Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis

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CRD summary
This review found that combined oral contraceptives were associated with an increased risk of venous thrombosis. The effect size depends on the progestogen used and the dose of ethinyl estradiol. Despite some concerns with the quality of the included studies these results are likely to be reliable, and the authors’ conclusions are appropriate.

Authors’ objectives
To review the risk of venous thrombosis in women using combined oral contraceptives.

Searching
Seven databases including PubMed, EMBASE and The Cochrane library were searched to April 2013 without language restrictions. Search strategies were presented. The reference lists of potentially relevant papers were searched for additional studies.

Study selection
Cohort or case-control studies that included healthy women who used combined oral contraceptives were eligible for inclusion. The primary outcome of interest was fatal or non-fatal first venous thrombosis, particularly deep venous thrombosis or pulmonary embolism. Only studies with at least ten events were included.

The contraceptives used were generally ethinyl estradiol (at a range of doses) combined with one of levonorgestrel, gestodene, desogestrel, norgestimate, cyproterone acetate or drospirenone. The age (where reported) of included women ranged from 12 to 50 years; age ranges were similar across studies. Just over half of studies were community based; the rest were based on GP databases, healthcare plans or other data sources. Venous thrombosis was diagnosed in various ways, including clinical criteria, anticoagulation and by ad hoc methods.

Two reviewers performed study selection, with disagreements resolved by a third, if necessary.

Assessment of study quality
Risk of bias was assessed by considering the following: adequacy of exposure and outcome measurement; loss to follow-up; adequacy of control selection; how contraceptive use was reported; and whether thrombosis was objectively confirmed.

It appeared that two reviewers performed assessment of study quality.

Data extraction
Two reviewers independently extracted data on numbers of events, sufficient to create 2x2 tables before calculating risk ratios, odds ratios or rate ratios, with corresponding variances. Authors were contacted for additional information, where necessary.

Methods of synthesis
Different types of contraceptive were grouped together and classified as first, second or third generations of progestogen, using definitions set out in the paper. Studies were then synthesised using random-effects network meta-analyses to generate summary relative risks with 95% confidence intervals. Interaction terms were included in the model to investigate possible differences between direct and indirect evidence. Sensitivity analyses based on study design, funding source, first-time users and risk of bias were performed.

Results of the review
There were 26 studies included (nine cohort, 14 case-control and three nested case-control studies). The total sample size was not clear, but there were over two million women. Eight studies used an interview or questionnaire to assess
contraceptive use (high risk of bias); only five objectively confirmed venous thrombosis (low risk). None of the cohort studies reported loss to follow-up. Generally none of the trials appeared to be at low risk for all potential causes of bias.

In 23 studies of progestogens, their use increased the risk of thrombosis compared to non-users, with relative risks of 3.2 for first-generation progestogens (95% CI 2.0 to 5.1), 2.8 for second generation (95% CI 2.0 to 4.1) and 3.8 for third generation (95% CI 2.7 to 5.4). The risk of thrombosis was similar for first and second generation users, but the risk was higher in third than in second generation users (RR 1.3, 95% CI 1.0 to 1.8). No evidence of inconsistency between direct and indirect evidence in the network was found.

Fourteen studies presented results that compared different types of oral contraceptive. All preparations at least doubled the risk of thrombosis compared to non-use. The risk was highest with 50LNG (50ug ethinyl estradiol with levonorgestrel, RR 5.2, 95% CI 3.4 to 7.9) and lowest for 20LNG (20ug ethinyl estradiol with levonorgestrel, RR 2.2, 95% CI 1.3 to 3.6) and 20GSD (20ug ethinyl estradiol with gestodene, RR 2.2, 95% CI 1.4 to 3.2). Higher doses of gestodene, desogestrel, and levonorgestrel were associated with increased risk. Full results of the analysis were presented.

Sensitivity analyses found that the risk of thrombosis in third generation users was lower in industry-funded studies and in cohort studies. Risk estimates were generally higher where venous thrombosis had been objectively confirmed.

**Authors’ conclusions**

All the combined oral contraceptives investigated were associated with an increased risk of venous thrombosis. The effect size depended on the progestogen used and the dose of ethinyl estradiol.

**CRD commentary**

This well-conducted review addressed a relevant research question using appropriate inclusion criteria. A suitable extensive search was conducted, but it did not appear that unpublished material was sought, so some relevant studies may have been missed. Action seemed to be taken to avoid reviewer error and bias. Risk of bias was assessed, with mixed results, with many potential causes of bias identified and no study appearing to be at low risk of bias across all risk categories. All included studies were observational in design, and so may be of lower quality than randomised trials; however the number of women and events included was very large. Studies were synthesised using network meta-analysis which combines both direct and indirect comparisons of treatments. Such indirect comparisons may be less reliable; however, the authors found no evidence of inconsistency between direct and indirect evidence. Sensitivity analyses suggested a number of issues such that the risks of thrombosis may be underestimated in this analysis.

Despite some concerns with the quality of the included studies, the large size of this review and its careful analysis suggest that the results are likely to be reliable, and the authors’ conclusions are appropriate.

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

**Practice:** The authors suggested that only contraceptives with the lowest risk of thrombosis should be prescribed, and that prescribing 50LNG in the case of spotting during the use of 30LNG may carry a serious risk of thrombosis.

**Research:** The authors made no recommendations for research.

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