Clinical and Applied Thrombosis/Hemostasis
2018, Vol. 24(5) 797-802

DOI: 10.1177/1076029617727857
journals.sagepub.com/home/cat
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Analysis of Risk Factors of Stroke and Venous Thromboembolism in Females With Oral Contraceptives Use

Petr Dulicek, MD, PhD[1], Eva Ivanova, MD[1], Milan Kostal, MD, PhD[1], Petr Sadilek, MA, PhD[1], Martin Beranek, MPharm, PhD[2], Pavel Zak, MD, PhD[1], and Jana Hirmerova, MD, PhD[3,4]

Abstract

Thrombotic diathesis has been a well-known complication of oral contraceptive use for more than 50 years. This is true not only for venous thrombosis but also for an arterial one. The etiology is usually multifactorial and depends on several additional risk factors. We analyzed the prevalence of inherited and acquired thrombophilia in a cohort of 770 females who had a thrombotic event in association with oral contraceptive use (700 women with venous thromboembolism [VTE], 70 with stroke). Moreover, we tried to identify additional risk factors. Inherited thrombophilia was found in 44.5% with higher frequency in the cohort with VTE (42%) than in females with stroke (24%). The most frequent finding was factor V Leiden. Cigarette smoking was significantly more frequent in the group with stroke (50% vs 25%). The prevalence of cigarette smoking in the group with VTE did not exceed the frequency in general population. Women on oral contraceptive pills have higher risk of venous as well as arterial thrombosis. The risk of venous thrombosis is increased in females with inherited thrombophilia, whereas those with some additional acquired risk factors (especially smoking) may be predisposed to arterial thrombosis. However, the absolute risk of thrombosis in healthy women is low, far less than the risk of unintended pregnancy. Moreover, the risk may be reduced by keeping some rules before the prescription of the pills, healthy life style, and a proper choice of contraception.

Keywords

stroke, venous thromboembolism, hormonal contraceptive pills, thrombophilia, smoking

Introduction

Venous thromboembolism (VTE) is a multifactorial disease. Incidence of VTE is 1-2/10 000 in the age category below 45 years.[1] The frequency of inherited thrombophilia is 5% to 8% in our country, and approximately 35% of Czech females in reproductive age are taking oral contraceptive (OC), a very popular and efficacious type of contraception. Among users, combined OC (COC) highly prevails. Combined OCs prevent not only unwanted pregnancy but also confer noncontraceptive benefits, including treatment of heavy menstrual bleeding, menstrual cycle irregularity, premenstrual syndrome, perimenopausal vasomotor symptoms, and hirsutism or acne.[2] Since their introduction in the 1960s, an increased risk of VTE has been associated with COCs: a 3-fold to 6-fold risk of venous thrombosis is reported in epidemiological studies.[3]

The absolute risk, however, remains low, that is, a baseline risk of about 2 cases per 10 000 woman-years may be increased to 12 cases per 10 000 woman-years in COC users.[4]

The risk of VTE depends on many factors: the duration of COC use, body mass index (BMI), the type of pill, the age of users, the presence of either inherited or acquired thrombophilia, or an exposure to the additional risk factor (RF).

Arterial thrombotic events (ATEs), such as ischemic stroke, transient ischemic attack (TIA), or myocardial infarction (MI), are other examples of COC adverse effects, fortunately less common. Risk of ischemic stroke is increased 2 to 3 times and is even higher in the presence of additional RFs such as arterial hypertension (AH)—8-fold, smoking—4-fold, and hypercholesterolemia—11-fold.[5] The absolute risk of ischemic stroke is 21.4/100 000 and that of MI 10/100 000.[6]

[1] 4th Department of Internal Medicine and Hematology, University Hospital and Medical Faculty in Hradec Kralove, Hradec Kralove, Czech Republic
[2] Department of Clinical Biochemistry, University Hospital and Medical Faculty in Hradec Kralove, Hradec Kralove, Czech Republic
[3] 2nd Department of Internal Medicine, Charles University Medical Faculty in Pilsen, Pilsen, Czech Republic
[4] Biomedical Centre, Charles University Medical Faculty in Pilsen, Pilsen, Czech Republic

Corresponding Author:
Jana Hirmerova, 2nd Department of Internal Medicine, Charles University Medical Faculty in Pilsen, Dr. E. Benese 13, 305 99 Pilsen, Czech Republic.
Email: hirmerova@fnplzen.cz

The risk of ATE depends on the type of contraception—the content of ethinyl estradiol, respectively; the age of a user; BMI; the presence of acquired RFs—smoking, diabetes mellitus (DM), and hypercholesterolemia; and some acquired thrombophilic disorders—hyperhomocysteinemia and antiphospholipid syndrome (APS), but not on the duration of COC use. Noteworthy, cigarette smoking is a very frequent habit in Czech population. Almost 25% of Czech women are regular smokers. Approximately half of them belong to heavy smoker category (≥20 cigarettes daily).

Cerebral vein thrombosis (CVT) is a very special type of stroke and represents only 0.5% to 1% of all strokes. It is characterized by the most prominent gender difference in incidence rates.[7] In adulthood, the majority of affected individuals are women, who represent >70% of cases in most studies.[8,9]

The aim of the study was to analyze:

- the frequency of inherited or acquired thrombophilia in the cohort of 70 females with stroke (ischemic stroke, TIA, and CVT) and in the cohort of 700 females with VTE in association with COCs,
- the age of thrombosis onset and the duration of COC use prior to an event, and
- the assessment of additional RFs, especially the role of smoking in respective types of thrombotic events.

Patients and Methods

We assessed 2 cohorts—70 females with stroke and 700 females with VTE. All women were recruited in the period 1997 to 2014 and most of them came from the eastern part of the Czech Republic. The participants provided a written informed consent.

All women had been COC users (none used progestin-only pills or an intrauterine system with levonorgestrel [IUS-LNG]). We obtained a family and personal history of thrombosis and information about their smoking habits.

The females with stroke had been examined with a computed tomography (CT) scan. Venous thromboembolism had been objectively confirmed by venous compression ultrasound (in the case of deep vein thrombosis) and perfusion/ventilation lung scan or/and helical CT pulmonary angiography (in the case of pulmonary embolism). Laboratory work-up included the assays of protein C; protein S; antithrombin (AT); factor V Leiden (FVL), prothrombin gene mutation (ie F II G20210A mutation); APS diagnostics—lupus anticoagulants (LAs), anticardiolipin antibodies (ACLA) and anti-β-2-glycoprotein I antibodies; and homocysteine level.

We planned thrombophilia work-up with regard to appropriate time of testing, to exclude potential influence of acute thrombosis, anticoagulation therapy and persisting effect of COC. For this reason, some laboratory tests were performed during anticoagulation therapy, and some had to be postponed after the cessation. Blood samples were collected by venipuncture into plastic tubes containing either 1/10 volume of 3.8% sodium citrate for coagulation assays or 1/10 volume of 0.5 mol/L sodium ethylenediaminetetraacetic acid for DNA extraction. Then, the samples underwent centrifugation (15 minutes at 2500 g) for prothrombin time (PT), activated partial thromboplastin time (aPTT), and AT assays or double centrifugation (10 minutes at 1500 g) for protein C, protein S, and LA assays. After centrifugation plasma was used either immediately for PT, aPTT, and LA or stored at −70°C until analyzed (AT, protein C, and protein S). Protein C was determined by a coagulation assay using Staclot Protein C (STAGO D, Asnières, France; normal value, 70%-130%). In the case of low protein C value, a second test from a new blood sample was carried out, and moreover, antigen of protein C was determined by the Asserachrom protein C kit (STAGO D; normal value, 70%-140%). Staclot Protein S kit (STAGO; normal value 65%-140%) was used for determination of protein S, and again in the case of a low value, the antigen of total protein S and free protein S was evaluated from the second sample by the Asserachrom protein S kit (STAGO D; normal value of total protein S antigen 70%-140%, normal value of free protein S antigen 70%-130%). Antithrombin was determined by chromogenic assay, we used the Stachrom AT kit (STAGO D; normal value 80%-120%). The normal range of levels for protein C, protein S, and AT was obtained by examination of 100 healthy individuals (50 men, 50 women) from our region, and normal values were compared with the normal range recommended by the manufactures. The diagnosis of protein C, protein S, or AT deficiency was accepted only after multiple testing. The diagnostics of APS included LA panel and immunologic assays. To detect LA, following screening assays were performed: aPTT, PTT Automate (STAGO D); aPTT with high sensitivity to LA, PTT-LA (STAGO D); tissue thromboplastin inhibition test; and diluted Russell Viper Venom Time. If one of these tests was positive, the second determination was performed 6 to 8 weeks later and the test with hexagonal phospholipids (Staclot LA, STAGO D) was carried out for confirmation. A solid-phase immunoassay technique was used to quantify the levels of ACLA and anti-β-2-glycoprotein I antibodies. Both antibodies were tested against the international standard in IgG and IgM isotypes. The polymerase chain reaction was used for FVL and F IIG20210A detection. Level of homocysteine was determined immunochemically after l2-hour fasting (normal range: 12.5-17 mmol/L) in an analyzer (DPC Immulite 2000, Siemens). Normal range for homocysteine was obtained by examining 100 healthy individuals (50 men, 50 women) from our region, and normal values were also compared with normal range recommended by the manufactures.

Results

Characteristics of Both Cohorts

Mean age of patients was 29 years in the stroke group and 26 years in the VTE group. Mean duration of COC use was 48 months and 45 months, respectively.

Table 1. Summary of Results in the Female Cohort With Stroke and COC Use.

Stroke	No. of Events: 70	No. of Thrombophilic Disorders: 20 (28.6%)	Inherited/Acquired
Ischemic stroke	13	3	½ F II 20210/APS
TIA	17	2	2/0 FVL
CVT	40	15	14/1 9× FVL 4× F II 20210 1× combined/MPD

Abbreviations: APS, antiphospholipid syndrome; COC, combined oral contraceptives; CVT, cerebral vein thrombosis; FVL, factor V Leiden; MPD, myeloproliferative disease; TIA, transient ischemic event.

The Cohort of Females With Stroke

In this group, 13 females had an ischemic stroke, 17 had TIA, and 40 women had been diagnosed with CVT. In the group of CVTs, in most cases, multiple sinuses had been affected (75% of cases). In the rest of the group, isolated thrombosis in sinus sagittalis superior had been found. At the time of thrombosis, none woman was on thromboprophylaxis with low-molecular-weight heparin (LMWH).

Thrombophilia was revealed in 20 (29%) patients —17 (24%) of detected disorders were inherited—FVL in 11 women, F II G20210A in 5, and combined FVL with F II G20210A mutation in 1 case. Acquired thrombophilia was identified in 3 patients (APS in 2 women, and in 1 case incipient/early stage of polycythemia vera, with JAK-2 kinase positivity). Results are summarized in Table 1.

Concerning smoking, all 13 females with ischemic strokes were smokers (7 of them were heavy smokers) and 75% of females with TIA also smoked. Among females with CVT, 10 were smokers. In 3 of them, additional RFs were identified (colitis ulcerosa, corticosteroid use, and surgery). Other RFs were quite rare in this cohort (diabetes, AH, dyslipidemia by 1 case, and all 3 cases in females with an ischemic stroke).

The Cohort of Females With VTE

Of 700 VTE cases, 385 (55%) were considered spontaneous (ie without any additional trigger), whereas 315 patients reported various provoking factors (long travel, immobilization, surgery, arthroscopy, plaster cast, calf injury, or strenuous sport activity). At the time of VTE onset, none of women had been on thromboprophylaxis with LMWH.

In the whole VTE group, 313 women (44.7%) were diagnosed with thrombophilia (inherited thrombophilia and APS, respectively). The prevalence of thrombophilia was significantly higher in the subgroup of females with spontaneous VTE in comparison with the subgroup of provoked VTE (56.3% vs 30.4%, $P < .0001$). Of detected inherited hypercoagulable disorders, FVL highly prevailed. On the other hand, hyperhomocysteinemia was not found in any case. In 20 women, we revealed combined thrombophilia, mostly FVL + APS (in 10 females). The frequency of respective types of thrombophilia, diagnosed in the VTE group, is shown in Table 2.

Table 2. Frequency of Respective Types of Thrombophilia in Female COC Users With VTE.[a]

Type of Thrombophilia	n (%)
F V Leiden mutation—overall	210 (30.0)
Heterozygous trait	195
Homozygous trait	15
FII 20210A	34 (4.9)
APS	24 (3.4)
Protein C deficiency	6 (0.9)
Antitrombin deficiency	13 (1.9)
Protein S deficiency	6 (0.9)
FVL + APS	10 (1.4)
Other combinations	10 (1.4)

Abbreviations: APS, antiphospholipid syndrome; COC, combined oral contraceptives; FVL, factor V Leiden; VTE, venous thromboembolism.
[a]n = 700.

Table 3. The Type of VTE and Frequency of Inherited Thrombophilia in the Subgroup of Female COC Users With Spontaneous VTE.[a]

Type of VTE	N = 385	No. of Women Diagnosed With Thrombophilia	% of Respective Group
Distal (calf) DVT	211	118	55.9
Proximal DVT	63	44	69.8
DVT + PE	56	30	53.6
PE	28	13	46.4
VTE at unusual site	27	12	44.4

Abbreviations: COC, combined oral contraceptives; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]N = 385 (55% of the cohort with VTE).

Concerning VTE at unusual site, 22 women had splanchnic vein thrombosis. In 20 cases, Budd-Chiari syndrome had been diagnosed with JAK-2 kinase positivity in half of them. Two females had portal vein thrombosis, in first case AT deficiency was detected, in the second case FVL in a homozygous trait. In 5 cases, thrombosis had affected the veins of upper extremity. The type of VTE and prevalence of inherited thrombophilia and APS in females with spontaneous and provoked events are shown in Tables 3 and 4.

Distal location of thrombosis in the subgroup of females with spontaneous events was less frequent than in the subgroup with events provoked by a transient RF; however, the difference did not reach statistical significance ($P = .0667$). On the other hand, the frequency of PE and thrombosis at unusual site was much lower in provoked cases.

Regarding smoking, 25% of females with VTE mentioned regular smoking, but only 3% of them could be considered heavy smokers.

Table 4. The Type of VTE and Prevalence of Thrombophilia in the Subgroup of Female COC Users With Provoked VTE.[a]

Type of VTE	N = 315	No. of Women Diagnosed With Thrombophilia	% of Respective Group
Distal (calf) DVT	194	60	30.9
Proximal DVT	49	17	34.7
DVT + PE	54	17	34.0
PE	9	1	11.1
Thrombosis at unusual site	9	1	11.1

Abbreviations: COC, combined oral contraceptives; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]N = 315 (45% of the cohort with VTE).

Discussion

We have analyzed the types of thrombotic events and their RFs in 2 cohorts of female COC users—70 women with stroke and 700 women with VTE. Different sizes of both cohorts correspond with the incidence of these events in association with COCs. Etiopathophysiology of these 2 types of thrombosis is different and so the frequency of inherited and acquired RFs is also different. Inherited thrombophilia was significantly more prevalent in the subgroup with VTE (42% vs 24%, respectively). Factor V Leiden was the most frequent hypercoagulable disorder in both cohorts. We explain this finding by the fact that this mutation is the most frequent inherited thrombophilia in our country (with the prevalence of 5% in general population). In women with stroke, even with CVT, we did not find any case of deficiency of natural coagulation inhibitors (eg protein C, protein S, and AT). The cases of CVT prevailed in comparison to ischemic stroke and TIA, and women with CVT had a higher frequency of F II 20210A mutation, in concordance with another study.[10]

The number of ischemic strokes was small. According to the literature data, stroke in young adults is infrequent (6.1% of all strokes) but represents the highest frequency of cerebral infarctions of unusual etiology (36%).[11] In our cohort, all females with ischemic strokes had at least 1 additional RF. All were smokers (7 of them heavy smokers), in 2 women APS was detected and 3 females had either DM or dyslipidemia or AH. Hyperhomocysteinemia was not detected in any cohort, which was surprising finding.

According to epidemiologic data, the relative risk of VTE is highest in the first 3 months of COC use (13-fold increase at the most).[12] The increased risk persists in the first year of use, mainly in the first 6 months, further goes down.[13,14] However, we have not observed this fact, mean time of duration of COC use prior to thrombosis onset was much longer than 1 year and comparable in both of our cohorts. Mean age at the time of an event was also similar in both cohorts (29 years in stroke and 26 years in VTE).

If we compare additional RFs in the 2 cohorts, traditional provoking factors for VTE (like immobility) were not found in the group with stroke.[15] On the other hand, smoking and even heavy smoking was significantly more frequent in females with stroke, while in the cohort with VTE smoking did not exceed the frequency in normal Czech female population. It corresponds with the literature data—in a meta-analysis, cigarette smoking was an independent RF for stroke in young adults (odds ratio: 4.23; 95% confidence interval: 3.02-5.93).[16]

We are aware of some shortcomings of our analysis. First, the cohort of women with stroke is quite heterogeneous. We decided to include CVT to this group, though many authors consider CVT as VTE at unusual site. However, the others mention CVT as an uncommon form of stroke, usually affecting young individuals.[17] Moreover, in the Czech Republic, patients with CVT are treated by neurologists. Second, we have not evaluated the role of obesity. Obesity is associated with an increased risk of thrombosis, with 5-fold higher relative risk of VTE in persons with BMI >25 kg/m2 and 10-fold higher risk with BMI >30.[18] Unfortunately, we do not have these data available for all women so we cannot comment contribution of this factor. Third, we also cannot assess exactly the differential influence of various types of COC because this information is available only for 75% of females. Results of meta-analyses of clinical trials, comparing the risk of VTE between the second and the third generation of COC proved 1.7-fold increased risk for users of the third generation and even 3-fold increased risk in the first time users.[19,20] The risk of stroke also depends on the type of contraceptive pill. With lower content of estrogen, the risk of ischemic stroke is also lower.[21]

We have not found any case of thrombotic event in females with an IUS-LNG—Mirena or Jaydess, which is reported as safe in terms of risk of thrombosis.[22-24] The same is true for progestin-only pills. They do not raise risks of VTE, ischemic stroke, or MI.[25,26]

We have not analyzed MI because during the time of recruitment we had found only 1 woman with the history of this event. She was a heavy smoker and APS was detected as well. This complication is less frequent than stroke in COC users.6,26

Most of our results are in concordance with other studies, but some of them are different. Hyperhomocysteinemia has been reported as additional RF for ischemic stroke in COC users[27]; however, we have not detected any single case of increased homocysteine level in our cohorts. Deficiency of natural coagulation inhibitors have not been found in the group of females with CVT.

Finally, we tried to summarize the rules how to minimalize the risk of thrombosis in association with COCs. Both parts (physicians and females) should play a role in this process.

Doctor has to:

- take a family and personal history of thrombosis and then assess additional RFs,
- provide information about symptoms of thrombotic event (stroke, MI, and VTE), and
- advice to use thromboprophylaxis with LMWH in the presence of an additional transient RF for VTE.

However, routine (unselective) screening for thrombophilia prior to the initiation of hormonal contraception is not useful (it

is not cost-effective, respectively). The most frequent finding is FVL and in most cases this finding does not have any consequence.

Women should:

- be familiar with family history of thrombosis properly,
- avoid smoking,
- keep BMI within a normal range, and
- visit a doctor in presence of first potential symptoms of thrombosis.

However, it is possible to eliminate the risk with introduction of IUS-LNG.

Conclusions

More than 100 million of women take COCs worldwide. It is a very popular and efficacious type of contraception. The COCs contribute not only to the risk of VTE but also to the risk of ATE in females in reproductive age. The etiology of thrombosis is multifactorial. In our group of female COC users, thrombophilia was found in 43.2% with higher frequency in the cohort with VTE (44.7%) than in females with stroke (28.6%). Cigarette smoking was significantly more frequent in the group with stroke than in the group with VTE (50% vs 25%, respectively). The absolute risk of thrombosis in healthy women with COC is low, far less than the risk of unintended pregnancy. The risk of thrombosis may be reduced by keeping some rules before the prescription of COCs, healthy life style, and a proper choice of contraception.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Charles University Research Fund (project number P37/08).

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