Combined oral contraceptives and the risk of venous thromboembolism carriers of antithrombin, protein C or S deficiency: Sub-analysis of a prospective cohort study

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ABSTRACT

Antithrombin, protein C and S defects are well-recognized inherited risk factors for venous thromboembolism (VTE). Although these defects have been reported to increase the risk of VTE in fertile women under combined oral contraceptives (COCs), the magnitude of this association is uncertain. In a sub-analysis of a prospective cohort study, we evaluated the incidence of VTE occurring during treatment with COCs in fertile women who were family members of a proband with an objectively diagnosed VTE event and a documented defect of antithrombin, protein C or S. Of the 197 women of child-bearing age from 88 families who qualified for this analysis in a 17-year period, 112 (57%) were carriers of an inherited defect (23 antithrombin, 41 protein C and 48 protein S), whereas the remaining 85 were free from these abnormalities. Estrogen-progestin therapy was used by 19 of the 112 (17%) carriers of inherited thrombophilia for an overall period of 276 months, and by 17 of the 85 (20%) non-carriers for an overall period of 992 months. VTE events developed in 12 of the 19 (63%) carriers, leading to a monthly event rate of 4.3% (95% CI: 2.2 to 7.6), and in 2 of the 17 (12%) non-carriers, leading to a monthly rate of 0.2% (95% CI: 0.02 to 0.7), for a relative risk of 21 (95% CI, 4.7 to 92). Among family members of probands with inherited defects of antithrombin, protein C or S defects, the use of estrogen-progestin therapy in carriers of these abnormalities results in a risk of VTE events that is more than 20 times as high as that expected in non-carriers. Accordingly, the systematic screening for thrombophilia in these families has the potential to identify those subjects in whom this kind of hormonal treatment should be strongly discouraged.

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INTRODUCTION

Since the 1960s, inherited coagulation disorders have been identified which predispose to a greater risk of developing thrombotic events. This predisposition was summarized in the term thrombophilia. Women carrying these thrombophilic conditions are expected to develop thrombotic events at a younger age than males, especially during pregnancy and estroprogestinic treatment.

It has been shown that the use of combined oral contraceptives (COCs), containing a combination of ethinylestradiol and progestagen, increases the risk of developing thrombotic events in women using them compared with non-users.[1-3] Although the amount of estrogens contained in these preparations has substantially decreased in recent years, the thrombotic risk associated with the use of COCs has not diminished accordingly, mainly due to the current use of progestin components (such as gestodene, desogestrel or drospirenone) that are far more thrombogenic than those (such as levonorgestrel) used in the past, or to the use of alternative routes of administration (transdermal or via vaginal ring).

Women who are carriers of major thrombophilic defects, such as the deficiency of antithrombin (AT), protein C (PC) or protein S (PS) have been repeatedly shown to exhibit a higher thrombotic risk than non-carriers during the administration of hormonal drugs.[4] However, although their use is generally discouraged, in clinical practice it is not infrequent to see young women who still use them.

In the framework of a prospective cohort study

launched in 1998 for assessing and quantifying the association of inherited deficiency of natural anticoagulants with the risk of spontaneous and risk related venous thromboembolism (VTE),[5] we had the opportunity to follow-up over time a considerable number of women in fertile age who were family members of probands with a defect of AT, PC or PS. We report here our experience on the risk associated with the use of the COCs in women with and without thrombophilia.

MATERIALS AND METHODS

Study subjects

All patients presenting to the Thrombosis Unit of the University-Hospital of Padua with a documented episode of VTE between April 1998 and October 2015 were screened for deficiencies of AT, PC, and PS. The presence of a deficiency was confirmed by testing the patients on two separate occasions. When possible, gene sequencing was also performed to identify the lesions responsible for the defects. Patients with a confirmed deficiency of AT, PC, or PS acted as probands. All women aged 15 to 50 years who were family members of index patients were retrieved and asked to participate in the study, provided they did not have active cancer, antiphospholipid antibody syndrome or previous VTE. A detailed medical history was obtained prior to the laboratory assessment of the deficiency status. Close attention was paid to the presence of cardiovascular risk factors such as hyperlipidemia, diabetes and smoking habit.

All consenting women were followed up until October 2017. Approval for this study was obtained from the local Ethical Committee at Padua University.

Study objective and design

The study objective was to assess the incidence of VTE complications in women in fertile age who were family members of probands with inherited deficiency of antithrombin, protein C or S defects while on combined estrogen-progestin therapy. To this purpose, women meeting the eligibility criteria were labelled as being or not carriers of these abnormalities and were followed up prospectively over time. The use of oral contraceptives was discouraged but not prohibited.

A follow-up was performed every 6 months, either by a visit to the study Center or by telephone contact. On each occasion, they were enquired about the use of hormonal therapy (type of drug, duration of its administration). In case of clinical signs or symptoms of thromboembolic events, they were instructed to undergo proper objective tests to confirm or rule out the clinical suspicion. Diagnosis of deep vein thrombosis of the lower or upper limbs was made by compression ultrasound, and that of pulmonary embolism was made by computed tomography pulmonary angiography or ventilation/perfusion lung scanning. Cerebral or splanchnic vein thromboses were diagnosed by a cerebral/abdominal angio-computed tomography scan or magnetic resonance.

Laboratory assays

Laboratory tests for AT, PC and PS were performed according to methods previously described.[6] The following reference values were considered: for AT antigen concentration, 70% to 120%; AT activity, 70% to 120%; PC antigen concentration, 65% to 130%; PC chromogenic or coagulometric activities, 65% to 130%; total PS antigen concentration, 60% to 120%; and free PS antigen concentration, 60% to 108%; protein S activity, 65 to 130%. DNA analyses for FVL and prothrombin variant G20210A and plasma homocysteine assay were performed using previously described methods.[6,7] The criteria used for the classification of the different types of AT, PC and PS defects were those previously reported.[6] Subjects who presented with the same defect in two consecutive laboratory determinations performed at an interval of at least one month were potentially carriers of an inherited defect. To confirm the inheritance, the same defect had to be present in at least one first-degree family member. Where possible, sequencing of AT, PC and PS genes was performed to identify the lesions responsible for the defects and confirm the hereditary pattern (40% of patients). In women under estrogen treatment or during pregnancy, blood samples were collected at least three months after withdrawal of hormonal treatment or delivery, respectively. In this study we included only quantitative defects. Type I defects (concomitant reduction of antigen and activity to about 50%) were considered for AT and PC deficiency and type I (concomitant reduction of total and free PS antigen and PS activity to about 40-50%) and type III defects (normal total PS antigen reduced free PS antigen and PS activity to about 40-50%) for PS deficiency.

Statistical analysis

The incidence of thromboembolic events occurring during the periods of hormonal therapy and its 95% CI was calculated in carriers and non-carriers of thrombophilia. The relative risk (RR) for the development of COC-related VTE was calculated by dividing the incidence rate of VTE in carriers by that found in non-carriers. Observation time was defined as the months of use of COCs from the beginning of use until the development of the first VTE or until the discontinuation of treatment. Kaplan-Meier survival analysis was conducted to compare VTE free survival for COCs users with and without thrombophilia. A log rank test was conducted to determine if there were differences in the VTE free survival distributions between groups.

RESULTS

Subjects and use of estrogen-progestin drugs

Out of approximately 2000 patients who were tested in the study period, 88 unrelated probands with an objectively documented VTE and a deficiency of AT, PC or PS were identified. Of the 205 eligible women of child-bearing age who belonged to these families, 197 gave their informed consent for participation in the study and were enquired for the presence of the same defects. Of them, 112 (57%) were carriers of an inherited defect, whereas the remaining 85 were not (Figure 1).

During the study period, 19 of the 112 (17%) carriers of inherited thrombophilia used estrogen-progestin preparations for an overall period of 276 months, compared with 17 of the 85 (20%) non-carriers for an overall period of 992 months. The mean age at the start of use of estrogen-progestogen therapy was 31 years in the carrier group and 39 years in the non-carrier group, respectively. All women included in the study had normal BMI, did not have cardiovascular risk factors.

Preparations containing cyproterone acetate, desogestrel, gestodene, drospirenone and etonogestrel were used in the two groups (Table 1). Most of the women included in the study used preparations with desogestrel and gestodene (14/19 in the carrier group and 13/17 in the non-carrier group).

The doses of ethinylestradiol present in the COCs used by the women included in the study ranged from 20 to 30 µg; these dosages were equally distributed within each observation group.

Table 1 also shows for each participant in the study, the data relating to the age at which estrogen-progestogen therapy was started, the months of use of the therapy and the months of exposure at the onset of the first VTE. The use of estrogen-progestogen therapy was continuous, and no women in the study discontinued and resumed therapy during the study period.

Incidence of combined oral contraceptives related VTE

VTE events developed in 12 of the 19 (63.2 %) carriers, leading to a monthly event rate of 4.3% (95% CI: 2.2 to 7.6), and in 2 of the 17 (11.8%) non-carriers, leading to a monthly rate of 0.2% (95% CI: 0.02 to 0.7), for a RR of 21 (95% CI, 4.7 to 92) (Table 2).

Carrier women developed the thrombotic event after an average of six months of combined oral contraceptive use versus nine months in the non-carrier group.

In both groups the thrombotic events occurred without

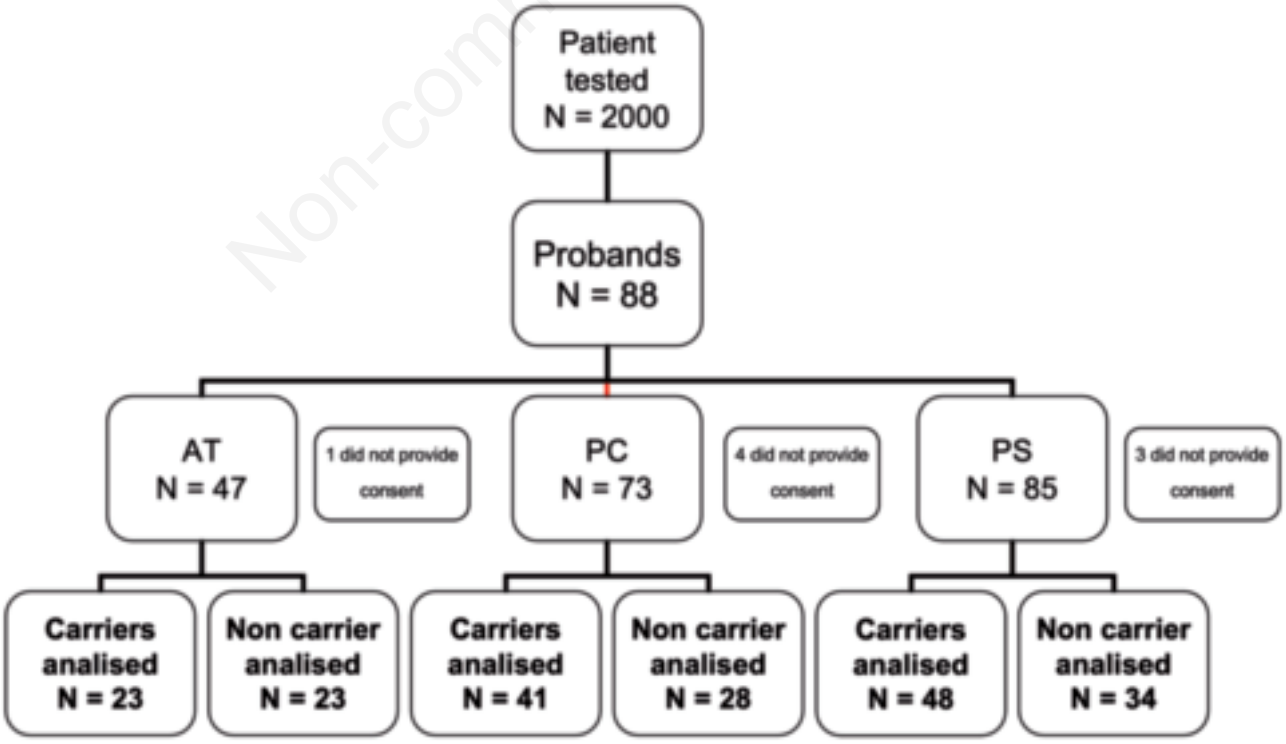

Figure 1. 88 unrelated patients with VTE and AT, PC or PS served as probands. 197 women (family members) of child-bearing age were enrolled. 112 out of 197 (57%) were carriers of an inherited defect and 85 were non-carriers.

other risk conditions for thrombosis such as surgery, plastercast/trauma or prolonged immobilization.

Of the 12 thrombotic events that occurred in carriers of inherited thrombophilia, 9 were isolated deep vein thrombosis (DVT) of the lower limbs, and 3 were DVT associated with pulmonary embolism (PE); the 2 events that occurred in non-carriers were isolated DVT (Table 1).

In Table 3, the incidence of COCs-related VTE is shown for each type of defect. The RR for VTE during COCs use in carriers as compared to non-carriers was 6.6 (95% CI, 1.0 to 47) for AT, 24.4 (95% CI, 4.8 to 124) for PC and 64 (95% CI, 13 to 318) for PS defects.

Figure 2 shows the VTE-free survival in carriers vs non-carriers of defects (Panel A) as well the VTE-free sur-

Table 1. Characteristics of women's relatives with and without AT, PC, PS deficiency. Exposure to COCs. VTE events.

Age at when starting to receive COCs	COCs type used at onset of VTE	Exposure months	Exposure months at first VTE	Type of VTE	Deficiency	Concomitant thrombophilic defects
20	Gestodene	6			AT	None
30	Desogestrel	120			AT	None
21	Gestodene	14	14	DVT	AT	None
20	Vaginal Ring	4			AT	None
40	Gestodene	1	1	DVT	AT	None
25	Drospirenone	72			NO	None
48	Gestodene	4	4	DVT	PC	None
42	Gestodene	4	4	DVT	PC	None
47	Gestodene	3	3	DVT + PE	PC	None
30	Desogestrel	8	8	DVT + PE	PC	None
40	Vaginal Ring	6	6	DVT	PC	None
20	Desogestrel	12			PC	None
38	Gestodene	24			PC	None
35	Gestodene	36			PC	None
28	Gestodene	36			NO	None
44	Gestodene	48			NO	None
36	Gestodene	8			NO	None
31	Gestodene	48			NO	None
34	Gestodene	12	12	DVT	NO	FVL
18	Ciproterone	12			NO	None
38	Desogestrel	12			NO	None
30	Drospirenone	2	2	DVT	PS	None
24	Gestodene	1	1	DVT	PS	G20210A PV
17	Drospirenone	1	1	DVT + PE	PS	None
20	Gestodene	4	4	DVT	PS	None
21	Ciproterone	14	14	DVT	PS	G20210A PV
43	Gestodene	12	12		PS	None
18	Desogestrel	180			NO	None
24	Desogestrel	72			NO	None
22	Vaginal Ring	6	6	DVT	NO	None
25	Ciproterone	48			NO	G20210A PV
22	Gestodene	36			NO	None
26	Gestodene	12			NO	None
18	Gestodene	180			NO	FVL
20	Desogestrel	30			NO	None
40	Desogestrel	180			NO	None

AT, antithrombin; PC, protein C; PS, protein S; COCs, combined oral contraceptives; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; FVL, Factor V Leiden.

vival according to the different type of defect (Panel B). The VTE-free survival distribution was statistically significant different (p=0.001 and p<0.001 respectively).

Figure 3 illustrates the incidence of thrombotic events and the RR related to the type of progestins used in combined oral contraceptive pills.

DISCUSSION

Despite the low incidence of venous thrombosis among women of reproductive age, the use of oral contraceptives and major inherited thrombophilic defects (*i.e.,* deficiency of antithrombin, protein C or protein S)

Table 2. Total cohort of women who have used COCs treatment and the risk of VTE.

	Carriers	Non-carriers
N women	19°	17*
Months of COCs treatment	272	992
Number of VTE	12°	2**
Proportion of pts with VTE	63.2% (95% CI, 33 to 110)	11.8% (95% CI, 1.4 to 42.5)
Incidence of VTE (%) per p/months of COCs	4.3% (95% CI, 2.2 to 7.6)	0.2% (95% CI, 0.02 to 0.7)
	RR 21 (95% CI, 4.7 to 92)	

*COCs, combined oral contraceptives; VTE, venous thromboembolism. °2 with G20210A prothrombin variant; * *2 with Factor V Leiden, 1 with G20210A prothrombin variant; **1 with Factor V Leiden.*

Table 3. Women who have used COCs treatment and the risk of VTE according to type of defect.

	AT	PC	PS	Non-carriers (N-C)
Number of women	5	8	6°	17*
Months of COCs treatment	148	97	34	992
Number of VTE	2	5	5°	2**
Incidence of VTE per % p/months of COCs		**RR (95% CI)**		
AT 1.4 (95% CI 0.16 to 4.8)		AT 6.6 (95% CI, 1.0 to 47)		
PC 5.2 (95% CI 1.7 to 12)		PC 24.4 (95% CI, 4.8 to 124)		
PS 15 (95% CI 5 to 34)		PS 64 (95% CI, 13 to 318)		
N-C 0.2 (95% CI, 0.03 to 0.7)				

*AT, antithrombin; PC, protein C; PS, protein S; COCs, combined oral contraceptives; VTE, venous thromboembolism. °2 with G20210A prothrombin variant; *2 with Factor V Leiden, 1 with G20210A prothrombin variant; **1 with Factor V Leiden.*

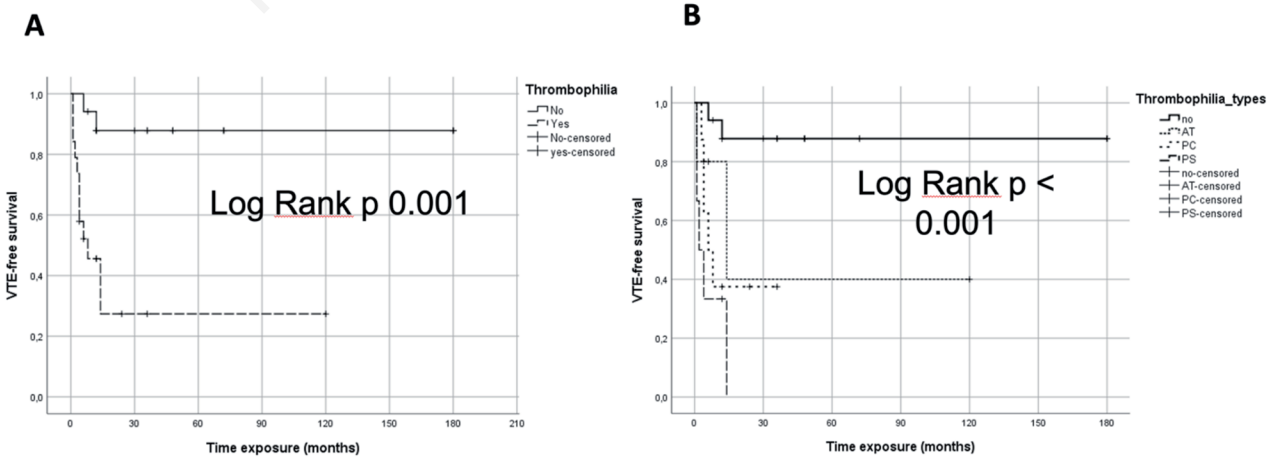

Figure 2. VTE-free survival in users of combined oral contraceptives with and without thrombophilia. A) VTE-free survival in patients with and without hereditary thrombophilia. B) VTE-free survival according to hereditary thrombophilia types.

interact synergistically to increase the thromboembolic risk. Although the use of contraceptive hormonal therapy is generally discouraged in carriers of these abnormalities, in clinical practice it is not infrequent to see women who use them. As we had the opportunity to follow-up over time a considerable number of women who were family members of probands with a deficiency in the natural anticoagulants, we could estimate and quantify the risk of COCs-related VTE through the comparison between carriers and non-carriers of these defects.

The rate of VTE events that was recorded during a follow-up of 276 and 992 months of COCs use in carriers and non-carriers, respectively, was considerably higher in the 19 carriers of these abnormalities, (4.3% patient-months) than in the 12 non-carriers (0.2% patient-months), leading to a RR for VTE of more than 20. The risk was similarly higher among users of pills containing desogestrel and gestodene (RR=26.6) and among users of pills containing drospirenone or cyproterone acetate (RR=20). All women developed the thrombotic event within approximately one year of COCs use, with an average of six months in the carrier group and nine months in the non-carrier group, suggesting that the thrombotic risk is to be expected earlier in the former than in the latter. Indeed, the use of estrogen-progestogen preparations is expected to further reduce the levels of coagulation inhibitors already genetically reduced.

The results of this prospective study are in line with those of our previous retrospective family cohort study, which showed an annual incidence of COCs-related VTE events of 4.3% and 0.7% in carriers and non-carriers, respectively.[6] These findings are consistent with those from a similar retrospective family cohort study, where VTE events were reported to occur almost ten times more frequently in deficient than in non-deficient females during the use of COCs;[8] and with those of old prospective studies, in which fertile women with defects of natural coagulation inhibitors were found to exhibit a more than a hundred-fold risk of VTE than control healthy women during use of estrogen-progestogen therapy.[9,10]

The strength of our study lies in its prospective design, in the recruitment of a broad number of women in fertile age who were family members of symptomatic carriers of deficiencies of natural anticoagulants, in the adoption of predefined criteria for the endpoint adjudication, and in a reasonably long follow-up that was conducted with an identical approach both in carriers and in non-carriers. Selection bias was prevented by including index patients on the basis of the occurrence of previous VTE and excluding family members with a previous episode of VTE. Confounding bias was prevented by screening all recruited subjects for other thrombophilic abnormalities (such as factor V Leiden, G20210 prothrombin mutation and hyperhomocysteinemia) potentially accounting for the thrombotic risk. Among the study limitations there are the small sample size correlated to the rarity of the thrombophilic defects considered and the relatively low number of subjects that used contraceptive pills. As regards the first point, also in a previously similar prospective multicenter study (the EPCOT study)[14] the number of women included, with AT/PC/PS defect, and users of estrogen-progestin therapy was slightly higher (34); the results of this study also highlighted a greater thrombotic risk in carriers compared with non-carriers using estrogen-progestin

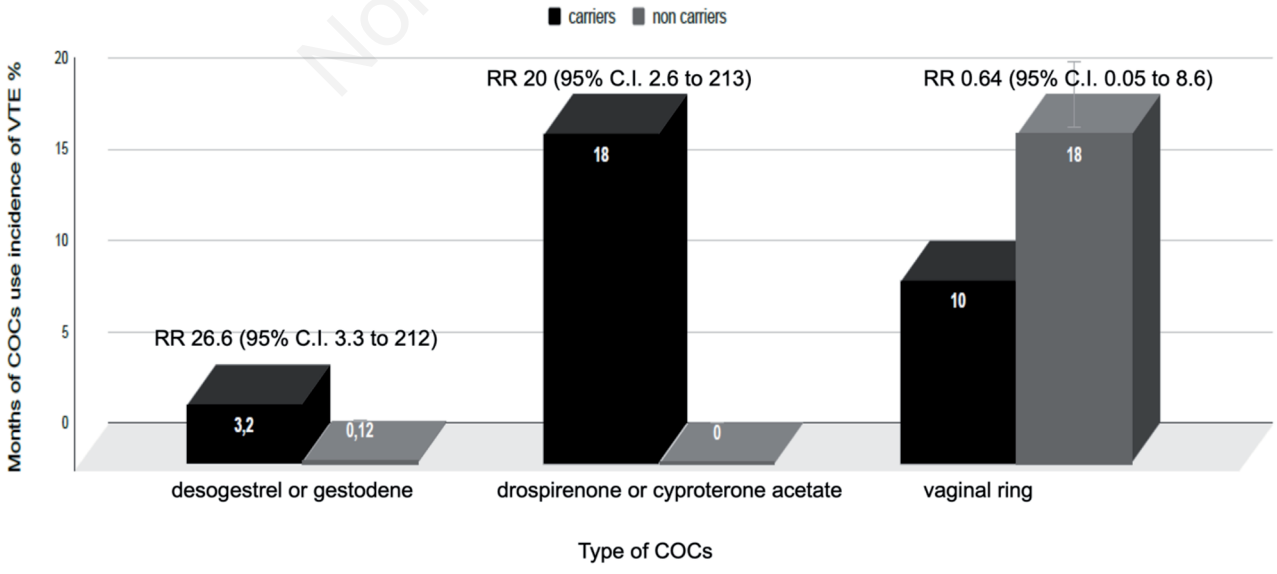

Figure 3. The incidence of thrombotic events and the RR related to the type of progestins used in combined oral contraceptive pills.

therapy (1/34 *versus* 0/135). As regards the second point is not surprising, as they had been discouraged from using them: in spite of this, the absolute number of events that were recorded in the follow-up of users of contraceptive pills was high enough to produce a valid estimation of the thromboembolic risk, as confirmed by the relative narrow confidence interval around the identified RR.

It should also be noted that the women enrolled in the study used, in most cases, preparations containing third-generation progestogens, cyproterone acetate and desogestrel, which cause a recognized greater thrombotic risk than second-generation preparations.[11]

The low number of women that used the vaginal ring and the fact that none of the women enrolled in the study used pills containing levonorgestrel or dienogest precludes firm conclusions about these contraceptive modalities. However, also these estroprogestin preparations are likely to increase the risk of VTE in women with major thrombophilia as previously shown.[4,11-13]

CONCLUSIONS

In conclusion, our study results strongly suggest that the thrombotic risk conferred by estro-progestin drugs in women in fertile age that are identified as carriers of AT, PC or PS defects is high enough to discourage their use.

An additional obvious implication of our results is the need for searching for inherited deficiencies of AT, PC or PS in all the family members of carriers of these abnormalities in order to increase protection against thromboembolic events triggered by several risk factors, including contraceptive pills.[15]

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