ELSEVIER

Contraception 73 (2006) 166–178

Contraception

Review article

Does use of hormonal contraceptives among women with thrombogenic mutations increase their risk of venous thromboembolism? A systematic review

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Received 17 July 2005; accepted 11 August 2005

Abstract

Because use of combined oral contraceptives (COCs) confers some risk of venous thromboembolism (VTE), there is concern that this effect may be greater among women with thrombogenic mutations. We searched the MEDLINE and EMBASE databases for all articles published from January 1966 through September 2004 for evidence relevant to hormonal contraception and thrombogenic mutations. Of 301 articles identified by the search strategy, 16 evaluated COCs, and no studies were found for other hormonal methods. We used standard abstract forms and grading systems to summarize and assess the quality of the evidence. A total of 10 studies together provided "good" evidence of a greater risk of VTE (risk ratios of 1.3–25.1) and cerebral vein or cerebral sinus thrombosis among COC users with factor V Leiden mutation when compared with nonusers who have the mutation. The evidence for prothrombin and other thrombogenic mutations was not as strong as for factor V Leiden mutation. It is unclear whether the type of COC or duration of use modifies the risk of VTE among women with thrombogenic mutations.

Keywords: Oral contraceptives; Venous thromboembolism; Thrombogenic mutations; Evidence-based guidelines

1. Introduction

In the 1990s, several gene mutations were found to substantially increase the risk of thrombosis. The factor V Leiden mutation, the most common genetic risk factor for venous thromboembolism (VTE), activates protein C resistance, inhibiting the blood's anticoagulant system and thereby enhancing the blood's susceptibility to thrombosis [1]. Globally, the highest prevalence of factor V Leiden is among European populations, ranging from 2.0% to 7.0%; prevalence is lower among Africans and Asians [2]. In the United States, the factor V Leiden mutation is carried in heterozygous form by about 5% of the white population and is less frequent among Hispanic-Americans (2.2%), African Americans (1.2%) and Asian-Americans (0.45%) [3]. Other thrombogenic mutations have been described including prothrombin (factor II 20210A; 1–3% in the general population and 6% among VTE patients) [4,5], and deficiencies of protein S (1.3% in both the general population and among VTE patients) [6], protein C (0.2% in the general population and 2.7% among VTE patients) [6,7] and antithrombin (0.2% in the general population, 1.1% in VTE patients) [6,8].

Cases of VTE are rare among women of reproductive age, fewer than 1 per 10,000 person-years [9]. Use of combined oral contraceptives (COCs) confers some risk of VTE, about three to six times that of nonusers. [9] Still, this relative risk increases the absolute risk of VTE to 3 to 4 per 10,000 person-years for current COC users [9]. While data are limited, evidence suggests there is no increased risk of VTE among women who use progestogen-only methods or combined injectable contraceptives [10,11].

We conducted this systematic review in preparation for an Expert Working Group of international family planning experts convened by the World Health Organization (WHO) in October 2003 to develop and revise medical eligibility

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0010-7824/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2005.08.011

criteria for contraceptive use. In this report, we describe the evidence obtained through our systematic review regarding whether women with a thrombogenic mutation (factor V Leiden mutation, prothrombin mutation, and deficiencies of protein S, protein C or antithrombin) further increase their risk of VTE by using hormonal contraceptive methods, as well as provide the WHO recommendations that were derived in part from this evidence. This review also includes evidence identified since the 2003 meeting through September 2004.

2. Materials and methods

We searched the MEDLINE and EMBASE databases for all articles (in all languages) published in peer-reviewed journals from January 1966 through September 2004 for evidence relevant to thrombogenic mutations and hormonal contraceptive use: ((exp Contraceptives, Oral/ or oral contracep:) or ((((combin: and inject:) and contracept:) or ((once a month or monthly) and inject: and contracept:) or (cyclofem or lunelle or mesigyna or cyclo provera or cycloprovera)) and female/) or ((exp Progestational Hormones/ or progestin:) and contracept: and (oral or pill or pills or tablet or tablets)) or ((Medroxyprogesterone 17-Acetate/ and (contracept: or inject: or depo or depot)) or (depot medroxyprogesterone or depo medroxyprogesterone or depotmedroxyprogesterone or depomedroxyprogesterone or dmpa) or (net en or norethisterone-enanthate)) or ((norplant: or uniplant or jadelle or implanon) or ((levonorgestrel or etonogestrel) and implant:)) or (mirena or (levonorgestrel and (exp intrauterine devices/ or (iud or iucd or ius) or (intrauterine adj3 system) or (intra-uterine adj3 system) or (intrauterine adj3 device) or (intra-uterine adj3 device)))) or ((exp Contraceptive Agents, Female/ and patch) or (orthoevra or ortho evra)) or ((exp Contraceptive Devices, Female/ and ring) or NuvaRing)) and ((thromb: or pulmonary embolism)) and (factor v or G20210A or thrombogenic mutation: or *"Activated Protein C Resistance"/ or *"Prothrombin"/ or Mutation/). We then limited the articles to human and nonreview. We searched reference lists from articles identified by the search, as well as key review articles, to identify additional articles. We did not attempt to identify unpublished articles or abstracts from scientific conferences.

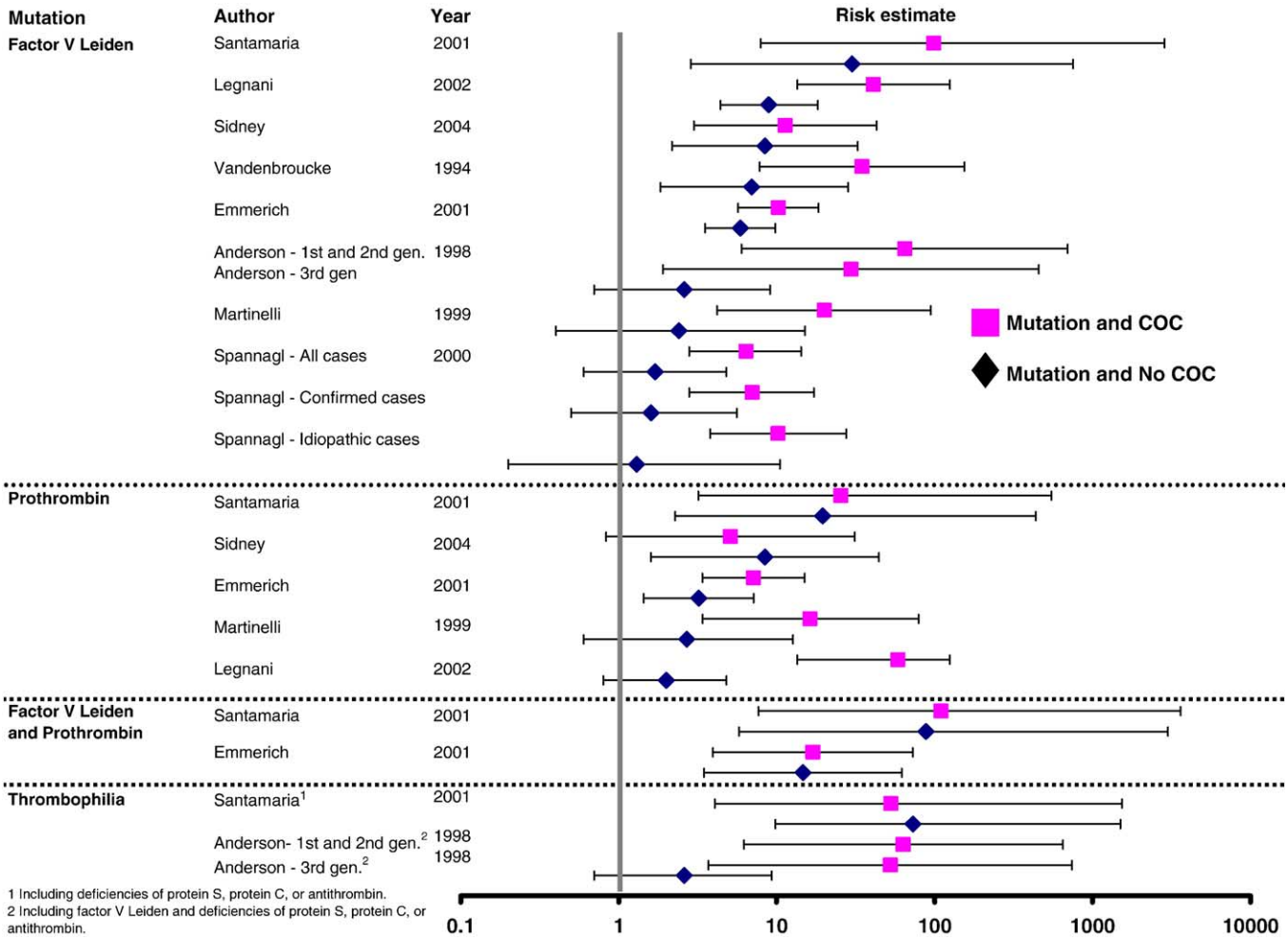

Fig. 1. Comparison of ORs for VTE. [1]Including deficiencies of protein S, protein C, or antithrombin. [2]Including factor V Leiden and deficiencies of protein S, protein C, or antithrombin.

Table 1
Evidence table for risk of VTE among women with thrombogenic mutations who used COCs

Author, year, source of support	Study design	Population	Exposure	Results		Weaknesses	Quality
Factor V Leiden (FVL) mutation							
Vandenbroucke et al. [1], 1994 Netherlands Heart Foundation	Case-control (LETS) Netherlands 1988–1992	155 DVT 169 controls (friends, acquaintances, partners of other cases)	COC use for month before thrombosis (type not specified). FVL Homozygous/ heterozygous	*OR for DVT:* No FVL/no COC No FVL/COC FVL/no COC FVL/COC Above ORs are unadjusted. FVL/COC interaction term was nonsignificant. *Incidence per 10,000 person-years* No FVL/no COC 0.8 FVL/no COC 5.7	 1.0 (ref.) 3.7 (2.2–6.1) 6.94 (1.84–28.31)[a] 34.7 (7.8–154) No FVL/COC 3.0 FVL/COC 28.5	Did not adjust for confounders	II-2 poor
Bloemenkamp et al. [13], 1995 Netherlands Heart Foundation	Case-control Netherlands 1988–1992 Analysis restricted to COC types that had ≥5 cases and controls	126 DVT 159 controls	COC use at time of DVT (different types of COCs) FVL carrier status not specified.	*RR for DVT among FVL+ women:* Desogestrel (30 μg) Levonorgestrel (30 μg) Levonorgestrel or lynoestrenol (50 μg) Levonorgestrel or norethisterone (30–40 μg) Norethisterone (35 μg) or lynoestrenol (37.5 μg) Reference for all comparisons is COC nonusers. Above ORs are adjusted for age. Adjustment for family history did not alter results.	 6.0 (1.9–19.0) 1.9 (0.4–8.5) 1.8 (0.2–16.3) 1.0 (0.1–9.4) 4.1 (0.7–24.0)	Did not clarify the true risk of FVL and COC use in the risk calculations.	II-2 fair
Andersen et al. [22], 1998 Helsefounden Danish Medical Research Council, Danish National Research Foundation	Case-control Denmark Matched for age	67 VTE 134 Controls (blood donors) Cases from hospital registries since 1977	COC use for 3 months before VTE (first-, second- and third-generation) FVL homozygous/ heterozygous	*OR for VTE:* No heritable thrombophilia present. Nonuser First and second Third Factor V Leiden mutation present. Nonuser First and second Third Heritable thrombophilia present (protein C, protein S or antithrombin deficiency; FVL) Nonuser First and second Third Above ORs are unadjusted. Reference for all comparisons is no FVL/no COCs.	 1.0 (ref.) 7.1 (2.0–25.2) 20.9 (3.1–141.3) 2.6 (0.7–9.1) 64.7 (6.0–693.8) 29.6 (1.9–456.1) 2.6 (0.7 -9.3) 63.3 (6.2–648.4) 52.5 (3.7–738.1)	Did not adjust for confounders (smoking, BMI and parity were different between types of COC users).	II-2 fair
Martinelli et al. [16], 1999 Not stated	Case-control Italy 1995–1998 Not matched	112 DVT 179 Controls (friends or partners) Ages 15–48 years	COC use ≤2 weeks before DVT (first-, second- and third-generation).	*OR for VTE:* No FVL/no COC) No FVL/COC FVL/no COC	 1.0 (ref.) 4.6 (2.6–8.0) 2.4 (0.4–15.1)	Selection of control group could lead to bias. Unclear if ORs were	II-2 fair

			FVL homozygous/ heterozygous	FVL/COC The interaction between FVL and COCs was 1.6 (95% CI, 0.2–18.0). Unclear if the above ORs are adjusted for age and presence of other thrombophilic defects.	20.0 (4.2–94.3)	adjusted for age.	
Spannagl et al. [20], 2000 Schering, Berlin	Case-control Germany 1995–1997 Matched by 5-year age group	80 DVT or PE 406 controls (random) Cases: from ambulatory and inpatient clinics Confirmed cases: positive imaging of thrombus and anticoagulant therapy Idiopathic cases: no prior VTE, pregnancy, delivery, accident, or operation ≤6 weeks before event	COC use at VTE (type not specified) FVL Carrier status not specified.	*OR for VTE:* All cases FVL/no COC: FVL/COC: Confirmed cases FVL/no COC FVL/COC Idiopathic cases FVL/no COC FVL/COC Above ORs are adjusted for varicose veins, family history of VTE and linear BMI. Reference for all comparisons is no FVL/no COC.	 1.7 (0.6–4.8) 6.4 (2.8–14.3) 1.6 (0.5–5.6) 7.0 (2.8–17.2) 1.3 (0.2–10.5) 10.2 (3.8–27.6)		II-2 good
Emmerich et al. [14], 2001 Not stated	Pooled analysis of 3 case-control studies	517 VTE 518 Controls recruited from health centers, same geographic area or identified by cases	COC type not specified FVL homozygous/ heterozygous	*OR for VTE:* No FVL/no COC FVL/no COC FVL/COC Above ORs are unadjusted.	 1.0 (ref.) 5.88 (3.52–9.82) 10.25 (5.69–18.45)	Did not adjust for confounders.	II-2 poor
Middeldorp et al. [17], 2001 Zorg Onderzoek Netherlands	Descriptive study 1997–2000 Not matched	236 Asymptomatic female carriers 9 Events in 1564 observation-years (5 females)	COC type not specified FVL homozygous/ heterozygous	*Annual incidence of VTE:* 0.58% (0.26–1.10%) *Incidence of VTE among 66 COC users:* 1.8% (0.4–5.2%) per year of COC use Above estimates are unadjusted.		Study design; could not estimate relative risk associated with COC use.	II-3 fair
Santamaria et al. [18], 2001 Not stated	Retrospective cohort Spain 1989–1999 Not matched	325 Women in 97 families 217 FVL 108 no FVL	COC use for 2 weeks before DVT (first-, second- and third-generation). FVL homozygous/ heterozygous	*105 DVT events* *OR for DVT:* No FVL/no COC FVL/no COC FVL/COC Above ORs are unadjusted.	 1.0 (ref.) 30.00 (2.87–749.43)[a] 99.00 (7.94–2857.17)[a]	Did not adjust for confounders. Selection of controls could lead to bias.	II-2 poor
Legnani et al. [15], 2002 Not stated	Case-control Italy 1994–2000	301 DVT 650 Controls (from general population in geographic areas of cases)	COC use at time of DVT (second- and third-generation). FVL homozygous/ heterozygous	*OR for DVT:* No FVL/no COC No FVL/COC FVL/no COC FVL/COC Above ORs are adjusted for age and presence of other thrombophilic defects.	 1.0 2.4 (1.7–3.5) 8.9 (4.4–18.2) 41.0 (13.5–125)	No adjustment for other confounders.	II-2 fair

(*continued on next page*)

Table 1 (*continued*)

Author, year, source of support	Study design	Population	Exposure	Results		Weaknesses	Quality
Factor V Leiden (FVL) mutation							
Vaya et al. [21], 2003 Not stated	Case-control Spain 1997–2001 Matched for age	43 Upper-extremity deep vein thrombosis (UEDVT) 97 Controls (hospitals)	COC use for 2 weeks before DVT (type not specified). FVL carrier status not specified.	*OR for UEDVT:* No COC use COC use Above OR is unadjusted. No cases among FVL carriers; risk estimates could not be calculated.	 (ref.) 5.78 (2.13–15.67)	Did not adjust for confounders.	II-2 poor
Martinelli et al. [24], 2004 Ministero dell'Università e della Ricerca Scientifica e Tecnología; Ministero della Sanità, Ricerca Finalizzata	Case-control Italy 1994–2003	65 UEDVT 288 Controls (friends or partners)	COC use for 2 weeks before thrombosis (type not specified). FVL or PT heterozygous	*OR for UEDVT:* No mutation/no COC No mutation/COC Mutation/no COC Mutation/COC Above ORs are adjusted for age.	 1.0 (ref.) 1.0 (0.5–2.0) 4.2 (1.4–12.6) 13.6 (2.7–67.3)	Did not provide separate estimates for FVL and PT carriers. Did not adjust for potential confounders.	II-2 poor
Sidney et al. [19], 2004 National Heart, Lung, and Blood Institute	Case-control California 1998–2000 Frequency matched on age	196 VTE 746 Controls (from same health care system) Ages 15–44 years	Current or past COC use (low estrogen) FVL homozygous/ heterozygous	*OR for VTE:* No FVL/no COC No FVL/COC FVL/no COC FVL/COC Above ORs adjusted for age; adjustment for BMI, family history of VTE, race/ethnicity did not change estimations. COC noncurrent use COC current use Above ORs are adjusted for age, race/ethnicity, income and BMI.	 1.0 (ref.) 3.20 (2.04–5.03) 8.42 (2.18–32.56) 11.32 (3.00–42.81) 1.0 (ref.) 4.07 (2.77–6.00)	Possible recall bias (COC use).	II-2 good
Prothrombin (PT) mutation							
Martinelli et al. [16], 1999 Not stated	Case-control Italy 1995–1998 Not matched	112 DVT 277 Controls (friends/partners) Ages 15–48 years	COC use ≤2 weeks before DVT (first-, second- and third-generation) PT heterozygous	*OR for DVT:* No PT/no COC No PT/COC PT/no COC PT/COC The interaction between PT and COCs was 1.1 (95% CI, 0.1–10.2). Above ORs are adjusted for age and presence of other thrombophilic defects.	 1.0 4.6 (2.6–8.0) 2.7 (0.6–12.7) 16.3 (3.4–79.1)	Selection of controls could lead to bias.	II-2 fair
Emmerich et al. [14], 2001 Not stated	Pooled analysis of three case-control studies	517 VTE 518 Controls recruited from health centers, same geographic area, or identified by cases.	COC type not specified PT homozygous/ heterozygous	*OR for VTE:* No PT/no COC PT/no COC PT/COC Above ORs are unadjusted.	 1.0 (ref.) 3.21 (1.44–7.15) 7.14 (3.39–15.04)	Did not adjust for confounders.	II-2 poor

Santamaria et al. [18], 2001 Not stated	Retrospective cohort Spain 1989–1999 Not matched	325 Women in 97 families 217 FVL 108 No FVL	COC use for 2 weeks before DVT (first-, second- and third-generation). PT homozygous/ heterozygous	105 DVT events *OR for DVT:* No PT/no COC PT/no COC PT/COC Above ORs are unadjusted.	 1.0 (ref.) 19.56 (2.28–437.25)[a] 25.55 (3.19–549.45)[a]	Did not adjust for confounders. Selection of controls could lead to bias.	II-2 poor
Legnani et al. [15], 2002 Not stated	Case-control Italy 1994–2000 Not matched	301 DVT 650 Controls (from general population in geographic areas of cases)	COC use at time of DVT (second- and third-generation) PT heterozygous	*OR for DVT:* No PT/no COC No PT/COC PT/no COC PT/COC Above ORs are adjusted for age and presence of other thrombophilic defects.	 1.0 (ref.) 2.4 (1.7–3.5) 2.0 (0.8–4.8) 58.6 (12.8–267)	No adjustment for additional confounders.	II-2 fair
Vaya et al. [21], 2003 None stated	Case-control Spain 1997–2001 Matched for age	43 Upper-extremity deep vein thrombosis (UEDVT) 97 Controls (hospitals)	COC use for 2 weeks before DVT (type not specified). PT Carrier status not specified.	*OR for UEDVT:* No COC use COC use Above ORs are unadjusted. The interaction term in the multivariate logistic regression analysis gave an OR of 927 (p=.715).	 1.0 (ref.) 5.78 (2.13–15.67)	Did not adjust for confounders.	II-2 poor
Martinelli et al. [24], 2004 Ministero dell'Università e della Ricerca Scientifica e Tecnologia Ministero della Sanità, Ricerca Finalizzata	Case-control Italy 1994–2003	65 UEDVT 288 Controls (friends/partners)	COC use for 2 weeks before thrombosis (type not specified). FVL or PT heterozygous	*OR for UEDVT:* No mutation/no COC No mutation/COC Mutation/no COC Mutation/COC Above ORs are adjusted for age.	 1.0 (ref.) 1.0 (0.5–2.0) 4.2 (1.4–12.6) 13.6 (2.7–67.3)	Did not provide separate estimates for FVL and PT carriers. Did not adjust for other potential confounders.	II-2 poor
Sidney et al. [19], 2004 National Heart, Lung and Blood Institute	Case-control California 1998–2000 Frequency matched on age	196 VTE 746 Controls (from same health care system) Ages 15–44 years	Current or past COC use (low-estrogen) PT homozygous/ heterozygous	*OR for VTE:* No PT/no COC No PT/COC PT/no COC PT/COC Above ORs are adjusted for age. COC noncurrent use COC current use Above ORs are adjusted for age, race/ethnicity, income and BMI.	 1.0 (ref.) 3.64 (2.30–5.77) 8.43 (1.60–44.41) 5.10 (0.83–31.18) 1.0 (ref.) 4.07 (2.77–6.00)	Possible recall bias (COC use).	II-2 good
Factor V Leiden and prothrombin							
Emmerich et al. [14], 2001 Not stated	Pooled analysis of three case-control studies	517 VTE 518 Controls recruited from health centers, same geographic area or identified by cases.	COC type not specified. PT and FVL homozygous/ heterozygous	*OR for VTE:* No FVL/no PT/no COC FVL+PT/no COC FVL+PT/COC Above ORs are unadjusted.	 1.0 (ref.) 14.67 (3.47–62.03) 16.97 (3.95–72.80)	Did not adjust for confounders.	II-2 poor

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Table 1 (*continued*)

Author, year, source of support	Study design	Population	Exposure	Results		Weaknesses	Quality
Factor V Leiden and prothrombin							
Santamaria et al. [18], 2001	Retrospective cohort	325 Women in 97 families	COC use for 2 weeks before DVT	105 DVT events		Did not adjust for confounders.	II-2 poor
Not stated	Spain	217 FVL	(first-, second- and	*OR for DVT:*		No matching.	
	1989–1999	105 no FVL	third-generation).	No FVL/no PT/no COC	1.0 (ref.)	Selection of controls	
	Not matched		PT and FVL	FVL+PT/no COC	88.00 (5.79–2996.25)[a]	could lead to bias.	
			homozygous/	FVL+PT/COC	110.00 (7.68–3607.48)[a]		
			heterozygous	Above ORs are unadjusted.			
Legnani et al. [15], 2002	Case-control	301 DVT	COC use at time	*OR for VTE:*		No adjustment for	II-2 fair
	Italy	650 Controls (from	of DVT (second-	No FVL+no PT/no COC	1.0 (ref.)	additional	
Not stated	1994–2000	general population in	and third-generation).	No FVL+no PT/COC	2.4 (1.7–3.5)	confounders.	
	Not matched	geographic areas of	PT and FVL	FVL+PT/no COC	Not estimable		
		cases)	heterozygous	FVL+PT/COC	86.5 (10.0–747)		
				Above ORs are adjusted for age and presence of other thrombophilic defects.			
Deficiencies in protein S, protein C or antithrombin							
Andersen et al. [22], 1998	Case-control	67 VTE	COC use for	*OR for VTE:*		Did not adjust for	II-2 fair
	Denmark	134 Controls (blood	3 months before	Heritable thrombophilia present		confounders	
Helsefounden	Matched for	donors)	VTE (first-, second-	(deficiency of protein C, protein S or		(smoking, BMI and	
Danish Medical	age	Cases from hospital	and third-generation).	antithrombin deficiency and FVL).		parity were different	
Research Council		registries since 1977	Heritable	Nonuser	2.6 (0.7 -9.3)	between type of	
Danish National			thrombophilia	First and second	63.3 (6.2–648.4)	COC users).	
Research			Homozygous/	Third	52.5 (3.7–738.1)		
Foundation			heterozygous	Reference group for above ORs is COC nonusers with no thrombophilia.			
Bloemenkamp et al. [23], 2000	Case-control (LETS study)	155 DVT	Duration of COC	*OR for DVT among COC users:*		Selection of controls.	II-2 fair
		169 Controls	use at time of DVT	First 6 months of COC use	3.0 (0.6–14.8)		
Netherlands Heart	Denmark	(friend/volunteer)	(different types of	First year of COC use	1.9 (0.6–6.1)		
Foundation	1988–1992		COCs).	≥13 months of COC use	1.0 (ref.)		
			Thrombophilia	*OR for DVT among women with thrombophilia:*			
			(protein C, protein				
			S and antithrombindeficiency;	First 6 months of COC use			
			FVL, PT)		18.5 (1.9–175.7)		

			Carrier status not specified.	First year of COC use ≥13 months of COC use Above ORs are adjusted for age; adjustment for history of pregnancy, positive family history did not change estimations.	11 (2.1–57.3) 1.0 (ref.)		
Santamaria et al. [18], 2001 Not stated	Retrospective cohort Spain 1989–1999 Not matched	325 Women in 97 families 217 FVL 108 no FVL	COC use for 2 weeks before DVT (first-, second- and third-generation). Protein C, protein S, antithrombin Homozygous/ heterozygous	105 DVT events *OR for DVT:* No thrombophilia/no COC Other/no COC Other/COC Above ORs are unadjusted.	 1.0 (ref.) 72.83 (9.81–1500.70)[a] 52.80 (4.06–1534.14)[a]	Did not adjust for confounders. Selection of controls could lead to bias.	II-2 poor
CVT or CST							
De Bruijn et al. [25], 1998	Case series compared to general population. Netherlands and UK 1992–1996	40 CST cases 2248 controls (randomly selected from the Netherlands) Information on mutation prevalence from previously published population estimates.	COC use at time of CST Protein C, protein S, antithrombin deficiency; FVL Carrier status not specified.	*OR for CST:* No mutation/no COC COC use mutation COC/mutation Above ORs are unadjusted. Mutation ORs based on population estimates of mutation prevalence.	 1.0 (ref.) 18.0 (5.0–59.0) 3.2 34.0	Exact OR and CIs not reported. Population estimates of mutations used to calculate ORs. No adjustment for confounders.	II-3 poor
Martinelli et al. [26], 1998 Not stated	Case-control Italy 1991–1997	27 CVT cases 93 Controls (friends/partners)	COC use during 2 weeks before CVT (type not specified). FVL homozygous/ heterozygous PT heterozygous	*OR for CVT:* No mutation/no COC PT/no COC No PT/COC PT/COC FVL/no COC No FVL/COC FVL/COC Above ORs are unadjusted.	 1.0 (ref.) No cases 13.4 (3.5–51.3) 149.3 (31.0–711) No cases 15.8 (4.3–57.2) 3 Cases, no controls	Too few cases to calculate some risk estimates and to adjust for confounders. Selection of controls could lead to bias.	II-2 poor

[a] Calculated for this systematic review.

2.1. Selection of studies

The search strategy identified a total of 301 articles. After reviewing the titles and abstracts of these articles as well as the full article when necessary, we included 16 studies. Most of those selected studies included odds ratios (ORs) for VTE among women with thrombogenic mutations by COC use. In addition, we included studies that did not report those risk estimates but added other valuable information such as duration of COC use and COC formulation.

We identified 11 studies that examined COC use and factor V Leiden [1,12–21]; six studies for the prothrombin mutation [14–16,18,19,21]; three studies for factor V Leiden, prothrombin or neither mutation [14,15,18]; and three studies for other thrombogenic mutations [18,22,23]. An additional study included carriers of factor V Leiden and prothrombin mutations for calculations of the risk, but did not differentiate between the two mutations [24]. We also identified two studies evaluating the risk of cerebral vein or cerebral sinus thrombosis (CST) among women with thrombogenic mutations [25,26]. We did not identify studies examining hormonal methods other than COCs.

Some of the studies indicated that they included women who were heterozygous, or who were either homozygous or heterozygous for the mutation of interest. When this information was not provided, it was assumed that both homozygotes and heterozygotes were included in the analysis. No study specifically focused on homozygotes.

2.2. Assessment of study quality and synthesis of data

We summarized and systematically assessed the evidence through the use of standard abstract forms [27]. We evaluated the quality of each individual piece of evidence using the system for grading evidence developed by the United States Preventive Services Task Force (Appendix A) [28].

We assessed the heterogeneity of the studies by examining the characteristics of the participants included in this review. Although the studies were too heterogeneous to calculate a summary statistic for VTE risk, we include a summary graph of relative risks (Fig. 1). We also constructed evidence tables according to mutation type and outcome (Table 1).

3. Results

3.1. Factor V Leiden

The Leiden Thrombophilia case-control study (LETS) in the Netherlands was the first to reveal that the factor V Leiden mutation increased the risk of VTE among women of reproductive age [OR, 7.9; 95% confidence interval (CI), 3.2–19.4] [1]. This study of 155 cases and 169 friend or partner controls also found an increased risk of VTE among COC users vs. nonusers (OR, 3.8; 95% CI, 2.4–6.0). Furthermore, women using COCs who also had the factor V Leiden mutation had more than a 30-fold risk of VTE (OR, 34.7; 95% CI, 7.8–154) when compared with non-COC users without the mutation; this translated to a four-fold risk for COC users with the mutation compared with nonusers with the mutation. These estimates were not adjusted for other risk factors such as age, body mass index (BMI) or smoking, although the authors reported that age adjustment served to increase the estimates. The authors also estimated that the background incidence of VTE among women aged 15–49 years was 0.8 per 10,000 person-years. The incidence increased to 3.0 among COC users without the mutation, to 5.7 among non-COC users with the mutation and to 28.5 among COC users with the mutation.

Following the LETS study, seven other studies [15,16,18–20,22,24] plus a pooled analysis [14] of three individual studies [4,29,30] have all shown an increased risk of VTE among women with factor V Leiden and further increased risk for COC users with the mutation, generally on a multiplicative scale (Table 1). The ORs for factor V Leiden alone ranged from 1.3 to 30.0. COC users with factor V Leiden had risk estimates of 1.3 to 25 times that of nonusers with factor V Leiden, but the CIs always overlapped. The ORs for COC users with factor V Leiden in comparison with women having neither risk factor ranged from 6.4 to 99.0. The quality of the studies and the pooled analysis varied, with three studies given a "poor" rating, another three "fair," and only two "good." Low-quality scores were generally due to indirect evidence, sparse data and lack of control for confounders. One of the good studies [20] found a smaller impact of factor V Leiden and COC use on VTE (OR, 6.4; 95% CI, 2.8–14.3) than in the LETS study and others. These discrepancies could be due to the selection of cases because this study included women from ambulatory and outpatient clinics while others included women from specialized clinics that would represent more severe cases. Other possible reasons include adjustment for confounders (varicose veins, family history of VTE and BMI) and the use of random controls rather than controls that were friends or acquaintances who might have had similar patterns of contraceptive use.

Two studies examined differences in VTE risk by formulation of the COC. Bloemenkamp et al. [13] examined data from the LETS study and found that among women with factor V Leiden who used COCs containing desogestrel (third-generation COCs), the risk of VTE was 6.0 (95% CI, 1.9–19.0) in a comparison with nonusers not having the mutation, which was higher than in similar comparisons for women with the mutation using first- or second-generation pills (OR range, 1.0–4.1, nonsignificant). In a case-control study in Denmark, third-generation pills, those containing desogestrel or gestodene, had a greater risk of VTE than other types of COCs [22]. Among women with factor V mutation, however, the risk estimate for the first- and second-generation pills was greater than for the third-generation pills (OR, 64.7; 95% CI, 6.0–693.8; OR, 29.6;

95% CI, 1.9–456.1, respectively). In a separate analysis examining the location of the DVT, for women using third-generation pills and having a factor V Leiden mutation the OR, for DVT in the left femoral vein was 2.5 times (95% CI, 0.2–33.4) than for women not having the mutation and not using COCs [12].

3.2. Prothrombin

Six studies [14–16,18,19,21] examined prothrombin mutations (Table 1). Five of these studies [14–16,18,19] found the risk ratio of initial VTE among women with prothrombin mutations to be from 2.0 to 19.6, with two of the studies having CIs including 1.00. Four of these studies [14–16,18] found a greater risk of VTE among women who had the mutation and used COCs (OR range, 7.14–58.6) in comparison with women having neither risk factor. One study of "good" quality evidence [19], however, found no such increase, and another study [21] did not report on the joint effect of the mutation and COC use. Three of these studies [15,16,19] adjusted for age and two [15,16] adjusted for the presence of other thrombophilic defects. Overall, three studies were of "poor" quality, primarily due to lack of controlling for confounders and selection of control groups that could lead to bias, two were "fair" and only one was "good".

A seventh study assessing risk of upper-extremity DVT among women with either factor V Leiden or prothrombin mutation reported an OR of 13.6 (95% CI, 2.7–67.3) for COC users when they were compared with women having neither risk factor, but it did not provide an estimate for prothrombin alone [24].

3.3. Factor V Leiden and prothrombin

Three studies examined the simultaneous presence of these two mutations among COC users and found ORs of 16.97 (95% CI, 3.95–72.80) [14], 110.00 (95% CI, 7.68–3607.48) [18] and 86.5 (95% CI, 10.0–747) [15], respectively, when compared with nonusers not having the mutations. The studies had too few cases to adjust for confounders.

3.4. Thrombophilia

We identified three studies that evaluated the risk of VTE with other thrombogenic mutations, specifically deficiencies of protein S, protein C and antithrombin. The first study found a greater risk of VTE among COC users with any one of these mutations (specific estimates for each mutation were not given) (OR, 52.80; 95% CI, 4.06–1534.14) in comparison with nonusers having no mutations [18]. The second study examined deficiencies of protein C, protein S, or antithrombin and the factor V Leiden mutation together and found greater risks for women with these mutations who used first- and second-generation COCs (OR, 63.3; 95% CI, 6.2–648.4) or third-generation COCs (OR, 52.5; 95% CI, 3.7–738.1) when they were compared with nonusers without thrombophilia [22]. Bloemenkamp et al. [23] examined duration of COC use and found that the first 6 months of COC use (OR, 18.5; 95% CI, 1.9–175.7) and the first year of COC use (OR, 11.0; 95% CI, 2.1–57.3) had higher risk estimates for VTE when compared to longer use (13 months or greater) among women with thrombophilia as the referent group.

3.5. Cerebral vein or cerebral sinus thrombosis

We identified two studies that evaluated cerebral sinus or cerebral vein thrombosis (CVT). The first study examined 40 women with CST in the Netherlands and UK and compared their oral contraceptive history with that of 2248 randomly selected women from the Netherlands [25]. Previously published estimates of the population prevalence of thrombogenic mutations (factor V Leiden and deficiencies in protein C, protein S or antithrombin) were assumed for the control population. They reported an increased risk of CST among COC users (OR, 18; 95% CI, 5–59) and also among women with a thrombogenic mutation (OR, 3.2; 95% CIs not reported). The authors then estimated that COC users with a mutation had 34 times the risk of CST as women with neither factor. The second study examined CVT among 40 cases and 120 controls in Italy [16]. COC users with the prothrombin mutation had greater risk of CVT (OR, 149.3; 95% CI, 31.0–711). For factor V Leiden and COC use, there were three cases of CVT but no controls.

4. Discussion

Ten studies provided overall "good" quality evidence that women with the factor V Leiden mutation who use COCs are at greater risk of developing VTE than nonusers without the mutation; ORs for VTE ranged from 6.4 to 99.0. For the prothrombin mutation, four studies of "fair" to "poor" quality found an increase in VTE risk for women who had the mutation and used COCs compared with nonusers without the mutation; however, one study of "good" quality did not find a statistically significant effect of both risk factors together. We found "fair" evidence from three studies that oral contraceptive users with both factor V Leiden and prothrombin mutations have an increased risk of VTE compared with nonusers having neither mutation. Finally, two studies of "poor" quality indicated that COC users with thrombogenic mutations have an increased risk of cerebral thrombosis.

Several key methodological issues must be considered in the review of these studies. As in all case-control studies, the selection of controls can be a key source of bias. For example, the use of blood donors as controls may be a problem if the contraceptive practices of blood donors differ from the general population from which the cases were drawn [22]. In the Vandenbroucke et al. [1] study, the selection of friends, acquaintances and partners of other cases as controls may be confounding because of a similarity in lifestyle to that of the cases. The authors postulated, however, that contraceptive use in the control

group was similar to that of the Danish entire population and thus it seems unlikely that the results would be skewed. On the other hand, the lack of control for confounders, either through matching or adjusting during analysis, could have biased these results.

Diagnostic bias may also be a concern as most of the cases were recruited from highly specialized hospitals or clinics. Women with VTE who used COCs may have been more likely to be admitted to the hospital because of the known association between VTE and COC use. Even so, Spannagl et al. [20], who included cases from both inpatient and ambulatory clinics, found in a sub-analysis of only severe cases that the OR did not vary from the ORs for all the cases. While only two studies examined differences between third-generation and other COCs, there may be confounding by indication, with women at higher risk of thrombosis preferentially prescribed third-generation pills.

It is unclear from the studies whether women who are homozygous for a thrombogenic mutation have a greater risk VTE when using COCs. Six of the papers specifically stated whether they included heterozygotes and homozygotes, but none computed a relative risk for homozygotes alone. In the study by Vandenbroucke et al. [1], the authors argued that because homozygous women have a greater risk at baseline of developing thrombosis, even a small increase in risk due to COC use would result in an overall risk of over 100 times than that of nonusers without a mutation. One must be cautious in the interpretation of this large increase in risk, however, because the relative risk for homozygotes is based purely on speculation.

In nearly all of the studies, the CIs were quite wide because of the small number of controls with mutations. Even though estimation of the risk was imprecise and CIs for thrombogenic mutation almost always overlapped with those for mutation plus use of oral contraceptives, the data overwhelmingly suggest that there is a multiplicative effect at work — the combination of factors produces greater risk than thrombogenic mutation alone.

We did not identify any studies that examined the use of other hormonal methods among women with thrombogenic mutations. Limited evidence, however, suggests there is no increased risk of VTE among women who use progestogen-only methods or combined injectable contraceptives [10,11].

Based on the large increase in risk for women who have thrombogenic mutations and use oral contraceptives, it has been suggested that all women should be screened for thrombogenic mutations before using oral contraceptives. It has been estimated that such a policy would deny oral contraceptives to at least 3–6% of women, while preventing a small number of cases of thrombosis; 99.9% of women who are carriers of factor V Leiden mutation would not have thrombosis if they received oral contraceptive pills [31,32]. Furthermore, a cost-effectiveness analysis of screening for factor V Leiden mutation found that more than 92,000 carriers would need to be screened to prevent one venous thrombogenic death attributed to oral contraceptive use at a cost of nearly $300 million. In addition, screening all 20-year olds for factor V Leiden mutation would cost $4.8 million per year of life saved, as compared to $21,400 per year of life saved for annual mammography screening in women aged 60–69 years [31]. These estimates are for the US population; such screening would be extremely difficult in low-resource settings.

In 2003, the WHO reviewed this evidence during a meeting of the Expert Working Group for medical eligibility criteria for contraceptive use (MEC) [33]. (Two of these studies were published in 2004 [19,24] and were therefore not included in the evidence presented to the Expert Working Group; evidence from both studies was consistent with the previous evidence.) The Expert Working Group concluded that a new condition, “known thrombogenic mutations,” should be added to the MEC. The group also recommended that women with known thrombogenic mutations should not use combined hormonal contraceptive methods (WHO Category 4), but that they can generally use progestogen-only methods, including levonorgestrel-releasing intrauterine devices (WHO Category 2). The Expert Working Group also issued a clarification with the recommendation that, “Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening.”

Acknowledgments

This review was supported by resources from the WHO, the US Centers for Disease Control and Prevention (CDC), US Agency for International Development and the US National Institute of Child Health and Human Development. We would also like to acknowledge the assistance of William Thomas, MLIS, Technical Information Specialist at CDC, for developing the literature search strategies. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the funding agencies.

Appendix A. Study quality assessment

A.1. Individual study

Each study was given a rating of either Level 1, Level II-1, Level II-2, Level II-3, or Level III based on the study design (Table 1). Each study was also given a rating of poor, fair, or good based on the criteria for grading the internal validity of a study (Table 2). A good study meets all criteria for that study design; a fair study does not meet all criteria but is judged to have no fatal flaw; and a poor study contains a fatal flaw. Also, the type of evidence was either identified as being direct (the evidence was based on data directly addressing the question) or indirect (the evidence was extrapolated from other relevant data).

A.2. Body of evidence

The quality of the body of evidence was the highest rating given to an individual study. If the results were inconsistent, the quality of the body of the evidence was lowered by one level. If results were consistent, then the quality of the body of the evidence was left at the original level.

Table 1. Levels of evidence [28]

	Levels of evidence
Level 1	Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1	Evidence obtained from well-designed controlled trials without randomization.
Level II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
Level II-3	Evidence obtained form multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regards as this type of evidence.
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Table 2. Criteria for grading the internal validity of individual studies [28]

Study Design	Criteria
Systematic Reviews	■ Comprehensiveness of sources/search strategy used ■ Standard appraisal of included studies ■ Validity of conclusions ■ Recency and relevance
Case-control studies	■ Accurate ascertainment of cases ■ Nonbiased selection of cases/controls with exclusion criteria applied equally to both ■ Response rate ■ Diagnostic testing procedures applied equally to each group ■ Appropriate attention to potential confounding variables
Randomized controlled trials (RCTs) and cohort studies	■ Initial assembly of comparable groups: ■ For RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups ■ For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts ■ Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) ■ Important differential loss to follow-up or overall high loss to follow-up ■ Measurements: equal, reliable, and valid (includes masking of outcome assessment) ■ Clear definition of interventions ■ All important outcomes considered ■ Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs
Diagnostic accuracy studies	■ Screening test relevant, available for primary care, adequately described ■ Study used a credible reference standard, performed regardless of test results ■ Reference standard interpreted independently of screening test ■ Handled indeterminate results in a reasonable manner ■ Spectrum of patients included in study ■ Sample size ■ Administration of reliable screening test

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