Risk factors for venous thromboembolism in women under combined oral contraceptive

The PILl Genetic Risk Monitoring (PILGRIM) Study

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Summary

Identifying women at risk of venous thromboembolism (VTE) is a major public health issue. The objective of this study was to identify environmental and genetic determinants of VTE risk in a large sample of women under combined oral contraceptives (COC). A total of 968 women who had had one event of VTE during COC use were compared to 874 women under COC but with no personal history of VTE. Clinical data were collected and a systematic thrombophilia screening was performed together with ABO blood group assessment. After adjusting for age, family history, and type and duration of COC use, main environmental determinants of VTE were smoking (odds ratio [OR] = 1.65, 95% confidence interval [1.30–2.10]) and a body mass index higher than 35 kg.m–2 (OR=3.46 [1.81–7.03]). In addition, severe inherited thrombophilia (OR=2.13 [1.32–3.51]) and non-O blood groups (OR=1.98 [1.57–2.49]) were strong genetic risk factors for VTE. Family history poorly predicted thrombophilia as its prevalence was similar in patients with or without first degree family history of VTE (29.3% vs 23.9%, p=0.09). In conclusion, this study confirms the influence of smoking and obesity and shows for the first time the impact of ABO blood group on the risk of VTE in women under COC. It also confirms the inaccuracy of the family history of VTE to detect inherited thrombophilia.

Keywords

Deep-vein thrombosis, oral contraceptives, thrombophilia

Introduction

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a complex disease resulting from numerous associated factors (1). In child-bearing age women, combined oral contraceptives (COC) are a major environmental risk factor. While the incidence of VTE is 16 VTE/100,000 women-years (WY) in nonpregnant non COC users, it can increase up to 99 VTE/100,000 WY according to the type of COC (2). During the past ten years, several studies showed a higher risk of VTE with 3rd and 4th compared to 1st and 2nd generations (3–6). Hypercoagulability, reflected by elevated activated protein C (APC) resistance was proposed as a plausible biological mechanism of the VTE risk during COC use. A higher APC resistance is thought to explain the increased risk observed in 3rd, 4th generation or cyproterone acetate users compared to 2nd generation users (7). Even though the incidence remains relatively low, the wide use of COC exposes a great number of women to VTE risk. Complications of VTE might be severe and include post-thrombotic syndrome, chronic PE, and a high mortality rate, mostly due to PE (8–11). Having young, healthy women exposed to those risks appears to be unacceptable. However, unwanted pregnancies related risks, both physical and psychological, are important and COC have proved their benefit on that matter (12–14). There is a major issue in identifying women using COC who will undergo VTE. Unfortunately, identifying those at an increased risk for VTE seems to be difficult. Several recommendations have been edited in order to lower the risk of VTE (15–17). Major surgery with expected immobilisation is an absolute contraindication in all recommendations. Despite the fact that smoking remains a controversial risk factor for VTE (18, 19), all recommendations agrees to contra-indicate COC in smokers aged
over 35 years beyond 15 cigarettes per day. For most of the recommendations, obesity does not contra-indicate COC. The Royal College of Obstetricians and Gynaecologists (RCOG) considers that COC shouldn’t be recommended in women with a severe obesity (i.e. body mass index [BMI] over 35 kg.m⁻²) (15). Out of these environmental and debated contexts, the main factors that can prevent a physician from prescribing COC to a woman are the positive personal or family history of VTE and the presence of inherited thrombophilia including antithrombin, protein C, protein S deficiencies, factor V Leiden (FVL) and prothrombin G20210A (PTG20210A) mutations. However, the issue as to who to screen for evidence of inherited thrombophilia is contentious, and systematic screening is not appropriate because of its poor cost effectiveness (20). Thus, thrombophilia screening is generally restricted to women with a positive family history of VTE. Despite widespread acceptance of this policy, the limited value of family history to detect inherited thrombophilia was shown in several studies and therefore the decision to test for inherited thrombophilia cannot be accurately guided by the presence or absence of family history (21–23). A better knowledge of the clinical and genetic risk factors of VTE in contraceptive users and the value of family history in the identification of inherited thrombophilia could help guiding more evidence-based decisions in the future. We therefore conducted a large case-control study where cases were women with a personal history of VTE under COC and controls were women under COC with no personal but family history of thrombosis. We aimed to identify environmental and genetic risk factors for a first episode of VTE and to evaluate the performance of family history for the screening of inherited thrombophilia in women using COC in a French case-control study.

Materials and methods

We conducted a case-control study, called the PILI Genetic RIsk Monitoring (PILGRIM) study, on patients referred to a single centre (Exploration Centre of hemorrhagic and thrombotic diseases [CEHT] of the Marseille University Hospital) between January 1, 2003 and December 31, 2013. Cases were all consecutive women who had a first objectively confirmed episode of VTE during COC use with no history of cancer or autoimmune disease. Controls were defined as consecutive women using COC who were referred to CEHT for thrombophilia screening as they presented a family history of thrombosis but with no personal history of the disease. During the consultation a standardised questionnaire (24) administrated by experienced physicians before screening for thrombophilic defects allowed us to collect the following data:

Personal history of VTE

VTE was considered established if DVT was confirmed by compression ultrasound or veinography, and PE by ventilation and perfusion lung scanning, spiral computer tomography scanning or pulmonary angiography, or when the patient had received full-dose heparin and a vitamin K antagonist for at least three months. Risk factors, including age, triggering circumstances at first VTE and family history of VTE were recorded. VTE was classified as provoked when occurring within three months after exposure to exogenous risk factors, including surgery, trauma, immobilisation for seven days. In the absence of these risk factors, VTE was defined as unprovoked.

Oral contraceptives

Progestogen only and first generation COC pills were excluded. We categorised the pills according to the generation of the progestogen. G2 group included second generation progestogens (levonorgestrel, norgestrel). G3 group included third generation progestogens (desogestrel, gestodene, norgestimate). G4 group included fourth generation progestogens (drospirenone, dienogest, nomegestrol). We also included cyproterone acetate (CA). Duration of use was collected, in months, without interruption. If the contraceptive was interrupted for more than four weeks, we calculated the duration from the date of restart. Considering the controls, if there was a switch in the contraception, we considered the most recent generation pill and we calculated the duration for this only pill.

Smoking

Current smoking was considered at the time of the VTE event for cases, and the time of the inclusion for controls. Five groups of smokers were obtained according to the number of cigarettes smoked per day: 0; 1 to 14; 15 to 24; 25 to 34; 35 or more (18).

Biometry

Height and weight were measured during the interview and BMI was calculated. BMI was stratified into four classes according to the WHO classification of obesity: below 25 kg.m⁻²; from 25 to 29.99 kg.m⁻² (pre-obese); from 30 to 34.99 kg.m⁻² (obese class I – mild obesity); 35 kg.m⁻² and more (obese class II and III – severe obesity).

Family history

The family history was qualified according to three different methods. For the first method, a positive 1st degree history was considered if at least one first-degree relative (parents, siblings, children) had had an episode of VTE. According to the second method, family history was positive when a VTE episode occurred in a first-degree relative aged under 45. We also calculated a family history score which is the ratio between the number of first-degree relatives who had had an episode of VTE and the total number of first-degree relatives. The family history score was divided into three groups according to Cohen et al. (24).
ABO blood group

ABO groups were obtained during the interview or phenotyped, in case individuals were unaware of their groups, with Qwaly’s 2 automate (Diagast, Loos, France). In all, ABO blood group was known for 955 (98.7%) cases and 864 (98.9%) controls.

Thrombophilia

Inherited thrombophilia was tested for all cases and controls. All haemostasis-related parameters were performed using the STA-R automate and commercially available kits and reagents from Diagnostica Stago (Asnieres, France), including the corresponding normal and pathologic control plasmas and standard plasmas. Anti-thrombin (AT) was measured with the AT chromogenic anti-thrombin heparin cofactor activity (Stachrom-ATIII). AT deficiency was defined by decreased levels of AT activity (<80 IU.dL⁻¹) (24). Protein S (PS) deficiency was defined by decreased free PS plasma antigen levels using specific ELISA assay (<55 IU.dL⁻¹) (25). Protein C (PC) deficiencies were defined by decreased levels of PC activity measured by Staclot Protein C (<70 IU.dL⁻¹) (26). Because PC and PS are vitamin K-dependent proteins and their plasma levels decrease by the concomitant use of vitamin K antagonists, PC and PS were measured at least one month after withdrawal of these drugs. Deficiencies were confirmed by measuring a second sample that was collected 3 months later. In controls, women with decreased plasma levels of AT, PC, PS were systematically verified at least 1 month after COC discontinuation.

FVL (rs6025) and PTG20210A (rs1799963) genotypes were obtained using light cycler technology (Roche Diagnostics, Indianapolis, IN, USA) (24).

We obtained informed consent from all participants, and the study met all institutional ethics requirement.

Statistical analysis

Qualitative variables were compared using the Chi² test (with Yate's continuity correction when appropriate) or Fisher's exact test when necessary. We used Student’s t-test for quantitative variables comparison. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Adjusted OR were calculated by logistic regression. For the multivariate analysis, we included the following confounding factors: age, type and duration of COC use, and family history score. Only significant (p<0.05) variables were maintained in the final model. A 5% two-tailed significance level was used for all tests.

According to previous recommendations (27, 28), inherited thrombophilia was separated into two groups depending on its severity. Moderate thrombophilia included heterozygosity for FVL or PTG20210A mutations. Severe thrombophilia was defined as natural anticoagulant inhibitor deficiencies, homozygosity for FVL or PTG20210A mutations, or heterozygosity for both mutations.

Results

Main characteristics of cases and controls

We included 968 women with a personal history of VTE during COC use and 874 controls. The main characteristics of the individuals are shown in Table 1. The mean age was 32.3 (range 14–55) for cases at the time of the VTE event, and 30.8 (range 14–55) for controls at the time of inclusion (mean difference (MD) =1.53 (95% CI 0.69–2.36), p=0.0004). While mean age was similar between cases and controls in the G2 group (MD=0.56 (-0.97–2.09, p=0.48), it was significantly higher in cases than in controls using G3 (MD=3.04 (1.79–4.30), p<10⁻⁴) and G4 (MD=5.35 (3.23–7.48), p<10⁻⁴) COC, and significantly lower in cases than in controls (MD=−3.44 (-5.45 – −1.43), p=0.0009) using CA (Suppl. Table 1, available online at www.thrombosis-online.com).

The distribution of COC type was significantly different (p<10⁻⁴) between cases and controls (Table 1), with 3rd generation COC more frequent (41.5%) in cases whereas 2nd generation COC being more often prescribed in controls (36.6%). Overall, the mean duration of COC use was slightly higher in cases than in controls (MD=0.69 (0.08–1.30), p=0.05) (Table 1) but shorter in controls using G2 COC (MD=−2.02 (0.86–3.17), p=0.0007), and shorter in cases using G4 (MD=−2.66 (-3.61 – −1.71), p<10⁻⁴) (Suppl. Table 1, available online at www.thrombosis-online.com).

Per design, all controls had a positive family history of thrombosis: 522 (59.7%) had a positive 1st degree family history of VTE (Table 1), 187 (21.4%) had a 2nd degree family history of VTE, 78 (8.9%) had a family history of arterial thrombosis, and for 87 (10.0%) the family history of thrombosis wasn’t documented. In cases, 270 (27.9%) women had a positive 1st degree family history of VTE.

Environmental risk factors for VTE

Cases were more frequently smokers than controls (32.5% vs 25.6%, p=0.001), and the association of smoking with VTE was not different (p=0.48) according to COC generations (Suppl. Table 1, available online at www.thrombosis-online.com). A trend towards an increased risk of VTE was observed according to the number of cigarettes (cig) smoked per day (cig/day): crude OR=1.13 (0.89–1.44) for 1 to 14 cig/day; OR=1.55 (1.10–2.21) for 15 to 24 cig/day; OR=1.99 (0.62–7.49) for 25 to 34 cig/day; OR=3.48 (0.84–23.44) for 35 cig/day or more (p for trend<10⁻⁴) when grouping 25 to 34 cig/day and >34 cig/day). BMI was significantly higher in cases than in controls (MD=1.64 (1.21–2.07), p<10⁻⁴) as was the percentage of women with BMI≥35 kg.m⁻² (5.0% vs 1.7%, p=0.0001). A trend towards an increased risk of VTE was observed according to the class of obesity: crude OR=1.51 (1.16–1.97) for pre-obesity, OR=2.67 (1.72–4.24) for mild obesity and OR=3.51 (1.97–6.66) for severe obesity (p for trend<10⁻⁴).

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Inherited thrombophilia and VTE

Two hundred forty-six (25.4 %) cases had an inherited thrombophilia compared to 183 (20.9 %) in controls (p=0.03) (Table 1); the effect being similar across the different COC generations (p for homogeneity=0.43, Suppl. Table 1, available online at www.thrombosis-online.com). Only PC deficiency and combinations of defects were significantly higher in cases than in controls (2.5 % vs 0.9 %, p=0.01 and 2.5 % vs 0.8 %, p=0.005, respectively) (Table 2). As a consequence, only severe thrombophilia was higher in cases than in controls (7.0 vs 3.5 %, p=0.0009). Besides, non-O blood groups were more prevalent in cases than in controls (Table 1), whatever the COC generation (p for homogeneity=0.73, Suppl. Table 1, available online at www.thrombosis-online.com). The effect of non-O blood groups was similar according to the presence of an inherited thrombophilia (OR: 1.77 [1.40–2.24], 2.86 [1.69–4.90] and 1.61 [0.57–4.43] for individuals without, with moderate- or severe thrombophilia, respectively).

In a multivariate analysis (Table 3), BMI≥35 kg.m⁻² (OR=3.46 [1.81–7.03]) and smoking (OR=1.65 [1.30–2.10]) remained significantly associated with the risk of VTE after adjustment for age, type and duration of COC, and the family history score. Significant genetic risk factors for VTE were severe thrombophilia (OR=2.13 [1.32–3.51]) and non-O blood groups (OR=1.98 [1.57–2.49]).

DVT vs PE

An univariate analysis (Suppl. Table 2, available online at www.thrombosis-online.com) was conducted according to the severity of the episode. The duration of COC was shorter in individuals with PE compared to those with DVT only (MD=1.36 [0.22–2.51], p=0.02). During the first 12 months of COC use, the percentage of VTE event was higher for PE than for DVT (34.9 % vs 18.6 %, p<10⁻⁴). The frequency of the FVL mutation was lower in PE women compared to DVT (6.1 % vs 13.9 %, p=0.002) (Suppl. Table 1).
Discussion

We conducted a case-control study in a large cohort of women using COC. Smoking, BMI, severe thrombophilia and ABO blood group were independently associated with the risk of VTE. We also confirmed, even assessing it by a family history score, that family history poorly predicts the presence of an inherited thrombophilia. In our group of women with VTE, following the RCOG recommendations for COC use would have putatively prevented 47% of VTE episodes.

Regarding environmental risk factors, BMI and smoking were both associated with an increased risk of VTE. Until now, smoking remained a controversial risk factor for VTE (18, 19). We confirmed that current smoking is associated with an increased risk of VTE in COC users and this risk increased according to the number of cigarettes smoked per day. In multivariate analysis, current smokers had a 1.65 increased risk of VT as compared to ever or ex smokers. This effect was similar in the different COC

Table 3: Risk factors for VTE in COC users derived from a multivariate model.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>VTE patients (n=893)</th>
<th>Controls (n=763)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥ 35 kg.m²</td>
<td>45 (5.0)</td>
<td>13 (1.7)</td>
<td>3.46 (1.81–7.03)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Current smokers</td>
<td>386 (32.0)</td>
<td>194 (25.4)</td>
<td>1.65 (1.30–2.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe thrombophilia</td>
<td>63 (7.1)</td>
<td>29 (3.8)</td>
<td>2.13 (1.32–3.51)</td>
<td>0.003</td>
</tr>
<tr>
<td>Non-O blood groups</td>
<td>680 (76.1)</td>
<td>483 (63.3)</td>
<td>1.98 (1.57–2.49)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Shown data are counts (%). Odds ratio were adjusted for age, type and duration of COC use, and the family history score.
generations. Severe obesity (BMI ≥ 35 kg m⁻²) was found to be associated with a 3.46 increased risk of VTE which is in line with previous findings in women (29). As for smoking, a trend towards an increased risk of VTE according to BMI was observed.

Inherited thrombophilia in asymptomatic individuals in all published recommendations is considered as a contraindication. However, specific studies on the impact of the main congenital thrombophilia defects and the risk of VTE in COC users are sparse and based on a relatively small number of individuals (20).

A much larger one has been recently published but severe thrombophilia defects were not reported (30). In the present study, we have used controls presenting a family history of thrombosis (first- and second-degree relatives, venous or arterial thrombosis). This mode of recruitment putatively enriched this group in genetic risk factors. This hypothesis is highlighted by the high prevalence of FVL, PTG20210A and non-O blood groups which was higher than expected in the general population from Marseille area (10.8% vs 4.3%, 6.8% vs 3.0% and 62.6% vs 56.0% for the prevalence of the three factors in PILGRIM controls and healthy women from Marseille area, respectively). Very interestingly, even with the use of this enriched population as controls, inherited thrombophilia was more frequent in cases. This difference was driven by severe thrombophilia, and mainly PC deficiency and combinations of defects, that explained the greater part of the difference in the thrombophilia testing whereas the prevalence of moderate thrombophilia (heterozygous FVL or PTG20210A) was similar between the two groups.

The prevalence of non-O blood groups was higher in cases than in controls, this effect being observed in all COC generations. This challenges conventional thoughts on genetic screening for thrombophilia, which presently does not include ABO blood type. The magnitude of effect of non-O blood group of VTE was in line with previous findings (31) and similar to smoking (respective ORs: 1.98 and 1.65, respectively). Inherited thrombophilia screening mention in the recommendations published so far does not include assessment of ABO blood group. The present result suggests the importance of the use of ABO blood group to select adequate contraception in women.

The severity of VTE in COC users might differ with the type of thrombophilia. Individuals with DVT are more likely to carry the FVL mutation than PE patients. This differential effect of FVL is known as the FVL paradox (32). We demonstrated that this FVL paradox also holds in COC users. By contrast, individuals with PE are more likely to carry the PTG20210A mutation or to have an AT deficiency than those with DVT. Although statistically significant, these two last results need to be confirmed in other studies. The difference of PE and DVT risk according to thrombophilia in COC users, if confirmed, might be taken into consideration as the outcome of PE and DVT is not similar.

We evaluated what could have been the impact of RCOG recommendations (if they have been applied) for the prevention of VTE in women on COC. We demonstrated that proper use of the clinical risk factors included in RCOG recommendations and which are considered not to recommend COC may have prevented 27.5% of VT events. Since the French crisis on COC prescriptions (6), we can expect a better compliance with recommendations and thus a decreased risk of VTE associated with COC use (6). The presence of asymptomatic thrombophilia is also a contraindication of COC in all international recommendations. When adopting a maximalist screening strategy for thrombophilia, by testing all women before the beginning of contraception, we could have theoretically prevented 186 more episodes, for a total of 452 women, i.e. 46.7% of cases. The fact that severe thrombophilia was found associated with the risk of VTE in the present study should not be taken as a justification to recommend thrombophilia screening in all women before prescribing COCs, as most international gynecologic guidelines do so (15, 17). Indeed such a strategy is not cost effective (20). Moreover, in the present study, 74.6% of women with a VTE event had no inherited thrombophilia and 20.9% of women who were free of VTE event had a positive thrombophilia screening.

As a consequence systematic thrombophilia screening is not recommended but usually restricted to individuals with a family history of VTE (30). However, we confirmed by using a much larger sample of VTE individuals and different manners of quantifying this VTE history the results of Cosmi et al. indicating that family history poorly predicts the presence of inherited thrombophilia (22). Indeed, only the family history score was associated with inherited thrombophilia with a trend towards an increase in prevalence according to the increase of the score. This score improves the specificity of family history for the thrombophilia screening but its sensitivity remains very low (sensitivity = 12%.

### Table 4: Distribution of thrombophilia and ABO blood group according to family history in VTE patients.

<table>
<thead>
<tr>
<th>Family history</th>
<th>P-value</th>
<th>Family history &lt;45 years</th>
<th>P-value</th>
<th>Family history score</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=270)</td>
<td>No (n=698)</td>
<td>0.09</td>
<td>Yes (n=113)</td>
<td>No (n=855)</td>
</tr>
<tr>
<td>Inherited thrombophilia</td>
<td>79 (29.3)</td>
<td>167 (23.9)</td>
<td></td>
<td>31 (27.4)</td>
<td>215 (25.1)</td>
</tr>
<tr>
<td>Moderate thrombophilia</td>
<td>58 (21.5)</td>
<td>120 (17.2)</td>
<td>0.12</td>
<td>22 (19.5)</td>
<td>156 (18.2)</td>
</tr>
<tr>
<td>Severe thrombophilia</td>
<td>21 (7.8)</td>
<td>47 (6.7)</td>
<td>0.57</td>
<td>9 (8.0)</td>
<td>59 (6.9)</td>
</tr>
<tr>
<td>Non-O blood group</td>
<td>206 (78.0)</td>
<td>522 (75.5)</td>
<td>0.42</td>
<td>90 (79.6)</td>
<td>638 (75.8)</td>
</tr>
</tbody>
</table>

(Note: Data available for 955 patients.)
What is known about this topic?
- International recommendations are against the use of COC in heavy smokers and obese women; however, the impact on the risk of venous thrombosis of these two factors are still debated in COC users.
- ABO blood group is a risk factor of venous thrombosis; however, its impact on the risk of VTE in COC users has not been specifically studied yet.
- Family history of venous thrombosis is believed to predict poorly the presence of a heritable thrombophilia.

What does this paper add?
- BMI and smoking were both associated with venous thrombosis risk in COC users in a dose-dependent manner.
- Non-O blood group is associated with the risk of venous thrombosis in COC users. The risk of venous thrombosis is of similar magnitude to that previously published in other settings.
- Using a family history score, we confirmed that family history of venous thrombosis is a poor predictor of the presence of inherited thrombophilia.

specifcity = 92%). This confirms that even if there is a significant correlation between family history of VTE and the presence of inhereted thrombophilia, one can not consider the approach based on the presence of a family history to perform thrombophilia screening as satisfactory.

These results maintain the question open as whom women might be screened for thrombophilia before COC use. Basing this strategy on women with a 1£ droe degree family history of VTE would have missed 182 (19.2%) of women with inherited thrombophilia of whom 54 (29.7%) had severe thrombophilia. In any case, even if we had performed a thrombophilia screening in all women we might have prevented only 50% of VTE. This confirms that additional factors causing VTE are still unknown and need to be identified.

The present study suffers from several limitations. Among them, the retrospective design and the mode of recruitment which has enriched the control group in genetic risk factors render impossible the extrapolation of the results in the general population. However, it allows us to show that women with a personal history of VTE under COC more often present a severe thrombophilia than women under COC with no personal event but with a family history of VTE whereas this is not the case for FVL or PTG20210A heterozygosity which could be rule out on the basis of the family history of VTE whereas this is not the case for FVL or PTG20210A heterozygosity. In any case, even if we had performed a thrombophilia screening in all women we might have prevented only 50% of VTE. This confirms that additional factors causing VTE are still unknown and need to be identified.

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In conclusion, this study confirms the influence of smoking and obesity and shows for the first time the impact of ABO blood group on the risk of VTE in women under COC. It also confirms the inaccuracy of the family history of VTE to detect inherited thrombophilia.

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Conflicts of interest
None declared.

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