

Venous Thrombosis, Oral Contraceptives and High Factor VIII Levels

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Summary

Recently, it has been described that elevated plasma levels of factor VIII are a strong risk factor for venous thrombosis We analysed the data of the Leiden Thrombophilia Study, a population based case-control study on the causes of venous thrombosis, to verify whether the risk due to oral contraceptive use was higher in women with higher factor VIII levels Furthermore we investigated the joint risk of high factor VIII levels and oral contraceptive use

We selected 155 premenopausal women with deep-vein thrombosis and 169 control subjects, aged 15-49, who were at the time of their thrombosis (or similar date in control) not pregnant, nor in the puerperium, did not have a recent miscarriage, and were not using injectable progestogens Of the patients, 109 (70%) women had used oral contraceptives during the month preceding their deep-vein thrombosis, in contrast to 65 (38%) of the control subjects (index date), yielding an odds ratio for oral contraceptive use of 3 8 (95% CI 2 4-6 0) Of the women who suffered a deep-vein thrombosis 56 (36%) had high factor VIII levels (≥150 IU/dl) as compared with 29 (17%) of the control subjects, yielding an odds ratio for high factor VIII of 4 0 (95% CI 2 0-8 0), relative to factor VIII levels <100 IU/dl The joint effect of oral contraceptive use and high factor VIII resulted in an odds ratio of 10 3 (95% CI 3 7-28 9), comparing women who had both with women who had neither We conclude that there is an increase in risk due to oral contraceptive use in women with higher factor VIII levels and that both factors have additive effects

Introduction

Oral contraceptive use increases the risk of venous thrombosis, with estimates of the relative risk varying from 2 11 (1) Recently, we described an interaction between oral contraceptive use and carrier-ship of factor V Leiden mutation, this combination leads to a 30-fold increase in risk of deep-vein thrombosis (2) This interaction is relevant, since both factor V Leiden and oral contraceptive use are common

Another common risk factor for venous thrombosis is elevated levels of procoagulant factor VIII (3-5) For men and women in the Leiden Thrombophilia Study, high factor VIII levels (≥150 IU/dl vs <100 IU/dl) had an odds ratio of 6 2 (95% CI 3 4-11) (3) This effect is not explained by elevated factor VIII levels as a post thrombotic acute phase reaction (4) It is plausible that high levels of factor VIII have a mixed genetic and environmental origin

We investigated whether the risk due to oral contraceptive use was affected by factor VIII levels

Patients and Methods

The patients and methods of our study have been described previously (2, 5) We invited 474 consecutive patients (both sexes) with a first episode of proven deep vein thrombosis (diagnosed by established objective methods) occurring between Jan 1 1988 and Dec 31, 1992 aged less than 70 years and without a known malignant disorder Patients had been selected from the files of three Anticoagulation Clinics in the Netherlands, which monitor anticoagulant treatment in all patients within a well defined geographical area For each thrombosis patient we invited one age and sex matched healthy control subject For patients we used the date of their deep-vein thrombosis, for the control subjects we used the date of their corresponding case in the original study (index date) Patients were seen only after anticoagulant treatment was discontinued for at least three months

For the present analysis we selected only premenopausal women, aged 15-49, who were at the time of their thrombosis (or similar date in control) not pregnant, nor in the puerperium, did not have a recent miscarriage, and were not using injectable progestogens

Blood collection Blood was collected into Sarstedt Monovette© tubes, containing 0 106 mmol/l trisodium citrate, and into a Becton Dickinson Vacutainer© tube for blood group determinations Plasma was prepared by centrifugation for 10 min at 2000 g at room temperature and stored at 70° C

Laboratory measurement Factor VIII coagulant activity (FVIII C) was measured by one stage clotting assays using factor VIII deficient plasma and automated APTT (Organon Teknica, Durham, USA) on a Electra 1000c (MLA, Pleasantville, USA) Pooled normal plasma, standard calibrated against the WHO standard for factor VIII was used as a reference The technicians did not know if the sample was from a patient or a control or from an oral contraceptive user or non user

Analysis and statistics We analysed data from 155 cases and 169 controls about current use of oral contraceptives at their thrombosis- or index date We started with univariate analysis by unconditional regression to estimate the odds ratio for respectively oral contraceptive use and high factor VIII (in different strata) or combinations Multivariate analysis by unconditional logistic regression was used to adjust for possible confounders, e g age, family history of venous thrombosis, history of pregnancy Oral contraceptive use was entered dichotomously (0 for non oral contraceptive user (currently) and 1 for current oral contraceptive use) Clotting factor VIII was entered dichotomously, 1 for factor VIII ≥150 IU/dl and 0 for factor VIII <150 IU/dl and also as categorized variables (strata factor VIII <100 IU/dl, 100 125 IU/dl, 125 150 IU/dl and ≥150 IU/dl)

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Table 1 Venous thrombosis risk for categories of factor VIII

FVIII C strata	IU/dl	Patients	Controls	Odds ratio	95% CI
	<100	20	41	1	
	100 125	40	55	1 5	0 8 2 9
	125 150	39	44	1 8	0 9 3 6
	>150	56	29	4	2 0 8 0
		155	169		

Although the original data were age matched we performed unmatched analysis Due to the inclusion criteria and age cut off many pairs were no longer intact in the database for this analysis Since the analysis was restricted to the matching factor sex we adjusted for confounding by the other matching factor age by controlling for age by logistic regression 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

Results

We selected from the original study 155 premenopausal women who had had a deep vein thrombosis and 169 control subjects

We used two types of analysis when analysing the factor VIII data, firstly we analysed simple dichotomy (factor VIII levels ≥150 IU/dl vs factor VIII levels <150 IU/dl, secondly we stratified in four different categories

Table 2 Distribution of women with deep vein thrombosis and control subjects by oral contraceptive use (OC) and presence of high factor VIII (factor VIII ≥150 IU/dl vs factor VIII <150 IU/dl

		Patients	Controls	Odds ratio	95% CI
OC ( )	FVIII ( )	26	89	1	
OC (+)	FVIII ( )	73	51	4 9	(2 8 8 6)
OC ( )	FVIII (+)	20	15	4 5	(2 1 10 2)
OC (+)	FVIII (+)	36	14	8 8	(4 1 18 8)
		155	169		

Table 3 Distribution of women with deep vein thrombosis and control subjects by oral contraceptive use (OC) and presence of high factor VIII (factor VIII ≥150 IU/dl vs factor VIII <100 IU/dl)

		Patients	Controls	Odds ratio	95% CI
OC ( )	FVIII ( )	7	28	1	
OC (+)	FVIII ( )	13	13	4 0	(1 3 12 4)
OC ( )	FVIII (+)	20	15	5 3	(1 8 15 5)
OC (+)	FVIII (+)	36	14	10 3	(3 7 28 9)
		155	169		

High Factor VIII

Dichotomous analysis showed that of the 155 women who suffered a deep-vein thrombosis, 56 (36%) had high factor VIII levels (above 150 IU/dl) as compared with 29 (17%) of the 169 control subjects, yielding an odds ratio of 2 7 (95% CI 1 6 4 6) Table 1 gives the results for the categorized levels of factor VIII It shows an increasing risk of venous thrombosis for increasing levels of factor VIII The results for VIII are most prominent if factor VIII levels are ≥150 IU/dl For levels exceeding 150 IU/dl, the risk was 4-fold increased (95% CI 2 0 8 0) as compared with women with factor VIII levels <100 IU/dl

Oral Contraceptive Use

Of the patients 109 women (70%) had used oral contraceptives during the month preceding their deep vein thrombosis in contrast to 65 (38%) of the control subjects yielding an odds ratio for oral contraceptive use of 3 8 (95% CI 2 4 6 0)

Oral Contraceptive Use and Factor VIII

Table 2 shows separate effects and combined effects of factor VIII (factor VIII levels ≥150 IU/dl vs <150 IU/dl) and oral contraceptive use As the table shows the separate effects of oral contraceptive use and high factor VIII levels are about the same 4 9 respectively 4 5 fold increased risk compared with those with normal factor VIII levels who did not use oral contraceptives The risk of the combination of oral contraceptive use and high factor VIII, compared with women with low factor VIII who did not use oral contraceptives was 8 8 fold increased

This subdivision for oral contraceptive use was also performed for the different strata of factor VIII (100-125 IU/dl, 125-150 IU/dl and ≥150 IU/dl) in comparison with low levels of factor VIII (<100 IU/dl) The results of the combined effects of oral contraceptive use and factor VIII (two extreme strata of factor VIII, ≥150 IU/dl compared with <100 IU/dl) are shown in Table 3, showing a slightly more pronounced effect of high factor VIII levels

The Logistic Model

The age-adjusted odds ratio for oral contraceptive use was 5 5 (95% CI 3 2-9 6) The age adjusted odds ratio for factor VIII differed only slightly from the crude odds ratio, with an odds ratio for those with high factor VIII levels (≥150 IU/dl) and oral contraceptive use of 13 8 compared with those with low levels of VIII (<100 IU/dl) and not using oral contraceptives (Table 3) Adjustment for family history of venous thrombosis or history of pregnancy did not change the estimators of interest

Incidence of Population

The combined effects of factor VIII levels and oral contraceptive use can be seen best by back-calculation to the population incidence rates, as shown in Table 4 To show the absolute effect of the cumulation of risk factors, we estimated the population incidence of thrombosis in young women with the four possible combinations of high factor VIII levels and use of oral contraceptives We estimated the total number of person years that had yielded the cases and partitioned these person-

Table 4 Current use of oral contraceptives (OC) among patients and control subjects according to presence of high factor VIII (≥150 IU/dl)

	Patients	Person years*	Incidence per 10000 person-years
Low factor VIII			
No OC use	26	389704	0 7
Current OC use	73	223313	3 3
High factor VIII			
No OC use	20	65680	3
Current OC use	36	61301	5 9

years according to the distribution of oral contraceptive use and high factor VIII levels in the control group Since we know that in the original study 117 female patients aged 15-49 came from the Leiden anticoagulation clinic, which has a geographical source population of 109824 women in that age group (data provided by the municipal administration), firstly the 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 10000 women-years (117/[5 × 109824]) Division of the number of women with venous thrombosis by the proportional number of person years in the categories in oral contraceptive use and high factor VIII levels (proportions taken from the control group) gives estimates of the population incidences As we know that the population incidence in this age bracket is about 2 1/10 000 py (2), the 155 cases were generated by 740 000 women years of follow-up These can be partitioned according to the distribution of the control group which represents this source population (89/51/15/14) Yielding 389704 women-years for the combination of high factor VIII (≥150 IU/dl) and oral contraceptive use The incidence of thrombosis increases from 0 7 per 10000 women per year for non-users of oral contraceptives without high factor VIII to 5 9 per 10000 for those with high factor VIII who also use oral contraceptives The absolute increase in thrombosis risk due to oral contraceptive use (i e , risk difference) is larger in women with high factor VIII than in women with low factor VIII (<150 IU/dl) The joint effect of the two risk factors is additive, in women with low factor VIII there are 2 6 additional cases per 10000 women per year when women use oral contraceptives and in women with high factor VIII (non-users) there are an additional 2 3 cases per 10000 women per year The combination of the two risk factors give an additional of 5 2 cases per 10000 person-years

Discussion

We previously reported that the effect of blood group and von Willebrand factor, were both mediated through factor VIII in their effect on venous thrombosis (3, 6) In the present study we have investigated the joint effect of factor VIII and oral contraceptive use and found that their effects are additive

In univariate analysis, high factor VIII and oral contraceptive use were associated with deep-vein thrombosis (Table 1, 2 and 3) The odds ratio for oral contraceptive use among low factor VIII was 4 0 The odds ratio for factor VIII among non-users was 5 3 From these odds ratios we can calculate what to expect under different models of interaction Under an additive interaction model the total excess risk of oral contraceptive use and factor VIII would be 8 3 (4 0 plus 5 3 minus 1) Under a multiplicative model, total risk of joint presence of factor VIII and oral contraceptive use would be 4 0 × 5 3 = 21 2 The observed data are very close to the additive expectation, as we found an odds ratio of 10 3 Apparently, both oral contraceptive use and high factor VIII increase the risk of venous thrombosis, while the joint presence of both risk factors does not lead to an excess of cases This can also be seen in the population incidences for the various risk factors combinations (Table 4)

This is different from the previously reported interaction between factor V Leiden mutation and oral contraceptive use, which interact in a way that exceeded the additive expectation (2)

When adjusting for factor V Leiden in the multivariate model with oral contraceptive use, high factor VIII, age, family history of venous thrombosis and parity (data not shown) the estimators of interest did not change This means that the risk of high factor VIII in combination with oral contraceptive use was not affected by factor V genotype It can be expected that the more risk factors (genetic or environmental) are present, the higher the risk of developing venous thrombosis will be (7, 8)

Blood group and von Willebrand factor, are both mediated through factor VIII in their effect on venous thrombosis (3) As we have shown previously, in univariate analysis bloodgroup (non-O), von Willebrand factor levels, and factor VIII levels were all associated with risk of venous thrombosis In multivariate analysis, only an effect of factor VIII levels remained (3) Our findings are in accordance with data reported in the 1960's, describing that the risk was higher in persons with blood group A as compared with persons with blood group O, or more generally "non-O" versus O (9-12), especially during the use of oral contraceptives or during pregnancy or puerperium (9, 13-16) In trying to understand the biochemical mechanism behind these clinical findings, lower levels of pro-coagulant factor VIII were found in normal individuals with blood group O as compared with persons with blood group non-O (17, 18) Subsequent research has shown that individuals with non-O blood group have higher levels of von Willebrand factor Von Willebrand factor serves as the carrier proton of factor VIII, and so there is a strong correlation between von Willebrand factor levels and factor VIII levels This led to our conclusion that factor VIII levels were the final effector of risk It is unclear, however, by which mechanism this occurs, although in analogy to other clotting abnormalities with a gain of function, e g factor V Leiden, increased thrombin activation seems likely The origin of high factor VIII levels is not entirely elucidated There exists additional familial clustery beyond the effects of blood group and von Willebrand factor, suggesting additional genetic determinants (6) In addition, acquired determinants are likely to play a role, too (3, 4), whether oral contraceptives increase factor VIII levels is controversial (19-24)

In the present study we actually did an analyses of high factor VIII levels, bloodgroup, oral contraceptive use and venous thrombosis, but especially among users the data were to scarce to draw conclusions (data not shown) Nevertheless, we found the expected relationship between high factor VIII and bloodgroup non-O in explaining venous thrombosis during oral contraceptive use, i e the known effect of blood group on venous thrombosis, could in our data almost entirely be explained by high factor VIII among non users This is in line with the old observation that there is a deficit of patients with blood group O in subgroups of young women who develop venous thromboembolism during the use of oral contraceptives (9)

We can conclude that there is an increase in risk due to oral contraceptive use in women with higher factor VIII levels and that both factors have additive effects

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References

1 Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP Evidence that currently available pills are associated with cardiovascular disease venous disease, In Hannaford PC, Webb AMC Evidence-guided Prescribing of the Pill Carnforth UK Parthenon Publishing 1996, 61 76
2 Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation Lancet 1994, 344 1453-7
3 Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis Lancet 1995, 345 152-5
4 O Donnell J, Tuddenham EG, Manning R, et al High prevalence of elevated factor VIII levels in patients referred for thrombophilia screening role of increased synthesis and relationship to the acute phase reaction Thromb Haemost 1997, 77 825-8
5 Koster T, Rosendaal FR, Ronde H de, Briet E, Vandenbroucke JP, Bertina RM Venous thrombosis due to poor anticoagulant response to activated protein C Leiden Thrombophilia Study Lancet 1993, 342 1503 6
6 Kamphuisen PW, Houwing Duistermaat JJ, van Houwelingen HC, Eikenboom JC, Bertina RM, Rosendaal FR Familial clustering of factor VIII and von Willebrand factor levels Thromb Haemost 1998, 79 323 7
7 Rosendaal FR Risk factors for venous thrombosis prevalence, risk, and interaction Seminars in Hematology 1997, 34 171-87
8 Rosendaal FR Thrombosis in the young epidemiology and risk factors A focus on venous thrombosis Thromb Haemost 1997, 78 1-6
9 Jick H, Slone D, Westerholm B, Inman WHW, Vessey MP, Shapiro S, Lewis GP, Worcester J Venous thromboembolic disease and ABO blood type A cooperative study Lancet 1969, 1 539-42
10 Talbot S, Wakley EJ, Ryrie D, Langman MJ ABO blood-groups and venous thromboembolic disease Lancet 1970 1 1257 9
11 Bates M Venous thromboembolic disease and ABO blood type Lancet 1971, 1 239
12 Talbot S, Wakley EJ, Langman MJ A19 A29 B, and O blood-groups Lewis blood groups, and serum triglyceride and cholesterol concentrations in patients with venous thromboembolic disease Lancet 1972 1 1152 4
13 Hill H, Loudon NB, Pitcher CS, Pocock VM Venous thromboembolic disease and ABO blood type Lancet 1969, 1 623
14 Mourant AE, Kopec AC, Domaniewska-Sobczak K Blood-groups and blood-clotting Lancet 1971, 1 223-7
15 Westerholm B, Wiechel B, Eklund G Oral contraceptives, venous thromboembolic disease, and ABO blood type Lancet 1971, Sept 18 664
16 Allan TM ABO blood groups and venous thromboembolism Lancet 1971 2 1209-10
17 Preston AE, Barr A Br J Haematol 1964, 10 238
18 Wahlberg TB, Blomback M, Magnusson D Influence of sex, blood group, secretor character, smoking habits, acetylsalicylic acid, oral contraceptives, fasting and general health state on blood coagulation variables in randomly selected young adults Haemostasis 1984, 14 312-9
19 Ballersen L, Bailey J, Epping PH, Schulte H, van de Loo Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population I Baseline data on the relation to age, gender, body weight, smoking, alcohol, pill-using, and menopause Thromb Haemost 1985, 54 475-9
20 Daume E Influence of modern low-dose oral contraceptives on hemostasis Adv Contraception 1990, 6 (Suppl) 51-68
21 Robinson GE Low dose combined oral contraceptives British J Obstet Gynaecol 1994, 101 1036-42
22 Fotherby K, Caldwell ADS New progestogens in oral contraception Contraception 1994, 49 1 32
23 Winkler UH Effects on hemostatic variables of desogestrel- and gestodene-containing oral contraceptives in comparison with levonorgestrel containing oral contraceptives, a review Am J Obstet Gynecology 1998, 179 551-61
24 Klutt C, Lansink M Effect of oral contraceptives on haemostasis variables Thromb Haemost 1997, 78 315-26

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