Articles

Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation

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Summary

We investigated whether the occurrence of venous thrombosis in young women who use oral contraceptives might be explained by the factor V Leiden mutation, which leads to resistance to activated protein C and enhances susceptibility to thrombosis.

We compared 155 consecutive premenopausal women, aged 15 to 49, who had developed deep venous thrombosis in the absence of other underlying diseases, with 169 population controls. The risk of thrombosis among users of oral contraceptives was increased 4-fold (relative risk 3·8 [95% CI 2·4–6·0]). The risk of thrombosis among carriers of the mutation compared with non-carriers was increased 8-fold (7·9 [3·2–19·4]). Compared with women who did not use oral contraceptives and were not carriers of the mutation, the risk of thrombosis among those with both risk factors was increased more than 30-fold (34·7 [7·8–154]).

Recalculation of population incidences from these relative risks shows that the absolute risk of venous thrombosis in young women who use oral contraceptives is much larger when they carry the factor V Leiden mutation. When a young woman develops thrombosis, her factor V Leiden status should be considered in counselling about her future method of contraception.

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Introduction

Ever since the first report in 1961,[1] the risk of venous thrombosis has been a much debated hazard of the use of oral contraceptives.[2,3] Venous thrombosis has become less common but has not disappeared with present-day low-dose preparations.[4–8] It is still unclear why oral contraceptives cause thrombosis, and why they do so only in a small number of women.

A hereditary abnormality in the protein C/protein S anticoagulant pathway, which leads to increased susceptibility to venous thrombosis, has been identified lately.[9] The abnormality is resistance to the anticoagulant effect of activated protein C (APC-resistance). Activated protein C inhibits clotting by cleavage of factors Va and VIIIa, and APC-resistance is caused by a point mutation at a cleavage site in factor Va which makes it inaccessible to activated protein C.[10] The mutation, a G/A substitution at nucleotide position 1691 of the factor V gene which has been called factor V Leiden,[10] has been confirmed by others.[11] It corresponds strictly with the presence of hereditary APC-resistance.[12]

We found APC-resistance in about 20% of patients with venous thrombosis and 3–5% of a general population sample in the Netherlands.[12,13] In a Swedish study, APC-resistance was present in 33% of thrombosis patients and 5% of controls.[14] These findings showed that APC-resistance is a strong risk factor for venous thrombosis and that it is much more prevalent than the other known hereditary abnormalities of the anticoagulant pathway that lead to increased risk of venous thrombosis (ie, protein C, protein S, and antithrombin deficiency).

We have investigated whether the presence of the factor V Leiden mutation could explain thrombosis in young women who use oral contraceptives. Specifically, we wanted to know whether the risk of thrombosis that exists in oral-contraceptive users is increased in those who carry the mutation. The investigation was part of a population-based case-control study on hereditary factors in venous thrombosis, the Leiden Thrombophilia Study.[13]

Patients and methods

The design of our population-based case-control study has been described previously.[13] Consecutive patients younger than 70, with an objective diagnosis of a first episode of deep venous thrombosis between 1988 and 1993 and without an underlying malignant disorder, were selected from the files of three anticoagulation clinics in the Netherlands which monitor anticoagulation treatment of virtually all patients in three well-

	Factor V Leiden mutation present		No factor V Leiden mutation	
	Patients	Controls	Patients	Controls
Current OC use	25	2	84	6
No current OC use	10	4	36	100
Relative risk (95% CI)	5 0 (0 8–31 8)		3 7 (2 2–6 1)	

OC=oral contraceptive

Table 1 **Current use of oral contraceptives among patients and controls according to presence of factor V Leiden mutation**

defined geographical areas Controls were friends and acquaintances, or partners of other patients, matched for age and sex with the cases Patients and controls were seen between 1990 and 1993 (6 to 19 months after the acute event) by one of us (TK) for an interview about risk factors, physical examination, and blood sampling for clotting factor and DNA analysis The presence of the factor V Leiden mutation was shown by *MlnI* digestion of amplified factor V DNA and visualisation of the cleavage products on ethidium-bromide-stained agarose gels [10]

For this investigation we selected from among our whole study population women aged 15–49 We found 190 patients and 194 controls We excluded women who were pregnant (10), within 30 days post partum (14), or with a recent miscarriage (2) at their study index date (the date of the clinical thrombotic event in the case, and the corresponding date for the control), we also excluded postmenopausal women (31) and those who had used only depot contraceptive preparations (3) Thus, 155 patients and 169 controls were left in the analysis

In most analyses we grouped homozygous and heterozygous carriers of the factor V Leiden mutation We contrasted current use of oral contraceptives during the month preceding the thrombosis index date with non-use in that month Previous and never use were grouped after we had verified that oral-contraceptive use that was stopped more than a month before the thrombosis index date gave no excess risk, which is in accordance with the known acute effect of oral contraceptives on venous thrombosis

Although the original data were age matched, we present analyses on unmatched data Undoing the matching permits analysis of subgroups of cases and controls selected for variables upon which they were not matched It also enables the presentation of the raw data A disadvantage is that the unmatched analysis will diminish the contrast between the groups, especially with respect to the effect of oral contraceptives Since, however, our analysis was already restricted to one of the matching factors (sex) and partly restricted to the other (age), we expect this attenuation to be slight We also expect little attenuation of the effect of the factor V Leiden mutation, since its prevalence is likely to be independent of age, except for sample fluctuation, because it is an autosomal genetic abnormality [15]

Relative risks of thrombosis among current users of oral contraceptives were estimated as odds ratios and their 95% CI according to Woolf [16] To show the absolute effect of the cumulation of risk factors, we also estimated the population incidence of thrombosis in young women with the four possible combinations of factor V mutation and use of oral contraceptives We estimated the total number of person-years that had yielded the cases and partitioned these person-years according to the distribution of pill use and the factor V mutation in the control group Since we know that in our original study 117 female patients aged 15–49 came from the Leiden anticoagulation clinic, which has a geographical source population of 109 824 in that age group (data provided by the municipal administration), first thrombosis incidence among young women without underlying disease in the Netherlands can be estimated over the 5 years of our study as 2 1 in 10 000 woman-years (117/[5×109 824]) Division of the number of women with venous thrombosis by the proportional number of person-years in the categories of pill use and carriage of the mutation (proportions taken from the control group) gives estimates of the population incidences This technique was used in one of the first case-control studies on smoking and lung cancer[17] and has since been refined [16] The method shows whether more events occurred in the presence of both factor V Leiden and oral-contraceptive use than would be expected by the sum of the individual effects of each of these risk factors

We carried out logistic regression to assess the direction and magnitude of the multiplicative interaction between recent use of oral contraceptives and the factor V Leiden mutation and to evaluate the effect of controlling for the matching factor age and the effects of other potential risk factors such as smoking, obesity (Quetelet index greater than 30 kg/m^2), surgery in the month before the thrombosis index date, and diabetes

Results

109 (70%) of the 155 women with first venous thrombosis and no other underlying disorder had been using oral contraceptives in the month before thrombosis compared with 65 (38%) of the 169 controls This amounts to an increase in risk (relative risk) of 3 8 (95% CI 2 4–6 0) Of the 155 women with thrombosis, 35 (23%) carried the factor V Leiden mutation (5 homozygotes and 30 heterozygotes) compared with 6 (3 6%) controls (all heterozygotes) This leads to an increase in risk of venous thrombosis among carriers of the factor V Leiden mutation of 7 9 (3 2–19 4) When the analysis was restricted to heterozygotes, the relative risk was 6 8 (2 7–16 8)

The relative risk of thrombosis associated with oral contraceptives was at least as high in carriers of the mutation as in women with the normal genotype (table 1, 5 0 *vs* 3 7) This result was similar after exclusion of the homozygotes from the analysis (5 women, of whom 3 used oral contraceptives, relative risk 5 5 [0 84–36]) The small difference in relative risk between carriers of the mutation and women with the normal genotype is statistically uncertain, however, owing to the small number of control women with the factor V Leiden mutation (only 6 women) As a first approximation, therefore, we conclude that the relative risk of thrombosis due to current oral-contraceptive use is similar among carriers and non-carriers of the mutation and does not significantly differ from the overall 4-fold relative risk associated with oral-contraceptive use However, the presence of the mutation itself causes a 7–8-fold increase in risk [10 13] This increase is also found for women in the absence of oral-contraceptive use, of the patients who did not use the pill, 10 carried the mutation and 36 did not compared with 4 and 100 controls, a relative risk of 7 0 (2 1–23 5) for the factor V Leiden mutation in the absence of oral contraceptives The additional use of oral contraceptives will multiply this 7-fold increase by 4, so that a woman who uses oral contraceptives and is a carrier of the mutation will have a risk of venous thrombosis about 30 times that of a non-user who does not carry the mutation This can also be calculated directly from table 1 by contrasting the relative frequency of having both risk factors versus none among patients and controls of the patients, 25 had both risk factors and 36 none, compared with 2 and 100 among the controls (relative risk 34 7 [7 8–154])

Since we know that first thrombosis in the absence of underlying disease has an approximate incidence of 2 1 in

	Patients	Person-years*	Incidence per 10 000 person-years
Factor V Leiden negative			
No OC use	36	437 870	0 8
Current OC use	84	275 858	3 0
Factor V Leiden positive			
No OC use	10	17 515	5 7
Current OC use	25	8757	28 5

*A total of 740 000 person years (yielding 155 patients) was partitioned according to the distribution of the control group 100/63/4/2

Table 2 **Estimated population incidence of first venous thrombosis in women aged 15–49, according to presence of factor V Leiden mutation and use of oral contraceptives**

10 000 person-years in this age group, we can calculate that the 155 cases originate from a population of about 740 000 person-years The distribution of these person-years over current use of oral contraceptives and factor V Leiden carriage can be derived from the control group, which is representative of the population from which these cases originated [18] The incidence of thrombosis increases from 0 8 per 10 000 women per year for non-users of oral contraceptives without the mutation to 28 5 per 10 000 for those with the mutation who also use oral contraceptives (table 2) The absolute increase in thrombosis risk due to oral contraceptives (ie, the risk difference) is much larger in women who carry the factor V Leiden mutation than in women who do not In women without the mutation, use of oral contraceptives yields an additional 2 2 cases per 10 000 women per year, whereas among carriers of the mutation oral contraceptives increase the number of cases by 22 8 per 10 000 women per year This finding indicates that the joint effect of the two risk factors is more than additive

The increased risk is seen when heterozygotes and homozygotes are taken together and is the same for heterozygotes only (the majority of the patients with the mutation) All 5 homozygotes were patients with deep venous thrombosis and 3 were current users of oral contraceptives However small the numbers, this proportion of oral-contraceptive use matches that in the rest of the patients Homozygotes have a baseline risk of thrombosis 50–80 times that of non-carriers,[15] so even a smaller increase in thrombosis risk by oral-contraceptive use—eg, a relative risk of 2—would carry the cumulative relative risk of homozygotes to more than 100

We carried out logistic modelling to assess several other potential risk factors, the influence of control for the matching factor age, and the interaction Recent surgery, diabetes, and obesity were moderate to strong independent risk factors, smoking carried no extra risk of deep venous thrombosis The small numbers of women with diabetes and recent surgery (2 and 17) led to inefficient fitting of the logistic model Obesity had a small independent effect As expected, statistical adjustment for age increased the estimates The following relative risks were obtained in a logistic model with fine stratification for age (entered in years) current use of oral contraceptives 6 0 (3 4–10 6) and factor V Leiden mutation 9 3 (3 6–24 1) With a multiplicative interaction term between oral contraceptive use and factor V Leiden mutation, the relative risks became 5 8 (3 2–10 5), 8 1 (2 3–28 2), and 1 2 (0 2–9 7) for the multiplicative interaction The analysis confirmed a near-multiplicative effect of oral contraceptive use and factor V Leiden mutation, since the relative risk for the interaction in this multiplicative model remained close to 1 0

Discussion

The combination of the use of oral contraceptives and carriage of the factor V Leiden mutation strongly increases the risk of venous thrombosis The combined effect of these risk factors seems close to a multiplication of the separate relative risks In terms of absolute effect, however, this means that the risk of venous thrombosis among women who use oral contraceptives is much greater when they carry the factor V Leiden mutation

Carriage of the factor V Leiden mutation and APC-resistance led to a 7–8-fold increase in venous thrombosis risk in our study in the Netherlands [10 13] A Swedish estimate was somewhat higher (10 [4 0–25 0], recalculated from Svensson and Dahlback[14]) The difference is possibly due to differences in patient samples—a proportion of the patients in the Swedish study had recurrent or familial thrombosis

Current oral-contraceptive use in our study gave a close to 4-fold risk, which increased to 6-fold after adjustment for age These estimates are similar to those of the few studies that have specifically addressed the risk of venous thrombosis among women using modern low-dose oral contraceptives, which were also predominant in the Netherlands during our study period The Oxford Family Planning Study[6] found a relative risk of 6 5 (1 2–16 2, recalculated), the Puget Sound study[4 5] 2 8 (0 9–8 2), and a study in Boston[7] 8 1 (3 7–18), with no indication of a decreased risk in the lowest dose group The confidence intervals from these studies are wide and overlapping, because of the small numbers Older studies on high-dose pills had relative risk estimates between 2 and 11 [19] Several of these older investigations used only a clinical diagnosis of venous thrombosis, which is now known to be highly unreliable with misclassification rates of up to 50% [20 21] In studies with comparable diagnostic criteria, however, low-dose preparations confer less risk than the older high-dose pills [4 6 8]

In our study the multiplication in risk caused by oral contraceptives was of similar magnitude in carriers and non-carriers of the factor V Leiden mutation Therefore our present best estimate is a cumulative 30-fold increase for oral-contraceptive users who also carry the genetic risk By a similar multiplicative effect, the risk increase for homozygotes is more than 100-fold [15] A difficulty in the interpretation of our data is that the confidence interval of the relative risk of oral-contraceptive use among carriers of the factor V Leiden mutation is large, mainly because of the small number of women without thrombosis who carry the mutation (table 1) To obtain a more reliable estimate we would need a study with larger numbers of controls positive for factor V Leiden Since the prevalence of factor V Leiden in the general population is 3–5%, a case-control study several times larger than this one would be needed However, we can offer two other and different approximations to estimate the use of oral contraceptives among women who carry the mutation The proportion of such women using oral contraceptives should not differ too much from that in the general population, since it is unlikely that a hitherto unknown mutation would influence the use of contraceptives, especially in women who have not yet had a thrombosis Therefore, a more stable estimate can be obtained by

comparing the use of oral contraceptives between factor-V-positive thrombosis patients (25 *vs* 10) and the total control group of our study (65 *vs* 104) This yields a relative risk of 4 0 (1 8–8 9), which is slightly higher after age stratification This estimate is strengthened by a comparison with independent population data from the Netherlands In repeated health surveys by the Netherlands Central Bureau of Statistics for the years 1989, 1990, and 1991 (corresponding to our study), the frequency of oral contraceptive use among women aged 15 to 49 was 37 7%, 34 2%, and 40 6% (random population samples of size 2245, 1971, and 1865) [27] These percentages are close to what is found among our population controls and also yield relative risks of about 4 0 for thrombosis patients positive and negative for factor V Leiden, which also increase on age stratification

A feature of our study is the use of friends and acquaintances of the affected women as controls (for about 60% of the patients[13]), and partners of other patients when a woman did not volunteer a friend This practice may diminish the contrast between the patients and their controls, since friends might share life-style characteristics such as use of oral contraceptives If anything, the effect would be to diminish the relative risk It is reassuring that the overall use of oral contraceptives among our control group is close to that of the general population of the Netherlands It seems very unlikely that the method for selection of controls affected the estimates for the genetic effect When the age matching is taken into account in a logistic model, all relative risk estimations become higher We do not want to emphasise any of these higher estimations whose cumulation would lead to a more than 50-fold increase, since they rest on model assumptions and might depend on subgroup sample fluctuations

Our analysis leads to the conclusion that the absolute increase in risk due to oral contraceptives is larger in women who carry the factor V Leiden mutation than in those who do not This difference is most clearly seen by approximate back-calculation to population incidence rates (table 2) Although such calculations are hypothetical, and rest on general assumptions, they offer insight into the absolute effect (ie, the risk difference) when oral contraceptives are used in woman with and without the genetic defect The difference in risk brought about by oral contraceptives in women who do not carry the mutation is about 2 2 per 10 000 woman-years, while the risk difference for the mutation in the absence of oral-contraceptive use is about 4 9 per 10 000 The combined presence of the mutation and oral-contraceptive use gives a risk difference of about 27 7 per 10 000 woman-years, which is much larger than the sum of the individual effects Thus, in the presence of both risk factors, venous thrombosis develops in a substantial number of women who would never have had thrombosis in the presence of either risk factor alone [18 23] They developed thromboses only because both risk factors were present In this reasoning it is not important to know whether or not the relative risks are exactly multiplicative, it is the additional number of cases of thrombosis, over and above the sum of the individual effects, that is counted

The biological interpretation follows from the same reasoning The consequences of the factor V Leiden mutation (APC-resistance) and the metabolic changes in the clotting cascade due to oral contraceptives probably enhance each others' effects This idea finds support in the strong absolute increase in venous thrombosis risk during oral-contraceptive use in a large protein-C-deficient kindred[24] and in case-reports of severe thrombosis in young oral-contraceptive users with protein S and antithrombin deficiency [25 26] These deficiencies, which are very rare in the general population, lead to a defect in the anticoagulant part of the clotting cascade that is functionally similar to APC-resistance

Whatever the ultimate biological explanation, it is clear that a young woman who starts using oral contraceptives is at a higher risk of venous thrombosis if she carries the factor V Leiden mutation Should young women who start using oral contraceptives be screened for the mutation and the resulting hereditary APC-resistance? It is difficult at this stage to propose a balance of benefits and risks About 4% of young women would be denied oral contraceptives if factor V Leiden mutation became a contraindication The absolute risk of deep venous thrombosis is low even among young women who have both risk factors Most episodes among the young are minor, although pulmonary embolism does occur Withholding oral contraceptives from all carriers might be a high price to pay, especially since other methods of contraception are more error-prone and cause greater medical, psychological, and social morbidity Although it might be tempting to screen for homozygotes, who have a greatly increased risk, such an undertaking would not be cost-effective since the population frequency of homozygosity of the factor V Leiden mutation is only about 1 in 5000 [15]

When a young woman has had venous thrombosis, however, her factor V Leiden status might be take into account in counselling about future methods of contraception If she is a homozygote, she should be strongly advised to discontinue oral contraception If she is a heterozygote, the increased risk should be clearly explained, since her thrombosis episode shows that she might be one of the women who are susceptible to the interplay between oral contraceptives and hereditary APC-resistance In addition, other environmental or hereditary mechanisms might be at play, such as combined genetic defects (eg, protein C deficiency combined with factor V Leiden) [27] This combination might result in relative risks that approximate those of homozygosity for the factor V Leiden mutation If screening for factor V Leiden is done in a young woman with an objective diagnosis of venous thrombosis, it makes good sense to investigate also protein C, protein S, and antithrombin deficiency [28] The result of screening for genetic risk factors might also have a bearing on contraceptive decisions of the patient's mother and sisters, and for possible anticoagulation prophylaxis at other times of high risk such as during immobilisation or post partum At first or repeat prescription of oral contraceptives, it might pay to take a thorough personal and family history of thrombosis and to investigate if positive [29]

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