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Combined Hormonal Contraceptives and First Venous Thrombosis in Young French Women: Impact of Thrombotic Family History

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Context: In UK and French, but not World Health Organization (WHO), guidelines for combined hormonal contraception (CHC), family history of a venous thromboembolism (VTE) is a condition for which the theoretical risks usually outweigh the advantages of using CHC.

Objective: We estimated the prevalence of inappropriate prescriptions of CHC according to several international guidelines and their impact on VTE.

Design: A single-center observational study.

Setting: Hemostasis unit outpatient clinic (Paris, France).

Population: A total of 2088 French CHC users of childbearing age with a first documented VTE who were referred to our unit between 2000 and 2009.

Methods: Data were collected by a standardized questionnaire during a medical consultation. Family history of VTE was analyzed according to definitions from international recommendations (VTE before age 45 years, United Kingdom; before age 50 years, France). A CHC prescription was considered inappropriate for women with vascular contraindications and/or a family history of VTE. Cross-sectional analysis of the clinical and biological characteristics was performed.

Main Outcome Measures: Prevalence of inappropriate prescription of CHC and potentially preventable events were estimated.

Results: According to the WHO, UK, or French guidelines, 8.8%, 18.9%, and 25.9%, respectively, of CHC prescriptions were considered inappropriate. Compliance with these guidelines could reduce the corresponding number of VTEs by 6.3%, 13.5%, and 18.5%, respectively. Characteristics of the women were similar.

Conclusion: Our results suggest inappropriate CHC prescriptions are prevalent among CHC users with first VTE. The appropriate way to take family history of VTE into account should be further clarified.

Abbreviations: CHC, combined hormonal contraception; HAS, French National Authority for Health; RCOG, Royal College of Obstetricians and Gynecologists; RR, relative risk; VTE, venous thromboembolism; WHO, World Health Organization.

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Combined hormonal contraception (CHC) is one of the most commonly prescribed methods of birth control and is used by several million women worldwide [1]. It is well tolerated and confers many noncontraceptive benefits [2]. Nevertheless, epidemiological studies have shown that the use of CHC increases the risk of venous thromboembolism (VTE) events, ischemic stroke, and myocardial infarction [3–6]. Even if these events are uncommon in premenopausal women, prescribers should take into account the risk of a vascular complication as part of the risk-benefit assessment for CHC use [4, 7, 8].To reduce these adverse events, international guidelines define medical eligibility criteria for contraceptive use into four categories, ranging from category 1 (no contraindication) to 4 (contraindication for CHC use) [9–13]. Previous studies among women of childbearing age [14, 15] have reported a prevalence of contraindication to CHC use of 13% to 16% in the general public and of 6% to 24% among CHC users [15–17]. The criteria used to define the contraindications for CHC use differed from one study to another. This could explain these differences in prevalence estimates. Indeed, medical eligibility criteria for CHC use differ according to the various guidelines.

Surprisingly, none of the studies reported a family history of VTE as a contraindication [14–17], despite the fact that a positive family history has been reported to increase significantly the risk of VTE, depending on the number of affected relatives [18]. Thus, family history of VTE is included in both the Royal College of Obstetricians and Gynecologists (RCOG) [12] and the French National Authority for Health (HAS) [10] guidelines as category 3. In contrast, the World Health Organization (WHO) recommendations [9] do not include family history of VTE as a contraindication for CHC use.

We conducted a cross-sectional study to assess the prevalence of vascular contraindications to CHC and first-degree family history of VTE among CHC users who had a first VTE event, to estimate the rate of inappropriate CHC prescriptions. Then, we evaluated the preventable cases associated with these different guidelines. We also compared the clinical and biological characteristics of women with and without an inappropriate prescription.

1. Methods

A. Participants and Study Design

Consecutive CHC users aged 18 to 45 years with a first confirmed episode of VTE and who were referred to the outpatient clinic of our Hemostasis Unit (Hotel-Dieu Hospital, Paris, France) between 1 January 2000 and 31 December 2009 were included. For all the women, data were collected at the time of the first visit to the unit. Cross-sectional analysis of the clinical and biological characteristics at the time of the first documented VTE was performed.

Cases of deep venous thrombosis, pulmonary embolism, and cerebral venous thrombosis were diagnosed with an imaging procedure. A standardized questionnaire was completed for all women during a medical consultation at the Hemostasis Unit. Baseline data included information about the first VTE event, medical history, medical comorbidities, treatments, family history, transient risk factors, reproductive factors, and factors such as height, weight, smoking status, and the use of exogenous hormones. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). Family history of VTE included self-reported events during the medical consultation. Superficial vein thrombosis was not taking into account.

Family history of VTE was analyzed according to the definitions from two sets of international recommendations. First, according to RCOG guidelines [12], family history of VTE was considered positive if at least one first-degree relative had had a VTE event when they were younger than age 45 years. Second, according to HAS guidelines [10], family history of VTE was considered positive if at least one first-degree relative had had a VTE event when

they were younger than age 50 years or if more than two relatives had had a VTE. In this last situation, the relationship of those relatives usually was that of one first-degree relative older than age 50 years with a one or more second-degree relative who had had VTE.

Each woman's socioeconomic level was also recorded and classified into one of four categories: low, student, middle, and high.

The study protocol was approved by the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (reference: 09.043; 22/01/2009) and the Commission nationale de l'informatique et des libertés (reference: 909046; 22/01/2009). Oral and written information were provided, and written consent forms were obtained for all women.

B. 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 event. Women who did not use CHC during the 3 months before VTE or used nonhormonal intrauterine devices, condoms, or no contraceptive methods were considered as nonusers. CHC included any type of progestin combined with ethinyl-estradiol and delivered by one of the three routes of administration: oral, vaginal, or transdermal. Only four women used CHC with transdermal ethinyl-estradiol.

C. Contraindications to CHC

The WHO [9] medical eligibility criteria for contraceptive use provide guidelines for prescribing contraception to women with medical comorbidities. These criteria classify medical criteria for CHC use into four categories (Table 1). Medical criteria in categories 3 and 4 constitute inappropriate use of CHC. Several countries adapted these recommendations [10–13]. A summary of the categories according to the various recommendations is provided in Table 2. All the recommendations [9–13] agree that the following criteria constitute contraindications for CHC use: early postpartum period, smokers older than age 35 years, hypertension, migraine headaches with aura or migraine headaches in women older than age 35 years (except for the RCOG [12]), and presence of multiple risk factors. Nevertheless, there are some differences between the various recommendations, especially regarding a first-degree family history of VTE, which is only considered as an increased risk over benefit (category 3) to CHC use by the RCOG [12] and the HAS [10] but not by the WHO (category 2) [9]. We recorded cardiovascular contraindications to CHC use and a first-degree family history of VTE by the RCOG and HAS guidelines.

Women with a category 3 or 4 contraindication [*i.e.*, early postpartum period, smokers over age 35, hypertension, and multiple risk factors (*i.e.,* the combination of at least two of the following factors: age ≥35 years, smoking, diabetes, dyslipidemias, BMI ≥30 kg/m^2)] were considered as having a medical contraindication to CHC use. Information on migraine headaches or diabetes-related complications was not available. CHC users with a category 3 or 4 contraindication and/or a family history of VTE were recorded as CHC users with inappropriate prescription. All other women were considered as CHC users without inappropriate prescription.

Table 1. Definitions of Medical Eligibility Criteria Categories for Contraceptive Use

Category	Category Definitions
1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used

Table 2. A Summary of Medical Eligibility Criteria per Category According to International Guidelines for Combined Hormonal Contraceptive Use

	WHO [9]	CDC [13]	RCOG [12]	HAS [10]	SOGC [11]
Country	World	United States	United Kingdom	France	Canada
Year of publication	2015	2016	2014	2013	2004
Early postpartum	¾	¾	¾	¾	¾
Hypertension	¾	¾	¾	¾	¾
Migraine over age 35 y	3	3	2	3	3
Smokers over age 35 y	¾	¾	¾	¾	¾
Diabetes (vascular disease or >20 years' duration)	¾	¾	¾	¾	¾
Multiple risk factors[a]	¾	¾	¾	¾	¾
First-degree family history of VTE	2	2	3	3	2

Abbreviations: CDC, Centers for Disease Control and prevention; SOGC, Society of Obstetricians and Gynecologists of Canada.
[a]Multiple risk factors constitute a combination of at least two of the following factors: age ≥35 years, smoking, diabetes, dyslipidemias, BMI ≥30 kg/m^2.

Finally, we defined three groups of inappropriate prescription: (1) according to the WHO, with inappropriate prescription defined by CHC users with category 3 or 4 contraindications; (2) according to the RCOG or (3) the HAS, with inappropriate prescription defined by CHC users with category 3 or 4 contraindications and/or a family history of VTE.

D. Laboratory Analysis

After the first VTE event, women were screened for acquired and hereditary thrombophilia at the baseline visit in the outpatient clinic. All tests were performed in our hospital laboratory in Paris. Women were considered as having thrombophilia if they had at least one of the following laboratory abnormalities: factor V Leiden or prothrombin G20210A mutations or hereditary deficiency in natural anticoagulant protein C, protein S, or antithrombin; or biological antiphospholipid syndrome (lupus-like anticoagulant, anticardiolipin, and antiß2Gp1 antibodies). Diagnosis of thrombophilia was confirmed on a second blood sampling.

E. Statistical Analysis

Baseline characteristics were analyzed with the following classic statistical tests for cross-sectional data: mean ± standard deviation for continuous variables and proportions for categorical variables. Variance analysis and the χ^2 test were performed to compare quantitative or qualitative variables among groups. The t test was used to compare quantitative variables between two groups. A two-tailed P value < 0.05 was considered to indicate statistical significance. Preventable events were computed using the standard formula of attributable fraction of risk, where RR is relative risk: [(1 − RR)/RR]. For this estimation, RR of VTE associated with CHC, evaluated by the most recent meta-analysis, was used (RR, 3.5; 95% confidence interval, 2.9 to 4.3) [4]. Statistical analysis used procedures available in SAS software (SAS Institute, Cary, NC).

3. Results

A total of 2088 CHC users with a first VTE event were included. Women were screened for thrombophilia at their first visit at the Hemostasis Unit, with a median delay since VTE of 9 months. Table 3 lists the clinical characteristics of CHC users and the prevalence of WHO vascular contraindications (category 3 or 4) to CHC use and family history of VTE among CHC users according to RCOG or HAS guidelines. CHC was prescribed to 184 women (8.8%) with

Table 3. Clinical Characteristics of Contraceptive Users With a First VTE and Vascular Contraindications to CHC Use (N = 2088)

Clinical Characteristics	Mean ± SD	No. (%)
Age, mean ± SD, y	29.0 ± 7.2	
≥35		527 (25.2)
≥40		212 (10.2)
BMI, kg/m^2	23.0 ± 4.4	
<25		1610 (77.1)
≤25 and <30		314 (15.0)
≥30		164 (7.9)
Smoking		177 (8.5)
Diabetes		6 (0.3)
Dyslipidemias		89 (4.3)
Vascular contraindications to CHC use		
WHO category 3 or 4		
Smokers over age 35		31 (1.5)
Early postpartum		30 (1.5)
High blood pressure		51 (2.5)
Multiple risk factors[a]		113 (5.4)
Family history of VTE		
According to RCOG (first-degree relative age <45 y)		233 (11.2)
According to HAS (first-degree relative age <50 y or multiple family history of VTE)		392 (18.8)
Total (WHO category 3 or 4 and/or family history of VTE)		
WHO		184 (8.8)
WHO + family history of VTE (according to RCOG)		395 (18.9)
WHO + family history of VTE (according to HAS)		541 (25.9)

Data given as no. (%) unless otherwise indicated.
[a]Multiple risk factors constitute a combination of at least two of the following factors: age≥35, smoking, diabetes, dyslipidemias, BMI ≥30 kg/m^2.

vascular contraindications (category 3 or 4) according to international recommendations. In contrast, according to RCOG and HAS guidelines, 395 (18.9%) and 541 (25.9%) women, respectively, could be classified as CHC users with inappropriate prescription, because they had vascular contraindications and/or a family history of VTE. A positive family history of VTE was present in 233 women (11.2%) and 392 (18.8%) when applying RCOG or HAS guidelines, respectively. Preventable VTE events were estimated, according to different guidelines, between 6.3% and 18.5% (Table 4).

Table 5 lists the clinical and biological characteristics of CHC users according to vascular contraindications and the two definitions of positive family history of VTE. Among CHC users, 184 women had vascular contraindications (category 3 or 4) to CHC use. Among them, 22 (12%) or 35 (19%) also had a family history of VTE according to the RCOG or HAS definitions, respectively. A total of 211 women (53.4%), according to RCOG guidelines, and 357 (66%), according to HAS guidelines, had a first-degree family history of VTE without other vascular contraindications. Thrombophilia was more frequent in CHC users with a family history of VTE than in CHC users with vascular contraindications—mainly carriers of the gene mutation factor V Leiden (RCOG, $P < 0.01$; HAS, $P = 0.01$). The socioeconomic level was lower in CHC users with WHO contraindications. VTE characteristics were not different between groups. No significant differences were observed between the different types of CHCs among our three groups of guidelines (*i.e.*, vascular contraindications and the two definitions of positive family history of VTE).

Clinical and biological characteristics of the two groups of CHC users with and without inappropriate prescription were not significantly different except for the socioeconomic classification, regardless of definition of a positive family history (Table 6). Women at a low socioeconomic level were more likely to have an inappropriate prescription ($P < 0.01$).

Table 4. Preventable Events According to the Different Guidelines

Guidelines	Rate of Inappropriate Prescription, %	Preventable Fraction of VTE Event (95% CI)
WHO	8.8	6.3 (5.8–6.8)
WHO + family history (RCOG)	18.9	13.5 (12.4–14.5)
Only family history (RCOG)	11.2	8.0 (7.3–8.6)
WHO + family history (HAS)	25.9	18.5 (17.0–19.9)
Only family history (HAS)	18.8	13.4 (12.3–14.4)

The prevalence of thrombophilia in CHC users with a first-degree family history of VTE when younger than 45 years was similar in CHC users without such a history in their first-degree relatives (33.5% vs 27.7%, respectively; $P = 0.07$). However, according to the HAS definition of family history of VTE, the prevalence of thrombophilia with or without family history of VTE was significant (33.9% vs 27.1%, respectively; $P = 0.007$).

4. Discussion

According to RCOG or HAS recommendations, between 18.9% and 25.9% of women in this large cohort of CHC users experienced a first VTE even though a contraindication (*i.e.*, vascular and/or familial VTE history) to CHC use was present, contrasting with 8.8% according to the WHO guidelines (*i.e.*, vascular contraindication only). Preventable events were estimated according to VTE risk associated with CHC use to be between 6.3% and 18.5%. There was no statistical difference between women with and without inappropriate prescription in terms of VTE characteristics and biological thrombophilia regardless of guidelines. CHC users with inappropriate prescription belonged to a lower socioeconomic level compared with CHC users without inappropriate prescription.

VTE, stroke, and myocardial infarction are multifactorial diseases resulting from numerous risk factors that are not yet fully understood. Vascular events are the most important determinant of the benefit-risk profile of hormonal contraceptive use. At the time of prescription, the choice of the contraceptive method must also take into account the risk of an unwanted pregnancy. Nevertheless, contraindications must be assessed to avoid vascular adverse events in women, because other contraceptive strategies can be proposed in these situations. Progestin-only or nonhormonal contraceptive methods are potential alternatives for women with VTE risk factors [5, 19].

Few studies have reported inappropriate prescription of CHC [14–17, 20]. Only one study [21], conducted in Swedish women of childbearing age, evaluated the incidence of VTE and possibly preventable cases. The authors observed that 26% of women with CHC-related VTE had relative contraindications for CHC use or should have had thromboprophylaxis during surgery. The authors concluded that a substantial proportion of CHC-related VTE events could have been avoided [21]. Our findings concerning preventable cases are consistent with this conclusion.

Previous studies [14, 15] of women of childbearing age found a prevalence of contraindication to CHC use of 13% to 16%. Lauring *et al.* [14] described a high prevalence of CHC use among women with a medical contraindication to CHC (39.2%), but in a small sample (51 of 130 women). The largest contraindication category was self-reported migraine with aura. Previous studies of CHC users have reported a prevalence of contraindication to CHC use at 6% to 24% [15–17]. Inclusion of different risk factors could explain these differences. Only one study [17], the largest of its kind with 2963 CHC users from international self-reported patient surveys, included multiple vascular risk factors as a contraindication to CHC use. In this study, 23.7% had at least one high-risk condition with multiple vascular risk factors in 9.3% of the women. This high prevalence could be explained by the self-reported approach. Indeed, Xu *et al.* [20] showed that the prevalence

Table 5. Clinical and Biological Characteristics of CHC Users According to Vascular Contraindications and the Two Definitions of Family History of VTE

	A	B	C		
	CHC Users With WHO Categories 3-4	CHC Users With Only a First-Degree Family History of VTE at Younger Than Age 45 Years[a]	CHC Users With Only a First-Degree Relative Younger Than Age 50 or History of VTE in Multiple Relatives[b]	*P* Value[c]	*P* Value[d]
Patients, No.	184	211	357		
Age, mean ± SD, y	34.8 ± 6.7	28.8 ± 7.1	28.8 ± 7.0	<0.01	<0.01
BMI, mean ± SD, kg/m^2	27.2 ± 6.8	23.1 ± 4.2	23.0 ± 4.2	<0.01	<0.01
Socioeconomic level,[e] no. (%)					
Low	91 (50.6)	77 (37.2)	123 (35.4)	0.12[f]	0.03[f]
Student	4 (2.2)	27 (13.0)	45 (13.0)		
Middle	67 (37.2)	75 (36.2)	128 (36.9)		
High	18 (10.0)	28 (13.5)	51 (14.7)		
Biological thrombophilia					
No thrombophilia	143 (77.7)	138 (65.4)	233 (65.3)	<0.01[g]	0.01[g]
Factor V Leiden	23 (12.5)	36 (17.1)	70 (19.6)		
Prothrombin mutation	8 (4.4)	11 (5.2)	21 (5.9)		
AT, PS, or PC deficiency	4 (2.2)	12 (5.7)	15 (4.2)		
Antiphospholipid syndrome	4 (2.2)	8 (3.8)	8 (2.2)		
Combinations	2 (1.1)	6 (2.8)	10 (2.8)		
VTE characteristics:					
DVT only	125 (67.9)	159 (75.4)	260 (72.8)	0.10	0.24
PE or CVT	59 (32.1)	52 (24.6)	97 (27.2)		
For patients with DVT only					
Proximal DVT	26 (20.8)	36 (22.8)	59 (22.8)	0.16[g]	0.15[g]
Distal DVT	91 (72.8)	121 (76.6)	197 (76.1)		
Upper-extremity DVT	8 (6.4)	1 (0.6)	3 (1.2)		

Data given as no. (%) unless otherwise indicated.
Abbreviations: AT, antithrombin; CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; PC, protein C; PE, pulmonary embolism; PS, protein S; SD, standard deviation.
[a]According to RCOG guidelines and without other vascular contraindications.
[b]According to HAS guidelines and without other vascular contraindications.
[c]*P* value between A and B.
[d]*P* value between A and C.
[e]Some data are missing: column A, n = 14; and column B, n = 8 for socioeconomic data.
[f]Adjusted for age.
[g]Mantel-Haenszel χ^2 test.

of comorbidities is higher by self-screening than by chart review. However, to our knowledge, no previous study of the prevalence of inappropriate CHC prescription has taken into account a first-degree family history of VTE. This is surprising because it would appear to be relevant to consider multiple risk factors and first-degree family history of VTE even if the international guidelines are not consensual.

Our findings concerning the first-degree family history of VTE are consistent with previously published literature in which 22% to 35% of CHC users with VTE had a first-degree relative with VTE without specifying the age [22–25]. In a recent case-control study, among 968 women with VTE associated with CHC use, 113 (11.7%) had a first-degree family history

Table 6. Clinical and Biological Characteristics of CHC Users by Inappropriate Prescription

	According to WHO Guidelines			According to RCOG Guidelines[b]			According to HAS Guidelines[c]		
	CHC Users With Inappropriate Prescription[a]	CHC Users Without Inappropriate Prescription	*P* Value	CHC Users With Inappropriate Prescription[a]	CHC Users Without Inappropriate Prescription	*P* Value	CHC Users With Inappropriate Prescription[a]	CHC Users Without Inappropriate Prescription	*P* Value
Patients, No.	184	1904		395	1693		541	1547	
Age, mean ± SD, y	34.8 ± 6.7	28.5 ± 7.0	<0.01	31.6 ± 7.5	28.4 ± 7.0	<0.01	30.9 ± 7.5	28.4 ± 7.0	<0.01
BMI, mean ± SD, kg/m^2	27.2 ± 6.8	22.6 ± 3.9	<0.01	25.0 ± 5.9	22.6 ± 3.8	<0.01	24.4 ± 5.6	22.5 ± 3.8	<0.01
Socioeconomic level,[d] no. (%)									
Low	91 (50.6)	613 (32.9)	<0.01[e]	168 (43.4)	536 (32.3)	<0.01[e]	214 (40.6)	490 (32.2)	0.01[e]
Student	4 (2.2)	282 (15.1)		31 (8.0)	255 (15.4)		49 (9.3)	237 (15.6)	
Middle	67 (37.2)	685 (36.7)		142 (36.7)	610 (36.8)		195 (37.0)	557 (36.7)	
High	18 (10.0)	286 (15.3)		46 (11.9)	258 (15.5)		69 (13.1)	235 (15.5)	
Biological thrombophilia[f]	41 (22.3)	545 (28.6)	0.06	114 (28.9)	472 (27.9)	0.7	165 (30.5)	421 (27.2)	0.2
VTE characteristics, no. (%)									
DVT alone	125 (67.9)	1414 (74.3)	0.06	284 (71.9)	1255 (74.1)	0.4	385 (71.2)	1154 (74.6)	0.3
PE or CVT	59 (32.1)	490 (25.7)		111 (28.1)	438 (25.9)		156 (28.8)	393 (25.4)	

Abbreviations: CVT, cerebral venous thrombosis; DVT, deep venous thrombosis; PE, pulmonary embolism.
[a]Inappropriate prescription was defined by a presence of a WHO category 3 or 4 criteria and/or VTE family history.
[b]RCOG defined VTE family history as having a first-degree relative experiencing VTE when younger than age 45 years.
[c]HAS defined VTE family history as having a first-degree relative experiencing VTE when younger than age 50 years or having multiple family members with a history of VTE.
[d]Some data are missing: socioeconomic data, n = 42.
[e]Adjusted for age.
[f]Biological thrombophilia screening was performed after the VTE event.

of VTE before the age of 45 years [22]. Furthermore, another study assessing the impact of male and female thrombotic family history on VTE risk [26] showed that the relatives of a person diagnosed with VTE when younger than 45 years were at significantly higher risk of VTE than if VTE had been diagnosed after age 45 years. Zöller *et al.* [27] also showed in a case-control study that a family history of VTE was a risk factor for VTE in CHC users (odds ratio, 6.02; 95% confidence interval, 5.02 to 7.22). Finally, we agree with the conclusion of Van Vlijmen *et al.* [23] that a positive family history seems to be an avoidable risk factor even if it is not currently considered as a contraindication for CHC use in all the guidelines [9, 11, 13]. Medical physicians should have access to clear, accurate information on contraceptive prescription. Information on medical history and a search for thrombosis risk factors before prescribing hormonal contraception are essential.

There was no statistical difference between women with and without inappropriate prescription in terms of VTE characteristics and biological thrombophilia whatever the guidelines taken in account. However, biological thrombophilia tends to be more frequent in CHC users with a family history; CHC users with inappropriate prescription were in a lower socioeconomic level compared with CHC users without inappropriate prescription. This could suggest inequity in access to well-trained health care providers.

To our knowledge, this is the largest study reporting the prevalence of inappropriate prescription and the clinical and biological characteristics of CHC users experiencing a first documented VTE. Another strength of this study is that the medical comorbidities were recorded during a medical consultation with a physician using a standardized questionnaire rather than being self-reported. We also included multiple risk factors and family history of VTE. All the medical charts were reviewed and family history of VTE was classified using definitions from both the RCOG and HAS guidelines. However, our study does suffer from the potential limitations of cross-sectional analyses such as recall bias or response bias. Furthermore, it was a single-center study and the women were recruited in a specialized hemostasis unit, leading to potential recruitment bias. Moreover, some contraindications to CHC were not systematically reported, especially migraine headaches. Thus, some women

may have been misclassified. Finally, the study population was French CHC users with a first VTE, which potentially limits generalization of the results.

In conclusion, between 8.8% and 25.9% of women with a VTE event associated with CHC use had an inappropriate prescription of CHC. Between 6.3% and 18.5% of these VTE events could have been preventable. Our results suggest that prescribers should be made more aware of the recommendations to reduce inappropriate prescription without increasing the number of unwanted pregnancies; other contraceptives strategies are available for these women. However, the appropriate way to take family history of VTE into account should be further clarified.

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