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Recurrent venous thrombosis in premenopausal women: effect of continuing or starting hormonal contraceptive use

Abstract

Background
There is a large body of literature available on hormonal contraceptive use and the risk of a first venous thrombotic event. Despite guideline recommendations to discontinue, a sizeable proportion of women continue or start using hormonal contraceptives after a venous thrombosis. The aim of this study was to evaluate the effect of this use on the risk of recurrence in premenopausal women.

Methods
Premenopausal female patients with a first venous thrombosis, included in the MEGA case-control study between 1999 and 2004, were followed for a recurrent venous thrombotic event up to 2010. Data on hormonal contraceptive use were available through a prescription database (from Dutch Foundation for Pharmaceutical Statistics). Time-dependent Cox-proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI), adjusted for age and BMI at baseline and anticoagulation use.

Results
650 women were linked to the prescription database and followed for a total of 3537 person-years (median 6.1 years; range, 41 days to 9.7 years). 57 women had a recurrence, of which 14 were during hormonal contraceptive use. Irrespective of contraceptive use at the first event, any type of hormonal contraceptive use increased the risk of recurrence about two-fold (HR 1.8, 95%CI: 0.9 to 3.3). Using combined oral contraceptives after the first event increased the risk almost three-fold (HR 2.6, 95%CI: 1.3 to 5.2). The recurrence rate among IUD users was found to be similar to the rate among non-users (HR 0.9, 95%CI: 0.3-3.1).

Conclusion
Hormonal contraceptive use after a first venous thrombosis increases the risk of a recurrent venous thrombotic event. A levonorgestrel-releasing intra-uterine device may be a safe alternative.

Introduction
A large body of literature is available about combined oral contraceptive use and the increased risk of a first venous thrombosis.[1-4] National[5,6] and international[7] guidelines state to discontinue hormonal contraceptive use after a venous thrombotic event, in particular combined preparations (oral contraceptive, transdermal patch and vaginal ring) with the idea of preventing recurrences. Despite these guidelines, a large proportion of women either continues or starts hormonal contraceptive use after a first venous thrombosis. One study found that 39% of women using hormonal contraceptives at the first event either continued or restarted afterwards.[8] In the present study about three months after stopping anticoagulation therapy, 21% of combined oral contraceptive users continued their contraceptive use.[9]

Discontinuation of hormonal contraceptives could be a small intervention on a woman’s lifestyle, with potentially large preventive effects with regard to the risk of recurrent venous thrombosis. Nevertheless, not much is known about the association between hormonal contraceptive use and recurrent venous thrombosis, except for one report by Christiansen et al.[10] In this study, the risk of recurrence was fourfold increased in users of hormonal contraceptives compared with non-users. The number of recurrences was too few to allow meaningful conclusions about the type of contraceptive.

The aim of the present study was to evaluate the effect of hormonal contraceptive use, administration route and type of combined oral contraceptive (dose of ethinylestradiol and type of progestagen) on the risk of recurrent venous thrombosis in premenopausal women with a first venous thrombosis.
Chapter 7

Materials and methods

Participants
Participants were cases from a population-based case-control study; the Multiple Environmental and Genetic Assessment of venous thrombosis (MEGA) study. Details of the study have been described elsewhere.[11] In short, between 1 March 1999 and 31 August 2004, 4956 consecutive patients with an objectively diagnosed first deep vein thrombosis of the leg or pulmonary embolism were included. Patients were aged 18-70 years and were enrolled from six anticoagulation clinics in the Netherlands. Anticoagulation clinics monitor all patients taking vitamin K antagonists in a well-defined geographical area. All patients filled in a questionnaire on risk factors for venous thrombosis. About three months after discontinuation of the anticoagulation therapy, patients were invited to the anticoagulation clinic for a blood sample. During this visit participants were interviewed regarding the period from the venous thrombotic event until venepuncture. This interview included items on possible change of hormonal contraceptive methods since the diagnosis of venous thrombosis.

Of 4956 eligible patients, 4731 gave informed consent for follow-up. Short answer forms, regarding recurrent venous thrombosis, were sent by mail to patients between January 2008 and December 2009. Questions were asked by telephone interview when answer forms were not returned. During the same period information about recurrences was retrieved from the anticoagulation clinics where patients were initially included for their first event and, in case they moved house, at the clinic nearest to their new address. Deaths due to recurrent venous thrombosis were obtained at the Central Bureau of Statistics (CBS). To obtain information on diagnostic procedures, discharge letters were requested from the clinician who diagnosed the recurrence according to the patient or the anticoagulation clinic. A detailed questionnaire on risk factors for venous thrombosis during follow-up was sent to participants after they gave permission for this in the short answer form. Details of the follow-up study have been described elsewhere.[12] This study was approved by the Medial Ethics Committee of the Leiden University Medical Center.

For the current analyses, we focussed on premenopausal women with venous thrombosis before age 50 (N=1584). Women who had cancer in the five years before the first venous thrombosis or undergoing chemo- or radiotherapy were excluded (N=60). Women who were unlikely to use contraceptives due to various reasons were excluded, i.e., pregnant or postpartum women (N=35), current HRT users (N=53), self-reported peri- or postmenopausal women (N=52), underweight women (N=1) and 32 women who had undergone a hysterectomy or oophorectomy. The population of interest consisted of 1351 premenopausal women.

Hormonal contraceptives
Hormonal contraceptive use was defined as use of a contraceptive that contains steroid hormones, administered orally, transdermally or vaginally. Users of a copper-IUD were considered non-users. Hormonal contraceptive use was categorised according to the route of administration into oral and non-oral preparations. Oral preparations were stratified into combined and progestagen-only preparations. Because many different preparations of combined oral contraceptives are available, these contraceptives were categorised according to the dose of ethinylestradiol and type of progestagen. Non-oral preparations were further stratified according to the specific application (vaginal ring, transdermal patch, implant, injectable, and levonorgestrel-releasing intrauterine device (IUD)).

Data on hormonal contraceptive use were available through two sources; a prescription database (the Dutch Foundation for Pharmaceutical Statistics (SFK) registry)[13] and the detailed questionnaire filled in at the end of follow-up. Participants in the MEGA follow-up study were linked to the prescription database via age, sex, 4 digits postal code and vitamin K antagonist use within the first month after the initial venous thrombosis. The national ID number was not available for linkage and abovementioned factors were not unique for every participant. Therefore, 650 (48%) of premenopausal women could be successfully linked to the prescription database. Linkage was a random process since being unique on the variables according to which linkage was performed is not associated with either recurrent venous thrombosis or use of contraceptives. The following information was available from SFK; date of prescription, name of the contraceptive and the amount and defined daily dosage (DDD) of the prescription. Periods of contraceptive use were defined as continuous use of contraceptive based on the normal duration of use. For instance, a prescription for 126 oral contraceptive pills was assumed to be taken for 24 weeks (three weeks of taking a contraceptive pill a day and a stopweek). An IUD was assumed to be used for five years. Women with a prescription for hormonal contraceptives just before the first venous thrombotic event, with enough contraceptive pills prescribed to continue after venous thrombosis, were considered exposed for these days after the event. This is because women are mostly advised to continue using contraceptives during the anticoagulant treatment period.[14] A prothrombotic effect of hormonal contraceptives is likely to be suppressed by anticoagulation, while the risk of menorrhagia associated with stopping hormonal therapy could be increased by anticoagulants.

The detailed questionnaire contained questions about hormonal contraceptive use after the first venous thrombosis; name of contraceptive used and starting date and date of discontinuation. Data on hormonal contraceptive use provided in the questionnaire was crosschecked with data retrieved at the time of the first venous thrombosis and at the time of venepuncture in the MEGA case-control study. 787 (58%) of premenopausal women filled in the detailed questionnaire and self-reported on their use of hormonal contraceptives after the first thrombotic event.

Recurrent venous thrombosis
A recurrent event was defined by information provided by patients through the questionnaire, anticoagulation clinics, discharge letters or causes of death. A decision
rule regarding certainty of the diagnosis was made according to the information collected per patient. Details of this decision rule have been described previously.[12] In short, reported recurrences were classified into certain recurrences when there was a discharge letter stating a diagnosis of a recurrent event based on clinical and radiological data, or when both the anticoagulation clinic and the patient reported a recurrent event at either a clearly different location than the first event or more than one year had passed since the first event, or when a registered death from a recurrent event at least six months after the first event was found. In the current analysis, certain recurrences were used as endpoint and patients with an uncertain recurrence were censored at time of their uncertain recurrence.

Statistical Analysis
Premenopausal women with information on hormonal contraceptive use after a first venous thrombosis were included. The start of follow-up was defined as the date of the first venous thrombosis. The end of follow-up was defined as the date of the recurrent event or when no recurrent event occurred, the date of returning the short answer form, or the last date until we knew patients to be recurrence free (last visit to the anticoagulation clinic, date of death, or emigration), whichever came first. Observation time was calculated as the time at risk from the first thrombotic event to the end of follow-up.

Hormonal contraceptive use was taken as a time-dependent exposure to allow women switching from use to non-use and vice versa during follow-up. Consequently, one woman could contribute follow-up time for hormonal contraceptive use as well as for non-use. Although anticoagulation use was not considered to be a confounder in the analysis, the risk of a recurrence is lower during a period of anticoagulation use. Therefore, analyses were adjusted for anticoagulation use (time-dependently) to obtain estimates of the incidence rate of a recurrence irrespective of anticoagulation use.

The relative risk of recurrent venous thrombosis was estimated separately for women using hormonal contraceptives at the first event and for women using hormonal contraceptives during follow-up. The effect of oral and non-oral preparations on the risk of recurrent venous thrombosis was assessed and compared with non-use. Data were analysed separately by data source (prescription database or questionnaire). Recurrence rates were calculated for combined oral contraceptives by dose of ethinylestradiol and progestagen.

All analyses were adjusted for the confounders age and BMI (at baseline) and for anticoagulation use. Time-dependent Cox-proportional hazards models were used to calculate hazard ratios (HR) with corresponding 95% confidence intervals. All statistical analyses were performed with STATA, version 13.0 (Statacorp LP, College Station, TX, USA).

Results
Of 1351 premenopausal women with a first venous thrombotic event, 650 were linked to the prescription database and followed for a total of 3537 person-years (median 6.1 years; range, 41 days to 9.7 years). 787 women filled in the detailed questionnaire and had a total follow-up of 5155 person-years (median 6.8 years; range 120 days to 9.9 years). Baseline characteristics of the study population by data source are given in Table 1. Characteristics were similar for the women linked to the prescription database and women who filled in the detailed questionnaire.

For 412 women data were available from both sources, and so could be checked for consistency. Based on the prescription data, 148 women (36%) did not use a contraceptive at any given time after the event and 109 women (26%) discontinued use some time after the event, for a total of 257 women (62%) who did not continue to use hormonal contraceptives after the first venous thrombosis. Data from the questionnaire are consistent with this, given that according to the questionnaire 241 of these 257 women (94%) did not continue to use hormonal contraceptives after the first event. However, the rest of the periods and types of hormonal contraceptive use reported by the prescription database and the questionnaire are not consistent. Out of the 155 women who continued or started using hormonal contraceptives according to the prescription database, 111 women (72%) did not self-report on such use in the detailed questionnaire. Because of this discrepancy and because we assumed data to be more accurate from the prescription database (women may not precisely remember their contraceptive use over the past few years), we focussed our analyses on data from the prescription database. Results based on the questionnaire data can be found in Supplementary Table 1.

Prescription database
Among the 650 women linked to the prescription database, 57 recurrences occurred, of which 14 were during hormonal contraceptive use. The overall rate of recurrent venous thrombosis among premenopausal women was 16.1 (95%CI: 12.4 to 20.9) per

| Table 1. Baseline characteristics of premenopausal women with venous thrombosis |
|-------------------------------|-------------------|-------------------|
| Variables                     | Prescription       | Questionnaire      |
| Age at 1st event, mean(range), yrs | 37 (18-49)        | 36 (18-49)        |
| BMI at 1st event               |                   |                   |
| >25 kg/m²                      | 246 (42)          | 334 (44)          |
| 25-30 kg/m²                    | 187 (32)          | 231 (31)          |
| ≥30 kg/m²                      | 156 (26)          | 190 (25)          |
| HC use at 1st event            | 455 (70)          | 590 (75)          |

BMI denotes: body mass index, HC: hormonal contraceptive
Hormonal contraceptives and recurrent venous thrombosis

1000 person-years. The recurrence rate in hormonal contraceptive users at the first event was similar (16.1, 95%CI: 11.8-22.0 per 1000 person-years) as in non-users at the first event (16.1, 95%CI: 10.0-25.9) (Table 2). This was also evident from the hazard ratio for users at the first event compared with non-users (HR 0.9, 95%CI: 0.5 to 1.5, adjusted for age, BMI and anticoagulation) (Table 2).

Among women using hormonal contraceptives during follow-up, we observed a recurrence rate of 22.3 (95%CI: 13.2-37.7) per 1000 person-years and among non-users during follow-up a rate of 14.8 (95%CI: 11.0-19.9) per 1000 person-years. This implied that hormonal contraceptive use after a first venous thrombosis increased the risk of recurrent thrombosis two-fold after adjustment for anticoagulation, age and BMI (HR 1.8, 95%CI: 0.9 to 3.3) (Table 2). Restriction to women who were using hormonal contraceptives at the first event, yielded a similar increased risk in women who continued to use hormonal contraceptives compared with those who stopped (HR 2.0, 95%CI: 1.0-4.0) (Table 2).

11 recurrences occurred during combined oral contraceptive use. The recurrence rate for combined oral contraceptive use during follow-up was 33.7 (95%CI: 18.7-60.9) per 1000 person-years, almost three-fold higher than for non-use during follow-up (HR 2.6, 95%CI: 1.3 to 5.2, adjusted for anticoagulation; HR 2.6 after adjustment for age, BMI and anticoagulation, 95%CI: 1.3 to 5.2). Notable was that out of 64 women using a levonorgestrel-releasing IUD (250 person-years of follow-up), only three had a recurrence (recurrence rate 12.0, 95%CI: 3.9-37.1 per 1000 person-years). The recurrence rate was similar for IUD users and non-users (HR 0.9, 95%CI: 0.3-3.1).

Recurrence rates were calculated by type of combined oral contraceptive. Numbers per type of combined oral contraceptive were, however, small. Incidence rates of recurrence were similar for the types of contraceptive mostly used in the Netherlands: IR 39.2 (95%CI: 17.6-87.1) for 30μg of ethinylestradiol and levonorgestrel, IR 33.4 (95%CI: 8.3-133.4) for 30μg of ethinylestradiol and desogestrel and IR 42.7 (95%CI: 6.0-303.5) for 30μg of ethinylestradiol and gestodene.

**Table 2. Recurrence rate in premenopausal women and the influence of hormonal contraceptive use**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>N</th>
<th>Follow-up</th>
<th>IR (per 1000)</th>
<th>HR* (95%CI)</th>
<th>HR† (95%CI)</th>
<th>HR‡ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use at first event</td>
<td>17</td>
<td>1057</td>
<td>16.1 (10.0-25.9)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>HC use at first event</td>
<td>40</td>
<td>2480</td>
<td>16.1 (11.8-22.0)</td>
<td>1.0 (0.6-1.7)</td>
<td>1.0 (0.6-1.7)</td>
<td>0.9 (0.5-1.5)</td>
</tr>
<tr>
<td>Non-use during follow-up</td>
<td>43</td>
<td>2910</td>
<td>14.8 (11.0-19.9)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>HC use during follow-up</td>
<td>14</td>
<td>627</td>
<td>22.3 (13.2-37.7)</td>
<td>1.7 (0.9-3.1)</td>
<td>1.7 (0.9-3.2)</td>
<td>1.8 (0.9-3.3)</td>
</tr>
<tr>
<td>Oral preparation</td>
<td>11</td>
<td>326</td>
<td>33.7 (18.7-60.9)</td>
<td>2.6 (1.3-5.2)</td>
<td>2.6 (1.3-5.2)</td>
<td>2.6 (1.3-5.2)</td>
</tr>
<tr>
<td>COC</td>
<td>11</td>
<td>326</td>
<td>33.7 (18.7-60.9)</td>
<td>2.6 (1.3-5.2)</td>
<td>2.6 (1.3-5.2)</td>
<td>2.6 (1.3-5.2)</td>
</tr>
<tr>
<td>POP</td>
<td>0</td>
<td>2</td>
<td>0 (0-1844.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Non-oral preparation</td>
<td>0</td>
<td>4</td>
<td>0 (0-922.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IUD</td>
<td>0</td>
<td>250</td>
<td>12.0 (5.9-22.1)</td>
<td>0.9 (0.3-2.9)</td>
<td>0.9 (0.3-3.1)</td>
<td>-</td>
</tr>
<tr>
<td>Injectable</td>
<td>13</td>
<td>529</td>
<td>24.5 (14.3-34.2)</td>
<td>1.0 (1.0-3.9)</td>
<td>1.0 (1.0-3.9)</td>
<td>1.0 (1.0-3.9)</td>
</tr>
</tbody>
</table>

COC denotes: combined oral contraceptive, HC: hormonal contraceptive, HR: hazard ratio, IR: incidence rate, POP: progestagen-only pill

*Adjusted for anticoagulation
†Age and anticoagulation adjusted
‡Anticoagulation, age and BMI adjusted

In women who used hormonal contraceptives after the first venous thrombosis the risk of recurrence was almost three-fold increased (HR 2.9, 95%CI: 1.6-5.1) compared with women who did not use hormonal contraceptives during follow-up. Restricting to women who were using hormonal contraceptives at the first event, a similarly increased risk was found with those who discontinued use as reference group (HR 2.9, 95%CI: 1.6-5.1). The risk of recurrent venous thrombosis was almost three-fold higher for combined oral contraceptive users than for non-users (HR 2.8, 95%CI: 1.6 to 5.0).
Discussion

Despite guideline recommendations, a large proportion of women either continues or starts hormonal contraceptive use after a first venous thrombotic event. This study assessed the association between the risk of recurrent venous thrombosis and hormonal contraceptive use after a first event. Information on hormonal contraceptive use was available from a large prescription database as well as from a detailed questionnaire filled in by premenopausal women from the MEGA follow-up study. Women using hormonal contraceptives, in particular combined oral contraceptives, after a first venous thrombosis had a two- to three-fold higher risk of recurrence than non-users. Use or non-use of hormonal contraceptives at the first event did not affect the risk of recurrent venous thrombosis. The use of a levonorgestrel-releasing intrauterine device appeared not associated with an increased risk of recurrent venous thrombosis.

To date, only one other study (LETS) evaluated the risk of recurrent venous thrombosis among women using hormonal contraceptives after their first event in a prospective follow-up study.[10] That analysis was restricted to women who used hormonal contraceptives at the first event. The authors observed a recurrence rate of 48.8 per 1000 person-years (95%CI: 24.3-87.2) among hormonal contraceptive users during follow-up and a recurrence rate of 10.5 per 1000 person-years (95%CI: 4.5-20.7) among those who had discontinued use. The recurrence rate among these non-users was similar as reported in the current study (14.8 per 1000 person-years); however, the recurrence rate in hormonal contraceptive users was higher (48.8 per 1000 person-years versus 22.3 per 1000 person-years). This difference may be due to differences in the distribution of types of contraceptives in the LETS and the MEGA study, between which a decade elapsed. The proportion of women using a second generation contraceptive had increased over time (MEGA study 55% vs LETS 25%), while the proportion of women using a third generation contraceptive and the proportion of women using triphasic preparations had decreased (35% vs LETS 49% and 5% vs LETS 11%). However, because of small numbers the difference in recurrence rates could be a chance finding as well.

Several limitations of this study should be mentioned. First, we aimed to combine data on hormonal contraceptive use from both the prescription database and the detailed questionnaires. 650 Women were linked to the prescription database and 787 women filled in the detailed questionnaire, with an overlap of 412 women. Combining both sources of information would have increased our power considerably. However, the lack of consistency between the two sources suggested that a substantial number of women had not correctly remembered periods of contraceptive use over the past years. Alternatively, as hormone use is actively advised against, women may have been reluctant to admit such use. We focussed our analyses on the objective data from the prescription database, where no misclassification is expected. Nevertheless, results for both data sources were similar.

A second limitation of our study is that only 48% of our population of interest could be uniquely linked to the prescription database. As a consequence, numbers were too small to assess reliably the risk of recurrence by type of contraceptive. The recurrence rate among women linked to the prescription database was similar (16.1, 95%CI: 12.4 to 20.9 per 1000 person-years) to the rate among women who could not be linked (17.9, 95%CI: 14.1-22.6), suggesting that bias due to the limited proportion that could be linked is unlikely.

A strength of our study is its size. Furthermore, as far as we know, we are the first to compare the risk of recurrent venous thrombosis between women using hormonal contraceptives versus those who did not throughout a long period of time after a first event, separately for those who used or not used hormones at the first event. Also we were the first to study the association for different administration routes of the contraceptive (oral vs non-oral). Furthermore, we used a decision rule to ascertain recurrence status by which we ensured that only certain recurrences were included in our analyses. Lastly, detailed information on participants hormonal contraceptive use during follow-up made it possible to perform a time-dependent survival analysis, allowing switches from exposed to non-exposed during follow-up and vice versa.

After a first venous thrombotic event recurrent venous thrombosis is common, with a five-year cumulative incidence of about 25%. [15,16,17] A large patient level meta-analysis has shown a one-year cumulative incidence of recurrence of 5% and a three-year cumulative incidence of 9% in women. [18] Recurrences are associated with considerable comorbidity (post-thrombotic syndrome, chronic pulmonary hypertension), mortality and health-care costs. Despite progress in identifying determinants of recurrence risk, its prediction and prevention in an individual patient remains a challenge. Prevention of recurrent venous thrombosis by extending anticoagulant treatment is dependent on a delicate balance between risk of thrombosis and bleeding. Discontinuation of hormonal contraceptives could be a small intervention on a woman’s lifestyle, with potentially large preventive effects with regard to the risk of recurrent venous thrombosis.

Current guidelines [5,6,7] recommend women to discontinue hormonal contraceptive use after a first venous thrombotic event. These guidelines however, are based on the assumption that risk factors for a first event also increase the risk of a recurrence. Not much was known on the risk of recurrences in women who continued their contraceptive use. Our study supports current guidelines which advise women to refrain from the use of hormonal contraceptives after a venous thrombotic event. We found that the risk of recurrent venous thrombosis is two- to threefold increased during periods of use of, particularly combined, hormonal contraceptives. Women should be urged to discontinue the use of hormonal contraceptives, since there are alternatives, e.g. a copper-IUD, available. This study suggests that the use of a levonorgestrel-releasing IUD may also be a safe option after a venous thrombotic event.

Given that out of 53 women who continue or restart using a combined oral contraceptive after a first venous thrombotic event one woman develops recurrent
venous thrombosis (Number Needed to Harm: 1/ risk difference = 1/ (0.0337-0.0148)) and given that currently 20-40% of women continue or start using hormonal contraceptives after a first event[8,9], the overall burden of recurrent venous thrombosis in women could be significantly reduced by adherence to the guidelines.

Reference List


13 http://www.sfk.nl/english.2015


