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ORIGINAL ARTICLE

Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis

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Essentials

- We performed a meta-analysis on thrombosis risk in thrombophilic oral contraceptive (COC)-users.
- The results support discouraging COC-use in women with a natural anticoagulant deficiency.
- Contrary, additive risk of factor V Leiden (FVL) or prothrombin-G20210A (PT) mutation is modest.
- Women with a FVL/PT-mutation as single risk factor can use COCs if alternatives are not tolerated.

Summary. *Background:* Combined oral contraceptives (COCs) are associated with an increased risk of venous thromboembolism (VTE), which is shown to be more pronounced in women with hereditary thrombophilia. Currently, WHO recommendations state that COC-use in women with hereditary thrombophilias (antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden and prothrombin-G20210A mutation) is associated with an unacceptable health risk. *Objective:* To perform a meta-analysis evaluating the additional risk of VTE in COC-users with thrombophilia. *Methods:* The MEDLINE and EMBASE databases were searched on 10 February 2015 for potential eligible studies. A distinction was made between 'mild' (factor V Leiden and prothrombin-G20210A mutation) and 'severe' thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, double heterozygosity or homozygosity of factor V Leiden and prothrombin-G20210A mutation). *Results:* We identified 12 case–control and three cohort studies. In COC-users, mild and severe thrombophilia increased the risk of VTE almost 6-fold (rate ratio [RR], 5.89; 95% confidence interval [CI], 4.21–8.23) and 7-fold (RR, 7.15; 95% CI, 2.93–17.45), respectively. The cohort studies showed that absolute VTE risk was far higher in COC-users with severe thrombophilia than in those with mild thrombophilia (4.3 to 4.6 vs. 0.49 to 2.0 per 100 pill-years, respectively), and these differences in absolute risks were also noted in non-affected women (0.48 to 0.7 vs. 0.19 to 0.0), but with the caveat that absolute risks were estimated in relatives of thrombophilic patients with VTE (i.e. with a positive family history). *Conclusion:* These results support discouraging COC-use in women with severe hereditary thrombophilia. By contrast, additive VTE risk of mild thrombophilia is modest. When no other risk factors are present, (e.g. family history) COCs can be offered to these women when reliable alternative contraceptives are not tolerated.

Keywords: combined oral contraceptives; hereditary; meta-analysis; thrombophilia; venous thromboembolism.

Introduction

Since their introduction in 1960, combined oral contraceptives (COCs), containing ethinylestradiol and a progestogen, are associated with an increased risk of venous thromboembolism (VTE) [1–4]. This association is considered to be related to COC-induced changes in coagulation, anticoagulation and fibrinolysis in a prothrombotic direction, which alter the hemostatic balance. These changes have more impact in women who are already at increased risk of VTE, for instance because of pre-existing hereditary thrombophilia (i.e. antithrombin, protein C and protein S deficiencies and factor (F) V Leiden and prothrombin G20210A mutation). In 1994, a first publication reported

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an increased risk of VTE in COC-users who are FV Leiden mutation carriers [5]. Many studies followed, the majority of which evaluated the risk of FV Leiden and prothrombin-G20210A mutation as these are more prevalent in the general population (5% [6,7] and 2% [8], respectively) than antithrombin, protein C and protein S deficiencies, which have an incidence of about 0.1% each [9–11]. Further, some studies evaluated the risk in COC-users with additional hereditary thrombophilias [12–14]. The number of cohort studies reporting the absolute VTE risk in COC-users with thrombophilia is limited and restricted to thrombophilic family cohort studies, which reported a higher risk with natural anticoagulant deficiencies than with FV Leiden or prothrombin G20210A mutation. Analyses are mostly based on small subgroups. Currently, WHO Medical Eligibility Criteria for contraceptive use state that COC-use in women with hereditary thrombophilias (antithrombin, protein C and protein S deficiencies, FV Leiden and prothrombin G20210A mutation) [15] is associated with an unacceptable health risk.

The aim of this systematic review and meta-analysis is to present summary statistics of the additional risk of first VTE in COC-users with mild and severe hereditary thrombophilia.

Methods

Identification of studies

The MEDLINE and EMBASE databases were searched for potential studies, published from inception to 10 February 2015 (date of search performed), presenting relevant evidence on VTE risk in COC-users with hereditary thrombophilia, with no restriction on language.

The PubMed database was searched by applying the following search terms:

('Thrombosis'[Mesh] OR 'thrombosis' OR 'thrombotic' OR thromboembolism*) AND ('Contraceptives, Oral'[Mesh] OR contracept*) AND ('Thrombophilia'[Mesh] OR 'thrombophilia' OR 'protein C' OR 'factor V Leiden' OR 'protein S' OR antithrombin* OR 'prothrombin' OR 'hereditary' OR 'inherited' OR 'family history' OR 'genetics' OR 'genetic').

The EMBASE database was searched by using the following search terms:

'thromboembolism'/exp OR thrombosis:ab,ti OR thrombotic:ab,ti OR thromboembolism*:ab,ti AND ('oral contraceptive agent'/exp OR contracept*:ab,ti) AND ('thrombophilia'/exp OR 'protein c deficiency'/exp OR 'protein s deficiency'/exp OR 'blood clotting factor 5 leiden'/exp OR 'antithrombin iii'/exp OR 'antithrombin'/exp OR 'prothrombin'/exp OR 'family history'/exp OR 'genetic predisposition'/exp OR thrombophil*:ab,ti OR 'protein c':ab,ti OR 'protein s':ab,ti OR 'factor v leiden':ab,ti OR 'factor 5 leiden':ab,ti OR antithrombin*:ab,ti OR prothrombin*:ab,ti OR 'family history':ab,ti OR familial:ab,ti OR genetic:ab,ti OR hereditary:ab,ti OR inherited:ab,ti) NOT [medline]/lim.

The search was developed with the expertise of a professional librarian of the Central Medical Library of the University Medical Center Groningen. The search was extended by manual review of the retrieved papers' reference lists.

Titles and abstracts of potentially relevant papers retrieved were checked independently on piloted forms by two investigators (E.F.W.v.V. and S.W.-V.) for eligibility of full paper evaluation. Discrepancies in opinion between the two principal reviewers regarding eligibility were resolved by discussion with a third investigator (K.M.). Likewise, the same two investigators performed full paper evaluation and discrepancies were resolved by the third investigator.

Study selection criteria

Regarding selection criteria, we anticipated including both case–control and cohort studies. Studies were considered eligible if the following criteria were met: original data presented; hereditary thrombophilia was considered (antithrombin, protein C or protein S deficiency, FV Leiden or prothrombin G20210A mutation, and double heterozygosity or homozygosity of factor V Leiden or prothrombin G20210A mutation); restriction to first VTE of any type; in case–control studies an analysis was performed comparing the prevalence of thrombophilia in COC-associated VTE cases vs. the prevalence in COC-using control persons; in cohort studies the incidence rate of VTE in thrombophilic COC-users was compared with non-thrombophilic COC-users; and odds ratios (OR) or rate ratios (RR) were provided with underlying data or retrievable based on available data. An additional inclusion criterion for cohort studies was that probands were not included in the analyses. Case series of patients were excluded and in the case of studies with multiple publications, the publication with the most inclusive dataset was included.

Quality assessment

The two investigators independently performed a quality assessment of the selected papers, in which components of the Newcastle–Ottawa tool for epidemiological studies were taken into account [16]. The following quality issues were considered relevant: the characteristics of the participants, inclusion and exclusion criteria for VTE cases, diagnostics of VTE, methods of collecting information on COC-use, source of control group, methods of matching cases to controls, and adjustment for confounding.

Statistical analysis

Data synthesis was conducted with Review manager (RevMan, version 5.3. Copenhagen: The Nordic

Cochrane Centre, The Cochrane Collaboration, 2014), which was used to pool the data for each risk factor, using the Mantel–Haenszel method with a random effects model. When risks of a certain disease are small, odds ratios (ORs) are considered to reliably estimate the relative risk (RR); therefore, the same method was used for case–control and cohort studies. A distinction is made between studies evaluating COC-users with severe (antithrombin, protein C or protein S deficiency, and double heterozygosity or homozygosity of FV Leiden or prothrombin G20210A mutation) and mild hereditary thrombophilia (FV Leiden or prothrombin G20210A mutation). Pooled results are presented as RR with corresponding 95% confidence intervals. Heterogeneity across studies was tested using the I^2 statistic; homogeneity was considered unlikely when $P < 0.10$. Funnel plots were performed to examine publication bias.

Results

The search resulted in 2087 hits, of which 2027 remained after deletion of 60 duplicates.

Based on title and abstract screening, 1929 papers were excluded, leaving 98 articles of possible relevance, which were retrieved for full paper evaluation. Additionally, 22 references were identified from these papers.

Based on the predefined inclusion and exclusion criteria, initially 25 studies (18 case–control studies and seven cohort studies) [5,13,14,17–38] were selected for detailed evaluation. Of these, six case–control studies [13,17,19,24,28,30] were excluded for the following reasons: no subdivision between men and women was provided for the prevalence of thrombophilia [30]; prevalence of COC-use and/or thrombophilia in controls was based on estimations only [17,19]; cases of VTE had occurred in patients who were all affected with thrombophilia [13]; information on the number of COC-users with thrombophilia in the patient and/or control groups was not provided or incomplete [28,30]; and a re-analysis based on the same dataset was used to assess the influence of duration of COC-use [24]. However, a subgroup analysis in COC-users with or without double heterozygosity of factor V Leiden and prothrombin 20210A mutation was excluded, as the study did not take into account the cases that were identified with homozygosity [14]. Additionally, four family cohort studies [32–34,36] were excluded for the following reasons: inclusion of probands with symptomatic VTE in risk estimations performed in thrombophilic family cohorts [32,36]; inclusion of women with personal history of VTE [32,34]; and a larger study dataset [38] available than present in the initial study [33]. There were no disagreements between the independent reviewers with respect to study eligibility that needed to be resolved by the third investigator. As a result, 15 studies, consisting of 12 case–control [5,18,20–23,25–27,29,31] and three cohort studies [35,37,38], were selected. A flow chart is presented in Fig. 1.

All 15 studies were written in the English language. Fourteen studies [5,14,20–23,25–27,29,31,35,38] evaluated the additional risk of mild thrombophilia (factor V Leiden, prothrombin G20210A mutation or both). Three studies evaluated the additional risk of severe thrombophilias (antithrombin, protein C or protein S deficiency [35,37], and double heterozygous or homozygous factor V Leiden or prothrombin G20210A mutation [38]). Characteristics of the studies are presented in Table 1. The number of COC-users with or without thrombophilia in cases and control groups, contributing to the analysis, is presented in Table 2; incidence rates of the cohort studies are presented in Table 3.

Study characteristics

COC-users with or without hereditary thrombophilia were the main population to be studied in only two of the selected studies [5,38]. All case–control studies collected cases from hospitals, except one that used a medical record database [14]. All cases occurred in women aged between 15 and 49 years, except for one study, which included women above 50 years [29]. All case–control studies matched controls for age, or an adjustment for age was performed, and five additionally matched according to region. All studies adjusted for various confounders, the majority adjusting for body mass index (BMI) and family history. Seven case–control studies tested also for antithrombin, protein C and protein S deficiency [14,18,20,21,23,26,27], of which three adjusted for other thrombophilias [14,21,26]. One cohort study adjusted for clustering of women within families [37]. The majority of studies included any VTE or cases of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). However, some studies selected cases based on specific VTE type; two included DVT of an upper

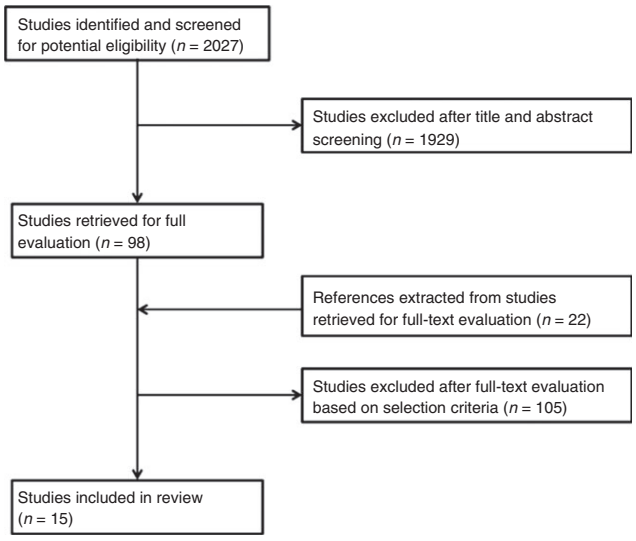

Fig. 1. Study flow diagram

Table 1 Study characteristics of case–control and cohort studies included in the analysis

Study	Inclusion criteria cases	Exclusion criteria cases	Thrombophilia testing	Mean/ median age case/ controls	Source cases/ controls	Diagnosis VTE*	Source COC-use	Definition COC-use	Matching factors	Study period	Adjustment
Case-control studies											
Bloemenkamp [5] Netherlands FVL	Women with first DVT, aged 15–49 years	Malignancy, pregnancy, postpartum, recent miscarriage	FVL	35/not stated	Cases: hospitals Controls: friends/ partner/other patients	Objectively confirmed	Cases: interview/ hospital discharge letter Controls: interview	Cases: COC-use at time of VTE Controls: COC-use at inclusion	No	1988–1992	Age, family history, FVL jointly
Andersen [18] Denmark FVL, ACS	Women with first VTE, aged 18–49 years	≤ 3 months: surgery, trauma, pregnancy, postpartum, malignancy, immobility, SVT, Crohn/ colitis, heart failure	FVL, ACS	33/28	Cases: hospital discharge registries Controls: blood donors	Not stated	Cases: interview Controls: questionnaire	Cases: COC-use ≤ 3 months prior to VTE Controls: COC-use ≤ 3 months prior to inclusion	Age, region	1977–?	BMI, smoking, parity, missing data
Martinelli [20] Italy FVL, FII	Patients with first CVT, aged 15–64 years	Malignancy, autoimmune disease, pregnancy, postpartum, post-menopause	FVL, FII, ACS	30/32	Cases: hospital Controls: friends/ partners	Objectively confirmed	Source COC-use not stated	Cases: COC use ≤ 2 weeks prior to VTE Controls: COC-use ≤ 2 weeks prior to inclusion	Age, region, education	1991–1997	Matching factors
Martinelli [21] Italy FVL, FII	Consecutive women with first DVT, lower extremities, aged 15–48 years	Malignancy, autoimmune disease, pregnancy, postpartum	FVL, FII, ACS	30/46	Cases: hospital Controls: friends/ partners other patients	Objectively confirmed	Source COC-use not stated	Cases: COC use ≤ 2 weeks prior to VTE Controls: COC-use at time of blood sampling	No	1995–1998	Age, other thrombophilias
Spannagl [22] Germany FVL	Consecutive women with DVT/PE, aged 15–49 years	Malignancy, infection, autoimmune/ liver/renal disease, history of drug abuse	FVL	34/34	Cases: hospitals Controls: random sample, population database	Objectively confirmed or anticoagulant treatment	Cases: questionnaire Controls: questionnaire	Cases: COC-use at time of VTE Controls: COC-use at inclusion	Age	1995–1997	Age, family history, BMI, varicose veins

Table 1 (Continued)

Study	Inclusion criteria cases	Exclusion criteria cases	Thrombophilia testing	Mean/ median age case/ controls	Source cases/ controls	Diagnosis VTE*	Source COC-use	Definition COC-use	Matching factors	Study period	Adjustment
Aznar [23] Spain FV, FII	Consecutive patients with first DVT/ PE, no age restriction	Malignancy	FII, FVL, ACS	Not stated	Cases: hospital Controls: blood donors	Objectively confirmed	Cases: interview Controls: interview	Cases: COC-use at time of the study Controls: COC-use at time of the study	Age, region	Not stated	Age
Legnani [14], Italy FVL, FII FVL+FII	Consecutive women with DVT/PE, aged 15–49 years	Isolated PE, SVT, DVT upper limb or unusual site	FVL, FII, ACS	30/33	Cases: hospital Controls: from general population	Objectively confirmed	Cases: interview Controls: interview	Cases: COC use at time of VTE Controls: COC at inclusion	Region	1994–2000	Age, other thrombophilias
Vaya [25] Spain FVL, FII	Consecutive patients with first DVT, upper extremity, aged 15–75 years	Malignancy, infection, autoimmune/ liver/renal disease, history of drug abuse	FVL, FII, AT	Not stated	Cases: hospital Controls: healthy volunteers from same hospitals	Objectively confirmed	Source COC-use not stated	Cases: COC-use $\leq$ 2 weeks prior to VTE Controls: COC-use $\leq$ 2 weeks prior to sampling	Age	1997–2001	Confounding factors not specified
Martinelli [26] Italy FVL, FII	Patients with first DVT of upper extremity, no age restriction	DVT due to central vein catheter, malignancy, related to thrombophilic family	FVL, FII, ACS	32/30	Cases: hospital Controls: partners or friends	Objectively confirmed	Source COC-use not stated	Cases: COC use at time of VTE Controls: COC use at inclusion	Age	1994–2003	Age, other thrombophilias
Sidney [27] USA FVL, FII	Women with first DVT/ PE, aged 15–44 years	Pregnancy, hysterectomy, ovariectomy, HRT-use, missing COC data, estrogen dose >50 mcg	FVL, FII	35/33	Cases: medical records database Controls: same database	Objectively confirmed or clinical suspicion PE	Cases: interview Controls: interview	Cases: COC-use at time of VTE Controls: COC use at inclusion	Age	1998–2000	Race/ethnicity, income, BMI

Table 1 (Continued)

Study	Inclusion criteria cases	Exclusion criteria cases	Thrombophilia testing	Mean/ median age case/ controls	Source cases/ controls	Diagnosis VTE*	Source COC-use	Definition COC-use	Matching factors	Study period	Adjustment
Roach [29] Netherlands FVL, FII	Women with first DVT/ PE, aged 50–63 years	Severe psychiatric problems, inability to speak Dutch	FVL, FII	53/53	Cases: hospital Controls: partners/ random digit dialing	Objectively confirmed	Cases: questionnaire Controls: questionnaire	Cases: COC-use ≤ 12 months prior to VTE Controls: ≤ 12 months prior to inclusion	Region	1999–2004	Age, BMI, smoking, family history
Bergendal [31] Sweden FVL, FII	Women with first DVT/ PE, aged 18–54 years	Pregnancy < 3 months, malignancy	FVL, FII	41/42	Cases: hospitals Controls: Swedish population register	Objectively confirmed	Cases: interview Controls: interview	Cases: COC-use ≤ 3 months prior to VTE Controls: ≤ 3 months prior to inclusion	Age	2003–2009	Smoking, BMI, immobilization
Cohort studies											
Simioni [35] Italy Netherlands FVL, ACS	Relatives, aged >15 years, of patients with VTE and ACS or FVL	Probands, double defect, malignancy, no consent	ACS, FVL	NA	NA	Objectively confirmed or anticoagulant treatment	Interview	COC-use and duration collected	NA	Not stated	No
van Vlijmen [37] Netherlands ACS	First-degree female relatives, aged 15–50 years, of patients with VTE and ACS	Probands, dead, geographic distance, no consent, laboratory results incomplete	ACS, FVL, FII	NA	NA	Idem	Interview and medical record and/or GP	Idem	NA	2000–2004	Clustering within families
van Vlijmen [38] Netherlands FVL or FII FVL+FII Homozygotes	First-degree female relatives, aged 15–50 years, of patients with VTE and FVL/F2	Probands, dead, geographic distance, no consent, laboratory results incomplete	FVL, FII, ACS	NA	NA	Idem	Interview and medical record and/or GP	Idem	NA	1995–1998 and 1998–2004	No

VTE, venous thromboembolism; PE, pulmonary embolism; CVT, cerebral vein thrombosis; SVT, superficial vein thrombosis; FVL, factor V Leiden mutation; FII, prothrombin G20210A mutation; ACS, antithrombin, protein C or protein S deficiency; FVIII, increased factor VIII levels (≥ 150%); BMI, body mass index; NA, not applicable. *Venography, pletysmography, Doppler ultrasound (DUS), duplex color US, intra-arterial angiography, computed tomography (CT) scan, intravenous (i.v.) digital angiographic imaging, magnetic resonance imaging (MRI), VP-ventilation-perfusion scan.

Table 2 Individual results of case–control studies

Studies	Thrombophilia examined	VTE cases COC-users with/ without thrombophilia	Controls COC-users with/ without thrombophilia	Odds ratio	(95% CI)
Bloemenkamp [5]	FVL	15/65	0/55	26.3	(1.5–449.0)
Andersen [18]	FVL	14/26	2/26	7.0	(1.4–33.9)
Martinelli [20]	FVL	3/14	0/27	13.4	(0.6–275.0)
	FII	7/14	1/27	13.5	(1.5–120.9)
Martinelli [21]	FVL	11/52	2/41	4.3	(0.9–20.7)
	FII	9/52	2/41	3.6	(0.7–17.3)
Aznar [23]	FVL or FII	9/10	0/10	19.0	(0.9–8.2)
Spannagl [22]	FVL	12/34	10/109	3.9	(1.5–9.7)
Legnani [14]	FVL	26/86	4/166	12.6	(4.2–37.1)
	FII	18/86	2/166	17.4	(3.9–76.6)
Vaya [25]	FII	4/9	0/12	11.8	(0.6–247.8)
Martinelli [26]	FVL or FII	5/18	3/82	7.6	(1.7–34.7)
Sidney [27]	FVL	10/56	3/59	3.5	(0.9–13.4)
	FII	3/56	2/59	1.6	(0.3–9.8)
Roach [29]	FVL	25/10	1/36	11.5	(1.5–87.1)
	FII	11/10	2/36	2.5	(0.5–11.8)
Bergendal [31]	FVL	89/221	6/91	6.1	(2.6–14.5)
	FII	29/273	2/97	5.2	(1.2–22.0)

COC, combined oral contraceptive; FVL, factor V Leiden mutation; FII, prothrombin 20210A mutation.

Table 3 Individual results of thrombophilic family cohort studies

Study	Thrombophilias examined	VTE cases/100 pill-years of use Incidence rate (95% CI)		Risk ratio	95% CI
		With thrombophilia	Without thrombophilia		
Simioni [35]	FVL	2/98	0/65	3.3	(0.4–120)
	ACS	2.0 (0.3–7.2)	0.0 (0.0–5.5)	6.4	(1.0–41.1)
		3/117	1/150		
		4.3 (1.4–9.7)	0.7 (0.0–3.7)		
Vlijmen [37]	ACS	13/281	3/629	9.7	(3.0–42.4)
		4.62 (2.5–7.9)	0.48 (0.1–1.4)		
Vlijmen [38]	FVL or FII	6/1218	6/3211	2.6	(0.85–8.17)
	Homozygosity or heterozygosity of FVL+FII	0.49 (0.18–1.07)	0.19 (0.07–0.41)	4.6	(0.93–22.86)
		2/232	6/3211		
		0.86 (0.10–3.11)	0.19 (0.07–0.41)		

ACS, antithrombin, protein C or protein S deficiency; FVL, factor V Leiden mutation; FII, prothrombin-G20210A mutation; CI, confidence interval.

extremity [25,26] and one study focused on cerebral vein thrombosis (CVT) [20]. The quality of the studies was high: the degree of information provided on methods applied to collect information on COC-use, the objective methods used in diagnosing VTE, source of controls, degree of matching to controls, adjustment, and description of inclusion and exclusion criteria, were generally considered adequate.

Risk of VTE

Mild thrombophilia Based on the combined results of 14 studies [5,14,18,20–23,25–27,29,31,35,38], the presence of mild thrombophilia increased the risk of VTE in COC-users almost 6-fold (RR, 5.89; 95% CI, 4.21–8.23) (Fig. 2). Heterogeneity between studies was low (I^2 = 0%; P = 0.47). In separate analyses, the presence of FV Leiden mutation increased the risk slightly more than 6-fold (RR, 6.14; 95% CI, 2.58–14.46). Between-study heterogeneity was low (I^2 = 0%; P = 0.81); the presence of prothrombin G20210A mutation increased the risk slightly more than 5-fold (RR, 5.24; 95% CI, 2.69–10.20). Heterogeneity between studies was low (I^2 = 4%; P = 0.40) (data not shown).

Severe thrombophilia Based on the combined results of three studies [35,37,38], the presence of severe thrombophilia increased the risk in COC-users more than 7-fold (RR, 7.15; 95% CI, 2.93–17.45) (Fig. 3). Heterogeneity between studies was low (I^2 = 0%; P = 0.77).

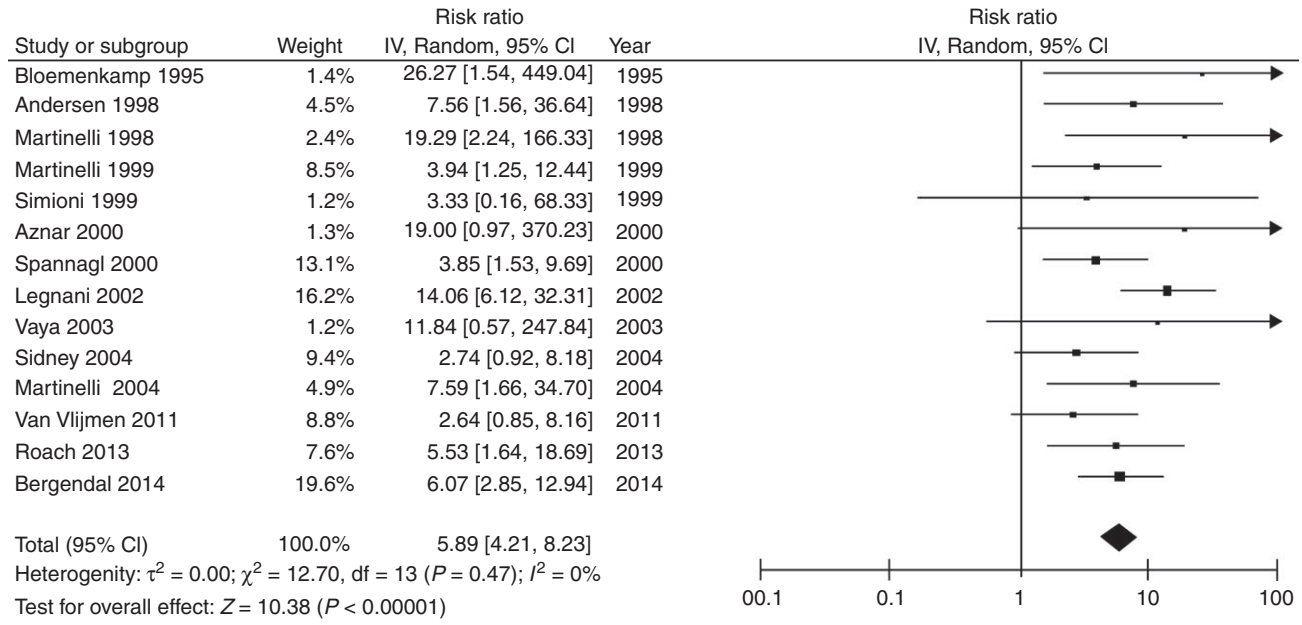

Fig. 2. Overall risk ratio for VTE among COC-users with mild thrombophilia (factor V Leiden or prothrombin G20210A mutation)

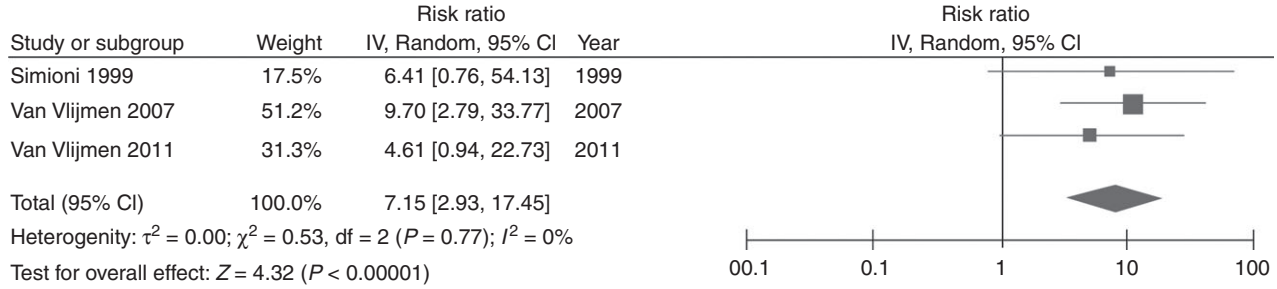

Fig. 3. Overall risk ratio for VTE in COC-users with severe thrombophilia (antithrombin, protein C or protein S deficiency, and homozygosity or heterozygosity of factor V Leiden or prothrombin-G20210A mutation).

Absolute risk of VTE

Mild thrombophilia The incidence of VTE in COC-users with mild thrombophilia (FV Leiden and prothrombin G20210A mutation) was 0.49 (95% CI, 0.18–1.07) to 2.0 (0.3–7.2) vs. 0.19 (95% CI, 0.07–0.41) to 0.0 (0–5.5) per 100 pill-years in COC-users without these mutations [35,38] (Table 3).

Severe thrombophilia The incidence of VTE in COC-users with double heterozygosity or homozygosity of FV Leiden or prothrombin-G20210A mutation was 0.86 (95% CI, 0.10–3.11) vs. 0.19 (95% CI, 0.07–0.41) per 100 pill-years in COC-users without these mutations [38].

The incidence of VTE in COC-users with antithrombin, protein C or protein S deficiency was 4.3 (95% CI, 1.4–9.7) to 4.62 (95% CI, 2.5–7.9) vs. 0.48 (95% CI, 0.1–1.4) to 0.7 (95% CI, 0.0–3.7) per 100 pill-years in non-deficient COC-users [35,38] (Table 3).

Potential sources of bias

As to evaluation of possible sources of bias, in the case–control studies the inclusion criteria applied in the analyses in COC-users were generally comparable (i.e. first VTE), although inclusion of cases in some studies depended on VTE type (CVT [20], DVT upper extremity [25,26] and DVT lower extremity [21]). One case–control study [29] had included older women (50–63 years) in comparison to the age range in the other studies (15–49); therefore, the meta-analysis for mild thrombophilia was re-performed without this study, but the outcome hardly changed (RR, 5.91; 95% CI, 4.10–8.51). Upper extremity DVT is viewed as somewhat different to lower extremity DVT (especially with respect to the possible influence of thrombophilia on the development of a first VTE). However, the results did not change if those studies [25,26] were excluded (5.73; 95% CI, 3.92–8.36). The majority excluded patients with recent risk factors (pregnancy,

postpartum, surgery, trauma or immobilization) [5,18,27] or co-morbidity (malignancy or systemic disease) [23,25,26] or both [18,20,21,31]. Information on COC-use was collected by interview, and also discharge letters in one study [5]; two studies used written questionnaires, similar for both cases and controls [22,29]. In three studies, the source was not stated [20,21,26].

In all three family cohort studies, only relatives were included, as including also probands would have introduced bias because they all had VTE; information on COC-use was collected by interviews and medical record review prior to the thrombophilia testing.

Venous thromboembolism was objectively established in all studies, but four studies [22,35,37,38] also had included patients based on clinical diagnosis and full-dose anticoagulants for ≥ 3 months. Several studies discussed missing data; one adjusted for missing data [18]. Finally, the funnel plots appeared symmetric, suggesting no publication bias.

Discussion

We performed a systematic review and meta-analysis based on 15 studies. In COC-users, mild thrombophilia (FV Leiden and prothrombin G20210A mutation) increased the risk of VTE 6-fold, whereas severe thrombophilia (antithrombin, protein C or protein S deficiency, and double heterozygosity and homozygosity of FV Leiden or prothrombin-G20210A mutation) increased the risk 7-fold.

However, to adequately assess the impact of the relative increase in risk, information on the absolute risk is needed. Two cohort studies reported a VTE incidence of 0.49 and 2.0 per 100 pill-years of use in COC-users with mild thrombophilia [35,38], indicating inconsistent outcomes. The noted high incidence of 2.0 per 100 pill-years could be because of the very small subgroup of COC-users with or without FV Leiden mutation providing pill-years and zero cases in non-thrombophilic COC-users. Two cohort studies [35,37] reported incidences of 4.3 and 4.6 per 100 pill-years in COC-users with severe thrombophilia, indicating a far higher risk (Table 3). These differences in absolute risks are also noted in non-affected women from families with severe vs. mild thrombophilias. Co-inheritance of other thrombophilic defects could explain the more heightened risk in non-affected women from families with severe thrombophilia; one of the family cohort studies indicated frequent co-existence of other thrombophilic defects [37]. The incidence of VTE in COC-users with double heterozygosity or homozygosity of FV Leiden or prothrombin G20210A mutation was 0.86 per 100 pill-years, suggesting that the absolute risk of this double defect is less serious than an antithrombin, protein C or protein S deficiency [38].

All absolute risks are estimated in family members of thrombophilic families (i.e. relatives of thrombophilic patients with VTE), who therefore also have a positive family history, which increases their baseline risk of VTE 2- to 3-fold [39–42]. To put observed risks into perspective, in COC-users with mild thrombophilia and positive family history the absolute VTE risk is increased 8- to 33-fold, and 70-fold in COC-users with severe thrombophilia, when compared with the VTE risk of about 0.06 per 100 person-years [1] estimated in the general population of COC-users.

This meta-analysis has some limitations; the risk of mild thrombophilia was largely estimated in a community setting, whereas the risk of severe thrombophilia was exclusively evaluated in a limited number of thrombophilic family cohorts. This is inherently because of the very low incidence of severe thrombophilia. Further, absolute risks were all estimated in members of thrombophilic family cohort studies; risks will therefore be more pronounced, because of the co-existing family history, than in the general population of COC-users who tested positive.

In conclusion, the presence of mild and severe thrombophilia increases the risk of VTE in COC-users 6-fold and 7-fold, respectively. However, absolute VTE risk estimates indicate that the contribution of severe thrombophilia to the VTE risk in COC-users is considerably higher (4.3–4.6 per 100 pill-years) than the additional risk with mild thrombophilia (0.49–2.0 per 100 pill-years), but with the caveat that these risks were estimated in thrombophilic COC-users who also had a positive family history. As a co-existing family history increases VTE risk 2- to 3-fold, estimated risks are more pronounced than in a general population of COC-users who tested positive for thrombophilia.

Clinical implications

Based on the high additive risk of VTE, it is recommended that COC-use should be avoided in asymptomatic women with known severe hereditary thrombophilia. Screening and identification may be useful in asymptomatic women from families with known severe thrombophilia. However, testing negative may give false reassurance, because female relatives without such deficiencies also have a markedly increased risk of COC-related VTE compared with the general population. Yet, the potential advantage is that testing makes it possible to identify affected family members in whom the risk of first VTE can be lowered by preventive measures such as avoiding COC-use [43]. Suitable alternatives to COC-use that have adequate contraceptive effectiveness are ovulation-inhibiting progestogen-only tablets, levonorgestrel-containing intrauterine devices (IUDs) and Cu-IUDs containing at least 300 mm^2 Cu [38,44].

By contrast, the additive risk of VTE with mild thrombophilia is only modest and therefore screening of asymptomatic women from families with known mild

thrombophilia is generally not indicated [43]. However, it is recommended to fully inform a female relative on the implications of screening so that she can decide whether or not to be tested. In women with known mild thrombophilia, detailed counseling on all contraceptive options is recommended to enable them to make an informed choice on the optimal contraceptive. When no other risk factors are present (e.g. family history), COC-use could be offered to these women when reliable alternative contraceptives are not tolerated, as in this situation the increased risk of pregnancy-related VTE outweighs the COC-associated risk. Similar to the general population, in women with mild thrombophilia, those COCs conferring the lowest risk of VTE are recommended as the first choice (i.e. levonorgestrel-, norgestimate- or norethisterone-containing COCs with a low ethinylestradiol dose [35 micrograms or less]) [1–4,44].

Addendum

E. van Vlijmen and S. Wiewel-Verschueren were responsible for the study concept and performed the literature research, data collection, data extraction and the quality assessment, which was supervised by K. Meijer. E. van Vlijmen, S. Wiewel-Verschueren and T. Monster analyzed and interpreted data. Statistical analyses were performed by T. Monster. E. van Vlijmen wrote the draft manuscript. K. Meijer, S. Wiewel-Verschueren and T. Monster provided input and critical review of the manuscript. All authors revised the manuscript.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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