Chapter 6

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

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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 hormonal contraceptive use after a thrombotic event, still 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 recurrence risk in premenopausal women.
Methods: 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 2009. Included in the current analyses were premenopausal female patients with a first venous thrombosis and for whom detailed information was available on hormonal contraceptive use during follow-up. 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
Results: 702 premenopausal women with a first venous thrombosis were followed for a total of 4673 woman-years (median 7.0 years; range, 12 days to 9.9 years) during which 74 recurrent events occurred resulting in a recurrence rate of 15.8 (95%CI: 12.6 to 19.8) per 1000 woman-years. 210 women used hormonal contraceptives, mainly orally administered, during follow-up with a total follow-up of 545 woman-years. They experienced 21 recurrent thrombotic events indicating a rate of 38.5 per 1000 woman-years, which was triple the rate of non-use during follow-up (HR 2.8, 95%CI: 1.7 to 4.7). None of the women (N=20, 70 woman-years of follow-up) using a levonorgestrel-releasing intra-uterine device developed a recurrent venous thrombosis.
Discussion: 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 contraceptive to use after a venous thrombosis.

Introduction

Combined oral contraceptives (containing ethinylestradiol and a progestagen) increase the risk of a first venous thrombosis two- to fourfold[1–4]. Several studies have assessed the risk of venous thrombosis associated with oral progestagen-only pills (POP)[5–9]; however, because these may be prescribed to a subset of women who are already at increased risk of venous thrombosis, no definite conclusions can be drawn.

Oral contraceptive use is the most common route of administration. However, steroid hormones for contraceptive use can also be administered via other administration routes or applications, i.e., intrauterinely (intrauterine device (IUD)), transdermally (patch), subcutaneously (injectable or implant), or transvaginally (ring). Regarding non-oral contraceptives, the use of combined preparations (i.e., a vaginal ring or a transdermal patch) is associated with an increased risk of a first venous thrombosis[10–12]. Progestagen-only non-oral preparations, i.e., the levonorgestrel-releasing IUD or the injectable preparation containing methoxyprogesterone acetate, appear to affect the risk of venous thrombosis differently. Whereas the risk of a first venous thrombosis is not increased in intra-uterine device (IUD) users[12,13], there is an association with a mildly elevated risk of venous thrombosis for the use of an injectable containing methoxyprogesterone acetate[8,13,14]. Overall, there is a large body of literature available about hormonal contraceptive use and the risk of a first venous thrombosis.

National[15,16] and international[17] guidelines advise to discontinue hormonal contraceptive use after a venous thrombotic event, in particular combined preparations (oral contraceptive, transdermal patch and vaginal ring). The guidelines are based on the assumption that risk factors for a first event also increase the risk of a recurrence. However, this is not necessarily so[18]. The absolute risk of recurrent venous thrombosis is higher than of a first venous thrombosis. The populations at risk differ and

therefore, possibly also the risk profiles.

Despite these guidelines, still 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 after the event [19]. Furthermore, we previously reported that in the participants of our study, 143 (21%) of 682 combined oral contraceptive users at the first event continued combined oral contraceptive use after the event [20].

Currently, there is only one report on recurrent venous thrombosis risk associated with hormonal contraceptive use [21]. The aim of the present study was therefore 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 recurrence risk of venous thrombosis in premenopausal women.

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 [22]. 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 the venipuncture. This interview included items on the change of

hormonal contraceptive methods since the diagnosis of venous thrombosis.

Of 4956 eligible patients, 4731 gave informed consent for follow-up. During follow-up, patients received a short questionnaire containing questions on recurrence of venous thrombosis and the use of oral anticoagulation therapy. Patients willing to fill in a detailed questionnaire on risk factors for venous thrombosis during follow-up received this questionnaire by mail or internet. This detailed questionnaire contained questions about hormonal contraceptive use after the first venous thrombosis, type of contraceptive used and when applicable starting date and date of discontinuation of hormonal contraceptives. Patients participating in a pilot study received only a detailed questionnaire which also included the question on recurrence.

Questionnaires were sent by mail to patients between January 2008 and December 2009. Questions were asked by telephone interview when questionnaires 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) and were included. Discharge letters, to obtain information on diagnostic procedures, were requested from the clinician who diagnosed the recurrence according to the patient or the anticoagulation clinic. Patients were followed from the date of their first episode of venous thrombosis until a second thrombotic event or until the end-of-study, defined as the date of filling in the short questionnaire. In case patients did not fill in the short questionnaire, they were followed until the last known visit to the anticoagulation clinic, death, or emigration. Details of the follow-up study have been described elsewhere[23]. This study was approved by the Medial Ethics Committee of the Leiden University Medical Center.

For the current analyses, we focussed on premenopausal wo-

men with venous thrombosis younger than 50 years (N=1526). Women who were pregnant (N=42), were postpartum (defined as four weeks after delivery) (N=18), or were users of hormone replacement therapy (N=16) at the time of the first event were excluded. Women with a diagnosis of cancer in the five years prior to the first event were also excluded (N=51). Of the remaining 1399 premenopausal women, 845 (60%) women provided information on hormonal contraceptive use by filling in the detailed questionnaire. Data on hormonal contraceptive use provided in the detailed questionnaire was crosschecked with data retrieved at the time of the first venous thrombosis and at the time of venipuncture in the case-control study. 143 (17%) women were inconclusive about their contraceptive use and were excluded from further analyses. A total of 702 women were included in the present analysis. 13 women only provided data regarding duration of use but not the type of contraceptive. These women were only included in the overall analysis of hormonal contraceptive use during follow-up.

Recurrent venous thrombosis A recurrent event was defined by information provided by patients through the short questionnaire, anticoagulation clinics, or discharge letters. A decision rule regarding certainty of the diagnosis was made according to the information collected per patient. 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 has passed since the first event, or when a registered death from a recurrent event at least six months after the first event was found. Details of this decision rule have been described previously [23]. In this study, certain recurrences were used as endpoint and patients with an uncertain recurrence were censored at time of their uncertain recurrence.

Hormonal contraceptives Hormonal contraceptive use was defined as use of a contraceptive that contains steroid hormones. Users of a copper-IUD were considered non-users. Hormonal contraceptive use was categorised according to the route of administration route, i.e., 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)).

Statistical analysis In this analysis premenopausal women with information on hormonal contraceptive use after a first venous thrombosis from a detailed questionnaire 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 a recurrent event or the date of filling in the short questionnaire or the detailed questionnaire, in case of participation in the pilot, when no recurrent event developed. 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 for 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. The risk of recurrent venous thrombosis was estimated for hormonal contraceptive use at the first event and for hormonal contraceptive use 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. All analyses were adjusted for the confounders' age and BMI (at baseline). Time-dependent Cox-proportional hazards models were used to

calculate hazard ratios (HR). All statistical analyses were performed with STATA, version 12.0 (Statacorp LP, College Station, TX, USA).

Results

702 women with a first venous thrombotic event were followed for a total of 4673 woman-years (median 7.0 woman-years; range, 12 days to 9.9 woman-years). Baseline characteristics of the study population are given in table 6.1. On average, women were 36 years of age (range 18 to 49 years) at baseline. 290 (43%) women had a BMI at baseline <25 kg/m^2. 533 (76%) women used hormonal contraceptives at the first venous thrombotic event, whereas 169 (24%) were non-users at the first event.

Table 6.1: Baseline characteristics of premenopausal women with venous thrombosis

Variables	**All N=702**
Age at 1st event, mean(range), yrs	36 (18-49)
BMI at 1st event	
<25 kg/m2	290 (43)
25-30 kg/m2	214 (32)
>30 kg/m2	163 (24)
Hormonal contraceptive use at 1^{st} event	533 (76)

BMI, body mass index

Among 702 women, 74 recurrences occurred, of which 21 recurrences were during hormonal contraceptive use. Overall, the rate of recurrent venous thrombosis was 15.8 (95%CI: 12.6 to 19.8) per 1000 woman-years. The recurrence rate in hormonal contraceptive users at the first event was similar (15.1, 95%CI:

11.6-19.8 per 1000 woman-years) as in non-users at the first event (18.0, 95%CI: 11.6-27.9) (Table 6.2). This was evident from the hazard ratio for users at the first event compared to non-users (HR 0.9, 95%CI: 0.5 to 1.5, adjusted for age and BMI) (Table 6.2).

Among women using hormonal contraceptives during follow-up, we observed a recurrence rate of 38.5 (95%CI: 25.1 to 59.1) per 1000 woman-years and among non-users during follow-up, a rate of 12.8 (95%CI: 9.8 to 16.8). This implied that hormonal contraceptive use after a first venous thrombosis tripled the risk of recurrent thrombosis (HR 3.0, 95%CI: 1.8 to 5.0). After adjustment for age and BMI at the first event, the hazard ratio did not change (HR 2.8, 95%CI: 1.7 to 4.7) (Table 6.2). Restricted to women who were using hormonal contraceptives at the first event, a similar risk increase was found associated with hormonal use during follow-up, with those who discontinued use as reference group (HR 3.4, 95%CI: 1.9-5.9, and after adjustment for age and BMI: HR 3.1, 95%CI: 1.7-5.4) (Table 6.2).

Hormonal contraceptive preparations were classified into oral and non-oral (Table 6.2). 16 recurrences occurred during oral contraceptive use (all combined oral contraceptives). The recurrence rate for combined oral contraceptive use during follow-up was 41.1 (95%CI: 25.1-67.1) per 1000 woman-years, again threefold higher than for non-use during follow-up (HR 3.2, 95%CI: 1.8 to 5.7; HR 2.9 after adjustment for age and BMI, 95%CI: 1.6 to 5.2). Only two women used a vaginal ring during follow-up of whom 1 had a recurrence, suggestive of a high recurrence risk. Because only one recurrence occurred among 31 non-oral preparation users, vaginal ring, levonorgestrel-releasing IUD, injectable and implanon users, no reliable risk estimates could be inferred. However, notable was that out of 20 women using a levonorgestrel-releasing IUD (70 woman-years of follow-up), none had a recurrence.

The recurrence rate per type (dose and content) combined oral contraceptive is reported in Table 6.3. Both dose of ethinyles-

Table 6.2: Recurrence rate in premenopausal women and the influence of hormonal contraceptive use

	N*	FU	IR (per 1000) (95% CI)	HR (95% CI)	HR‡ (95% CI)	HR§ (95% CI)
Non-use at 1^{st} event	20	1109	18.0 (11.6-27.9)	1	1	1
HC use at 1^{st} event	54	3564	15.1 (11.6-19.8)	0.8 (0.5-1.4)	0.8 (0.5-1.4)	0.9 (0.5-1.5)
Non-use during FU	53	4129	12.8 (9.8-16.8)	1	1	1
HC use during FU†	21	545	38.5 (25.1-59.9)	3.0 (1.8-5.0)	3.0 (1.8-5.0)	2.8 (1.7-4.7)
Oral preparation						
COC	16	389	41.1 (25.2-67.1)	3.2 (1.8-5.6)	3.2 (1.8-5.6)	2.9 (1.6-5.2)
POP	0	12	-	-	-	-
Non-oral preparation						
Vaginal ring	1	4	269.0 (37.9-1909.4)	-	-	-
IUD	0	70	-	-	-	-
Injectable	0	32	-	-	-	-
Implanon	0	1	-	-	-	-
HC use at 1^{st} event	54	3046	11.2 (8.0-15.6)	1	1	1
HC use at 1^{st} event and during FU	20	518	38.6 (24.9-59.8)	3.4 (1.9-5.9)	3.4 (2.0-6.0)	3.1 (1.7-5.4)

COC, combined oral contraceptive; FU, follow-up time in woman-years; HC, hormonal contraceptive; HR, hazard ratio; IR, incidence rate; POP, progestagen-only pill

* Number of recurrences

† No data on the type of contraceptive used was available in two women

‡ Age-adjusted

§ Age and BMI adjusted

Table 6.3: Overview of number of women and recurrences per combined oral contraceptive

Preparation	N*	N†	FU	IR (95%CI)	HR (95%CI)	HR§ (95%CI)
COC‡						
37.5 µg EE+LYN	5	0	7	-		
20 µg EE+LNG	3	0	6	-		
30 µg EE+LNG	67	3	141	21.3 (6.9-66.1)	1	1
50 µg EE+LNG	11	2	21	96.4 (24.1-385.4)	3.5 (0.6-20.9)	2.3 (0.3-16.7)
20 µg EE+DSG	8	0	24	-		
30 µg EE+DSG	33	5	58	86.7 (36.1-208.3)	3.7 (0.9-15.5)	3.4 (0.8-14.9)
20 µg EE+GSD	2	0	5	-		
30 µg EE+GSD	18	0	46	-		
35 µg EE+NRG	2	0	3	-		
35 µg EE+CPA	11	1	36	27.9 (3.9-197.8)	1.3 (0.1-12.7)	1.1 (0.1-11.6)
30 µg EE+DRSP	3	0	5	-		
Triphasic	17	5	25	200.0 (83.2-480.4)	8.6 (2.0-37.2)	7.5 (1.7-33.6)

COC, combined oral contraceptive; CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; FU, follow-up in woman-years; GSD, gestodene; HR, hazard ratio; LNG, levonorgestrel; POP, progestagen-only pills; Triphasic, contraceptive with varying dose of ethinylestradiol over 21 days with either norethisterone (N=1) or levonorgestrel (N=16)

* Number of women

† Number of recurrences; the total number exceeds the total number of women, because a woman could have used multiple preparations during follow-up

‡ Preparation 35 µg ethinylestradiol with norethisterone was not reported because none of the women used this contraceptive during follow-up

§ Age-adjusted

tradiol and progestagen were associated with the risk of recurrent venous thrombosis. Within users of combined oral contraceptives containing levonorgestrel, users of 50 µg ethinylestradiol had a two-fold higher recurrence rate than users of 30 µg ethinylestradiol with levonorgestrel (HR 2.3, 95%CI: 0.3-16.7, adjusted for age). Within contraceptives with 30 µg ethinylestradiol, contraceptives with desogestrel were associated with a higher risk of recurrence than contraceptives with levonorgestrel (HR 3.4, 95%CI: 0.8-14.9, adjusted for age). The risk of a recurrence was about equal in users of cyproterone acetate compared with users of 30 µg ethinylestradiol with levonorgestrel (HR 1.1, 95%CI: 0.1-11.6, adjusted for age). Out of 17 users of a triphasic preparation, 5 women had a recurrence leading to an eight-fold higher rate than in users of 30 µg ethinylestradiol with levonorgestrel (HR 7.5, 95%CI: 1.7-33.6, adjusted for age). One woman was using a triphasic contraceptive with norethisterone and 16 women with levonorgestrel. After excluding the user of norethisterone, the results were unchanged (age-adjusted HR 7.5, 95%CI: 1.7-33.6).

Discussion

In a study comprising 702 premenopausal women with venous thrombosis, we assessed the association between hormonal contraceptive use and recurrent venous thrombosis. Women using hormonal contraceptives, in particular combined oral contraceptives, after a first venous thrombosis have a threefold higher risk of recurrence than non-users. The use or non-use of hormonal contraceptives at the first event did not affect the risk of recurrent venous thrombosis. Among combined oral contraceptives users during follow-up, both the dose of ethinylestradiol as well as the progestagens influenced the recurrence rates. Users of triphasic contraceptives were found to have the highest recurrence rates among combined oral contraceptives. Interestingly, among 20 levonorgestrel-releasing IUD users, none had a recurrent venous thrombosis.

To date, only one other study (LETS) evaluated the risk of recurrent venous thrombosis among women using hormonal contraceptives in a prospective follow-up study [21]. That analysis was restricted to women who used hormonal contraceptives at the first event. The authors observed a recurrence rate of 48.8 (95%CI: 24.3-87.2) among hormonal contraceptive users during follow-up and a recurrence rate of 10.5 (95%CI: 4.5-20.7) among non-users. The recurrence rate among non-users was similar as reported in the current study (10.5 versus 11.2); however, their recurrence rate in hormonal contraceptive users was slightly higher (48.8 versus 38.6). This is most likely due to differences in the distribution of types of contraceptives in the LETS and the MEGA study, between which a decade elapsed. In both the LETS and the present study, the recurrence rate among triphasic contraceptive users was increased compared with non-users (138.9 (95%CI: 16.8-501.7) versus 200.0 per 1000 women-years (95%CI: 83.2-480.4)). Why the risk of a recurrence is higher for these types of contraceptives is currently unexplained, in particular because there is no difference reported between monophasic and triphasic contraceptives regarding the risk of a first venous thrombosis.

A limitation of our study is that data on hormonal contraceptive use were obtained through a detailed questionnaire which not every patient of the MEGA follow-up study was willing to fill in, reducing the number of women included in our analyses. The reason for not returning the questionnaire may have introduced selection bias. We therefore assessed the recurrence rate in patients who filled in the detailed questionnaire (responders) and patients who did not (non-responders) and this proved to be similar ($IR_{responders}$ 17.6, 95%CI: 14.5-21.5 and $IR_{non-responders}$ 17.3, 95%CI: 12.3-24.1). Most likely, selection bias did not influence our results. A further limitation of the present study is the assessment of menopausal status. Menopausal status was based on statements from the women at baseline and not on medical data. Potentially, peri- or postmenopausal women could have

been included. However, menopausal status is to our knowledge not related to thrombotic risk and therefore, this potential misclassification cannot have affected our risk estimates. Strengths of our study are its size, and that we used a decision rule to ascertain recurrence by which we ensured that only certain recurrences were included in our analyses. Furthermore, detailed information on participants' hormonal contraceptive use obtained 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.

In conclusion, hormonal contraceptive use after a first venous thrombotic event increased the risk of a recurrence. Although numbers are small, results suggest that the use of an levonorgestrel-releasing IUD may be a safe option after a venous thrombotic event. Among combined oral contraceptive users, the increase in risk depended on the ethinylestradiol dose, progestagen and whether the contraceptive was triphasic or not.

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