Hormonal contraceptive therapy is known to increase risk of venous thrombosis. It is important to identify the specific risks between different agents and combinations.

**Key findings**

- The review compared different generations of combined oral contraceptives (COCs) and their associated risk of VTE. Findings included:
  - First generation – RR 3.2 (95%, 2.0-5.1)
  - Second generation – RR 2.8 (95%, 2.0-4.1)
  - Third generation – RR 3.8 (95%, 2.7-5.5)
- Compared to non-users, all preparations of COCPs were associated with at least a twofold increase of VTE risk.
- A network meta-analysis of 23 studies indicated that COCPs increased the risk of VTE four-fold compared to non-users.
- Higher doses of progestogens were associated with an increased risk of VTE.
  - The highest risk of VTE was associated with 50?g ethinylestradiol with levonorgestrel preparations.
  - The lowest risk of VTE was 20?g ethinylestradiol with levonorgestrel and 20?g ethinylestradiol with gestodene preparations.

**Evidence included in this review**

The review did not exclude studies according to study design. 26 studies, reporting on 25 articles, were included. This comprised of nine cohort studies, three nested case-control studies and 14 case-control studies. Out of all studies, only five specifically confirmed VTE diagnosis using pre-set criteria for each event recorded.

**Quality assessment**

Apart from the five trials that confirmed VTE diagnosis, the remainder had a high or uncertain risk of bias concerning outcome assessment. Eight studies assessed VTE occurrence through a questionnaire. None of the nine cohort studies included mentioned loss to follow-up.
Clinical implications

All types of COCPs were associated with some degree of increased risk of VTE. However, the authors recommend that when prescribing COCPs the dose should be kept as low as possible, while remaining efficacious.

Further research

Further research could focus on identifying underlying mechanism/s of increased VTE risks. Further studies can also aim to ensure accurate outcome assessment (i.e. ensuring accurate diagnosis of VTE in all patients).

Cochrane review


Abstract

Combined oral contraceptive (COC) use has been associated with venous thrombosis (VT) (i.e., deep venous thrombosis and pulmonary embolism). The VT risk has been evaluated for many estrogen doses and progestagen types contained in COC but no comprehensive comparison involving commonly used COC is available.

To provide a comprehensive overview of the risk of venous thrombosis in women using different combined oral contraceptives.

Electronic databases (Pubmed, Embase, Web of Science, Cochrane, CINAHL, Academic Search Premier and ScienceDirect) were searched in 22 April 2013 for eligible studies, without language restrictions.

We selected studies including healthy women taking COC with VT as outcome.

The primary outcome of interest was a fatal or non-fatal first event of venous thrombosis with the main focus on deep venous thrombosis or pulmonary embolism. Publications with at least 10 events in total were eligible. The network meta-analysis was performed using an extension of frequentist random effects models for mixed multiple treatment comparisons. Unadjusted relative risks with 95% confidence intervals were reported. Two independent reviewers extracted data from selected studies.

3110 publications were retrieved through a search strategy; 25 publications reporting on 26 studies were included. Incidence of venous thrombosis in non-users from two included cohorts was 0.19 and 0.37 per 1 000 person years, in line with previously reported incidences of 0.16 per 1 000 person years. Use of combined oral contraceptives increased the risk of venous thrombosis compared with non-use (relative risk 3.5, 95% confidence interval 2.9 to 4.3). The relative risk of venous thrombosis for combined oral contraceptives with 30-35 ?g ethinylestradiol and gestodene, desogestrel, cyproterone acetate, or drospirenone were similar and about 50-80% higher than for combined oral contraceptives with levonorgestrel. A dose related effect of ethinylestradiol was observed for gestodene, desogestrel, and levonorgestrel, with higher doses being associated with higher thrombosis risk.
All combined oral contraceptives investigated in this analysis were associated with an increased risk of venous thrombosis. The effect size depended both on the progestogen used and the dose of ethinylestradiol. Risk of venous thrombosis for combined oral contraceptives with 30-35 ?g ethinylestradiol and gestodene, desogestrel, cyproterone acetate and drospirenone were similar, and about 50-80% higher than with levonorgestrel. The combined oral contraceptive with the lowest possible dose of ethinylestradiol and good compliance should be prescribed—that is, 30 ?g ethinylestradiol with levonorgestrel.


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