD use: OR 1.40 (95% CI: 1.23, 1.59), chi-squared homogeneity 19.99 (P > 0.05); adjusted for confounder, OR 1.42 (95% CI: 1.25, 1.62), chi-squared homogeneity 14.92 (P > 0.05).

Weighting by quality scores and inverse variance, and including confounding, OR 1.42 (95% CI: 1.24, 1.64).

The average quality scored was 0.78.

Funnel plots used to assess the possibility of publication bias showed asymmetry round the estimated pooled OR for current IUD use and pregnant controls, and approximate symmetry round the pooled OR for current IUD use and pregnant controls, and for past IUD use regardless of controls.
Authors' conclusions
Current IUD use does not increase the risk of ectopic pregnancy. However a pregnancy with an IUD in situ is more often ectopic than a pregnancy with no IUD. Past use could mildly elevate the risk of ectopic pregnancy. Further research is needed to clarify the risk of ectopic pregnancy with the duration of past IUD use.

CRD commentary
This is a thoughtful, well-written and clearly-presented review. By limiting the literature search to published articles some relevant studies may have been omitted. Predefined forms were used to assess study quality according to specified criteria, but no details are given of the methodology used to select studies for inclusion, to assess quality or to extract data. The potential bias inherent in quality assessment is acknowledged by the authors.

Sensitivity analysis investigated the effect of the quality of the studies on the results, and assessed the influence of confounding factors. Details were lacking on the diagnostic criteria used to define ectopic pregnancy and the length of follow-up period after insertion of the IUD. The complexities of selecting an appropriate control group for case-control studies of ectopic pregnancies are discussed in detail, as are the potential influences of various factors on the incidence of ectopic pregnancy, e.g. the different types of IUD and the increasing use of more effective medicated IUDs. The authors comment that although they found no statistical differences between different IUD types, it was impossible to analyse the innovation in IUDs in recent years with respect to the risk of ectopic pregnancy, due to lack of information about the type of IUD and the problems of recall bias. Potential causes of heterogeneity between studies such as study quality, IUD type, health and socioeconomic conditions, contraceptive use, abortion, and ethnic and behavioural differences were included in the discussion.

Implications of the review for practice and research
The incidence of ectopic pregnancies associated with the use of innovative IUDs requires continued monitoring.

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