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First venous thromboembolism and hormonal contraceptives in young French women

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Abstract

Information on the clinical and biological characteristics of combined hormonal contraceptives (CHC) users experiencing a venous thromboembolism (VTE) event is scarce. Better knowledge of factors determining the VTE risk in CHC users could help identify women at high risk.

Data were obtained from a large cohort of consecutive women with the first documented VTE event. Cross-sectional analysis of clinical and biological characteristics of the women was performed.

Of the 3009 women with the first VTE included, 31% were nonusers and 69% CHC users at time of VTE. CHC users were significantly younger (29.0 ± 7.2) than nonusers (31.6 ± 7.1) ($P < .001$). No difference in VTE familial history was observed between the 2 groups. Compared with nonusers, the CHC users experienced more frequently pulmonary embolism: odds ratio (OR) = 1.28 (1.06–1.55; 95% confidence interval [CI]), factor V Leiden mutations were more frequent in this group (OR = 1.41 [1.11–1.80; 95% CI]). Venous sclerotherapy and travel were associated with VTE in CHC users, whereas surgery and bed rest were significantly associated with VTE in nonusers. Finally, 2/3 of CHC users with VTE had additional VTE risk factors.

CHC users experiencing the first VTE differ from nonusers with respect to clinical and genetic background. Better understanding of the characteristics of VTE and associated risk factors could allow more appropriate management of these women and contribute to more accurate benefit-risk assessment before prescribing a CHC.

Abbreviations: BMI = body mass index, CHC = combined hormonal contraceptives, CI = confidence interval, CPA = cyproterone acetate, CVT = cerebral thrombosis, DVT = deep vein thrombosis, OR = odds ratio, PE = pulmonary embolism, POC = progestin only contraceptive, SD = standard deviation, VTE = venous thromboembolism.

Keywords: combined hormonal contraceptives, risk factors, thrombophilia, venous thromboembolism

1. Introduction

Venous thromboembolism (VTE) event—including deep vein thrombosis (DVT), pulmonary embolism (PE), and cerebral thrombosis (CVT)—is uncommon before the menopause. Its incidence markedly increases with age.[1] A substantial part of VTE in women of childbearing age is the use of hormonal contraceptives. The risk of VTE is, thus, a key factor to take into account when assessing the risk-benefit profile for hormonal contraceptives.[2–4]

Hormonal contraception is one of the most commonly prescribed birth control method and is used by several million women worldwide.[5] For many years, epidemiological studies have shown that the use of a combined hormonal contraceptive (CHC), whatever the route of administration, increases the risk of VTE.[3,6,7]

Previous studies have shown that VTE is a multifactorial disease resulting from numerous risk factors.[8] Moreover, it is not yet fully understood which women are at risk of developing a CHC-associated VTE. Better information about the factors determining the VTE risk in CHC users is thus necessary to optimize the CHC risk-benefit profile. However, to date, only a few small studies have been conducted comparing the clinical and biological characteristics of women with the first VTE who use CHC with those who do not.[9–12] Consequently, larger studies will help specify clinical and biological characteristics of CHC-associated VTE. In this perspective, we conducted a cross-sectional study to assess the characteristics of women with the first documented VTE according to hormonal

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contraceptive with the COREVE (COntraception and REcurrent Venous Event) data.

2. Subjects and methods

2.1. Participants and study design

We included consecutive women aged 18 to 45 years with the first confirmed episode of VTE referred to the outpatient clinic of our Hemostasis Unit (Hotel-Dieu Hospital, Paris, France) between January 1, 2000, and December 31, 2009. Women were excluded if they: presented with central retinal vein obstructions or cancer-related VTE; were on a progestin only contraceptive (POC) (n = 71); or did not remember which contraceptive they used at time of VTE (n = 41). For all women included, data were collected at the time of their first visit at the Hemostasis Unit. A cross-sectional analysis of the clinical and biological characteristics was first performed.

Cases of DVT, PE, and CVT were diagnosed with an appropriate imaging procedure.[13] PE was defined as the presence of a positive computed tomographic pulmonary angiography or a high-probability ventilation/perfusion lung-scintigraphy. DVT was diagnosed by use of compression ultrasonography or venography. DVT of a calf vein was considered as distal, and DVT involving the remaining vein segment (popliteal, femoral, or iliac) was considered as proximal.[13] CVT was diagnosed by positive cerebral MRI. The presence of the following transient risk factors was recorded: surgery (last 3 months before VTE), plaster cast, prolonged bed rest (≥4 days), hormonal contraceptive use, pregnancy, early postpartum period (6 weeks), venous sclerosis, or lengthy air travel. Caesareans were counted in the surgery group. The characteristics of women were extracted from their medical charts using a standardized questionnaire which was completed during a medical consultation by a physician at the Hemostasis Unit. Data included information on medical history, use of all treatments, family history, reproductive factors, other factors such as height and weight, smoking status, the use of exogenous hormones, and the first VTE event. The body mass index (BMI) was calculated as weight (kg) /(height [m]).[2] A positive 1st degree history was considered if at least 1 first-degree relative had had an episode of VTE under the age of 65 years.

The study protocol was approved by the CCTIRS (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé) and the CNIL (Commission nationale de l'informatique et des libertés). Oral and written information was provided, and written consent forms were obtained for all women.

2.2. Hormonal contraceptive classification

Women were classified as CHC users if they had used CHC at any time during the 3 months before the date of VTE; otherwise, they were considered as nonusers. CHC included any generation of progestin combined with ethinyl-estradiol (EE) and delivered by 1 of the 3 routes of administration (oral, vaginal, or transdermal). CHC were classified into generation according to the type of progestogens associated to EE. The first-generation pills contained norethisterone acetate. Second-generation pills contained norgestrel or levonorgestrel and the third-generation pills contained desogestrel or gestodene. We classified separately pills containing EE associated with norgestimate or drospirenone or cyproterone acetate (CPA) because the VTE risk associated with

these associations seemed to be different. Women were classified as nonusers if they used nonhormonal intrauterine devices, condoms, or no contraceptive methods.

2.3. Laboratory analysis

After the first event of VTE, women were screened for acquired and hereditary thrombophilia at the baseline visit in the outpatient clinic.[13] Tests included prothrombin time, activated partial thromboplastin time, antithrombin activity, protein C activity, protein S (activity and free antigen), activated PC resistance, factor V Leiden mutation, and factor II G20210A mutation after DNA extraction and polymerase chain reaction analysis, lupus-like anticoagulant, anticardiolipin, and antiβ2Gp1 antibodies. All tests were performed at the Hotel-Dieu Hospital laboratory. Women were considered as having biological thrombophilia if they presented at least one of the following laboratory abnormalities: mutation of the Factor V Leiden or prothrombin G20210A mutation or hereditary deficiency in natural anticoagulant protein C, protein S, or antithrombin or biological antiphospholipid syndrome. Diagnosis of thrombophilia was confirmed on a second blood sampling.[13]

2.4. Statistical analysis

Baseline characteristics were analyzed with the classic statistical tests for cross-sectional data: mean ± standard deviation (SD) for continuous variables and proportions for categorical variables. To compare qualitative variables, the chi-square test was used. T-test or Variance analysis were performed to compare quantitative variables among groups. Statistical significance was associated with a 2-tailed P-value below .05. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated by logistic regression. Statistical analysis used procedures available in SAS software (SAS Institute, Inc, Cary, NC).

3. Results

A total of 3009 consecutive premenopausal women with the first VTE were included in the COREVE study. Data were collected during the 1st visit at the Hemostasis Unit with a median time since VTE of 9 months. Among these women, 2088 (69.4%) used CHC and 921 (30.6%) were nonusers at the time of their first VTE. Table 1 shows the clinical and biological characteristics of the women included (CHC users and nonusers).

CHC users were significantly younger and leaner compared with the nonusers (respectively [mean ± SD] 29.0 ± 7.2, 31.6 ± 7.1 years old, and 23.0 ± 4.4, 23.9 ± 4.8 kg/m²). There was no difference in VTE family history between the 2 groups. CHC users had significantly less history of deliveries than the nonusers, even after the age adjustment. Biological thrombophilia screening was performed after the first VTE. CHC users were more frequent carriers of the factor V Leiden mutation than nonusers (OR = 1.41 [1.11–1.80; IC95%]). This result did not change after adjustment for age, BMI, and type of thrombosis (OR = 1.46 [1.14–1.87]).

Forty-one percent of the CHC users were first users of CHC with a median duration of 48 months (range 0.1–356 months). The time between the start of first CHC use and the first episode of VTE was less than 1 year in 25% of first CHC users and less than 3 months in 10% of first CHC users.

Table 1

Clinical and biological characteristics of combined hormonal contraceptive users and nonusers.

	CHC users n = 2088	Nonusers n = 921	Odds ratio, 95% CI	P
Mean age, years ± SD	29.0 ± 7.2	31.6 ± 7.1	–	<.001
Age				
≥35 y	527 (25.2)	345 (37.5)	0.56 (0.48–0.67)	<.001
≥40 y	212 (10.2)	141 (15.3)	0.63 (0.50–0.79)	<.001
BMI, kg/m^2 ± SD	23.0 ± 4.4	23.9 ± 4.8	–	<.001
BMI≥30	164 (8.0)	90 (10.2)	0.77 (0.59–1.01)	.06
Family history	477/2059 (23.2)	225/911 (24.7)	0.92 (0.77–1.10)	.4
History of delivery	650/2063 (31.5)	432/720 (60.0)	0.31 (0.26–0.37)	<.001
Biological thrombophilia	586/2066 (28.4)	219/910 (24.1)	1.25 (1.04–1.50)	.01
Factor V Leiden	312 (15.1)	103 (11.3)	1.41 (1.11–1.80)	.01
Prothrombin mutation	113 (5.5)	51 (5.6)	1.03 (0.73–1.46)	.8
Antithrombin deficiency	4 (0.2)	1 (0.1)	1.86 (0.21–16.69)	.6
Protein S deficiency	23 (1.1)	14 (1.5)	0.77 (0.40–1.5)	.4
Protein C deficiency	43 (2.1)	14 (1.5)	1.43 (0.78–2.64)	.2
Antiphospholipid syndrome	44 (2.1)	17 (1.9)	1.21 (0.69–2.13)	.5
Combinations	47 (2.3)	19 (2.1)	0.92 (0.53–1.60)	.8

BMI = body mass index, CHC = combined hormonal contraceptive, CI = confidence interval, SD = standard deviation.

VTE characteristics by hormonal use are described in Table 2. More than 70% of the events in both groups were DVT. CHC users experienced more frequently PE compared with nonusers with an OR of 1.28 (IC95%: 1.06–1.55). For women with DVT only, CHC users experienced more frequently distal DVT than nonusers with an OR of 2.3 (IC95%: 1.9–2.8). Associated risk factors were different between the 2 groups with more frequently VTE related to plaster cast, travel, and venous sclerotherapy in CHC users compared with nonusers. In contrast, VTE in nonusers was more frequently related to bed rest and surgery (Table 2). Analysis was repeated after exclusion of distal DVT. In this subgroup (n = 1439), clinical and biological characteristics of CHC and nonusers were similar to the population overall for VTE-related risk factors, except for venous sclerotherapy. Results were similar when CVT were excluded (n = 61).

Thirty-six percent of the CHC users had none of the classic VTE risk factors (i.e., age ≥ 40 years old, BMI ≥ 30, first degree family history of VTE, plaster cast, bed rest, surgery, travel, postpartum, and venous sclerotherapy), 42% had 1 risk factor, and 22% had 2 or more risk factors. Among the nonusers, 23% had none of the classic VTE risk factors, 40% had 1, and 37% had 2 or more. There were fewer CHC users with 2 or more associated risk factors than nonusers (respectively 22% and 37%; P < .001). Among the CHC users, more than 30% with none or one other risk factor had a biological thrombophilia detected after the first VTE. Moreover, biological thrombophilia was less frequent in women with at least 2 risk factors than in those with 1 or none (P = .04). The percentage of women aged under 25 with none or one VTE risk factor (as defined in the study design paragraph) was significantly greater than in women aged over 35 years (89.3% vs 81.8%, respectively, P < .001). Moreover, young women had more frequently biological thrombophilia, 32.8% versus 25.8% in women aged over 35 years (P = .01).

Clinical, biological, and VTE characteristics according to the type of CHC are described in Table 3. Among CHC users, 26.6%

Table 2

VTE characteristics according to the hormonal use.

	CHC-users n = 2088	Nonusers n = 921	Odds ratio, 95% CI	P
VTE characteristics:				
DVT	1539 (73.7)	728 (79.0)	0.74 (0.62–0.90)	<.01
PE	503 (24.1)	183 (19.9)	1.28 (1.06–1.55)	.01
CVT	46 (2.2)	10 (1.1)	2.05 (1.03–4.09)	.03
For patients with DVT only				
Proximal DVT	319 (20.8)	271 (37.3)	0.44 (0.36–0.54)	<.001
Distal DVT	1156 (75.2)	414 (57.0)	2.31 (1.92–2.79)	<.001
Upper extremity DVT	58 (3.8)	41 (5.7)	0.66 (0.44–0.99)	.04
Risk factors for VTE				
Plaster cast	217 (10.4)	75 (8.1)	1.31 (0.99–1.72)	.05
Bed rest	62 (3.0)	99 (10.8)	0.25 (0.18–0.35)	<.001
Surgery	175 (8.4)	190 (20.6)	0.35 (0.28–0.44)	<.001
Travel	410 (19.6)	94 (10.2)	2.15 (1.69–2.73)	<.001
Postpartum	30 (1.4)	213 (23.1)	0.05 (0.03–0.07)	<.001
Venous sclerotherapy	105 (5.0)	23 (2.5)	2.07 (1.31–3.27)	<.01

CHC = combined hormonal contraceptive, CVT = cerebral venous thrombosis, DVT = deep venous thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism.

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Table 3

Clinical, biological, and VTE characteristics according to the type of CHC.

	First-generation CHC	Second-generation CHC	CHC containing norgesimate	Third-generation CHC	CHC containing cyproterone acetate	CHC containing drospirenone	P
Patients, N=2037	66 (3.2)	542 (26.6)	51 (2.5)	886 (43.5)	376 (18.5)	116 (5.7)	
Clinical characteristics							
Mean age, years ± SD	30.7 ± 7.2	28.2 ± 7.3	29.6 ± 7.0	30.3 ± 7.2	26.6 ± 6.4	29.3 ± 7.5	<.001
BMI, kg/m² ± SD	25.2 ± 6.2	23.4 ± 4.8	23.0 ± 4.3	22.8 ± 4.0	22.4 ± 4.0	23.1 ± 4.5	<.001
Family history; N, %	20 (31.3)	133 (24.9)	10 (20.0)	200 (22.9)	75 (20.2)	31 (27.0)	.2
VTE characteristics: N (%)							
DVT	45 (68.2)	407 (75.1)	43 (84.3)	655 (73.9)	265 (70.5)	81 (69.8)	.2*
PE	20 (30.3)	122 (22.5)	7 (13.7)	214 (24.2)	101 (26.9)	32 (27.6)	
CVT	1 (1.5)	13 (2.4)	1 (2.0)	17 (1.9)	10 (2.6)	3 (2.6)	
For patients with DVT only							
Proximal DVT	4 (8.9)	95 (23.6)	5 (11.6)	126 (19.3)	57 (21.5)	21 (25.9)	.4*
Distal DVT	39 (86.7)	285 (70.9)	36 (83.7)	508 (77.7)	200 (75.5)	56 (69.2)	
Upper extremity DVT	2 (4.5)	22 (5.5)	2 (4.7)	20 (3.0)	8 (3.0)	4 (4.9)	
Biological thrombophilia	12 (18.2)	154 (28.8)	10 (19.6)	246 (27.9)	117 (31.3)	41 (37.6)	.003*
Risk factors for VTE: N (%)							
Plaster cast	10 (15.2)	59 (10.9)	7 (13.7)	91 (10.3)	37 (9.8)	8 (6.9)	.2*
Bed rest	2 (3.0)	19 (3.5)	1 (2.0)	22 (2.5)	12 (3.2)	5 (4.3)	.8*
Surgery	10 (15.2)	61 (11.3)	2 (3.9)	70 (7.9)	20 (5.3)	6 (5.2)	<.001*
Travel	10 (15.2)	87 (16.1)	4 (7.8)	177 (20.0)	96 (25.5)	26 (22.4)	<.001*
Venous sclerotherapy	1 (1.5)	26 (4.8)	3 (5.9)	52 (5.9)	14 (3.7)	6 (5.2)	.8*

Biological thrombophilia included a mutation of the Factor V Leiden or prothrombin G20210A mutation or hereditary deficiency in natural anticoagulant protein C, protein S, or antithrombin or biological antiphospholipid syndrome. Type of CHC was unknown for 51 women.

CHC = combined hormonal contraception, CVT = cerebral venous thrombosis, DVT = deep venous thrombosis, PE = pulmonary embolism, SD = standard deviation, VTE = venous thromboembolism.

* khi-2 Mantel–Haenszel.

used a second-generation CHC, more than 40% used a third-generation CHC and 18.5% used CHC containing EE and CPA. Women taking a CHC containing CPA at the time of thrombosis were significantly younger and leaner as compared with other CHC users (P < .001 and P = .01, respectively). They had a weaker family history of VTE and the main associated risk factor was long travel.

4. Discussion

In this large cohort of consecutive women experiencing a first VTE event, CHC users differed from nonusers with respect to clinical and genetic background. More than 69% of women included in our cohort were CHC users at the time of their first VTE. Compared with nonusers, CHC users were younger and leaner, experienced more frequently PE, and were more frequent carriers of factor V Leiden mutation. Two-thirds of the women using CHC had additional VTE risk factors.

Only a few small studies have previously evaluated the characteristics of CHC users with VTE.[9–12,14] A study by Blanco-Molina et al,[10] based on the RIETE observational registry, assessed 593 CHC users and 1074 nonusers at the time of a VTE event. In contrast to their study, we included only the first VTE and excluded recurrences. As in our study, CHC users were also younger and leaner than nonusers. Nonusers were also more likely to have undergone surgery and bed rest. Another small prospective cohort study compared the baseline characteristics of CHC users and nonusers at the time of a first VTE event.[11] While the CHC users were younger than nonusers, no difference was found between the 2 groups for BMI, site of VTE and transient risk factors (including only surgery, traumatism and immobilization). These differences could potentially explain our divergent results. As in the study of Blanco-Molina et al[10] the CHC users in our study experienced more frequently PE

compared with nonusers. In contrast with previous studies, the CHC users in our study experienced more frequently distal DVT than nonusers. It could be because hormonal contraceptive users are more likely to be referred for venous thrombosis check up in the presence of VT symptoms. However, in a large prospective study of patients with a suspicion of PE, the proportion of proximal DVT versus distal DVT was about 50%. Indeed, in patients with suspected PE, compression ultrasonography was positive in 21% patients of whom 10% had proximal DVT and 11% isolated distal DVT.[15] In Le Moigne et al study,[11] there was no difference between the 2 groups concerning the initial VTE site. Moreover, in most countries, diagnosis of VTE is limited to proximal DVT, with no exploration of distal veins. For example, the Blanco-Molina et al[10] study only provided data on proximal but not distal DVT. However, DVT typically starts in the calf veins, from where it may extend to the proximal veins and subsequently cause PE.[16] Indeed, our results were similar when we excluded distal DVT, except for the results concerning venous sclerotherapy which was usually associated with distal DVT.

Routine screening for biological thrombophilia before CHC use is not currently recommended.[17] In our study, thrombophilia tests were performed after the first VTE for all women: 99% of women were tested as compared with 50% in the cohort of Blanco-Molina et al.[10] In their study,[10] there was no statistical difference between the 2 groups concerning the presence of a factor V Leiden mutation but the percentages were similar to ours with 14% of CHC users found to have factor V Leiden and 10% in the nonuser group. Le Moigne et al[11] found that CHC users were more likely to be factor V Leiden mutation carriers than nonusers. Moreover, women with hormone-related VTE were more likely to be carriers of the factor V Leiden mutation than women with nonhormone-related VTE.[18,19] More recently, Suchon et al[9] evaluated the risk factors for VTE in CHC-users. In their cohort, 12.1% of women

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with VTE were carriers of the factor V Leiden mutation. Unfortunately, we are unable to precise whether factor V mutations were present in the homozygous or heterozygous state. But the above-mentioned studies did not have this information either.

Finally, our findings concerning the first-degree family history of VTE were consistent with previous published literature in which 22% to 35% of women with VTE in CHC-users had a first-degree family member with VTE.[11,12,20] In our study, the percentage was 23%. We agree with the conclusion of Van Vlijmen et al[12] that a positive family history seems to be an avoidable risk factor even if it is not currently considered as a contra-indication for CHC use. Zöller et al[21] also showed in a case-control study that family history of VTE was a risk factor for VTE in CHC users.

VTE is a multifactorial disease resulting from numerous associated factors which are not yet fully understood. A better characterization of CHC users at time of VTE could help to understand who will develop a VTE. However, our results showed that 64% of CHC users had at least 1 associated risk factor and 6% of them had more than 3 risk factors irrespective of biological thrombophilia. In younger CHC-users, VTE was associated with weaker VTE risk factors. An explanation could be the greater frequency of biological thrombophilia diagnosed in younger CHC-users than in older ones.

Women using CHC containing CPA with a 1st VTE differed from others CHC users. They are younger, leaner and they have more frequently travel-associated risk factors, which probably reflect different lifestyles. This CHC is often used in young women with symptoms of clinical hyperandrogenism such as acne. This particular clinical profile could contribute to explain these differences.

As far as we know, this is the largest study that reports the clinical and biological characteristics of VTE according to hormonal use. The strengths of the study were also to have included only first documented VTE and to have performed biological tests in 99% of the cohort. However, our study does suffer from potential limitations including the intrinsic limitations of cross-sectional analysis. Furthermore, the fact that it was a single-center study a specialized hemostasis unit might have led to some recruitment bias.

In conclusion, CHC users with the first VTE differ from nonusers with respect to clinical and genetic background. Two-thirds of women using CHC and experiencing a VTE event had additional VTE risk factors. Better understanding of the characteristics of VTE and associated risk factors could help identify women at high risk of VTE and contribute to more accurate benefit-risk assessment before prescribing a CHC.

Acknowledgments

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