The pill and thrombosis
van Vlijmen, Elizabeth Femma Willemien

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Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis

Elizabeth F.W. van Vlijmen
Sophie Wiewel-Verschueren
Taco B. M. Monster
Karina Meijer

Submitted
ABSTRACT

Case presentation
A 29-year-old woman previously tested heterozygote for Factor V Leiden mutation (in a research setting 6 years ago) asks: what is my risk of thrombosis if I would start using combined oral contraceptives (COCs)?

Methods
We performed a meta-analysis to evaluate the risk of VTE in COC-users with thrombophilia. A distinction was made in ‘mild’ (factor V Leiden, prothrombin-G20210A mutation) and ‘severe’ thrombophilia (antithrombin-, protein C-, protein S-deficiency, double heterozygosity or homozygosity of factor V Leiden and prothrombin-G20210A mutation). We identified 12 case-control- and three cohort studies.

Results
In COC-users, mild thrombophilia increased VTE risk six-fold (relative risk (RR) 5.89, 95% Confidence Interval [CI]: 4.21-8.23), while severe thrombophilia increased VTE risk seven-fold (RR 7.15, 95% CI: 2.93-17.45). The cohort studies showed that absolute VTE risk was far higher in COC-users with severe than with mild thrombophilia (4.3-4.6 versus 0.49-2.0 per 100 pill-years, respectively), but with the caveat that absolute risk was estimated in relatives of thrombophilic patients with VTE, i.e. with positive family history.

Conclusion
We recommend discouraging COC-use in all women with severe thrombophilia. Contrary, additive VTE risk of mild thrombophilia is modest and with no other risk factors present, e.g. family history, COC-use should not be denied in women who consider alternative adequate contraception not acceptable.
INTRODUCTION

Since their introduction in 1960, combined oral contraceptives (COCs), containing ethinylestradiol and a progestogen, are associated with an increased risk of venous thromboembolism (VTE).\(^1\)\(^-\)\(^4\) This association is considered related to COC-induced changes in coagulation, anticoagulation, and fibrinolysis in a prothrombotic direction, which alters hemostatic balance. These changes have more impact in women who are already at increased risk of VTE, for instance because of pre-existing hereditary thrombophilia, i.e. protein C, protein S and antithrombin deficiencies and factor V Leiden and prothrombin G20210A mutation. In 1994, a first publication reported increased VTE risk in COC-users who are factor V Leiden mutation carriers.\(^5\) Many studies followed of which the majority evaluated the risk of factor V Leiden and prothrombin G20210A mutation as these are more prevalent in the general population, 5\(^%\)\(^6\)\(^-\)\(^7\) and 2\(^%\)\(^8\), respectively, than protein C-, protein S- and antithrombin deficiencies, which have a prevalence of about 0.1\(^%\) each.\(^9\)\(^-\)\(^1\)\(^1\) Further, some studies evaluated the risk in COC-users with additional hereditary thrombophilias.\(^1\)\(^2\),\(^2\)\(^6\),\(^2\)\(^7\) The number of cohort studies reporting the absolute VTE risk in COC-users with thrombophilia is limited and restricted to thrombophilic family cohort studies, which reported higher risk with natural anticoagulant deficiencies than with factor V Leiden or prothrombin G20210A mutation. Analyses are mostly based on small subgroups. Currently, WHO Medical Eligibility Criteria for contraceptive use state that COC-use in women with hereditary thrombophilias (antithrombin-, protein C-, protein C-deficiency, factor V Leiden, prothrombin G20210A mutation)\(^1\)\(^3\) is associated with an unacceptable health risk.

The aim of this systematic review and meta-analysis is to present summary statistics of the risk of 1st VTE in COC-users with mild and severe hereditary thrombophilia.
METHODS

Identification of studies

MEDLINE and EMBASE databases were searched for potential studies published from inception to February 10, 2015 (date of search performed) presenting relevant evidence on VTE risk in COC-users with hereditary thrombophilia, with no restriction in language.

The PubMed database was searched by applying the following search terms: (“Thrombosis”[Mesh] OR “thrombosis” OR "thrombotic" OR thromboembolism*) AND (“Contraceptives, Oral”[Mesh] OR contracept*) AND (“Thrombophilia”[Mesh] OR "thrombophilia" OR "protein C" OR "factor V Leiden" OR "protein S" OR antithrombin* OR "prothrombin" OR "hereditary" OR "inherited" OR "family history" OR "genetics" OR "genetic").

The EMBASE database was searched by using the search terms: 'thromboembolism'/exp OR thrombosis:ab,ti OR thrombotic:ab,ti OR thromboembolism*:ab,ti AND ('oral contraceptive agent'/exp OR contra- cept*:ab,ti) AND ('throm-bophilia'/exp OR 'protein c deficiency'/exp OR 'protein s deficiency'/exp OR 'blood clotting factor 5 leiden'/exp OR 'antithrombin iii'/exp OR 'antithrombin'/exp OR 'prothrombin'/exp OR 'family history'/exp OR 'genetic predisposition'/exp OR thrombophil*:ab,ti OR 'protein c':ab,ti OR 'protein s':ab,ti OR 'factor v leiden':ab,ti OR 'factor 5 leiden':ab,ti OR antithrombin*:ab,ti OR prothrombin*:ab,ti OR 'family history':ab,ti OR familial:ab,ti OR genetic:ab,ti OR hereditary:ab,ti OR inherited:ab,ti) NOT [medline]/lim.

The search was developed with the expertise of a professional librarian of the Central Medical Library of the University Medical Center Groningen. The search was extended by manual review of the retrieved papers’ reference lists.

Titles and abstracts of potentially relevant papers retrieved were checked independently by two investigators (E.F.W.v.V. and S.W.-V.) for eligibility of full paper evaluation. Discrepancies in opinion between the 2 principal reviewers regarding eligibility were resolved by discussion with a third investigator (K.M.). Likewise, the same two investigators performed full paper evaluation, and discrepancies were resolved by the third investigator.
Study selection criteria

Regarding selection criteria, we anticipated to include both case-control and cohort studies. Studies were considered eligible if the following criteria were met: original data presented, hereditary thrombophilia was considered (antithrombin-, protein C-, or protein S deficiency, factor V Leiden or prothrombin G20210A mutation, double heterozygosity or homozygosity of factor V Leiden or prothrombin G20210A mutation), restriction to 1st VTE of any type, in case-control studies an analysis was performed comparing the prevalence of thrombophilia in COC-associated VTE cases versus the prevalence in COC-using control persons, in cohort studies the incidence rate of VTE in thrombophilic COC-users was compared to non-thrombophilic COC-users, odds ratio (OR) or rate ratio (RR) provided with underlying data or retrievable based on available data. An additional inclusion criterion for cohort studies was that probands were not included in the analyses. Case series of patients were excluded and in case of studies with multiple publications, the publication with the most inclusive dataset was included.

Quality assessment

The two investigators independently performed a quality assessment of the selected papers, in which components of the Newcastle-Ottawa tool for epidemiological studies were taken into account. The following quality issues were considered as relevant: the characteristics of the participants, in- and exclusion criteria for VTE cases, diagnostics of VTE, methods collecting information on COC-use, source of control group, methods of matching cases to controls, and adjustment for confounding.

Statistical analysis

Data synthesis was conducted with Review manager (RevMan, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), which was used to pool the data for each risk factor, using the Mantel-Haenszel method with a random effects model. When risks of a certain disease are small, Odds ratios (ORs) are considered to reliably estimate the Relative risk (RR); therefore the same method was used for case-control and cohort studies. A distinction is made between studies evaluating COC-users with severe (antithrombin-, protein C-, or protein S deficiency, and double heterozygosity or homozygosity of factor V Leiden or prothrombin G20210A mutation) and mild hereditary thrombophilia
(factor V Leiden or prothrombin G20210A mutation). Pooled results are presented as RR with corresponding 95% confidence intervals. Heterogeneity across studies was tested using the I² statistic, homogeneity was considered unlikely when p<0.10. Funnel plots were performed to examine publication bias.

RESULTS

The search resulted in 2087 hits, of which 2027 remained after deletion of 60 duplicates. Based on title and abstract screening, 1929 papers were excluded, leaving 98 articles of possible relevance, which were retrieved for full paper evaluation. Additionally, 22 references were identified from these papers.

Based on the predefined in- and exclusion criteria, initially 25 studies (18 case-control studies and seven cohort studies) were selected for detailed evaluation. Of these, six case-control studies were excluded for the following reasons: no subdivision between men and women was provided for the prevalence of thrombophilia; prevalence of COC-use and/or thrombophilia in controls was based on estimations only; cases of VTE had occurred in patients who were all affected with thrombophilia; information on the number of COC-users with thrombophilia in the patient- and/or control-groups was not provided or incomplete, and a re-analysis based on the same dataset was used to assess influence of duration of COC-use. Additionally, a subgroup analysis in COC-users with or without double heterozygosity of FVL and prothrombin G20210A mutation was excluded, as the study did not take into account the cases that were identified with homozygosity.

Further, four family cohort studies were excluded for the following reasons: inclusion of probands with symptomatic VTE in risk estimations performed in thrombophilic family cohorts; inclusion of women with personal history of VTE and a larger study dataset available than present in the initial study. As a result, 15 studies, consisting of 12 case-control and three cohort studies were selected. There were no disagreements between the independent reviewers with respect to study eligibility that needed to be resolved by the third investigator. A flow chart is presented in Figure 1.
All 15 studies were written in the English language. Fourteen studies evaluated additional risk of mild thrombophilia (factor V Leiden, prothrombin G20210A mutation or both). Three studies evaluated additional risk of severe thrombophilias (antithrombin-, protein C-, or protein S deficiency, and double heterozygous, or homozygous factor V Leiden or prothrombin G20210A mutation). Characteristics of the studies are presented in Table 1. The number of COC-users with or without thrombophilia in cases- and control-groups contributing to the analysis is presented in Table 2; incidence rates of the cohort studies are presented in Table 3.

Study characteristics

Characteristics of the studies are presented in Table 1. Except for two in none of the studies selected COC-users with or without hereditary thrombophilia were the main population to be studied. All case-control studies collected cases from hospitals, except one which used a medical record database. All cases occurred in women aged between 15 or 18 to 49 years, except for one study, which included
women above 50 years. All case-control studies matched controls for age, or an adjustment for age was performed, and five additionally matched according to region. All studies adjusted for various confounders, of which the majority adjusted for BMI and family history. Seven case-control studies tested also for antithrombin-, protein S-, and protein C deficiency, of which three studies adjusted for other thrombophilias. One cohort study adjusted for clustering of women within families. The majority of studies included any VTE or cases of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). However, some studies selected cases based on specific VTE type; two included DVT of upper extremity, and one study focused on cerebral vein thrombosis (CVT). The quality of the studies was high: degree of information provided on methods applied to collect information on COC-use, the objective methods used in diagnosing VTE, source of controls, degree of matching to controls, adjustment, and description of in- and exclusion criteria were generally considered adequate.

The number of COC-users with or without thrombophilia in cases- and control-groups contributing to the analysis is presented in Table 2.
Risk of VTE

Mild thrombophilia

Based on combined results of 14 studies,\(^6,^{15-26,28}\) presence of mild thrombophilia increased the risk of VTE in COC-users almost six-fold (RR 5.89, 95%CI: 4.21-8.23) (Figure 2). Heterogeneity between studies was low (I\(^2\) = 0%; P=0.47). In separate analyses, presence of factor V Leiden mutation increased risk slightly more than six-fold (RR 6.14 [95%CI: 2.58-14.46]). Between-study heterogeneity was low (I\(^2\) = 0%; P = 0.81); presence of prothrombin G20210A mutation increased risk was slightly more than five-fold (RR 5.24 [95%CI: 2.69-10.20]). Heterogeneity between studies was very low (I\(^2\) = 4%; P = 0.40) (data not shown).
Severe thrombophilia

Based on combined results of three studies,³⁵,³⁷,³⁸ presence of severe thrombophilia increased the risk in COC-users more than seven-fold (RR 7.15, 95%CI:2.93-17.45) (Figure 3). Heterogeneity between studies was low (I² = 0%; P = 0.77).

Figure 3. Overall risk ratio for VTE in COC-users with severe thrombophilia (antithrombin-, protein S-, or protein C deficiency, and homozygosity or heterozygosity of factor V Leiden or prothrombin G20210A mutation).
Absolute risk of VTE

*Mild thrombophilia*

Incidence of VTE in COC-users with mild thrombophilia (factor V Leiden, prothrombin G20210A-mutation) was 0.49 (95%CI:0.18-1.07) and 2.0 (95%CI:0.3-7.2) versus 0.19 (95%CI: 0.07-0.41) and 0.0 (95%CI:0-5.5) per 100 pill-years in COC-users without these mutations28 (Table 3).

*Severe thrombophilia*

Incidence of VTE in COC-users with double heterozygosity or homozygosity of factor V Leiden or prothrombin G20210A mutation was 0.86 (95%CI:0.10-3.11) versus 0.19 (95%CI:0.07-0.41) per 100 pill-years in COC-users without these mutations.38

Incidence of VTE in COC-users with antithrombin-, protein C-, or protein S deficiency was 4.3 (95%CI:1.4-9.7) and 4.62 (95%CI:2.5-7.9) versus 0.48 (95%CI:0.1-1.4) and 0.7 (95%CI:0.0-3.7) per 100 pill-years in non-deficient COC-users35,38 (Table 3).

**Table 3: Individual results of thrombophilic family cohort studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Thrombophilas examined</th>
<th>VTE cases/100 pill-years of use</th>
<th>Risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Incidence rate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>With thromophilia</td>
<td>Without thromophilia</td>
<td></td>
</tr>
<tr>
<td>Simioni 199935</td>
<td>FVL</td>
<td>2/98</td>
<td>0/65</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>2.0 (0.3-7.2)</td>
<td>0.0 (0.0-5.5)</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>3/117</td>
<td>1/150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>4.3 (1.4-9.7)</td>
<td>0.7 (0.03-3.7)</td>
<td></td>
</tr>
<tr>
<td>Vlijmen 200737</td>
<td>ACS</td>
<td>13/281</td>
<td>3/629</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>4.62 (2.5-7.9)</td>
<td>0.48 (0.1-1.4)</td>
<td></td>
</tr>
<tr>
<td>Vlijmen 201138</td>
<td>FVL or FII</td>
<td>6/1218</td>
<td>6/3211</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>FVL or FII</td>
<td>0.49 (0.18-1.07)</td>
<td>0.19 (0.07-0.41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Homozygosity or heterozygosity of FVL + FII</td>
<td>2/232</td>
<td>6/3211</td>
<td>0.19 (0.07-0.41)</td>
</tr>
<tr>
<td></td>
<td>Homozygosity or heterozygosity of FVL + FII</td>
<td>0.86 (0.10-3.11)</td>
<td>0.19 (0.07-0.41)</td>
<td></td>
</tr>
</tbody>
</table>

**Potential sources of bias**

As to evaluation of possible sources of bias, in the case-control studies the inclusion criteria applied in the analyses in COC-users were generally comparable, i.e. 1st VTE, although inclusion of cases in some studies depended on VTE type (CVT,\textsuperscript{18} DVT upper extremity,\textsuperscript{24,25} DVT lower extremity).\textsuperscript{19} One case-control study\textsuperscript{29} had included older women (50-63 years) in comparison to the age range in the other studies (15-49), therefore the meta-analysis for mild thrombophilia was re-performed without this study, but the outcome hardly changed (RR: 5.91 [95%CI:4.10-8.51]). Upper extremity DVT is viewed as somewhat different than lower extremity DVT (especially with respect to possible influence of thrombophilia on the development of a first VTE). However, the results did not change if those studies\textsuperscript{24,25} are excluded (5.73 [95% CI: 3.92-8.36]). The majority excluded patients with recent risk factors (pregnancy, postpartum, surgery, trauma, immobilization),\textsuperscript{5,16,27} or co-morbidity (malignancy, systemic disease),\textsuperscript{21,24,25} or both.\textsuperscript{16,18,19,31} Information on COC-use was collected by interview and also discharge letters in one study,\textsuperscript{5} except for two, which used written questionnaires, and similar for both cases and controls.\textsuperscript{20,29} In 3 studies, the source was not stated.\textsuperscript{18,19,25}

In all three family cohort studies, only relatives were included, as including also probands would have introduced bias since they all had VTE; information on COC-use was collected by interviews and medical record review prior to the thrombophilia testing. VTE was objectively established in all studies, but 4 studies,\textsuperscript{20,35,37,38} also had included patients based on clinical diagnosis (full-dose anticoagulants for ≥ 3 months). Several studies discussed missing data; one adjusted for missing data.\textsuperscript{15} Finally, the funnel plots appeared symmetric, suggesting no publication bias.

**DISCUSSION**

We performed a systematic review and meta-analysis based on 15 studies. In COC-users, mild thrombophilia (factor V Leiden, prothrombin G20210A mutation) increased the risk of VTE six-fold, whereas severe thrombophilia (antithrombin-, protein C- or protein S deficiency, double heterozygosity and homozygosity of factor V Leiden or prothrombin G20210A mutation) increased risk seven-fold.
However, to adequately assess the impact of the relative increase in risk, information on the absolute risk is needed. Two cohort study reported a VTE incidence of 0.49 and 2.0 per 100 pill-years of use in COC-users with mild thrombophilia\textsuperscript{35,38}, indicating inconsistent outcomes. The noted high incidence of 2.0 per 100 pill-years could be due to the very small subgroup of COC-users with or without factor V Leiden mutation providing pill-years and zero cases in non-thrombophilic COC-users. Two cohort studies\textsuperscript{35,37} reported incidences of 4.3 and 4.6 per 100 pill-years in COC-users with severe thrombophilia, indicating a far higher risk (\textbf{Table 3}). These differences in absolute risks are also noted in non-affected women from families with severe versus mild thrombophilias. Co-inheritance of other thrombophilic defects could explain the more heightened risk in non-affected women from families with severe thrombophilia; one of the family cohort studies indicated frequent co-existence of other thrombophilic defects.\textsuperscript{37} The heightened risk in non-deficient users may also explain that the increase in relative risk is not clearly different from that seen in COC-users with mild thrombophilia. The incidence of VTE in COC-users with double heterozygosity or homozygosity of factor V Leiden or prothrombin G20210A mutation was 0.86 per 100 pill-years, suggesting that the absolute risk of this double defect is less serious than an antithrombin-, protein C-, or protein S deficiency.\textsuperscript{38}

All absolute risks are estimated in family members of thrombophilic families, i.e. relatives of thrombophilic patients with VTE, and therefore also have a positive family history, which increases their baseline risk of VTE two- to three-fold.\textsuperscript{39-42} To put observed risks into perspective, in COC-users with mild thrombophilia and positive family history the absolute VTE risk is increased eight- to 33-fold, and 70-fold in COC-users with severe thrombophilia, when compared to the VTE risk of about 0.06 per 100 person-years,\textsuperscript{1} estimated in the general population of COC-users.

This meta-analysis has some limitations; the risk of mild thrombophilia was largely estimated in a community setting, while risk of severe thrombophilia was exclusively evaluated in a limited number of thrombophilic family cohorts. This is inherently due to the very low prevalence of severe thrombophilia. Further, absolute risks were all estimated in members of thrombophilic family cohort studies, risks will therefore be more pronounced because of the co-existing family history, than in the general population of COC-users tested positive.
In conclusion, the presence of mild and severe thrombophilia increases the risk of VTE in COC-users six, and seven-fold, respectively. However, absolute VTE risk estimates indicate the contribution of severe thrombophilia to the VTE risk in COC-users as considerably higher (4.3 and 4.6 per 100 pill-years) than the additional risk of mild thrombophilia (0.49 and 2.0 per 100 pill-years), but with the caveat that these risks were estimated in thrombophilic COC-users who also had a positive family history. As a co-existing family history increases VTE risk two- to threefold, estimated risks are more pronounced than in a general population of COC-users tested positive for thrombophilia.

Recommendations
According to GRADE quality of evidence grading, sound epidemiological studies as included in this meta-analysis would be graded as low evidence, but when observed effects are large and there is no obvious bias explaining those effects, the evidence may be rated as moderate or even high, as further research is very unlikely to change our confidence in the estimate of effect (http://gradeworkinggroup.org). From this standpoint the strong recommendation is given based on the high additive risk, to avoid COC-use in women with severe hereditary thrombophilia in all cases. The additive VTE risk of mild thrombophilia is modest and when no other risk factors are present, e.g. family history, COC-use should not be denied in women who consider alternative adequate contraception not acceptable, as in this situation the increased risk of pregnancy-related VTE and increased risk of pregnancy outweigh the COC-associated risk.
References


### Table 1. Study characteristics of case-control- and cohort studies included in the analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria Cases</th>
<th>Exclusion criteria Cases</th>
<th>Thrombophilia testing</th>
<th>Mean/median age case/controls</th>
<th>Source cases/controls</th>
<th>Diagnosis VTE*</th>
<th>Source COC-use</th>
<th>Definition COC-use</th>
<th>Matching factors</th>
<th>Study period</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-control studies</strong></td>
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<tr>
<td><strong>Bloemenkamp</strong></td>
<td>Women with 1&lt;sup&gt;st&lt;/sup&gt; DVT, aged 15-49 years</td>
<td>Malignancy Pregnancy Postpartum, Recent miscarriage</td>
<td>FVL</td>
<td>35/Not stated</td>
<td>Cases: hospitals Controls: Friends/partner/other patients</td>
<td>Objectively confirmed</td>
<td>Cases: interview/hospital discharge letter Controls: interview</td>
<td>Cases: COC-use at time of VTE Controls: COC-use at inclusion</td>
<td>No</td>
<td>1988-1992</td>
<td>Age, Family history, FVL jointly</td>
</tr>
<tr>
<td><strong>Andersen</strong></td>
<td>Women with 1&lt;sup&gt;st&lt;/sup&gt; VTE, aged 18-49 years</td>
<td>≤ 3 months: Surgery Trauma Pregnancy Postpartum Malignancy Immobility SVT Crohn/collitis Heart failure</td>
<td>FVL, ACS</td>
<td>33/28</td>
<td>Cases: hospital discharge registries Controls: blood donors</td>
<td>Not stated</td>
<td>Cases: interview Controls: Questionnaire</td>
<td>Cases: COC-use ≤ 3 months prior to VTE Controls: COC-use ≤ 3 months prior to inclusion</td>
<td>Age, Region</td>
<td>1977-?</td>
<td>BMI, Smoking, Parity, Missing data</td>
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<tr>
<td><strong>Martinelli</strong></td>
<td>Patients with 1&lt;sup&gt;st&lt;/sup&gt; CVT aged 15-64 years</td>
<td>Malignancy Autoimmune disease Pregnancy Postpartum Postmenopause</td>
<td>FVL, FII ACS</td>
<td>30/32</td>
<td>Cases: Hospital Controls: friends/partners</td>
<td>Objectively confirmed</td>
<td>Source COC-use not stated</td>
<td>Cases: COC use ≤ 2 weeks prior to VTE Controls: COC-use ≤ 2 weeks prior to inclusion</td>
<td>Age, Region, Education</td>
<td>1991-1997</td>
<td>Matching factors</td>
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<td><strong>Martinelli</strong></td>
<td>Consecutive women with 1&lt;sup&gt;st&lt;/sup&gt; DVT lower extremities aged 15-48 years</td>
<td>Malignancy Autoimmune disease, Pregnancy Postpartum</td>
<td>FVL, FII ACS</td>
<td>30/46</td>
<td>Cases: Hospital Controls: friends/partners/other patients</td>
<td>Objectively confirmed</td>
<td>Source COC-use not stated</td>
<td>Cases: COC use ≤ 2 weeks prior to VTE Controls: COC-use at time of blood sampling</td>
<td>No</td>
<td>1995-1998</td>
<td>Age, Other thrombophilies</td>
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<td>Study</td>
<td>Inclusion criteria Cases</td>
<td>Exclusion criteria Cases</td>
<td>Thrombophilia testing</td>
<td>Mean/median age case/controls</td>
<td>Diagnosis VTE*</td>
<td>Source COC-use</td>
<td>Definition COC-use</td>
<td>Matching factors</td>
<td>Study period</td>
<td>Adjustment</td>
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<tr>
<td>Aznar</td>
<td>Consecutive patients with 1st DVT/PE No age restriction</td>
<td>Malignancy</td>
<td>FII FVL ACS</td>
<td>Not stated</td>
<td>Cases: hospital Controls: blood donors</td>
<td>Cases: Interview Controls: Interview</td>
<td>Cases: COC-use at time of the study Controls: COC-use at time of the study</td>
<td>Age, Region</td>
<td>Not stated</td>
<td>Age</td>
<td></td>
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<td>Spain Fv, Fl</td>
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<tr>
<td>Spannagl</td>
<td>Consecutive women with DVT/PE aged 15-49 years</td>
<td>Malignancy Infectious, autoimmune/ liver/renal disease History drug abuse</td>
<td>FVL</td>
<td>34/34</td>
<td>Cases: hospitals Controls: random sample population - database</td>
<td>Objectively confirmed or anticoagulant treatment</td>
<td>Cases: Questionnaire Controls: Questionnaire</td>
<td>Cases: COC-use at time of VTE Controls: COC-use at inclusion</td>
<td>Age</td>
<td>1995-1997</td>
<td>Age, Family history, BMI, Varicose veins</td>
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<tr>
<td>Germany FVL</td>
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<tr>
<td>Legnani</td>
<td>Consecutive women with DVT/PE aged 15-49 years</td>
<td>Isolated PE SVT DVT upper limb or unusual site</td>
<td>FVL FII ACS</td>
<td>30/33</td>
<td>Cases: hospital Controls: from general population</td>
<td>Objectively confirmed</td>
<td>Cases: Interview Controls: Interview</td>
<td>Cases: COC use at time of VTE Controls: COC at inclusion</td>
<td>Region</td>
<td>1994-2000</td>
<td>Age, Other thrombophilias</td>
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<tr>
<td>Italy FVL, FII FVL+FFI</td>
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<td>Vaya</td>
<td>Consecutive patients with 1st DVT upper extremity aged 15-75 years</td>
<td>Malignancy Infection Autoimmune/ Liver/renal disease History drug abuse</td>
<td>FVL FII AT</td>
<td>Not stated</td>
<td>Cases: hospital Controls: healthy volunteers from same hospitals</td>
<td>Objectively confirmed</td>
<td>Source COC-use not stated</td>
<td>Cases: COC-use ≤ 2 weeks prior to VTE Controls: COC-use ≤ 2 weeks prior to sampling</td>
<td>Age</td>
<td>1997-2001</td>
<td>Confounding factors not specified</td>
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<td>Spain FV, Fl</td>
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<tr>
<td>Martinelli</td>
<td>Patients with 1st DVT of upper extremity No age restriction</td>
<td>DVT due to central vein catheter Malignancy Related to thrombophilic family</td>
<td>FVL FII ACS</td>
<td>32/30</td>
<td>Cases: hospital Controls: partners or friends</td>
<td>Objectively confirmed</td>
<td>Source COC-use not stated</td>
<td>Cases: COC use at time of VTE Controls: COC use at inclusion</td>
<td>Age</td>
<td>1994-2003</td>
<td>Age, Other thrombophilias</td>
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<tr>
<td>Italy FVL, Fl</td>
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<tr>
<td>Study</td>
<td>Inclusion criteria Cases</td>
<td>Exclusion criteria Cases</td>
<td>Thrombophilia testing</td>
<td>Mean/median age case/controls</td>
<td>Source cases/controls</td>
<td>Diagnosis VTE (^a)</td>
<td>Source COC-use</td>
<td>Definition COC-use</td>
<td>Matching factors</td>
<td>Study period</td>
<td>Adjustment</td>
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<td>Sidney</td>
<td>Women with 1(^1)st DVT/PE aged 15-44 years</td>
<td>Pregnancy Hysterectomy, Ovariotomy HRT-use Missing COC data, estrogen dose &gt;50 mcg</td>
<td>FVL, FII</td>
<td>35/33</td>
<td>Cases: medical records Database Controls: same database</td>
<td>Objectively confirmed or clinical suspicion PE</td>
<td>Cases: interview Controls: interview</td>
<td>Cases: COC-use at time of VTE Controls: COC use at inclusion</td>
<td>Age</td>
<td>1998-2000</td>
<td>Race/ethnicity, Income, BMI</td>
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<td>Roach</td>
<td>Women with 1st DVT/PE aged 50-63 years</td>
<td>Severe psychiatric problems, Inability to speak Dutch</td>
<td>FVL, FII</td>
<td>53/53</td>
<td>Cases: hospital Controls: Partners/ Random digit dialing</td>
<td>Objectively confirmed</td>
<td>Cases: Questionnaire Control: Questionnaire</td>
<td>Cases: COC-use ≤ 12 months prior to VTE Controls: ≤ 12 months prior to inclusion</td>
<td>Region</td>
<td>1999-2004</td>
<td>Age, BMI, Smoking, Positive family history</td>
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<tr>
<td>Bergendal</td>
<td>Women with 1st DVT/PE aged 18-54 years</td>
<td>Pregnancy &lt; 3 months Malignancy</td>
<td>FVL, FII</td>
<td>41/42</td>
<td>Cases: Hospitals Controls: Swedish population register</td>
<td>Objectively confirmed</td>
<td>Cases: interview Controls: interview</td>
<td>Cases: COC-use ≤ 3 months prior to VTE Controls: ≤ 3 months prior to inclusion</td>
<td>Age</td>
<td>2003-2009</td>
<td>Smoking, BMI, immobilization Cohort studies</td>
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**Cohort studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria Cases</th>
<th>Exclusion criteria Cases</th>
<th>Thrombophilia testing</th>
<th>Mean/median age case/controls</th>
<th>Source cases/controls</th>
<th>Diagnosis VTE (^a)</th>
<th>Source COC-use</th>
<th>Definition COC-use</th>
<th>Matching factors</th>
<th>Study period</th>
<th>Adjustment</th>
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<tbody>
<tr>
<td>Simioni</td>
<td>Relatives, aged &gt;15 years, of patients with VTE and ACS or FVL</td>
<td>Double defect Malignancy No consent</td>
<td>ACS, FVL</td>
<td>NA</td>
<td>NA</td>
<td>Objectively confirmed or anticoagulant treatment</td>
<td>Interview</td>
<td>COC-use and duration collected</td>
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<td>Not stated</td>
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<tr>
<td>van Vlijmen</td>
<td>1st degree female relatives, aged 15-50 years, of patients with VTE and ACS</td>
<td>Probands Dead Geographic distance No consent Laboratory incomplete</td>
<td>ACS, FVL, FII</td>
<td>NA</td>
<td>NA</td>
<td>Idem</td>
<td>Idem</td>
<td>NA</td>
<td>2000-2004</td>
<td>Clustering within families</td>
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<tr>
<td>van Vlijmen</td>
<td>1st degree female relatives, aged 15-50 years, of patients with VTE and FVL/F2 Homozygotes</td>
<td>Probands Dead Geographic distance No consent Laboratory incomplete</td>
<td>FVL, FII, ACS</td>
<td>NA</td>
<td>NA</td>
<td>Idem</td>
<td>Idem</td>
<td>NA</td>
<td>1995-1998 1998-2004</td>
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</table>

**Notes:**
- *Venography, plethysmography, Doppler US, duplex color US, Intravenous-arterial angiography, CT-scan, IV digital angio graphic imaging, MRI, VP-lung scan, pulmonary angiogram.*