Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception

Running short title: Oral contraceptives, pregnancy and mild thrombophilia

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ABSTRACT

Current guidelines discourage combined oral contraceptive (COC) use in women with hereditary thrombophilic defects. However, qualifying all hereditary thrombophilic defects as similarly strong risk factors might be questioned. Recent studies indicate the risk of venous thromboembolism (VTE) of a factorVLeiden mutation as considerably lower than a protein C, protein S-, or antithrombin deficiency. In a retrospective family cohort study, the risk of VTE during COC-use and pregnancy-postpartum was assessed in 798 female relatives of symptomatic probands with heterozygous, double heterozygous or homozygous factorVLeiden or prothrombin G20210A mutation. Overall absolute VTE risk in women with no, single or combined defects was 0.13 (95%CI:0.08-0.21), 0.35 (95%CI:0.22-0.53), and 0.94 (95%CI:0.47-1.67) per 100 person-years, while these were 0.19 (95%CI:0.07-0.41), 0.49 (95%CI:0.18-1.07), and 0.86 (95%CI:0.10-3.11) during COC-use, and 0.73 (95%CI:0.30-1.51), 1.97 (95%CI:0.94-3.63), and 7.65 (95%CI:3.08-15.76) during pregnancy-postpartum. COC-use and pregnancy-postpartum were independent risk factors for VTE, with highest risk during pregnancy-postpartum, as demonstrated by adjusted HRs of 16.0 (95%CI:8.0-32.2) versus 2.2 (95%CI:1.1-4.0) during COC-use, respectively. Rather than strictly contra-indicating COC-use, we advocate that detailed counseling on all contraceptive options, including COCs, should be performed, addressing the associated risks of both VTE and unintended pregnancy, in order to enable these women to make an informed choice.
Introduction

The risk of venous thromboembolism (VTE) in women using combined oral contraceptives (COCs) is attributed to changes in hemostasis.\textsuperscript{1-3} These changes may have greater impact in women with thrombophilic defects. Therefore, WHO recommendations state COC-use in women with thrombophilic mutations, i.e. antithrombin-, protein C-, or protein S-deficiency, factorVLeiden, and prothrombin-20210A, as associated with an unacceptable health risk.\textsuperscript{4} These recommendations are mainly based on case-control studies reporting increased relative risks of VTE during COC-use in women with hereditary thrombophilic defects.\textsuperscript{5-11} However, to qualify all hereditary thrombophilic defects as similarly strong risk factors might be questioned. The absolute risk of VTE in factorVLeiden-carriers is estimated being 0.15 per 100 person-years,\textsuperscript{12} whereas in antithrombin-, protein C, or protein S-deficient persons these estimates range from 0.7 to 1.7 per 100 person-years, indicating a considerably higher degree of risk.\textsuperscript{12,13}

We previously demonstrated that women with severe hereditary thrombophilic defects, i.e. antithrombin-, protein C-, or protein S-deficiency are at very high risk during actual COC-use, particularly when concomitant thrombophilic defects are present (4.6 per 100 pill-years), and the use of COCs should be strongly discouraged in these women.\textsuperscript{14,15}

As the absolute risk in women with mild thrombophilic defects is substantially lower than in women with severe thrombophilic defects, withholding COCs in women with mild hereditary thrombophilic defects might be less favourable. When discouraging COC-use, an increased risk
of unintended pregnancy must be taken into account as alternative non-hormonal contraception is less reliable.\textsuperscript{16,17}

Pregnancy and especially the postpartum period is a strong risk factor for VTE, with an absolute risk of VTE in the general population that is higher than noted for COCs, i.e. 0.2 per 100 pregnancy-years\textsuperscript{18} versus 0.06 per 100 pill-years.\textsuperscript{19} To balance the risk and benefits of COCs, reliable estimates of the VTE risk associated with both COC-use and pregnancy are needed.

In order to evaluate whether mild thrombophilic defects indeed have lower risk of VTE during COC-use, which would be the basis for counseling, the risk of first VTE during COC-use and pregnancy-postpartum was assessed in a large retrospective family cohort of women with heterozygous, double heterozygous or homozygous factorVLeiden or prothrombin-G20210A mutation. Women were divided into those with no, single, or combined mild thrombophilic defects, as we recently demonstrated that aggregation of defects is often noted in thrombophilic families, and that especially the presence of multiple defects may significantly increase the absolute risk of VTE.\textsuperscript{13-15}

In order to put results into perspective, obtained absolute risks are compared with those during use of alternative contraception.

**Methods**

**Subjects**

In the present retrospective family cohort study, all female relatives were included from four family cohorts, which were described in detail elsewhere.\textsuperscript{20-23} These were first-degree relatives of consecutive patients (proband) with VTE or premature atherosclerosis (<50 years) and
factorVLeiden, prothrombin-G20210A, high factor VIII levels (>150 IU/dL) or hyperhomocysteinemia, respectively (Figure 1). Probands and their first degree relatives were enrolled between 1995 and 1998 (factorVLeiden study) and 1998 and 2004 (prothrombin-G20210A, hyperhomocysteinemia and factor VIII studies) in 3 university hospitals in The Netherlands. Probands were excluded to avoid bias, as they have experienced VTE by definition. Relatives of probands with premature atherosclerosis were not included in the present study. First-degree relatives aged ≥15 years were identified by pedigree analysis. Relatives were contacted through the probands and were all seen in person at our clinics.

Information on VTE, exposure to exogenous risk factors for VTE, and anticoagulant treatment was collected by physicians and research nurses through medical interviews using a validated questionnaire, and by reviewing medical records.

All relatives were tested for the presence of factorVLeiden, prothrombin-G20210A, high factor VIII levels, and hyperhomocysteinemia (original index defects), and for antithrombin-, protein C- and protein S-deficiency.

Due to the retrospective nature of the study, collection of medical history took place at the end of the observation period. As thrombophilia testing was performed after collection of these data, medical history taking of relatives was not influenced by the results of thrombophilia testing. For the same reason, any decisions on diagnostic outcome and treatments during the observation periods were made without knowledge on presence of thrombophilia.

Female relatives with antithrombin, protein C, or protein S deficiency were excluded, as these deficiencies are strong risk factors for VTE. As hyperhomocysteinemia is no longer considered an independent thrombophilic risk factor, this defect was not taken into account, but these women were not excluded from our cohort.
For the purpose of our study, information on contraceptive use and pregnancies (including pregnancy losses) was reconfirmed by a written questionnaire sent by mail. In addition, also GPs were contacted for further information. All relatives gave informed consent in accordance with the Declaration of Helsinki and the studies were approved by the institutional review boards of the three participating Dutch hospitals.

**Diagnosis of venous thromboembolism**

VTE was considered established when diagnosed by compression ultrasound or venography (deep vein thrombosis), by ventilation/perfusion lung-scan, spiral CT-scan or pulmonary angiography (pulmonary embolism), or when the patient had received full-dose heparin and vitamin K antagonists for at least 3 months without objective testing at a time when these techniques were not available. VTE was classified as ‘provoked’ when occurring up to 3 months after exposure to exogenous risk factors, which included surgery, trauma, immobilization for at least 7 days, COC-use, pregnancy-postpartum up to 3 months, and malignancy. In the absence of these risk factors, VTE was defined as ‘unprovoked’. Superficial phlebitis was not considered a thrombotic event.

**Laboratory studies**

FactorVLeiden and prothrombin-G20210A were demonstrated by polymerase-chain-reactions. Factor VIII:C was measured by one-stage clotting assay and considered increased at levels above 150 IU/dL. Protein S- and protein C-antigen levels were measured by Enzyme-Linked-Immuno-Sorbent-Assay (DAKO, Denmark); protein C activity (Behring, Germany) and antithrombin levels (Chromogenix, Sweden) by chromogenic substrate assays. Normal ranges were determined in healthy volunteers without a (family) history of VTE, who were neither
pregnant nor used COCs within 3 months prior to blood sampling. Antithrombin-, protein S- and protein C-deficiency were defined by levels below the lower limit of their normal ranges. In probands and symptomatic relatives, blood samples were collected at least 3 months after VTE had occurred. If they were still treated with vitamin-K-antagonists, samples were taken after temporary change of this therapy to low molecular weight heparin for at least 2 weeks.

Statistical analysis

We estimated the overall absolute risk of first VTE in female relatives with no defects, a single defect, or a combination of factorVLeiden and prothrombin-G20210A. Homozygosity for factorVLeiden or prothrombin-G20210A was classified as a combined defect, as their prevalence is too low to calculate reliable estimates separately.

Furthermore, the absolute risk during actual COC-use and during the pregnancy/postpartum period was estimated.

The absolute risk was expressed as the incidence rate per 100 person-years. Corresponding 95% confidence intervals (CI) were calculated by using the binomial probability model (conditional-small-sample-approach). Person-years were counted from age 15 until age 50 years, first VTE, or end of study. A minimum age of 15 years was chosen since VTE is rare at younger age, and a maximum age of 50 years as end of fertile lifetime. The duration of exposure to COCs (pill-years) included actual use including a 3-month exposure window after COC-use was discontinued. For pregnancy, including pregnancy losses, exposure was defined as the gestation time plus 3-month postpartum.

We used a time-varying exposure Cox-proportional-hazard model to estimate adjusted hazard ratios of actual COC-use and the pregnancy-postpartum period next to the presence of single or combined hereditary mild thrombophilic defects. With this model we specifically took into
account that both COC-use and the pregnancy-postpartum period are temporary risk periods during fertile lifetime. Effect modification (interactions) of mild thrombophilic defects on both COC-use and the pregnancy-postpartum period were also considered. Additionally, the influence of an increased factor VIII level (>150IU/mL) as an acquired independent risk factor for VTE was estimated.

Furthermore, the absolute risk of VTE during COC-use in women with or without mild hereditary thrombophilia was put into the perspective of contraceptive failure of COC and alternative contraceptives. Alternative contraceptives include condom, the copper-IUD (380 mm²), and the levonorgestrel intrauterine device (LNG-IUD). The LNG-IUD is presented as having no increased risk of VTE, as recently reported in a large study.¹⁹

Continuous variables were expressed as mean values and standard deviation (SD) or median values and range, and categorical data as counts and percentages. A two-sided p-value of less than 0.05 indicated statistical significance.

Analyses were performed using SAS software, version 9.1 (SAS-Institute-Inc.,USA).

**Results**

**Clinical characteristics**

The study consisted of 639 unrelated families including 271 probands with factorVLeiden, 109 with prothrombin-G20210A, 156 with high factor VIII levels, and 103 with hyperhomocysteinemia (Figure 1). Of their 4315 relatives aged 15 years or older, 2292 relatives could not be enrolled; 1371 were non-responders (no consent, geographical distance) and 921 had deceased. Of the 2023 relatives enrolled, 989 were female. Of these women, 54 were not eligible
as they had antithrombin-, protein C-, or protein S-deficiency, leaving 935 eligible female relatives. One-hundred-thirty-seven eligible women were excluded for incomplete thrombophilic tests. The remaining 798 women were available for analysis (Figure 1).

Table 1 lists the characteristics of the 798 female relatives. Of those, 301 had one or more defects. Among these women, 14 were homozygous for factorVLeiden, of whom three were also heterozygous for prothrombin-G20210A mutation, and four women were homozygous for the prothrombin-G20210A mutation.

Two-hundred-and-five of the 301 (68%) women with single or combined defects and 366 of the 497 women (74%) without a defect reported COC-use during their lifetime. The majority of women (76%) had only one period of COC-use. Seventy-two percent of women had one or more pregnancies, with a median number of 3 (range 1-10) pregnancies. Sixty-nine percent of the women who had used COCs and 75% of women who never used COCs had one or more pregnancies (Table 1).

A total of 50 first episodes of VTE were reported, of which 44 (88%) were provoked by exogenous risk factors. The majority, i.e. 35 provoked episodes of VTE, occurred during COC-use (11), of which four in the presence of another risk factor, or during the pregnancy-postpartum period (21), and three VTEs occurred after starting COC-use during the 12 weeks postpartum (Table 1).

Absolute risk of first venous thromboembolism

Table 2 lists the absolute risk of VTE associated with COC-use and the pregnancy-postpartum period. The crude overall absolute risk of first VTE in our cohort was 0.25 per 100 person-years (95%-CI, 0.18-0.32), based on 50 VTEs in 798 women with 20317 person-years. In women with
no, a single or combined defects, these were 0.13 (95%-CI, 0.08-0.21), 0.35 (95%-CI, 0.22-0.53), and 0.94 (95%-CI, 0.47-1.67) per 100 person-years, respectively.

Restricting the observation time to actual COC-use, the crude incidence of VTE was 0.30 (95%-CI, 0.16-0.50) per 100 pill-years, based on 14 VTEs during 4661 pill-years. In women with no, a single or combined defects, the incidences were 0.19 (95%-CI, 0.07-0.41), 0.49 (95%-CI, 0.18-1.07), and 0.86 (95%-CI, 0.10-3.11) per 100 pill-years, respectively (Table 2).

When considering only the pregnancy-postpartum periods, the crude incidence of first VTE was 1.55 (95%-CI, 0.99-2.30) per 100 pregnancy-years, based on 24 VTEs during 1553 pregnancy years. In women with no, a single or combined defects, the incidences rose from 0.73 (95%-CI, 0.30-1.51) and 1.97 (95%-CI, 0.94-3.63) to 7.65 (95%-CI, 3.08-15.76) per 100 pregnancy-years, respectively.

**Relative risk of first venous thromboembolism**

The increased risk of VTE in women with single and combined defects in comparison to women without defects was confirmed in our time-dependent multivariable Cox regression analysis (also including pregnancy and COC-use). The hazard ratios were 2.7 (95%CI, 1.4 to 5.1) for a single defect and 8.5 (95%CI, 3.8 to 19.2) for combined defects. The substantially higher risk of VTE during the pregnancy-partum period was confirmed by a hazard ratio of 16.4 (95%CI, 8.2 to 32.8). For actual COC-use the hazard ratio was 2.1 (95%CI, 1.1 to 4.1).

When adjusted for factor VIII, hazard ratios were 2.7 (95%-CI,1.4-5.0) and 10.1 (95%-CI, 4.4-23.0) for a single and combined defects, 2.2 (95%-CI, 1.1-4.0) for COC-use and 16.0 (95%-CI, 8.0-32.2) for pregnancy.

A high factor VIII level was present in 197 (40%), 99 (39%), and 8 (22%) of women with no, single and combined defects, respectively. Independently of the presence of factorVLeiden or
prothrombin-G20210A mutation, the presence of high factor VIII level was associated with an increased risk of VTE (adjusted HR 2.3 (95%-CI, 1.3-4.2)).

**Absolute risk of venous thromboembolism in COC-users versus users of alternative contraception**

The absolute VTE incidence in COC-users and in users of alternative contraceptive methods, i.e. LNG-IUD-users, copper-IUD users and male condom-use, for a hypothetical group of 100,000 women over one year is presented in **Table 3**. In addition to the absolute risk related to COC-use, the hypothetical risks of VTE associated with contraception failure were estimated.

In this analysis, both the direct risk of VTE due to the contraceptive method (only present in COC-users) and the additional risk of VTE due to contraceptive failure resulting in unintended pregnancies are taken into account. In Table 3, the absolute risk of VTE of 0.55 per 100 pill-years in COC-users with thrombophilic defect(s) is derived from combining both the number of VTEs and observation years in women with single and combined defects as presented in table 2. The absolute risk of VTE of in users of alternative contraceptives is 2.2 fold lower, 0.25 per 100 years in users of alternative contraceptive methods, i.e. based on the adjusted HR of 2.2 for COC-use. The absolute risk of VTE of 2.8 per 100 pregnancy years is derived from combining both the number of VTEs and observation years noted in pregnant women with single and combined defects, see table 2. A similar approach is used in the calculations in women without thrombophilic defects.

In women with a thrombophilic defect, the total number of VTEs is 556 in COC-users, 270 in LNG-IUD-users, 290 in copper-IUD-users and 586 in condom-users. In women without thrombophilic defects, the total number of VTEs is 192, 174, 95 and 100, respectively. In these
estimations, the possibility that ‘unintended’ pregnancies are interrupted is not taken into consideration; in that situation, it is expected that the risk of VTE is lower than presented here.

**Discussion**

In a cohort of women with a positive family history of VTE, the presence of single or combined factor V Leiden and prothrombin-G20210A mutation, including homozygotes, resulted in a modest increase in absolute risk of VTE. COC-use and the pregnancy-postpartum period were confirmed as risk factors for VTE. Although the absolute risk of VTE significantly increased during COC-use, [up to 0.86 (95%-CI, 0.10-3.11) per 100 pill-years] in women with combined defects, the absolute risk during the pregnancy-postpartum period was by far the most important [up to 7.65 (95%-CI, 3.08-15.76) per 100 pregnancy years]. The substantially higher risk of VTE during the pregnancy-postpartum period was confirmed by an adjusted HR of 16.0 (95%-CI, 8.0-32.2), as compared to an adjusted HR of 2.2 (95%-CI, 1.1-4.0) for COC-use.

Our results further show that, in line with recent publications, the a-priori absolute risk of VTE during the pregnancy-post-partum period noted in women without any thrombophilic defect is higher than noted in COC-users, i.e. 0.73 versus 0.19 per 100 person-years. However, as these risks were observed in thrombophilic families, the absolute risk during the pregnancy-postpartum period and during COC-use in our study was approximately 3.5 to 5 times higher than reported in the general community, incidences of 0.2 per 100 pregnancy-years. and 0.06 per 100 pill-years.

As our cohort also included women from one of the original family studies with familial high factor VIII level, which is an acquired risk factor for VTE, the effect of high factor VIII level was
also estimated. Independently of the presence or absence of factorVLeiden or prothrombin-G20210A, the presence of high factor VIII level was associated with an increased risk of VTE (adjusted HR 2.3 (95%-CI, 1.3-4.2).

Several studies have reported COC-use and pregnancy-postpartum as contributing factors to the risk of VTE in women with factorVLeiden and/or prothrombin-G20210A. However, adequate interpretation of risks is hampered as most studies only reported relative risks and these estimates differ considerably. In carriers of factorVLeiden or prothrombin-20210A, odds ratios for COC-use ranged from 1.3 to 30, while for the pregnancy-postpartum period these ranged from 2 to 53. Additionally, it is often unclear whether the presence of other thrombophilic defects was excluded. Further, although COCs prevent from pregnancy, the clinical consequences of both hormonal risks of VTE are seldom considered simultaneously within one study.

The major finding in the present study is the high pregnancy-related risk of VTE, relative to the observed risk during COC-use. Therefore, if it is decided against COC-use, adequate alternative contraception is needed in order to keep the risk of unintended pregnancy in these women as low as possible. The actual choice in alternative contraception is very limited; only copper-intrauterine devices (IUDs) and condoms. All hormonal contraceptives are considered to increase the risk of VTE, including progestagen-only contraceptives (desogestrel-only pill (Cerazette®), etonogestrel implant (Implanon®), medroxyprogesterone-acetate injections (Depoprovera®), and LNG-IUD (Mirena®)), though this is merely on theoretical grounds by means of extrapolation of data from combined hormonal contraceptives. However, a recent large cohort study reported the LNG-IUD to not increase the risk of VTE, based on more than 100,000 women-years of use.
In order to put our results into a risk-benefit perspective, we estimated absolute VTE risk of COC-use and alternative contraceptive methods, i.e. LNG-IUD, copper-IUD and condoms for a hypothetical group of 100,000 women over one year of use, together with VTE risk associated with contraception failure (Table 3). Although COC-use results in COC-related VTEs, due to its excellent contraceptive efficacy,\textsuperscript{37} the number of unintended pregnancies and subsequent number of pregnancy-related VTEs (6) is very low. The pregnancy-related VTE risk associated with the LNG-IUD and Cu-IUD (380 mm\textsuperscript{2} Cu) is estimated to be higher, due to their slightly lesser contraceptive efficacy.\textsuperscript{38,16} Condom-use has the lowest contraceptive efficacy, with an up to 60-fold increased risk of unintended pregnancy,\textsuperscript{17} which makes this option the least favourable alternative. Summarising these extrapolations, the LNG-IUD and copper-IUD both carry a lower overall risk of VTE and are therefore good alternatives to COCs. The reported higher rate of unintended pregnancies versus COC-use is expected not clinically relevant in daily practice as these contraceptives are not dependent on compliance. However, the specific side effects of LNG-IUD and copper-IUD related to changes in bleeding pattern, that often lead to discontinuation of use, and women’s preferences need be taken into account.

Our study has its limitations. With the retrospective design, not all events were established by objective techniques, because these were not yet available at the time. Consequently, the reported absolute risk of VTE may have been overestimated. On the other hand, due to the retrospective design, treating physicians were unaware of the presence of any thrombophilic defects. Furthermore, there was a potential for recall bias on COC-exposure. Therefore, extensive efforts were made to minimize the recall bias on COC-exposure by verification of patient information through medical files and treating physicians. Not all relatives were tested for all thrombophilic defects. Furthermore, the overall risk of VTE might be overestimated due to the family cohort
design by selecting symptomatic affected probands. The risk of VTE associated with these mild hereditary thrombophilic defects will probably be even lower when unselected women are tested for those defects as part of counselling prior to COC-use.

Strong points of our study are its size and the testing for all known thrombophilic defects. Further, we estimated the absolute and relative risk of VTE and took both COC-use and pregnancy into account. Moreover, these risks were put into perspective in a modelling exercise, in which both the risks of contraceptive-related VTE and the risk of pregnancy-related VTE (resulting from contraceptive failure) are considered.

In conclusion, factorVLeiden and prothrombin-G20210 are mild risk factors for VTE in fertile women. Although in the women with a factor Leiden and prothrombin-G20210 mutation, the absolute risk of VTE increased during COC-use, this risk was importantly lower than the absolute risk observed during the pregnancy-postpartum period. These data provide evidence that the policy to contra-indicate COC-use in these women needs reconsideration. The results of the study do not allow to “promote” a COC use in asymptomatic family-carriers of FVL or PT G20210A, but indicate that when COC-use is discontinued the need for adequate alternative contraception has high priority.

Rather than strictly contra-indicating COC-use, we advocate that detailed counseling on all contraceptive options, including COCs, should be performed, addressing the associated risks of both VTE and unintended pregnancy, in order to enable these women to make an informed choice.
Acknowledgement

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Authorship

Contributions: van Vlijmen, Veeger, Middeldorp, Hamulyák, Prins, Büller, and Meijer had full access to the database

Study concept and design: van der Meer†, van Vlijmen and Veeger

Acquisition of data: van Vlijmen, Middeldorp, Hamulyák, and Büller

Analysis and interpretation of data: van Vlijmen, Veeger and Meijer

Drafting of the manuscript: van Vlijmen

Critical revision of the manuscript for important intellectual content: Veeger, Middeldorp, Hamulyák, Prins, Büller, and Meijer

Statistical analysis: Veeger

Study supervision: van der Meer†, Meijer

All authors have read and approved the final version of the manuscript.

Conflict of interest disclosures:

None reported

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REFERENCES


Table 1. Characteristics of 798 female 1st degree relatives with either factor V Leiden, prothrombin G20210A, or a combination of these defects, including homozygosity

<table>
<thead>
<tr>
<th>All female relatives</th>
<th>No defects</th>
<th>Single defects</th>
<th>Combined defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female relatives, n</td>
<td>497</td>
<td>251</td>
<td>50</td>
</tr>
<tr>
<td>Follow-up, y(^a)</td>
<td>32 (0.1 – 35)</td>
<td>28 (0.1 - 35)</td>
<td>24 (2 - 35)</td>
</tr>
<tr>
<td>Factor V Leiden (%)</td>
<td>NA</td>
<td>160 (64)</td>
<td>46 (92)</td>
</tr>
<tr>
<td>Prothrombin G20210A (%)</td>
<td>NA</td>
<td>91 (36)</td>
<td>39 (81)</td>
</tr>
<tr>
<td>Ever COC users, n (%)</td>
<td>366 (74)</td>
<td>171 (68)</td>
<td>34 (68)</td>
</tr>
<tr>
<td>Age at start of COC, y</td>
<td>19 (15 - 47)</td>
<td>20 (15 - 49)</td>
<td>19 (15-49)</td>
</tr>
<tr>
<td>Duration of COC use, y</td>
<td>8 (0.1 - 30)</td>
<td>6 (0.1 - 27)</td>
<td>6 (0.5 - 16)</td>
</tr>
<tr>
<td>Ever pregnant, n (%)</td>
<td>364 (73)</td>
<td>175 (70)</td>
<td>36 (72)</td>
</tr>
<tr>
<td>Age at first pregnancy</td>
<td>24 (15-41)</td>
<td>24 (15-36)</td>
<td>23 (17-38)</td>
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<tr>
<td>Number of pregnancies, n</td>
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<tr>
<td>Total pregnancy time, y</td>
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<td>3 (0.3 - 9)</td>
<td>2 (0.8 - 6)</td>
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<td>Age at time of VTE, y</td>
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<tr>
<td>Provoked, n</td>
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<tr>
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<td>Pregnancy/post partum</td>
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<tr>
<td>COC use + other risk factor</td>
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<td>0</td>
</tr>
<tr>
<td>Major trauma, surgery, immobilisation</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

High factor VIII level was present in 8 (22%), 99 (39%) and 197 (40%) of women with combined defects, single defects and no defects, respectively (in 14 women Factor VIII levels were not available).

Abbreviations: COC, combined oral contraceptive; NA, data not applicable; VTE, venous thromboembolism. Data are given as median (min - max) unless otherwise indicated.

\(^a\) Restricted to those aged 15 to 50 years.

\(^b\) Including 14 homozygote carriers of factor V Leiden, of whom 3 were also heterozygous for prothrombin G20210A, and 4 homozygote carriers of the prothrombin G20210A mutation, respectively
Table 2. Absolute risk of venous thromboembolism in all 798 female relatives with no defects, a single defect (factor V Leiden or prothrombin G20210A), or a combination of these defects (including homozygosity) and during actual use of COCs and during actual pregnancy.

<table>
<thead>
<tr>
<th>Defects</th>
<th>None</th>
<th>Single</th>
<th>Combineda</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>Total No.</td>
<td>497</td>
<td>251</td>
</tr>
<tr>
<td></td>
<td>No. with event</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Observation period, y</td>
<td>12908</td>
<td>6234</td>
</tr>
<tr>
<td></td>
<td>Incidence Rate per 100 person-years (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.08-0.21)</td>
<td>(0.22-0.53)</td>
<td>(0.47-1.67)</td>
</tr>
<tr>
<td>Actual pill use</td>
<td>Total No.</td>
<td>366</td>
<td>171</td>
</tr>
<tr>
<td></td>
<td>No. with event</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Observation period, pill years</td>
<td>3211</td>
<td>1218</td>
</tr>
<tr>
<td></td>
<td>Incidence rate per 100 pill-years (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.07-0.41)</td>
<td>(0.18-1.07)</td>
<td>(0.10-3.11)</td>
</tr>
<tr>
<td>Actual pregnancy</td>
<td>Total No.</td>
<td>364</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td>No. with event</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Observation period, pregnancy-years</td>
<td>955</td>
<td>507</td>
</tr>
<tr>
<td></td>
<td>Incidence Rate per 100 pregnancy-years (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.30-1.51)</td>
<td>(0.94-3.63)</td>
<td>(3.08-15.76)</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; CI, confidence intervals
a: Including 14 homozygote carriers of factor V Leiden, of whom 3 were also heterozygous for prothrombin G20210A, and 4 homozygote carriers of the prothrombin G20210A mutation, respectively
Table 3. Comparison of thrombosis outcome in women with factor V Leiden or prothrombin G20210A, or a combination of these defects (including homozygosity) According to the method described by Koster et al.\(^3\)

<table>
<thead>
<tr>
<th>Defects</th>
<th>COC</th>
<th>LNG-IUD</th>
<th>Copper IUD (380 mm(^2))</th>
<th>Condom*</th>
<th>COC</th>
<th>LNG-IUD</th>
<th>Copper IUD (380 mm(^2))</th>
<th>Condom*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of first VTE per 100 py</td>
<td>0.55(^b)</td>
<td>0.25(^c)</td>
<td>0.25(^c)</td>
<td>0.25(^c)</td>
<td>0.19</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Cases of VTE per 100,000 py</td>
<td>550</td>
<td>250</td>
<td>250</td>
<td>250</td>
<td>190</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Contraceptive failure rate, per 100 wy(^d)</td>
<td>0.2</td>
<td>0.7</td>
<td>1.4</td>
<td>12</td>
<td>0.2</td>
<td>0.7</td>
<td>1.4</td>
<td>12</td>
</tr>
<tr>
<td>Unintended pregnancies per 100,000 py</td>
<td>200</td>
<td>700</td>
<td>1,400</td>
<td>12,000</td>
<td>200</td>
<td>700</td>
<td>1,400</td>
<td>12,000</td>
</tr>
<tr>
<td>Incidence of VTE per 100 pregnancy-years(^e)</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Additional cases of VTE</td>
<td>6</td>
<td>20</td>
<td>40</td>
<td>336</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>84</td>
</tr>
<tr>
<td>Total number of VTE</td>
<td>556</td>
<td>270</td>
<td>290</td>
<td>586</td>
<td>192</td>
<td>95</td>
<td>100</td>
<td>174</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism

\(^a\): US data

\(^b\): (6+2) events during (1218+232) pill-years (see Table 2)

\(^c\): based on an adjusted HR of 2.2 for COC-use when compared to no COC-use

\(^d\): Pearl Index for correct use (method failure), wy=women-years

\(^e\): (10+7) events during (507+92) pregnancy-years (see Table 2)
Legend for the figure:

Figure 1. Recruitment of the study population from families with factor V Leiden, prothrombin G20120A mutation, high factor VIII levels, and hyperhomocysteinemia, respectively.
Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception

Elizabeth F. W. van Vlijmen, Nic J. G. M. Veeger, Saskia Middeldorp, Karly Hamulyák, Martin H. Prins, Harry R. Büller and Karina Meijer