Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis

Denti F, Crowther M, Ageno W

CRD summary
This review assessed the risk of cerebral vein thrombosis (CVT) associated with oral contraceptive (OC) use. The authors concluded that OC users are at increased risk of CVT, particularly those with a pre-existing prothrombotic condition. However, these findings were based on a diverse group of studies with inherent biases, suggesting that the authors' findings should be interpreted with caution.

Authors' objectives
To evaluate the prevalence and risk of cerebral vein thrombosis (CVT) associated with the use of oral contraceptives (OCs). The review also assessed the risk of CVT associated with various inherited and acquired thrombophilic states, and evaluated the possible interactions between the various prothrombotic factors. This abstract only considers the risk of CVT with the use of OCs.

Searching
MEDLINE (1994 to March 2005, week 5), EMBASE (1994 to week 15, 2005) and the Cochrane Library (Issue 2, 2005) were searched; the search terms were reported. The reference lists of retrieved articles were also checked for additional studies and content experts were contacted for other published or unpublished data. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Any study that compared patients with CVT with a non-CVT control group was eligible for inclusion. Case series were excluded from the review.

Specific interventions included in the review
Studies assessing OC use were eligible for inclusion. The types of OCs assessed in the review were not specified.

Participants included in the review
Studies that compared women aged 18 years or older who were or were not taking OCs were eligible for inclusion. Data relating to OC use in pregnant, postpartum and postmenopausal women were excluded. Studies that included patients with a history of thromboembolic disease were also excluded from the review, as were those that had patients in case and control groups who were genetically related. Where stated the mean or median age of the participants included in the review ranged from 28 to 37 years for cases and from 28 to 39 years for controls. One study assessed a group of healthy blood donors and another volunteers from a group of healthy women, physicians and health care workers; other studies used either a group of randomly selected women or did not state how the participants were recruited.

Outcomes assessed in the review
Studies that assessed OC use and the incidence of CVT were eligible for inclusion. CVT had to be confirmed by objective imaging methods.

How were decisions on the relevance of primary studies made?
Two independent reviewers assessed studies for inclusion in the review, with any disagreements resolved by consensus or through discussion with a third reviewer. Agreement between reviewers was assessed using the kappa statistic (k=0.99; reported as excellent agreement).
Assessment of study quality
Two independent unmasked reviewers performed the validity assessment. Studies were considered low quality if they arbitrarily excluded patients from either the control or study groups and if they did not match the baseline characteristics (age and gender) of the participants in the control and study groups. Otherwise, studies were considered to be of higher quality.

Data extraction
Two independent reviewers extracted the data, with any disagreements resolved by consensus or through discussion with a third reviewer. Authors were contacted by e-mail to enquire about missing data. Incidences of CVT were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
The studies were combined by risk factor to give a pooled OR (with 95% CI) using primarily a fixed-effect model; a random-effects model was used in the presence of significant heterogeneity. Where appropriate, the risk of publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic. A secondary analysis was used to assess the association between different inherited and acquired risk factors and OC use.

Results of the review
The review included 17 case-control studies in total, but only eight of these studies reported data on OC usage (263 women with CVT and 2,862 women without CVT).

Most of the studies were described as high quality. Six of the 8 OC studies used matched case and control participants.

Participants who used OCs showed a significantly increased risk of CVT in comparison with controls who did not use OCs (OR 5.59, 95% CI: 3.95, 7.91, p<0.001). Significant heterogeneity was detected (I-squared 68.4%, p=0.002), but a similar result was found when using a random-effects analysis (OR 4.79, 95% CI: 2.40, 9.58, p<0.001). A funnel plot suggested the possible presence of publication bias. Only 2 studies reported separate analyses for women with thrombophilic conditions who were using OCs: one found a significantly increased OR for CVT in women with hyperhomocysteinemia (OR 19.5, 95% CI: 5.7, 67.3), factor V Leiden (OR 30.0, 95% CI: 3.4, 263.0) and prothrombin mutation (OR 79.3, 95% CI: 10.0, 629.4), compared with control participants; the other reported an independent association between CVT, prothrombin mutation and OC use.

Authors’ conclusions
Users of OCs are at an increased risk of CVT, particularly if they have a pre-existing prothrombotic condition.

CRD commentary
This review addressed a clear research question that was defined in terms of the population, intervention, outcomes and study design. Searches were carried out for both published and unpublished studies, and no language restrictions were applied. However, a funnel plot suggested the presence of publication bias with an absence of smaller unpublished studies. Steps were taken to reduce bias and error in the study selection, quality assessment and data extraction processes.

Differences between the studies were assessed statistically, and where significant heterogeneity was detected analyses were carried out using both random-effects and fixed-effect models. No prospective studies were identified and only case-control studies were included in the analysis. Such study designs have inherent biases which, when combined with the presence of significant heterogeneity and publication bias, suggest that the authors’ conclusions regarding OC use
should be interpreted with caution. The authors' recommendations for good-quality prospective studies that assess CVT risk with OC use appear appropriate.

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

Practice: The authors stated that women with CVT should avoid the use of OCs, while women with known prothrombotic conditions who use OCs should be evaluated on an individual basis to assess the risk of CVT.

Research: The authors stated that further good-quality prospective research is needed to further assess the risk of CVT among women who use OCs or who have prothrombotic conditions.

**Bibliographic details**


**PubMedID**

16397131

**DOI**

10.1182/blood-2005-09-3578

**Original Paper URL**

http://bloodjournal.hematologylibrary.org/cgi/content/full/107/7/2766

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adolescent; Adult; Aged; Cerebral Veins; Confidence Intervals; Contraceptives, Oral /adverse effects; Female; Humans; Intracranial Thrombosis /epidemiology; Middle Aged; Reproducibility of Results; Risk Factors; Thrombophilia /epidemiology

**AccessionNumber**

12006001688

**Date bibliographic record published**

31/08/2007

**Date abstract record published**

31/08/2007

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.