REVIEW ARTICLE

Risk of Venous Thromboembolic Disease Associated With Hormonal Contraceptives and Hormone Replacement Therapy

A Clinical Review

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Venous thromboembolic events (VTEs) represent a serious complication related to hormonal contraception and hormone replacement therapy (HRT). Evidence on hormonal contraceptive– and HRT-related VTEs is derived almost exclusively from observational studies and points to a 2- to 6-fold increased relative risk of VTEs with either therapy. Oral contraceptive pills that contain third-generation progestins (desogestrel or gestodene) seem to be associated with greater VTE risk than those that contain levonorgestrel. Oral contraceptive pill use and HRT are associated with exponentially higher VTE relative risks when used by women who carry an inherited hypercoagulable state. The indication of a lower or a lack of VTE risk associated with the use of progestin-only contraceptives and with transdermal HRT suggests that these therapies may be safer than combination oral contraceptive pills and oral HRT for women in whom oral estrogen therapy is considered contraindicated. Data that support such safety advantages are limited and should be interpreted with caution. *Arch Intern Med. 2004;164:1965-1976*

Venous thromboembolic events (VTEs) are among the most feared complications associated with oral contraceptive pill (OCP) use and hormone replacement therapy (HRT) because VTEs carry substantial morbidity and have the potential to be fatal. Venous thromboembolic events typically manifest as deep venous thrombosis (DVT) with or without pulmonary embolism (PE), but the spectrum of VTEs also includes upper extremity and intra-abdominal DVT, cerebral sinus thrombosis (venous stroke), and superficial venous thrombophlebitis. Population-based studies[1-4] have shown that the annual incidence of VTEs increases from approximately 1 in 100 000 persons younger than 20 years to 1 in 10 000 persons aged 20 to 40 years, 1 in 1000 persons aged 41 to 75 years, and 1 in 100 persons older than 75 years. Therefore, any exposure that increases the relative risk of VTEs will result in greater absolute risk and will likely be of greater clinical significance in older rather than young persons.

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Because hormonal therapy is often withheld in women with a history of VTEs and in those who carry an inherited hypercoagulable state or are perceived to be at greater baseline risk of VTEs, better understanding of the data on which such practice is based is important and should help guide more evidence-based decisions in the future. In addition, because hormonal contraception and HRT can be accomplished by a variety of different compounds, with different types and doses of estrogens and progestins, it is important to identify whether the data on VTE risk apply to all compounds or only to certain substances and dosages.

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Most hormonal contraceptives contain a combination of an estrogen (mestranol or ethinyl estradiol) and a progestin, but progestin-only oral, injectable, and implantable products are also available. Combination OCPs and progestin-only contraceptives have efficacy greater than 99% with "perfect" compliance.[5] However, progestin-

Table 1. Types of Estrogen and Progestin Used in Combination OCPs and Progestin-Only Contraceptives in the United States*

	Estrogen†								
	Ethinyl Estradiol, µg								
Progestin†	15	20	25	30	35	40	50	Mestranol, 50 µg	Progestin Only
First generation									
Norethindrone (acetate)		X		X	X		X	X	X (POP)
Ethynodiol diacetate					X		X		
Second generation									
Levonorgestrel		X		X		X			X (IP)‡
Norgestrel				X			X		X (POP)
Third generation									
Desogestrel	X	X	X	X					
Norgestimate§			X		X				
Unclassified									
Drospirenone				X					
Medroxyprogesterone acetate									X (IM)‖
Norelgestromin¶		X							
Etonogestrel#	X								

Abbreviations: IM, intramuscular injection only; IP, subdermal implants; OCPs, oral contraceptives; POP, progestin-only pill.

*The following progestins are not available in the United States: gestodene (third generation), norgestrione (second generation), lynestrenol, norethynodrel (first generation), and cyproterone acetate (unclassified).

†Varying doses in multiphasic preparations.

‡No longer available in the United States.

§Classified as a second-generation progestin in some studies.

‖Also available as an injectable contraceptive in combination with estradiol cypionate.

¶Available only as a transdermal (patch) contraceptive.

#Available only as a once-a-month contraceptive vaginal ring.

only contraceptives are less popular because they are associated with higher pregnancy ("failure") rates with "typical use" and with considerable breakthrough bleeding.[5] According to estimates by the World Health Organization, there currently are more than 100 million women using some form of hormonal contraception worldwide,[6] of whom 12 million and 1 million are users of progestin-only injectable contraceptives and progestin-only pills (POPs), respectively.[7]

The first OCP was approved in the United States in 1960 and contained 150 µg of mestranol and 10 mg of norethynodrel.[8] Mestranol is metabolized in the liver into the active agent ethinyl estradiol,[5] and OCPs containing 35 µg of ethinyl estradiol are equivalent to those containing 50 µg of mestranol.[9] Through the years, the estrogen content of OCPs has been reduced with the goal of minimizing adverse effects, and some currently available OCPs contain only 15 µg of ethinyl estradiol. Progestins are classified as first-, second-, and third-generation drugs based on when they were produced,[10] but some recent studies defined first-generation OCPs as those containing more than 50 µg of ethinyl estradiol in combination with any progestin. Second- and third-generation OCPs were introduced in the early 1970s and early 1980s (1990s in the United States), respectively.[10,11] Specific estrogens and progestins that are used in combination and progestin-only contraceptives are listed in **Table 1**.

The use of HRT increased exponentially between the 1960s and the middle of the 1990s, and in 1999 an estimated 20 million postmenopausal women were using HRT worldwide.[12] Hormone therapy–HRT can be accomplished by 3 regimens: estrogen alone and estrogen plus continuous or cyclical progestin.[13] Because unopposed estrogen replacement is associated with increased rates of endometrial hyperplasia and cancer, it is best reserved for women who have undergone a hysterectomy. Combination HRT is the regimen of choice for women with a uterus.[13] The 2 types of estrogen commonly used in oral HRT are conjugated equine estrogens and micronized estradiol, and transdermal preparations of 17β estradiol are also available. In the United States, the most prescribed HRT regimen contains conjugated equine estrogens combined with medroxyprogesterone acetate.[14] Conjugated equine estrogens have a complex composition of at least 9 different estrogens, some of which do not even occur in humans.[15] At the doses used clinically, the potency of estrogens included in HRT preparations is 6 times lower than the potency of ethinyl estradiol contained in currently available OCPs, with 1.25 mg of conjugated equine estrogens being equivalent to much less than 50 µg of ethinyl estradiol.[16]

This review updates, summarizes, and discusses the strengths and limitations of the available evidence on the association between VTEs and OCPs and HRT. Readers are referred to recent reviews[10,17] of the association between OCPs, HRT, and arterial thromboembolism.

METHODS

We performed single keyword and Boolean PubMed searches for English-language articles relating to humans published between January 1, 1966, and September 30, 2003, using the following keywords and phrases: *(deep) venous thrombosis, thrombophlebitis, venous thromboembolism, pulmonary embolism, estrogen, (oral) contraceptives, progesterone-only pills,* and *hormone (estrogen) replacement (therapy).*

Table 2. Studies Comparing the Risk of VTEs Between OCP Users and Nonusers

Source	RR or OR (95% CI)*	VTE Risk According to Estrogen Content	Study Design	Patient Age, Range, y	Outcomes Studied
Studies in Which VTEs Were Objectively Confirmed in All Included Cases					
Valla et al,[19] 1986	2.37 (1.05-5.34)		Case-control	15-45	Hepatic vein thrombosis
Thorogood et al,[20] 1992	2.1 (0.8-5.2)†		Case-control	16-39	Fatal PE
	1.6 (0.7-3.4)‡				
Quinn et al (PIOPED),[21] 1992	0.89§		Case-control	18-37	All PE
Vandenbroucke et al (LETS),[22] 1994	3.8 (2.4-6.0)		Case-control	15-49	All DVT, PE
Spitzer et al (Transnational),[23] 1996	4.0 (3.1-5.3)		Case-control	16-44	Idiopathic DVT, PE
Grodstein et al (NHS),[24] 1996	2.2 (0.8-5.9)		Cohort	30-55	Idiopathic PE
Realini et al,[25] 1997	6.38 (1.19-34.2)		Case-control	<40	All DVT, PE
Martinelli et al,[26] 1998	22.1 (5.9-84.2)		Case-control	15-54	Cerebral sinus thrombosis
de Bruijn et al,[27] 1998	13 (5.0-37.0)		Case-control	18-54	Cerebral sinus thrombosis
Bloemenkamp et al,[28] 1999	5.0 (3.1-8.2)†	OR = 8.7 (EE = 50 µg)	Case-control	15-49	All DVT
	3.9 (2.6-5.7)‖	OR = 3.7 (EE = 30 µg)			
Martinelli et al,[29] 1999	4.6 (2.6-8.0)		Case-control	<50	All DVT
Bloemenkamp et al,[30] 2000	4.0§		Case-control	15-49	All DVT
Parkin et al,[31] 2000	9.6 (3.1-29.1)		Case-control	15-49	Fatal PE
Studies in Which VTEs Were Confirmed in Only a Percentage of Cases¶					
Helmrich et al,[32] 1987	8.1 (3.7-18)		Case-control	18-49	Idiopathic DVT, PE
Gerstman et al,[33] 1990		RR = 2.6 (1.2-5.5) (EE>100 µg vs <50 µg)	Cohort	15-44	All DVT, PE
Hirvonen et al,[34] 1990	1.2 (0.37-3.68)		Cohort	15-39	Fatal PE
Gerstman et al,[35] 1991		RR = 3.2 (2.4-4.3) (EE>50 µg vs <50 µg)	Cohort	15-44	All DVT, PE
Poulter et al (WHO),[36] 1995	3.95 (2.95-5.28)#		Case-control	20-44	Idiopathic DVT, PE
	3.25 (2.59-4.08)**				
Jick et al (UK-GPRD),[37] 1995	5.9 (3.7-9.8)††		Cohort	<40	Idiopathic DVT, PE
Heinemann et al,[38] 2002	5.4 (4.0-7.4)†		Case-control	15-49	All DVT, PE
	3.4 (2.7-4.2)‡				

(*continued*)

We also identified original articles by back-referencing from original and relevant review articles published after 1995. If an original study did not provide a measure of VTE risk (such as relative risk or odds ratio), we calculated the unadjusted risk whenever the study presented raw data that allowed us to reconstruct 2 × 2 tables. Abstracts and articles from non–peer-reviewed journals were not included in this review.

RESULTS AND DISCUSSION

Combination Oral Contraceptives and VTEs

The first case report of an OCP-related VTE was published in 1961, when a nurse developed PE while using an OCP containing 100 µg of mestranol and 5 mg of norethynodrel.[18] Data on OCP-related VTE risk consist of 46 original studies (**Table 2** and **Table 3**).[19-65] Except for 1 randomized controlled trial[40] and 3 prospective cohort studies,[46,49,51] all remaining data were derived from case-control and nested case-control studies. The latter were derived from cohorts identified through computerized medical records from large public or private clinics, health maintenance organizations, or pharmacy network database programs.

The 37 original studies[19-56] comparing the risk of VTEs between users of any combination OCP and nonusers are given in Table 2. Studies differ in terms of definition of VTE outcomes, age range of studied women, types of OCPs used, and criteria for selection of controls. Although most studies included at least 2 age-matched controls per case, different age strata were used to match cases and controls among studies. Also, because a 35-year span exists between the first and last published studies, the OCPs under investigation are different regarding estrogen dose (higher in earlier studies) and progestin type.

Most important, in only 15 (33%) of the 46 studies was the VTE diagnosis objectively confirmed in 100% of included cases. All 3 prospective cohort studies[46,49,51] and some recent landmark studies[37,38,59] are included among those in which the diagnosis of VTEs was not objectively confirmed in all included cases. In the World Health Organization Collaborative Study,[36,59] the investigators reported that the overall study results were upheld even when the analysis was restricted to the 42% of cases with confirmed VTEs.

Because it has been demonstrated that less than half of the patients with clinically suspected DVT or PE will have the diagnosis confirmed by objective imaging,[66-69] inclusion of cases diagnosed without objective confirmation is likely to be associated with many false-positive diagnoses and, hence, to have the potential to overestimate VTE risk in prospective studies. However, in observational studies, such an excess of cases may tend to bias the estimated risk toward the null hypothesis, thus resulting in underestimation of risk. This may explain the remarkable consistency of findings across multiple studies, where estimated relative risks of OCP-related VTE risk are similar despite some methodological flaws and substantial heterogeneity among studies. Such heterogeneity makes it difficult to apply meta-analytic mod-

Table 2. Studies Comparing the Risk of VTEs Between OCP Users and Nonusers (cont)

Source	RR or OR (95% CI)*	VTE Risk According to Estrogen Content	Study Design	Patient Age, Range, y	Outcomes Studied
Studies in Which the Tests Used for VTE Diagnosis Were Not Specified and the Percentage of Cases Objectively Confirmed Is Unknown					
Sartwell et al,[39] 1969	4.4 (3.1-6.8)		Case-control	15-44	Idiopathic DVT, PE, SVT
Fuertes-de la Haba et al,[40] 1971	1.12 (0.4-2.9)		RCT	21-40	All DVT, PE
Greene and Sartwell,[41] 1972	6.5		Case-control	15-44	Situational DVT, PE
Boston Collaborative,[42] 1973	11.0 (5.2-25.0)		Case-control	20-44	Idiopathic DVT, PE, SVT
Grounds,[43] 1974	0.35§		Cohort	15-45	Idiopathic DVT, PE
Stolley et al, 1975/Maguire et al,[44,45] 1979	4.1 (1.3-13.1)† 2.0 (1.1-3.8)‡	OR = 4.7 (EE<100 µg) OR = 10.1 (EE>100 µg)	Case-control	15-49	All DVT, PE, SVT
Royal College of General Practitioners,[46] 1978	4.17 (2.1-10.9)	OR = 3.2 (EE>100 µg) OR = 1.7 (EE<50 µg)	Prospective cohort	15-49	Idiopathic DVT, SVT
Petitti et al,[47] 1978	7.7 (2.9-20.7)† 1.9 (0.9-4.1)‡		Case-control	18-54	All DVT, PE, SVT
Petitti et al (Walnut Creek),[48] 1979	6.7 (2.6-17.2)	OR = 7.6 (EE>50 µg) OR = 0.3 (EE<50 µg)	Case-control	18-54	Idiopathic DVT, PE
Porter et al,[49] 1982	8.3 (3.0-23.0)		Prospective cohort	20-44	Idiopathic DVT, PE
Porter et al,[50] 1985	2.8 (0.9-8.2)		Cohort	15-44	Idiopathic DVT, PE
Vessey et al,[51] 1986	4.1§	RR = 1.58 (EE>50 µg vs <50 µg)	Prospective cohort	25-56	All DVT, PE
Farmer et al (UK-MediPlus),[52] 1997	4.10 (3.26-5.08)††		Cohort	14-49	All DVT, PE
Lidegaard et al,[53] 2002	2.6§	OR = 0.6 (0.4-0.9) (EE = 20 µg vs 30-40 µg) OR = 1.6 (0.9-2.8) (EE = 50 µg vs 30-40 µg)	Case-control	15-44	All DVT, PE
Studies in Which the Diagnosis of a VTE Was Made on Clinical Grounds Alone in Most Cases					
Royal College of General Practitioners,[54] 1967	2.5§		Case-control	15-49	All DVT, PE, SVT
Vessey and Doll,[55] 1968	8.61§		Case-control	16-40	Idiopathic DVT, PE
Vessey and Doll,[56] 1970	3.8		Case-control	16-40	Situational DVT, PE

Abbreviations: CI, confidence interval; DVT, deep venous thrombosis; EE, ethinyl estradiol; LETS, Leiden Thrombophilia Study; NHS, Nurses' Health Study; OCP, oral contraceptive pill; OR, odds ratio; PE, pulmonary embolism; PIOPED, Prospective Investigation of PE Diagnosis Study; RCT, randomized controlled trial; RR, relative risk; SVT, superficial venous thrombophlebitis; UK-GPRD, United Kingdom General Practice Research Database; VTE, venous thromboembolic event; WHO, World Health Organization.

*Risk in OCP users compared with nonusers. Risk is expressed as RR in cohort studies and the RCT and as OR in case-control studies.
†Risk of idiopathic VTE only.
‡Risk of situational VTE only.
§Risk calculated from data reported in the study.
‖Risk of idiopathic and situational VTE combined.
¶Percentage of VTEs objectively diagnosed varied from 28% to greater than 90% of cases, depending on the study.
#Estimated risk in women from European countries only.
**Estimated risk in women from South America, Asia, and Africa.
††Study consisted of cohort and nested case-control analyses; RR, of VTE in OCP users vs nonusers as reported from the cohort study.

els to address some of the issues pertaining to OCP-related VTE risk. This can be illustrated by the fact that no more than 15 studies have been included in the meta-analyses addressing the risk of VTEs associated with OCP use.[70-72]

Despite all the limitations discussed previously, several findings can be extracted from the available data:

1. The risk of VTEs is higher in the first 6 months to 1 year of OCP use, particularly among first-time users,[23,30,36,53,73-76] and the risk associated with reexposure after a period of no use is similar to, and not higher than, that associated with first-time use.[77] The increased risk of VTE is apparent by the fourth month of OCP use, does not increase further with duration of use, and disappears by the third month after OCP discontinuation.[36,39]

2. The incidence rates of VTEs are higher in OCP users aged 40 to 49 years or 45 to 49 years compared with younger users,[52,54,65] which reflects the increased baseline age-associated absolute risk of VTE in older users.

3. One prospective cohort study[51] found a non–statistically significant doubling of the risk of postoperative VTEs in women who used OCPs during the month of surgery compared with those who stopped their OCP use more than 1 month before surgery.

4. One prospective cohort study[46] demonstrated that the risk of a first, isolated idiopathic superficial venous thrombophlebitis event is increased 3-fold in users of OCPs.[78]

5. Most studies* comparing OCPs with higher estrogen doses relative to lower estrogen doses have revealed that the risk of VTEs is approximately twice as high in users of OCPs containing higher estrogen doses (Table 2). Such a relationship between estrogen dose and VTE risk was not found in other studies.[32,49,50,57,81] Bloemenkamp et al[28] and Lidegaard et al[53] have shown that the risk of VTEs is greater in users of OCPs containing 50 µg as opposed to less than 35 µg of ethinyl estradiol and

References 11, 28, 33, 35, 44, 46, 51, 53, 73, 79, 80.

Table 3. Studies Comparing the Risk of VTEs Between Second- and Third-Generation OCPs

Source	Study Design	Odds Ratio (95% CI)			
		Third- vs Second-Generation OCPs*	Desogestrel vs Levonorgestrel	Gestodene vs Levonorgestrel	Norgestimate vs Levonorgestrel
Studies in Which VTEs Were Objectively Confirmed in All Included Cases					
Bloemenkamp et al (LETS),[57] 1995	Case-control	2.2 (0.9-5.4)	NA	NA	NA
Spitzer et al (Transnational),[23] 1996	Case-control	1.5 (1.1-2.1)	1.5 (1.1-2.2)	1.5 (1.0-2.2)	NA
Bloemenkamp et al,[28] 1999	Case-control	1.9 (0.8-4.5)	NA	NA	NA
Jick et al (UK-GPRD),[58] 2000	Cohort/case-control	2.3 (1.3-3.9)	NA	NA	NA
Studies in Which VTEs Were Confirmed in Only a Percentage of Cases†					
Farley et al (WHO),[59] 1995	Case-control	2.7 (1.6-4.6)	2.4 (1.3-4.6)	3.1 (1.6-5.9)	NA
Jick et al (UK-GPRD),[37] 1995	Cohort/case-control	2.2 (1.0-4.7)‡	2.2 (1.1-4.4)	2.1 (1.0-4.4)	NA
Lidegaard et al,[60] 1998	Case-control	1.44 (0.83-2.50)	NA	NA	NA
Andersen et al,[61] 1998	Case-control	9.7 (0.4-259.6)	NA	NA	NA
Heinemann et al,[38] 2002	Case-control	1.7 (0.9-3.6)§ 0.9 (0.6-1.4)‖	NA	NA	NA
Studies in Which the Tests Used for VTE Diagnosis Were Not Specified and the Percentage of Cases Objectively Confirmed Is Unknown					
Farmer et al (UK-MediPlus),[52] 1997	Cohort/case-control	1.68 (1.04-2.75)¶ 1.34 (0.74-2.39)#	1.76 (0.91-3.48) 0.87 (0.41-1.83)	1.32 (0.70-2.49) 0.84 (0.38-1.85)	NA
Farmer et al,[62] 1998	Case-control	0.77 (0.38-1.57)	NA	NA	NA
Herings et al,[63] 1999	Cohort	4.2 (1.7-10.2)	4.2 (1.7-10.6)	3.9 (1.2-12.9)	NA
Burnhill (PPFAC),[64] 1999	Cohort	11.8 (1.4-11.9)**	1.9 (0.6-5.9)††	NA	NA
Farmer et al,[65] 2000	Cohort/case-control	NA	1.0 (0.6-1.6)	1.3 (0.8-1.6)	1.1 (0.6-2.3)
Lidegaard et al,[53] 2002	Case-control	1.4 (1.0-1.9)	1.6 (1.0-2.4)	1.0 (0.7-1.4)	0.4 (0.2-0.8)

Abbreviations: CI, confidence interval; LETS, Leiden Thrombophilia Study; NA, not applicable; PPFAC, Planned Parenthood Federation of America Clinics; OCPs, oral contraceptive pills; UK-GPRD, United Kingdom General Practice Research Database; VTE, venous thromboembolic event.

*Norgestimate is included as a second-generation OCP in some studies.

†Percentage of VTEs objectively diagnosed varied from 42% to 88% of cases, depending on the study.

‡Based on confirmed VTE cases only.

§Analysis restricted to hospitalized cases and controls.

‖Analysis of all cases and controls.

¶Analysis adjusted by age only.

#Multiple regression analysis.

**Risk of deep venous thrombosis in women using OCPs containing desogestrel relative to norgestimate.

††Risk of pulmonary embolism in women using OCPs containing desogestrel relative to norgestrel (not levonorgestrel).

that OCPs containing 30 µg or more of ethinyl estradiol confer a higher risk than OCPs containing 20 µg of ethinyl estradiol.[53] However, the true risk of VTEs associated with OCPs containing very low estrogen doses (≤20 µg of ethinyl estradiol) remains unknown.[7,28,52,59,65,82-85]

Because of the retrospective nature of data acquisition in observational studies, a variety of biases or even the methods used could affect the results. For example, underestimation of the risk of VTEs may have occurred in some studies in which the analyses were restricted to idiopathic or fatal PE, thus excluding patients who may have developed other forms of VTE while exposed to OCPs. In addition, the single existent randomized controlled trial did not detect an association between OCP use and VTEs, probably owing to lack of adequate power to detect such an association and questionable compliance and evidence of crossover between the OCP and the "alternative contraception" groups.[40,86]

Because OCP use has been perceived as a risk factor for VTEs for many years, diagnostic suggestion and referral bias could have led to an overestimation of the OCP-related VTE risk because physicians may be prone to pursue an objective diagnosis of VTE in women taking OCPs.[87,88] However, Realini et al[25] and Bloemenkamp et al[28] demonstrated that such bias cannot explain the association between OCP use and VTEs (Table 2). In both studies,[25,28] cases and controls were selected from among women who had undergone objective imaging for DVT and thus were subject to similar diagnostic suggestion by referring physicians, regardless of history of OCP use.

Studies[20,28,39,41,45,47,55,56] have also shown that the OCP-related VTE risk is increased for situational VTEs (ie, after exposure to a known risk factor, such as surgery or pregnancy) and for idiopathic VTEs (ie, spontaneous), albeit the point risk estimate for situational VTEs is approximately 50% lower than that for idiopathic VTEs (Table 2). Exclusion of patients with known situational and acquired (eg, active cancer) risk factors for VTEs increases the likelihood that VTEs were triggered solely by exposure to OCPs. Moreover, assuming that there was no synergistic interaction between OCP use and the other situational risk factor, the weaker risk seen for situational VTEs is to be expected and should not be viewed as a potential bias that affects the study results.[86,89]

Before 1995, it was believed that the type and potency of progestins did not increase the risk of DVT and PE.[33] Since then, 13 of 15 studies found greater VTE risk in users of third-generation OCPs than in users of second-generation OCPs, although the difference has not always reached sta-

Table 4. Risk of VTEs Associated With Progestin-Only Contraceptives

Source	Study Design	VTE Risk*		
		Contraceptive POPs†	Therapeutic POPs‡	Progestin-Only Injectable§
Lewis et al,[11] 1996	Case-control	1.28 (0.66-2.5)	NA	NA
Farmer et al (UK-MediPlus),[52] 1997	Cohort/nested case-control	0.84/10 000‖	NA	NA
Lidegaard et al,[60] 1998	Case-control	2.61 (0.69-9.8)	NA	NA
WHO et al,[7] 1998	Case-control	1.74 (0.8-3.99)	NA	2.19 (0.66-7.3)
Vasilakis et al (UK-GPRD),[104] 1999	Nested case-control	1.3 (0.3-6.8)	5.3 (1.5-8.7)	NA
Heinemann et al (Transnational),[105] 1999	Case-control	0.68 (0.3-2.6)	NA	NA
Poulter et al (WHO),[106] 1999	Case-control	NA	5.9 (1.2-30.1)	NA
Lidegaard et al,[53] 2002	Case-control	2.0 (0.8-5.1)	NA	NA

Abbreviations: NA, not applicable; POPs, progestin-only pills; UK-GRPD, United Kingdom General Practice Research Database; VTE, venous thromboembolic event; WHO, World Health Organization.
*All risks are expressed as odds ratio (95% confidence interval) except where otherwise noted.
†Prescribed for contraception.
‡Prescribed for the treatment of menstrual disorders.
§Mostly medroxyprogesterone acetate (Depo-Provera; Pfizer Inc, New York, NY).
‖Risk is expressed as crude risk from the cohort analysis (number of events per women – years at risk).

tistical significance (Table 3). However, that criteria for grouping progestins into "generations" have varied: because norgestimate is partially metabolized into levonorgestrel, many studies included norgestimate as a second-generation OCP.[23,37,38,53,59,60] Based on limited data, the risk of VTEs associated with norgestimate use seems to be similar to that of levonorgestrel use and lower than that of desogestrel and gestodene (Table 3).

Concerns that the findings of a differential VTE risk between second- and third-generation OCPs were not a result of true association but of bias and confounding led to a fierce and lengthy debate in the literature[90-99] and to many reanalyses of the original data.[11,74-77,82,83] Prescription bias, "attrition of susceptibles" or "starter effect" bias, and recall and "switching pill" bias are among the many biases and confounding factors that have been implicated as accounting for the differential risk. Arguments supporting and refuting the presence of these biases have been extensively exchanged.* Independent reviews[85,102,103] of all available data have concluded that the biases may partially account for, but do not seem to entirely explain, the differential risk. In addition, 2 meta-analyses[71,72] have concluded that there is a small but real differential risk of VTEs between third- and second-generation OCPs. An interesting but concerning finding of one of the meta-analyses[71] is that results differ depending on the study funding sources: a significant differential risk between third- and second-generation OCPs was found by non–industry-sponsored studies, whereas industry-sponsored studies showed a point risk estimate of approximately 2.0 but with wide confidence intervals that included the unity.

Most epidemiologic studies have reported VTE risk in users of monophasic OCPs. Monophasic combination OCPs provide a constant daily dose of estrogen and progestin, whereas biphasic or triphasic OCPs provide varying doses of both components given through a 21-day cycle.[5] The limited data[22,57] suggesting that the risk of VTEs associated with multiphasic levonorgestrel OCPs is similar to that of monophasic levonorgestrel OCPs do not allow definitive conclusions. In addition, there are no studies, to our knowledge, that address the risk of VTEs in users of OCPs containing drospirenone, a progestin analogue of spironolactone. Likewise, the risk of VTEs in users of the combination contraceptive vaginal ring NuvaRing (Organon USA, Roseland, NJ) is unknown.

Progestin-Only Contraceptives and VTEs

Data on POP-related risk of VTEs are derived exclusively from 8 case-control studies, with none of the VTE risk estimates reaching statistical significance (**Table 4**). The VTE risk associated with injectable contraceptives was assessed by only 1 case-control study,[7] in which most women were using medroxyprogesterone acetate (Depo-Provera; Pfizer Inc, New York, NY), and a non–statistically significant odds ratio of 2.19 was found (Table 4). There are no data pertaining to the risk of VTEs associated with implantable subdermal levonorgestrel rods (Norplant; Wyeth, Madison, NJ, and Implanon; Organon, Roseland, NJ) and with a levonorgestrel-releasing intrauterine device (Mirena; Berlex Inc, Montville, NJ). Only 1 case and 5 controls were using subdermal levonorgestrel rods in the World Health Organization Collaborative Study,[7] and they were excluded from the analysis.

When POPs are used to treat menstrual disorders, they may contain different progestins or higher doses of progestins than those found in POPs used for contraception.[104,106] Unlike contraceptive POPs, therapeutic POPs have been associated with a 5- to 6-fold increased risk of VTE compared with nonusers (Table 4). This finding possibly reflects a progestin dose-response effect, although the results may have been impacted by confounding in at least 1 of the studies,[106] in which women using therapeutic POPs were older than those using contraceptive POPs.

References 11, 23, 28, 37, 52, 57, 61, 63, 74-76, 82, 84, 85, 87, 100, 101.

Table 5. Studies Comparing the Risk of VTEs Between HT Users and Nonusers

Source	Study Design	RR or OR (95% CI)*			
		Overall	Oral HT		Transdermal HT
			Combined	Estrogen Only	
Boston Collaborative,[16] 1974	Case-control	1.75†	NA	NA	NA
Petitti et al (Walnut Creek),[48] 1979	Case-control	0.7 (0.2-2.5)	NA	NA	NA
Nachtigall et al,[124] 1979	Double-blind, prospective	0.77‡	NA	NA	NA
Quinn et al (PIOPED),[21] 1992	Case-control	1.03 (0.60-1.75)	NA	NA	NA
Devor et al,[110] 1992	Case-control	0.79 (0.30-2.08)	NA	NA	NA
Daly et al,[111] 1996	Case-control	3.5 (1.8-7.0)	5.3 (1.9-14.6)	3.2 (1.4-7.4)	2.0 (0.5-7.6)
Jick et al,[112] 1996	Case-control	3.6 (1.6-7.8)	2.4 (0.8-7.3)	4.1 (1.8-9.3)	NA
		4.0 (1.6-9.7)§	NA	NA	NA
		2.5 (0.5-12.2)‖	NA	NA	NA
Grodstein et al (NHS),[24] 1996	Cohort	2.1 (1.2-3.8)	NA	NA	NA
Daly et al,[113] 1996	Case-control	2.3 (0.6-8.1)	NA	NA	NA
Perez-Gutthann et al (UK-GPRD),[114] 1997	Case-control	2.1 (1.4-3.2)	2.2 (1.4-3.5)	1.9 (1.0-3.8)	2.1 (0.9-4.6)
		2.2 (1.4-3.6)§	NA	NA	NA
		1.9 (1.0-3.9)‖	NA	NA	NA
Varas-Lorenzo et al,[115] 1998¶	Case-control	2.3 (1.0-5.3)	5.0 (1.5-16.7)	1.4 (0.4-4.6)	NA
		2.7 (1.2-6.5)**	NA	NA	NA
Høibraaten et al,[15] 1999#	Case-control		NA	1.22 (0.76-1.94)	0.57†
Grady et al (HERS),[116] 2000	RCT	2.7 (1.4-5.0)	NA	NA	NA
		2.8 (1.3-6.0)§	NA	NA	NA
		2.8 (0.9-8.7)‖	NA	NA	NA
Lowe et al,[117] 2000	Case-control	4.09 (1.3-13.3)	NA	NA	NA
Herrington et al (ERA),[118] 2000	RCT		0.50†	1.44†	NA
Viscoli et al (WEST),[119] 2001	RCT		NA	0.5 (0-5.8)§	NA
			NA	1.0 (0.10-7.10)‖	NA
Rosendaal et al,[120] 2002	Case-control	3.2 (1.7-6.0)	NA	NA	NA
Hulley et al (HERS II),[121] 2002	RCT	2.1 (1.3-3.4)	NA	NA	NA
		1.98 (1.14-3.45)§	NA	NA	NA
		2.86 (1.13-7.26)‖	NA	NA	NA
WHI,[122] 2002	RCT	2.11 (1.58-2.82)	NA	NA	NA
		2.07 (1.49-2.87)§	NA	NA	NA
		2.13 (1.39-3.25)‖	NA	NA	NA
Scarabin et al,[123] 2003	Case-control	NA	NA	3.5 (1.8-6.8)	0.9 (0.5-1.6)

Abbreviations: CI, confidence interval; ERA, Estrogen Replacement and Atherosclerosis study; HERS, Heart and Estrogen/progestin Replacement Study; HT, hormone therapy; NA, not available; NHS, Nurses' Health Study; OR, odds ratio; PIOPED, Prospective Investigation of PE Diagnosis study; RCT, randomized controlled trial; RR, relative risk; UK-GPRD, United Kingdom General Practice Research Database; VTE, venous thromboembolic event; WEST, Women's Estrogen for Stroke Trial; WHI, Women's Health Initiative.

*Risk is expressed as OR in case-control studies and as RR in cohort studies and RCTs.
†Risk was calculated from data reported in the study.
‡No cases of pulmonary embolism; risk of "thrombophlebitis" was calculated from study data.
§Risk of deep venous thrombosis only.
‖Risk of pulmonary embolism only.
¶Most women (>79%) used transdermal HT.
#All women used estrogen-only replacement therapy.
**Analysis restricted to women older than 50 years.

Interaction of Contraceptives and Inherited Hypercoagulable States

Data on the risk of VTEs in women who are OCP users and carry an inherited hypercoagulable state consist of 8 case-control studies [22,26-29,57,61,107] and 2 retrospective controlled cohort studies.[108,109] In OCP users, the risk of VTEs seems to be increased 35- to 99-fold in carriers of factor V Leiden[22,57,61,107,109] and 16-fold in carriers of the prothrombin G20210A mutation[29] compared with non-OCP users, noncarriers. This increase in risk is exponential, that is, the resulting odds ratios are much higher than if the separate risks associated with the hypercoagulable state and with OCP use were to be merely added or multiplied. In addition, the risk of VTEs seems to be exquisitely higher within the first year of OCP use[30] and seems greatest with OCPs containing desogestrel or gestodene.[57,61]

The risk of cerebral vein thrombosis seems to be increased 150-fold in carriers of the prothrombin G20210A mutation who use OCPs compared with nonusers, noncarriers.[26] The risk of VTE in carriers of protein C and antithrombin deficiency who use OCPs was increased 2-fold and 9-fold, respectively, compared with carriers who do not use OCPs.[108]

Oral HRT and VTEs

Studies comparing the risk of VTEs in HRT users compared with non-HRT users are listed in **Table 5**.[15,16,21,24,48,110-124] Similar to OCP studies, those assessing HRT-related VTE risk are heterogeneous in their methods. The age range of studied women varies, as does the definition of VTE outcomes. Nonetheless, all but 3 studies[16,48,124] used

objective diagnostic testing for VTE ascertainment. Included among the 9 studies that showed an increased risk of VTE in HRT users are 2 large randomized controlled trials, which enrolled 2500 patients (the Heart and Estrogen/progestin Replacement Study[116]) and 16 000 patients (the Women's Health Initiative[122]).

Although selection, diagnostic suggestion, and referral bias could all have accounted for the positive association between HRT and VTEs found in observational studies, level 1 data from the Heart and Estrogen/progestin Replacement Study and the Women's Health Initiative have confirmed not only that the risk of VTEs is indeed increased in HRT users but also that the risk is of the same magnitude as that found in case-control studies.

Underestimation of the risk of VTEs may have resulted from a small number of HRT-exposed cases[16,48,110,124] and from restricting the analyses to PE outcomes.[21] Two randomized controlled trials[118,119] assessing the effects of HRT on progression of coronary artery atherosclerosis and stroke recurrence likely lacked adequate power to accurately assess VTE risk, having included only 667 and 223 patients, respectively. Whether the type of oral HRT regimen (combination or estrogen only) or the estrogen dose in individual products has any effect on the VTE risk is unknown because data are inconsistent. The oral estrogen–only HRT arm of the Women's Health Initiative is still ongoing.

The risk of VTEs is higher in the first 6 months to 1 year after initiation of HRT and tends to decrease and even disappear over time.* The risk of VTE in past users is not increased compared with that of never users.[24,111-115] In studies[112,114,116,121,122] that analyzed the risks of DVT and PE separately, HRT was consistently associated with increased DVT risk, but results were conflicting regarding the risk of PE (Table 5). A recent meta-analysis[12] showed a summary odds ratio of 2.16 (95% confidence interval, 1.47-3.18) for PE in HRT users.

*References 15, 24, 111, 112, 114, 122, 123.

Høibraaten et al[125] published the only placebo-controlled randomized trial of HRT in women with a previous history of VTE. This study enrolled 140 patients using oral combination HRT (estradiol plus norethisterone acetate) but was terminated early owing to incidences of VTE of 10.7% and 2.3% in the HRT and placebo groups, respectively.[125]

Transdermal Hormonal Replacement and VTEs

Clinical data on transdermal HRT are derived from 4 case-control studies (Table 5). In the studies by Daly et al[111] and Perez-Gutthann et al,[114] transdermal HRT was associated with a nonsignificant increased risk of VTEs. In these studies,[111,114] as in the study by Høibraaten et al,[15] results were based on only 2 to 7 HRT-exposed cases. Recently, Scarabin et al[123] showed that the estimated risk of VTEs in users of estrogen-only oral HRT compared with transdermal HRT was 4.0 (95% confidence interval, 1.9-8.3). In the study by Varas-Lorenzo et al,[115] 79% of women received transdermal HRT, but the analysis did not discriminate the risk of VTEs based on route of HRT administration.

Interaction of HRT and Inherited Hypercoagulable States

There have been 3 case-control studies[117,120,126] of the association between HRT, inherited hypercoagulable states, and VTEs. All 3 studies included only patients with activated protein C resistance caused by the factor V Leiden mutation. The odds ratios for VTEs among HRT users who carried factor V Leiden heterozygosity compared with nonusers, noncarriers ranged from 13.3 to 15.5, which represents an exponential increase in risk beyond what would be expected by adding the individual risks associated with HRT and factor V Leiden heterozygosity.[117,120,126]

CONCLUSIONS

Associations between exposure and disease observed in case-control studies[84,127] do not constitute proof of causality. Epidemiologic evidence for causality typically requires the fulfillment of a variety of criteria, including the strength of the findings, consistency, statistical significance, replication, and biological plausibility of the observed association.[84,127,128] In addition, although the magnitude of an association between risk and disease is usually expressed as relative risk or odds ratio, the importance of any given association for the individual patient is best determined by the absolute risk.

Although it is unlikely that a randomized controlled trial of OCP use will ever be performed, owing to reasons that include the need to enroll hundreds of thousands of women and some ethical considerations,[84,129] it is the lack of such prospective data that gives rise to debates and uncertainties, some of which may go on indefinitely. Thus, it must be kept in mind that any interpretations from the literature are strictly based on observational data. In this regard, the lessons learned from the literature pertaining to the HRT-related VTE risk are invaluable. Until 2000, observational data on the risk of VTEs were somewhat conflicting (Table 5). It was not until 2 large randomized controlled trials[116,122] were conducted that it became clear not only that there is indeed an increased risk of VTE associated with HRT but also that HRT is associated with increased risk of arterial cardiovascular events. The latter data have dissipated the earlier view, based strictly on observational (but consistent) data, that HRT was associated with cardiovascular disease prevention.

The following series of conclusions can be derived from the currently available evidence:

Hormonal Contraceptives and VTEs

1. The overall observational data are consistent, pointing to a 3- to 6-fold increased risk of VTEs among all OCP users compared with nonusers and to a real, albeit small, increased VTE risk with the use of desogestrel- or gestodene-containing OCPs, compared with OCPs containing levonorgestrel. The increase in relative risk translates into a low absolute risk, estimated to be

1 to 3 cases per 10 000 woman-years. Nevertheless, because venous thromboembolic disease is 5 times more common than arterial thromboses in women younger than 40 years,[130] it is appropriate for clinicians to prescribe OCPs that carry the lowest possible risk of VTEs.

2. Current evidence suggests that combination OCPs containing 35 µg or less of ethinyl estradiol and a second-generation progestin are associated with the lowest risk of VTEs and thus should be preferable in first-time OCP users. The true risk associated with OCPs containing less than 20 µg of ethinyl estradiol is unknown.

3. Given the low absolute risk associated with the use of third-generation OCPs for the individual patient, current evidence does not support a recommendation that women already using third-generation OCPs stop taking them.[131] In fact, some women may benefit from the further minimization of androgenic activity provided by these products.[131,132]

4. The true VTE risk associated with the use of norethindrone and norgestimate, which are among the most commonly used progestins in the United States, is essentially unknown.

5. Limited observational data suggest that progestin-only contraceptives are associated with a lower risk of VTEs than combination OCPs, but the 2 types of OCPs have never been directly compared. Moreover, although progestin-only contraceptives seem to be a safer option for effective hormonal contraception in women with a known inherited hypercoagulable state or a previous history of VTEs, the safety of using progestin-only contraceptives in those settings remains unknown.

6. Although estrogen-containing OCPs are considered contraindicated in women with a previous history of VTEs, there currently are no objective data to support or refute an increased rate of VTE recurrence in women who use OCPs after VTEs compared with those who do not use OCPs after VTEs.[70]

7. In women with a deficiency of antithrombin or protein C, it is prudent that OCPs be avoided because of the reported 4% annual absolute risk of VTEs associated with OCP use in those women.[108] The OCP-related VTE risk in carriers of protein S deficiency is uncertain but is likely increased.

8. In women who carry the factor V Leiden or the prothrombin G20210A mutation, a recommendation of complete avoidance of OCPs cannot necessarily be made. Despite the exponentially increased relative risk, the estimated absolute risk of VTEs (28-50 cases per 10 000 woman-years) still remains relatively low.[22,57] Moreover, the use of alternative, nonhormonal contraception may lead to more (unplanned) pregnancies and their attendant VTE risk. In healthy women, VTEs are more frequent during pregnancy than during OCP use, with an estimated incidence of 1 case per 1000 deliveries and a 1% to 2% case-fatality rate.[133] In carriers of the factor V Leiden or prothrombin G20210A mutation, the pregnancy-related VTE risk also seems to be exponentially increased.[134]

HRT and VTEs

1. Best available evidence points to a 2- to 4-fold increased relative risk of VTEs among oral HRT users compared with nonusers. Based on the Heart and Estrogen/progestin Replacement Study[116] prospective data, the increased relative risk translates into an absolute risk of 2.3 cases per 1000 woman-years. Such absolute risk could still be considered acceptable, as long as HRT were associated with an overall favorable benefit-risk ratio. However, current evidence suggests that the risks of VTEs, cardiovascular disease, and breast cancer associated with oral combination HRT outweigh the benefits of reduction in osteoporosis and prevention of colon cancer.[122] Moreover, because HRT does not seem to improve quality of life in women without postmenopausal symptoms, it has been suggested that HRT seems to be best indicated only for women who require postmenopausal symptom control.[135]

2. In women with postmenopausal symptoms, the risk of VTEs associated with short-term (ie, for a few months) oral HRT for symptom control is uncertain. Although it could be assumed that the absolute risk would be low, this has not been formally studied, and the available evidence shows that the risk of VTEs seems greatest within the first months to 1 year after initiation of HRT. Therefore, even short-term HRT may still be associated with an unfavorable benefit-risk ratio from a VTE standpoint.

3. The fact that oral HRT increases the risk of VTE recurrence provides evidence against the use of HRT in women with a previous history of VTEs.[125]

4. In women who carry an inherited hypercoagulable state, the exponentially increased risk of VTEs, in addition to the unfavorable effects of HRT in arterial cardiovascular disease events, likely makes oral HRT an unattractive option. In carriers of hypercoagulable states who have severe postmenopausal symptoms, data are still limited to support a firm recommendation of strict short-term HRT avoidance. However, it is prudent to first consider the use of alternative therapies for symptom relief.

5. There are limited observational data suggesting a lower risk of VTEs in users of transdermal relative to oral HRT. Although transdermal HRT may be a safer option for the short-term control of postmenopausal symptoms than oral HRT, such therapy has unknown effects on arterial cardiovascular events. Moreover, the safety of transdermal HRT in women who carry an inherited hypercoagulable state or have had previous VTEs remains uncertain.

6. Although phytoestrogens may relieve postmenopausal symptoms,[136] to our knowledge there are no studies on the safety and potential adverse effects associated with the use of these products. Some phytoestrogens, such as the isoflavonoid genistein, also have "selective estrogen-receptor modulator–like" activity. Because selective estrogen-receptor modulators have also been associated with increased VTE risk, phytoestrogens should not be viewed as being safer than HRT in the lack of properly conducted studies.

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