

# Higher Risk of Venous Thrombosis During Early Use of Oral Contraceptives in Women With Inherited Clotting Defects

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**Background:** Results of recent studies show that the risk for venous thrombosis is highest during initial oral contraceptive use. This suggests a subgroup of females who are at immediate risk of thrombosis when exposed to oral contraceptives.

**Objective:** To determine whether women with inherited clotting defects who use oral contraceptives develop venous thrombosis at an earlier stage than do those without inherited clotting defects.

**Methods:** Analysis of the data from the Leiden Thrombophilia Study, a population-based case-control study with data on duration of oral contraceptive use and recently detected genetic coagulation disorders. Patients had a first episode of objectively proven deep vein thrombosis. Patients and controls were considered thrombophilic when they had protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden mutation, or prothrombin 20210 A mutation.

**Results:** Risk of developing deep vein thrombosis was

greatest in the first 6 months and the first year of oral contraceptive use. Compared with prolonged use, the risk of developing deep vein thrombosis was 3-fold higher in the first 6 months of use (95% confidence interval [CI], 0.6-14.8) and 2-fold higher in the first year of use (95% CI, 0.6-6.1). Patients who developed venous thrombosis in the early periods of use were more often thrombophilic. Among women with thrombophilia, the risk of developing deep vein thrombosis during the first 6 months of oral contraceptive use (compared with prolonged use) was increased 19-fold (95% CI, 1.9-175.7), and in the first year of use, it was increased 11-fold (95% CI, 2.1-57.3).

**Conclusions:** Women with inherited clotting defects who use oral contraceptives develop venous thrombosis not only more often but also sooner than do those without inherited clotting defects. Venous thrombosis in the first period of oral contraceptive use might indicate the presence of an inherited clotting defect.

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**R**ESULTS OF recent studies<sup>1-4</sup> show that the risk for venous thrombosis is highest during the initial period of oral contraceptive use. This confirms a clinical impression that has not been studied extensively.<sup>5-7</sup> It was previously reported<sup>3,8</sup> that factor V Leiden mutation, which leads to resistance to activated protein C and was found in about 1 of 5 patients with venous thrombosis, displays a strong interaction with use of oral contraceptives. Other inherited clotting defects that are themselves risk factors for venous thrombosis, such as protein C deficiency, protein S deficiency, antithrombin deficiency, and prothrombin 20210 A mutation, might also lead to a high risk of venous thrombosis when combined with oral contraceptive use.<sup>9</sup>

A higher risk of venous thrombosis during the first months of oral contraceptive use might be specific to people with genetic risk factors. To test this hypothesis, we analyzed data from the Leiden Thrombophilia Study.<sup>10,11</sup> In the original study, oral contraceptive use led to a 4-fold increased risk of venous thrombosis (6-fold on age adjustment). In the present analysis, with new data on duration of use and recently detected genetic risk factors, we first looked at whether patients with venous thrombosis were more often in their first 6 months or their first year of oral contraceptive use compared with control subjects who also used oral contraceptives. Second, we investigated whether patients who developed venous thrombosis early had hereditary clotting defects more often than those who developed venous thrombosis during prolonged use.

## PARTICIPANTS, MATERIALS, AND METHODS

### STUDY SETTING

The patients and methods of this study have been described previously.<sup>10</sup> We invited 474 consecutive patients (both sexes; age, <70 years; without a known malignant disorder) with a first episode of proven deep vein thrombosis (diagnosed by established objective methods) between January 1, 1988, and December 31, 1992. Patients had been selected from the medical files of 3 anticoagulation clinics in the Netherlands, which monitor anticoagulant treatment in all patients within well-defined geographic areas. Each patient with thrombosis invited 1 age- and sex-matched control subject (a friend or acquaintance; if not possible, volunteering partners of patients were age- and sex-matched to serve as controls); age matching was within 5-year bands. After anticoagulant drug treatment was discontinued for at least 3 months, patients underwent a structured interview about risk factors for venous thrombosis and collection of blood samples. Controls were seen around the time of enrollment of the patients and underwent the same interview and blood sample collection.

In the present analysis, we selected premenopausal females, aged 15 to 49 years, who at the time of their thrombosis (or the corresponding date in the control group, their index date [see the next section]) were not pregnant or in the puerperium, did not have a recent miscarriage, and were not using injectable progestogens. Data about use of oral contraceptives at the thrombosis or index date were available from 155 patients and 169 controls.

### TIME WINDOW ASSESSMENT

Information on the duration of oral contraceptive use was newly abstracted from the interview data and supplemented with data from hospital discharge letters and original investigation records (for patients and controls). We analyzed all periods of oral contraceptive use (different types) and compared first-ever use with prolonged use. For the present analysis, we checked whether the date of venous thrombosis was in the first 6 months or in the first year of oral contraceptive use for patients. For controls, we used their index date, ie, the date of venous thrombosis of their corresponding patient in the original study. This ensures that use of oral contraceptives among the controls reflects the same calendar years as patients. We ascertained whether this index date was within the first 6 months or the first year of oral contraceptive use of the control. In this way, we could verify whether patients who used oral contraceptives were more often in their early periods of pill use compared with controls who used oral contraceptives. When a participant who had used oral contraceptives at the time of thrombosis or the index date had temporarily stopped using them in the year before this date, this renewed use was not counted as first use because there

had been previous exposure to oral contraceptives; such use was categorized as "prolonged" because the participant had already had her first exposure to oral contraceptives more than 1 year before the thrombosis or index date ( $n = 12$ ). This categorization will, if anything, lower the effect of early use in our data.

### GENETIC RISK FACTORS

Blood samples were collected from all participants, and plasma samples were stored at  $-70^{\circ}\text{C}$ . High-molecular-weight DNA was isolated from leukocytes and stored at  $4^{\circ}\text{C}$ . Presence of the mutant factor V Leiden gene, protein C deficiency, protein S deficiency, antithrombin deficiency, and prothrombin 20210 A mutation<sup>11-14</sup> was determined by technicians who did not know if the sample was from a patient or control, or from an oral contraceptive user or nonuser. Criteria for diagnosing clotting deficiencies were used as described previously.<sup>11-13</sup>

### STATISTICAL ANALYSIS

Because of the age cutoff value and other restrictions in this analysis (see the "Study Setting" subsection), we had to break the original one-to-one matching. However, we stratified for age in the analysis because of confounding by age: new oral contraceptive users are often young, and long-term users are mostly older. Lack of adjustment for age will lead to underestimation of the effect of new use because older persons have a higher risk of venous thrombosis. Because age matching was in 5-year bands, an analysis that stratifies for age takes potential confounding and the effect of matching into account.

First, we restricted analysis to patients and controls who had been using oral contraceptives (at the thrombosis or index date) to investigate the effect of duration of oral contraceptive use. We analyzed whether patients who used oral contraceptives had their venous thrombosis more often during the first 6 months or first year of oral contraceptive use compared with the index date of the controls by estimating the odds ratio (OR) (95% confidence interval [CI]) of being in an early time window of use.

Second, we restricted analysis to patients who used oral contraceptives to investigate whether patients who had developed venous thrombosis in the early periods of use more often had thrombophilia compared with those who developed venous thrombosis during prolonged use, also by calculating the OR. Patients and controls were considered thrombophilic when they had protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden mutation, or prothrombin 20210 A mutation.

Multivariate analysis by unconditional logistic regression was used to adjust for possible confounders, eg, age, family history of venous thrombosis, and history of pregnancy. Age was entered into the models as a continuous variable (in years) after assessing that using a categorized dummy variable model led only to trivial differences for the estimators of interest. Family history and history of pregnancy were entered as dichotomous variables.

## RESULTS

Of 155 premenopausal patients with deep vein thrombosis (age, 15-49 years), 109 used oral contraceptives at

the time of thrombosis. Of 169 controls, 65 used contraceptives at their index date. On average, patients who were using oral contraceptives were slightly older than controls using oral contraceptives (age [mean  $\pm$  SD],

32.2 ± 9.6 vs 29.8 ± 8.9 years); long-term users were older than short-term users (age [mean ± SD], 32.1 ± 9.1 vs 24.4 ± 9.6 years at the cutoff point of 1 year of use). Stratification of oral contraceptive use by duration of use is shown in **Table 1**. The date of venous thrombosis was more often in the first 6 months or first year of use than was the corresponding index date of the controls. Age-adjusted OR (95% CI) of oral contraceptive use, compared with longer use, for females using oral contraceptives up to 6 months was 3.0 (95% CI, 0.6-14.8). When 1 year was taken as a cutoff point, the age-adjusted OR for use shorter than 1 year became 1.9 (95% CI, 0.6-6.1). Further adjustment for history of pregnancy or positive family history did not change the estimations. Prolonged users (ie, >1 year of use) had an age-adjusted 5-fold increase in risk relative to nonusers of oral contraceptives (data not shown). In the original study,<sup>8</sup> the age-adjusted OR of oral contraceptive use (all times together) was 6-fold.

Of 109 oral contraceptive–using patients, 37 were thrombophilic: 5 had a protein C deficiency, 3 had a protein S deficiency, 2 had an antithrombin deficiency, 25 had the factor V Leiden mutation, and 4 had the prothrombin 20210 A mutation (2 had both the factor V Leiden and prothrombin 20210 A mutations). Of 65 oral contraceptive–using controls, 10 were thrombophilic: 5 had a protein S deficiency, 2 had the factor V Leiden mutation, and 3 had the prothrombin 20210 A mutation. **Table 2** shows that, among patients who developed venous thrombosis during early use, thrombophilia was more often present than among those who developed venous thrombosis during prolonged use. The age-adjusted OR for coagulation defects was 18.5 (95% CI, 1.9-175.7) for use up to 6 months. For the cutoff point of 1 year, the OR was 11.0 (95% CI, 2.1-57.3).

Four patients who developed deep vein thrombosis in the first year of use took preparations containing monophasic ethinyl estradiol and desogestrel (30 µg), and 2 used ethinyl estradiol- and levonorgestrel-containing oral contraceptives (30 µg); among controls, these numbers were 1 and 2, respectively. Although these numbers are too small to arrive at stable conclusions, they support those in the literature<sup>15-17</sup> about difference in venous thrombosis risk for different types of contraceptives. They also indicate that the “starter effect” does not explain the difference between different types of contraceptives.<sup>17</sup>

#### COMMENT

In this case-control study, we first confirm the high risk of venous thrombosis during the early stages of oral contraceptive use. Second, we find that the high risk in the first 6 months and first year of use can be explained in part by the presence of inherited coagulation defects.

Several potential biases that are often believed to exist in case-control studies do not apply to studies of genetic risk factors. For genetic risk factors, it is not important that they are assessed only after diseases develop because they do not change. Moreover, the most important genetic risk factors for venous thrombosis, factor V Leiden and factor II mutations, were not yet discovered at the time of data collection. Even their clinical manifestation (ve-

**Table 1. Patients and Controls Using Oral Contraceptives at the Thrombosis or Index Date According to Duration of Use**

Duration of Use, mo	Patients, No.	Controls, No.
1-6	8	2
7-12	4	3
≥13	97	60
<b>Total</b>	<b>109</b>	<b>65</b>

**Table 2. Patients With or Without Inherited Clotting Defects According to Duration of Oral Contraceptive Use**

Duration of Use, mo	Inherited Clotting Defect, No.		Total No.
	Yes	No	
1-6	7	1	<b>8</b>
7-12	3	1	<b>4</b>
≥13	27	70	<b>97</b>
<b>Total</b>	<b>37</b>	<b>72</b>	<b>109</b>

nous thrombosis) cannot have affected any prescription of oral contraceptives because we only studied first venous thrombosis. Assessment of the time windows was performed retroactively on existing data, but without knowledge of the participants' genetic status. Finally, patients came from a routine care situation wherein all patients from a certain geographic area are given care; patients were consecutively included on meeting the study and analysis requirements. The CIs in our study remain large—despite the fact that we started with ample numbers of patients and controls—as a consequence of looking at narrow time windows with specific genetic risk factors.

Earlier studies<sup>5-7,18,19</sup> on duration of oral contraceptive use described that the association between oral contraceptive use and venous thrombosis was unrelated to duration of use. Earlier negative findings might be explained by the use of different cutoff points, with larger time windows. From our study results, we conclude that risk of oral contraceptive use is higher during the first year of use, especially during the first 6 months of use. However, females who use oral contraceptives longer than 1 year are still at risk of developing venous thrombosis; their age-adjusted risk was still 5-fold higher compared with nonusers (data not shown). These results are similar to those of the World Health Organization study<sup>1</sup> and the Transnational Study,<sup>2</sup> in which women who had used oral contraceptives for the first time were compared with those who had never used them; a 10-fold increased risk during the first year of use was found, which declined to a 2-fold increase in subsequent years.<sup>20,21</sup> Once use of an oral contraceptive is discontinued, risk of venous thrombosis disappears within about 3 months; there is no elevated risk among past users.<sup>1,7,19,22,23</sup>

Among patients who developed deep vein thrombosis within 1 year of starting use of oral contraceptives, most inherited clotting defects were found. Risk of developing deep vein thrombosis during the first year of oral contraceptive use was 11-fold for patients with thrombosis. An explanation for the higher risk is that these

patients already have 1 inherited risk factor, of which the effect is augmented by oral contraceptives. The exact nature of the biochemical interaction is unknown, although there are interesting leads about the role of acquired activated protein C resistance.<sup>24-28</sup>

From the results of this study and others,<sup>1-4</sup> we conclude that duration of oral contraceptive use affects the association between oral contraceptives and venous thrombosis: the relative risk is highest in first-ever users. Furthermore, we find that this starter effect is explained in part by the presence of inherited clotting defects: females with inherited clotting defects are more likely to develop venous thrombosis during oral contraceptive use in the first year of use. Together with the overall interaction between oral contraceptive use and inherited clotting defects,<sup>8,9</sup> this implies that females with inherited clotting defects who use oral contraceptives develop venous thrombosis not only more often but also sooner. However, the inherited clotting defects explain only part of the starter effect. When females continue using oral contraceptives, their risk of developing venous thrombosis does not disappear, and it also is present in those without clotting defects. Also, the starter effect cannot explain differences between different contraceptives in observational studies.<sup>17</sup>

It is uncertain whether routine screening for genetic clotting disorders before starting oral contraceptive use is useful or feasible, even when there is a family history of inherited thrombophilia in a first-degree relative.<sup>29,30</sup> Still, taking a careful family history and providing information to patients about signs and symptoms of venous thromboembolism might well be in order. When a female develops venous thrombosis during the first year of oral contraceptive use, this could be an indication that she has an inherited clotting defect.

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