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Hormonal contraception and venous thromboembolism

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Key words
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Conflict of interests
Øjvind Lidegaard has, within the last three years, received honoraria for speeches on pharmacoepidemiological issues, including fees from Bayer Pharma Denmark, and was expert witness in a US legal case in 2011.
Finn Egil Skjeldestad received compensation for his work on a Steering Committee supervising a supplementary analysis of Danish registry data on oral contraceptive use and venous thromboembolism.
Ian Milsom has participated in International Advisory Board Meetings sponsored by Organon/Schering Plough/MSD and Schering/Bayer Pharma. Ian Milsom has received lecture fees for presentations sponsored by Organon/Schering Plough, Schering/Bayer Pharma and Pfizer.
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Abstract

Background. New studies about the influence of hormonal contraception on the risk of venous thromboembolism (VTE) have been published. *Aim.* To evaluate new epidemiological data and to propose clinical consequences. *Design.* A literature survey. *Methods.* Studies assessing the risk of specific types of hormonal contraception were evaluated, compared and set into a clinical perspective. *Results.* The majority of newer studies have demonstrated a threefold increased risk of VTE in current users of medium- and low-dose combined oral contraceptives (COCs) with norethisterone, levonorgestrel (LNG) or norgestimate compared with non-users. The same studies have demonstrated a sixfold increased risk of VTE in users of combined pills with desogestrel, gestodene, drospirenone or cyproteroneacetate, and in users of the contraceptive vaginal ring, compared with non-users. The rate ratio of VTE between users of COCs with newer progestogens compared with users of COCs with LNG was 1.5–2.8 in seven studies and 1.0 in two studies. Progestogen-only contraception did not confer an increased risk of VTE in any study. The incidence rate of VTE in non-pregnant women aged 15–49 years using non-hormonal contraception is three per 10 000 years. *Conclusions.* For women starting on hormonal contraception, we recommend medium- or low-dose combined pills with norethisterone, LNG or norgestimate as first-choice preparations. For the many women who are users of COCs with newer progestogens, although the absolute risk of VTE is low, a change to combined pills with norethisterone, LNG or norgestimate may halve their risk of VTE. Finally, we recommend COCs with 20 μg estrogen combined with the older progestogens to be launched in the Scandinavian countries. Women at an increased risk of VTE should consider progestogen-only contraception or non-hormonal contraception.

Abbreviations: BMI, body mass index; CI, confidence interval; COC, combined oral contraception; DRSP, drospirenone; EE, ethinylestradiol; EURAS, European Active Surveillance study; HC, hormonal contraception; LNG, levonorgestrel; IUS, intrauterine system; n.a., not available; OC, oral contraception; RR, relative risk; SHBG, sex hormone-binding globulin; wy, women years; VTE, venous thromboembolism.

Key Message

New research suggests a doubling of the risk for venous thromboembolism with combined contraceptives containing desogestrel, gestodene, drospirenone or cyproteroneacetate, compared with women using norethisterone, levonorgestrel or norgestimate; a sixfold risk compared with non-users. The rate ratio has been 1.5–2.8 in seven studies, but 1.0 in two. The overall risk is still low. Progestogen-only contraception did not confer increased risk. The preference for first-time users should be contraceptives with norethisterone, levonorgestrel or norgestimate. Women already on the newer progestogens might benefit from changing contraceptive in order to halve their risk of venous thromboembolism.

Introduction

Until a decade ago, hormonal contraception (HC) was primarily based on oral contraceptives (OCs). Today, HC includes hormone patches, the hormone vaginal ring, the subcutaneous hormone implant, the levonorgestrel (LNG)-releasing intrauterine system and intramuscular depot preparations.

Many short-term benefits and adverse effects of combined OCs (COCs) are well known, affecting primarily well-being and compliance (1). Among the potentially serious adverse effects, fear of an influence on cancer, in particular breast cancer, has been a concern. There is, however, good epidemiological evidence to show that the overall risk of cancer is reduced with OC use, and the influence on breast cancer risk is minimal, if present at all (2,3). The greatest clinical concern is still the increased risk of venous thromboembolism (VTE) in women taking combined hormonal contraceptive products with semi-synthetic progestogens and the artificial estrogen, ethinylestradiol.

Although this risk has been known for more than 50 years, and other risk factors have been identified and quantified, healthy women on COCs are still diagnosed with VTE. There is controversy about the magnitude of this risk for the different types of COCs according to progestogen type. This overview aims to update knowledge about the risk of VTE in users of different HCs, to promote clinical recommendations and to discuss clinical aspects in women at particular risk.

Material and methods

The PubMed database was searched for articles relevant to the key words "hormonal contraception" or "oral contraceptives" and "venous thromboembolism" or "deep venous thrombosis." Of more than 200 published articles in the English language, only 19 studies were found assessing the risk of VTE in users of specific types of newer combined pills with different progestogen types (4–22). Small case series or case reports were excluded.

We also obtained information on hormonal products marketed in the Nordic countries from official sources, such as Web-based national pharmacological lists.

Results

The different HC products available on the Nordic market are summarized in Table 1. The overall trend has been the same in all countries, i.e. a shift from high-estrogen pills with 50 μg ethinylestradiol (EE), which were predominant until the early 1980s, towards lower dose pills, with 30 and later 20 μg EE. Through the 1980s, COCs with 30 μg EE gradually replaced COCs with 50 μg EE, and from the early 1990s, the 20 μg pills pushed the high-dose pills out of the market. Since the start of 2010–2019, low-dose pills with 20 μg EE have been the leading formulations.

Parallel with this change in estrogen dose, new generations of progestogens have been developed. The first-generation progestogen, norethisterone (and later dienogest), has been in use since the 1970s. In the 1980s, the second-generation pills, with norgestrel and levonorgestrel (LNG), were predominant. Through the 1980s and 1990s, the two third-generation progestogens, desogestrel and gestodene, together with COCs with norgestimate were launched. The last of these products belongs, nevertheless, to the second-generation OCs. In the decade after 2000, the new fourth-generation progestogen, drospirenone (DRSP), replaced other products for many users, and is now a market leader in some countries.

Overall, about one-third of women of reproductive age are current users of hormonal contraception in Denmark, Finland and Iceland, slightly fewer in Norway and Sweden. The use is highest in the younger age groups, in whom more than every other woman is on the pill.

Venous thromboembolism

In Denmark, the incidence rate of venous thromboembolism in non-pregnant women who are not using hormonal contraception increased from 0.7 in women 15–19 years of age to 5.8 per 10 000 women years (wy) in women 45–49 years old, or 8.3-fold through fertile age (20).

At the same time, the incidence rate increased from overall 2.8 per 10 000 wy in 2001 to 4.1 per 10 000 wy in 2009, or 4.1% per year. This increase may be explained by improvements in diagnostic accuracy and the increasing proportion of adipose women. Adiposity is a well-established risk factor of VTE, together with family disposition, varicose veins, coagulation disorders, such as activated protein C resistance or factor V Leiden mutation, immobilization, pregnancy and other factors causing physical pressure on pelvic or limb veins (Table 2).

Table 1. Different types of hormonal contraception on the Nordic market according to estrogen dose and progestogen type (not all combinations are available in all countries).

	Norethisterone	Levonorgestrel	Norgestimate	Desogestrel or etonogestrel	Gestodene	Drospirenone	Cyproterone
High-dose EE			(a)				
30–40 g EE	First	Second	Second	Third (b)	Third	Fourth	
20 g EE				Third	Third	Fourth	
POP	3)			(c)			
Estradiol/dienogest	Fifth (d)						
Levonorgestrel intrauterine system		(e)					
Depot progestogen	(f) 3)			(g)			

Note: (a) patch contraception (Evra®); (b) NuvaRing®; (c) Cerazette®; (d) Qlaira®; (e) levonorgestrel-releasing intrauterine system (Mirena®); (f) an intramuscular depot medroxyprogesterone acetate (DepoProvera®); and (g) Implanon®.
Abbreviations: EE, ethinylestradiol; HC, hormonal contraception; first, first-generation HC; second, second-generation HC; third, third-generation HC; fourth, fourth generation HC; POP, progestogen-only pills 3).

Table 2. Risk factors of venous thromboembolism.

Risk factor	Prevalence (%)	Relative risk
Genetic		
Age (≥30 vs. <30 years)	50	4
Family disposition (close relative)	5	2
Leiden factor V mutation heterozygote	6–10	8
Leiden factor V mutation homozygote	0.4–1	64
Prothrombin G20210A	2–3	2
Protein C deficiency	0.05	11
Protein S deficiency	0.1	32
Antithrombin deficiency	0.03	18
Acquired		
Pregnancy	4	4–28
Adiposity (body mass index >30 kg/m^2)	8	2
Oral contraceptives	35	3–6
Immobilization (travel or surgery)	?	2–5
Connective tissue diseases	4	3
Varicose veins	8	2

About two-thirds of VTE is deep venous thrombosis and one-third pulmonary embolism (with or without detected deep venous thrombosis).

Venous thrombosis and hormonal contraception

The influence of HC on the risk of VTE has been continuously debated since the 1960s, although with varying intensity. Now the issue is 'hot' again, due to apparently conflicting scientific results. Table 3 lists 19 studies, assessing specifically the risk of VTE in current users of COCs with levonorgestrel and with use of COCs with third- or fourth- generation pills (4–22). In all these studies, an increased risk of VTE was associated with use of COCs. The risk has only decreased slightly over recent decades, despite the reduction in the dose of estrogen used in the pills (Table 3). The relative risk (RR) of VTE with use of COCs with levonorgestrel has been found in recent studies to be about three when compared with non-users.

Of 13 studies specifically assessing the risk in users of COCs with desogestrel or gestodene, 12 found a higher risk with use of these products when compared with use of second-generation pills. The difference was significant in eight of the 12 studies. Of five studies not demonstrating a significant difference, two were re-analyses (8,10) of primary studies demonstrating a significant difference (7,9), while one study by Dinger et al. did not find any difference (14). The two re-analyses do not appear more statistically robust than the analyses in the primary studies. In the most recent Danish study with validated end-points, the rate ratio between third- and second-generation pills was 2.2 [95% confidence interval (CI) 1.7–2.8] for desogestrel vs. LNG and 2.1 (95% CI 1.7–2.5) for gestodene vs. LNG (20).

Likewise, of nine studies specifically assessing the risk of VTE in users of fourth-generation COCs with drospirenone and in users of second-generation pills, six found significant differences, whereas two (both by Dinger et al.) showed no difference (14,17). In all seven studies demonstrating a difference, the rate ratio of VTE between users of COCs with DRSP vs. LNG was 1.5–2.8, and the RR compared with

Table 3. Relative risk of venous thromboembolism in current users of different combined oral contraceptives compared with non-users unless otherwise specified according to recent studies.

Study first author (reference)	Data sampling period	Venous thrombosis (*n*)	COCs with levonorgestrel [RR (95% CI)]	COCs with desogestrel/ gestodene [RR (95% CI)]	COCs with drospirenone [RR (95% CI)]
Blomenkamp (4)	1988–1992	126	3.8 (1.7–8.4)	8.7 (3.9–19.3)	–
WHO (5)	1989–1993	433	3.6 (2.5–5.1)	7.4 (4.2–12.9)	–
Jick (6)	1991–1994	80	1 (reference)	1.8 (1.0–3.2)	–
Spitzer (7)	1991–1995	471	3.7 (2.2–6.2)	6.7 (3.4–13.0)	–
Lewis (8)	1993–1995	502	2.9 (1.9–4.2)	2.3 (1.5–3.5)	–
Farmer (9)	1991–1995	85	3.1† (2.1–4.5)	5.0‡ (3.7–6.5)	–
Todd (10)	1992–1997	99	1 (reference)	1.4 (0.7–2.8)	–
Bloemenkamp (11)	1994–1998	185	3.7 (1.9–7.2)	5.6 (not given)	–
Parkin (12)	1990–1998	26	5.1 (1.2–21.4)	14.9 (3.5–64.3)	–
Lidegaard (13)	1994–1998	987	2.9 (2.2–3.8)	4.0 (3.2–4.9)	–
Dinger (14)	2000–2004	118	1 (reference)	1.3 (*n.a.*)	1.0 (0.6–1.8)
van Hylckama Vlieg (15)	1999–2004	1524	3.6 (2.9–4.6)	7.3 (5.3–10.0)/ 5.6 (3.7–8.4)	6.3 (2.9–13.7)
Lidegaard (16)	1995–2005	4213	2.0 (1.8–2.3)	3.6 (3.3–3.8)	4.0 (3.3–4.9)
Dinger (17)	2002–2008	680	1 (reference)	*n.a.*	(0.6–1.8)
Parkin (18)	2002–2009	61	1 (reference)	*n.a.*	2.7 (1.5–4.7)
Jick (19)	2002–2008	186	1 (reference)	*n.a.*	2.8 (2.1–3.8)
Lidegaard (20)	2001–2009	4246	2.2 (1.7–2.8)	4.2 (3.6–4.9)	4.5 (3.9–5.1)
Confirmed only	2001–2009	2707	2.9 (2.2–3.8)	6.8 (5.7–8.1)	6.3 (5.4–7.5)
FDA (21)	2001–2007	625	1 (reference)	*n.a.*	1.5 (1.2–1.9)
Gronich (22)	2002–2008	518	1 (reference)	1.4 (0.9–2.1)	1.7 (1.0–2.7)

†Absolute risk per 10 000 women years.
Abbreviations: CI, confidence interval; COC, combined oral contraception; n.a., not available; and RR, relative risk.

non-users was 6.3 in both the Dutch (15) and the Danish (20) study.

However, all studies except one agree on one point, which is that the risk of VTE in users of third- and fourth-generation pills is the same (14–16,20). The new study from Israel found a 43% (95% CI 1.2–1.8) higher risk in users of fourth-generation pills compared with users of third-generation OCs and a rate ratio of 1.65 (95% CI 1.02–2.65) when compared with second-generation COCs (22).

Comments on recent studies

EURAS study

The EURAS (European Active Surveillance) study by Dinger et al. included 25 events of VTE in users of COCs with LNG, 26 events in users of COCs with DRSP and only five events in non-pregnant non-users (14). Surprisingly, the users of the old second-generation pills were slightly younger (25.3 years old) than the users of the new fourth-generation pills with DRSP (25.9 years old; 14). Taking this into account, the absolute risk of VTE among second-generation OC users was surprisingly high; 8.0 per 10 000 wy, compared with 5.5 per 10 000 wy in the Danish study with mainly older fertile women who were using LNG-containing products (16).

Despite high priority of case ascertainment in the EURAS study, the panel of blinded adjudicators rejected 17 of 118 diagnoses of VTE, whereas an unpublished proportion of the remaining cases were only agreed upon by one of three experienced specialists (14). It is rather unusual that a panel decision on validity of a diagnosis is based on such a minority decision. Furthermore, assessment of duration of use, allocation rules of events at time of shifting from one product to another, and allocation of cases of VTE at study end were not clearly described. Apparently, no adjustment was made for length of use or for estrogen dose.

German case–control study

The other retrospective German case–control study by Dinger et al. had several methodological problems (17). First, the validation rules were the same as in the EURAS study (minority decision). Second, the comparison between OC with DRSP vs. LNG was not adjusted for estrogen dose. Among both cases and controls, women with previous thrombosis were included; in addition, among controls pregnant and puerperal women and women with genetic predisposition were included. All these methodological circumstances have biased the results towards an underestimation of the risk difference between cases and controls, and between users of

COCs with DRSP vs. users of COCs with LNG. The rate ratio of VTE between users of COCs with DRSP and LNG was 1.0 (95% CI 0.6–1.6) without adjustment for body mass index (BMI) and family history, and 1.0 (95% CI 0.5–1.8) after adjustment, confirming that BMI and family disposition do not have any confounding influence on rate ratios between users of different product groups.

Danish study 1995–2005

Taking advantage of the special Danish register opportunities, all women 15–49 years old through the period 1995–2005 were identified (16). Women with previous cancer or cardiovascular diseases, and all pregnant or puerperal women throughout the study period were excluded, leaving 10.4 million women years of observation in non-pregnant women free of previous cardiovascular disease and previous cancer. From the prescription registry, an individual daily updated exposure line of OC use throughout the study period was made. Women were allocated daily to never use, previous use or current use of hormonal contraception along three dimensions: estrogen dose, progestogen type, and length of use.

The total number of first-time VTE episodes recorded through the study period was 4213. As compared with non-users of HC (never and previous users together), women on COCs with DRSP and 30 μg EE experienced a 7.9-fold (95% CI 5.7–11.0), 2.7-fold (95% CI 1.9–3.9) and 3.3-fold (95% CI 2.4–4.5) increased risk of VTE for the three duration of use strata (less than one year, one to four years, and more than four years). Users of COCs with third-generation progestins had similar risk estimates, while users of COCs with LNG increased their risk 1.9–2.2 times (16). The rate ratio estimate between COCs with DRSP vs. COCs with LNG was, after adjustment for length of use, 1.64 (95% CI 1.27–2.10) based on 103 and 201 VTE events in the two user groups, respectively.

The Danish study was criticised for the lack of confounder control for BMI. But studies with access to this potential confounder, such as the Dutch study (15), the UK study (18) and the new Israeli study (22), found no confounding influence from BMI on the influence of COCs for VTE. Similar findings were reported from EURAS (14).

Danish study 2001–2009

For validation of end-points, the Danish results were in a new analysis with four more study years stratified into confirmed and non-confirmed VTE depending on whether the women received anticoagulation therapy or not (a measure of reliability of the clinical VTE diagnoses; 20). A higher rate ratio between fourth- and second-generation pills for confirmed events was demonstrated [RR 2.1 (95% CI 1.6–2.8)] than for the non-confirmed events of VTE [RR 1.8 (95% CI 1.1–2.9)]. Thus, the risk estimates between the two product types decreased when non-validated VTE events were included.

The new analysis also delivered the first risk estimates for low-dose fourth-generation COCs with 20 μg EE, with a rate ratio of 2.2 (95% CI 1.3–3.9) compared with second-generation COCs and not different from the rate ratio of 2.1 (95% CI 1.5–3.0) for the 30 μg pill with drospirenone.

Dutch case–control study

The Dutch study included 1524 women of reproductive age with VTE and 1760 control women (partners of male VTE patients and community controls; 15). The absolute risk of VTE in non-pregnant non-users of OCs was 1.2 per 10 000 in women <30 years old. Confounder control was made for BMI and family disposition (to account for preferential prescribing). With non-users as a reference, RRs of VTE in users of COCs were 3.6 (95% CI 2.9–4.6) for LNG, 7.3 (95% CI 5.3–10.0) for desogestrel, 5.6 for gestodene and 6.3 (2.9–13.7) for DRSP. The rate ratio of VTE between users of COCs with DRSP vs. LNG was 1.7 (95% CI 0.7–2.2). These estimates were almost identical to the Danish results. This well-sized Dutch study also demonstrated a reduction in risk with reduced estrogen dose and with higher risk during the first year of use.

A strength of this study was that the included cases were consecutive women admitted with VTE to one of six coagulation clinics. Much of the information was obtained by questionnaires and might therefore be influenced by recall bias.

Nevertheless, the Dutch (15) and the Danish studies (16,20) reached similar risk estimates within quite different settings, with different study populations, different designs and different methods.

PharMetrics case–control analysis

Jick and Hernandez analysed OC use in 186 young women with idiopathic VTE and in a 1:4 control population (19). The adjusted rate ratio of VTE between the women using DRSP compared with women on a second-generation pill was 2.8 (95% CI 2.1–3.8). Adjustment was made for age and duration of use, and stratified according to estrogen dose. Women using COCs with DRSP were, in fact, slightly less likely to be obese (5.8%) than women using COCs with LNG (6.5%), which may be regarded as a further documentation against preferential prescribing of COCs with DRSP to women at risk.

Sixty-one per cent of VTE events were non-idiopathic and were excluded, explaining (at least partly) why the absolute incidence rate of VTE was lower than in the Danish and Dutch studies, at 3.1 per 10 000 exposure years in users of DRSP COCs and 1.3 per 10 000 exposure years in women using COCs with LNG.

UK general practice research database

This database has generated several studies on the influence of OC on the risk of VTE. Parkin et al. followed all women 15–44 years old starting on COCs with DRSP or LNG, and counted 61 idiopathic VTE events from May 2002 through September 2009 (18). A nested case–control analysis demonstrated an adjusted rate ratio of VTE between users of COCs with DRSP vs. LNG of 2.7 (95% CI 1.5–4.7). Confounder control included adjustment for BMI.

This study also found relatively small absolute risks of idiopathic VTE in current users of 2.3 per 10 000 exposure years among women using COCs with DRSP and 0.9 in women on COCs with LNG, figures slightly lower than the USA figures (19).

Food and drug administration

This multicenter study collected data from two medical care programs and two state Medicaid programs in the USA and encompassed a retrospective cohort study including only users of different types of hormonal contraception (21). The precision of exposure data was comparable with data from prescription databases, and the analysis applied a six week prolongation of each exposure beyond the end date of prescription, with detailed rules in the case of switching. Detailed records were made for different user groups for other health indicators, showing that users of COCs with DRSP were generally as healthy as, or healthier than, users of other types of COCs.

The study included 898 251 person years on hormonal contraception through the period 2001–2007 and 625 events of VTE. With users of LNG COCs as reference, all women on COCs with DRSP experienced a 49% higher risk of all VTE, and for new users and women hospitalized for VTE, the RR among users of COCs with DRSP was 1.72 (95% CI 1.14–2.59). The prolongation of exposure periods with six weeks may have slightly underestimated the risk estimates of VTE.

The FDA study also delivered the first risk estimate of VTE in users of the contraceptive vaginal ring, with 9.8 events per 10 000 exposure years, compared with users of COCs with LNG having a rate ratio of 1.48 (95% CI 0.96–2.27), a rate ratio identical with that for users of COCs with DRSP. Danish data found a rate ratio of 1.9 (95% CI 1.3–2.7) for the same comparison (23).

Israeli study

Finally, Gronich et al. conducted a historical cohort study during the period 2002–2008 with data from the largest healthcare provider in Israel (22). Within 819 749 women years, 1017 VTE events were recorded. The exposure strings in this study were prolonged by six months. With users of LNG COCs as reference, users of COCs with DRSP had a RR of 1.65 (95% CI 1.02–2.65) and users of third-generation pills a RR of 1.38 (95% CI 0.90–2.11). The slightly lower estimates in this study compared with the Danish results could be influenced by the extension of the exposure periods by six months.

Table 4. Different definitions of the end-point venous thromboembolism, different comparison groups and different confounder controls and their consequences for the risk estimates.

Diagnosis validation	Consequence for the relative risk estimates
Non-standardized case selection	May depend on interests
Diagnoses from registries	Underestimates risk
Diagnoses confirmed by the affected women	Underestimates risk a little
Diagnosis confirmed by chart review	Valid estimates
Diagnosis confirmed by anticoagulation therapy	Valid estimates
Only idiopathic events included	Valid, but selected
Exposure definition	
Prolonging OC use beyond current use	Underestimates risk
Confounder control	
Age	New OC ↑, older OC ↓
Body mass index	No effect
Family disposition	No effect today
Comparison group (reference group)	
Never users of OC	Selected controls
Non-users of OC (never + previous users)	Best reference group
Inclusion of pregnant women in reference group	Underestimates risk
Inclusion of puerperal women in reference group	Underestimates risk
Inclusion of predisposed women	Underestimates risk
Inclusion of women with cancer	Underestimates risk

Abbreviation: OC, oral contraception.

Discussion

Generally, the risk estimates of VTE with the use of OC are largely dependent on the precision of the exposure information and the validity of the end-point VTE (Table 4).

For each misclassification of COC use and for each inclusion of a non-valid VTE, the risk estimates among users of COCs will be underestimated. According to the number of potential biases in epidemiological studies on OC and VTE, the studies finding the lowest risk estimates and the lowest rate ratios had more methodological uncertainties than the studies demonstrating differences in risk of VTE between users of COCs with DRSP and LNG.

According to the Danish data, the risk of VTE in non-pregnant non-users in 2010 was on average 3 per 10 000 wy. Current users of COCs with levonorgestrel, norethisterone or norgestimate have an approximately threefold increase in risk

Table 5. Relative risk of venous thromboembolism in current users of different types of hormonal contraception (reference group: non-pregnant non-users).

	Norethisterone	*Levonorgestrel*	*Norgestimate*	*Desogestrel or Etonogestrel*	*Gestodene*	*Drospirenone*	*Cyproterone*
High dose EE[1]			7-8*				
30-40 ug EE	3	3	3.4	6†	6	6	6
20 ug EE				5	5	6	
POP	0.6			0.6			
Estradiol/dienogest	na						
Levonorgestrel IUS		0.8					
Depot progestogen	0.5			1.4			

Abbreviations: EE, ethinylestradiol; IUS, intrauterine system; n.a., not available; and POP, progestogen-only pill.
* Transdermal patch.
† Vaginal ring.

of VTE compared with non-users, while users of COCs with desogestrel, gestodene, DRSP or cyproteroneacetate have a six- to sevenfold increased risk of VTE, implying at least twice the risk in the latter groups compared with users of second-generation pills.

In absolute terms, women on COCs with newer progestogens have an absolute risk of VTE of 20 per 10 000 wy. Thus, 2.0% of women on COCs with the newer progestogens may expect to experience a VTE after 10 years of use, although there will be fewer events in the youngest women and more among older fertile women. Thus, in absolute terms the risk is still small, but not negligible.

In Table 5 we summarize an average "state of the art" for the different types of hormonal contraception with non-users as the reference, and in Figure 1 we show the rate ratios for third- and fourth-generation COCs compared with second-generation pills.

The results of these new studies indicate that the risk of VTE is doubled in COCs with third- or fourth-generation progestogens compared with COCs containing second-generation progestogens. The question then arises, why are there differences in VTE incidence when using different progestogens?

Why are there differences in VTE incidence when using different progestogens?

An increased risk of VTE among users of combined oral contraceptives was reported within a decade of the introduction of COCs (24). Later studies demonstrated that the increased risk of VTE was correlated in a dose-dependent manner to the estrogen dose of the COC, findings which resulted in the development of pills with a lower estrogen content in comparison to the original COCs (25,26). The low-dose COCs (containing <50 μg or less ethinylestradiol) were introduced around 1974, and subsequent studies showed that they were associated with less risk of VTE than COCs containing ≥ 50 μg EE (25). Thus, there is evidence to support the hypothesis that the risk of VTE is associated with the estrogenicity of the product used.

In the mid-1990s, several studies indicated that low-dose OCs containing a combination of 30 μg EE in combination with 150 μg desogestrel had a higher risk for VTE than a low-dose OC containing 30 μg EE in combination with 150 μg levonorgestrel (5–7,27). Thus, the risk of VTE apparently also varied according to the progestogen type. There is evidence to suggest that different progestogens may differentially influence the estrogenicity of the combined preparation. Odlind et al. (28) utilized data available about the influence of oral contraceptives on changes in sex hormone-binding globulin (SHBG) to assess the estrogenicity of different COCs. These analysis revealed that there appeared to be a relationship between the risk of VTE and the effect of COCs on SHBG, which is a surrogate marker for estrogenicity. Monophasic preparations containing levonorgestrel, having the lowest risk of VTE, caused an average SHBG increase of around 50%. Combined oral contraceptives containing desogestrel or gestodene caused an average SHBG increase of 200–300% and had a higher risk of VTE. A preparation with cyproteroneacetate caused a 300–400% SHBG increase. There was a 150% SHBG increase with norgestimate and a 250–300% increase with drosperinone and dienogest.

A recent Dutch study confirmed these differential changes in SHBG related to different progestogens (29).

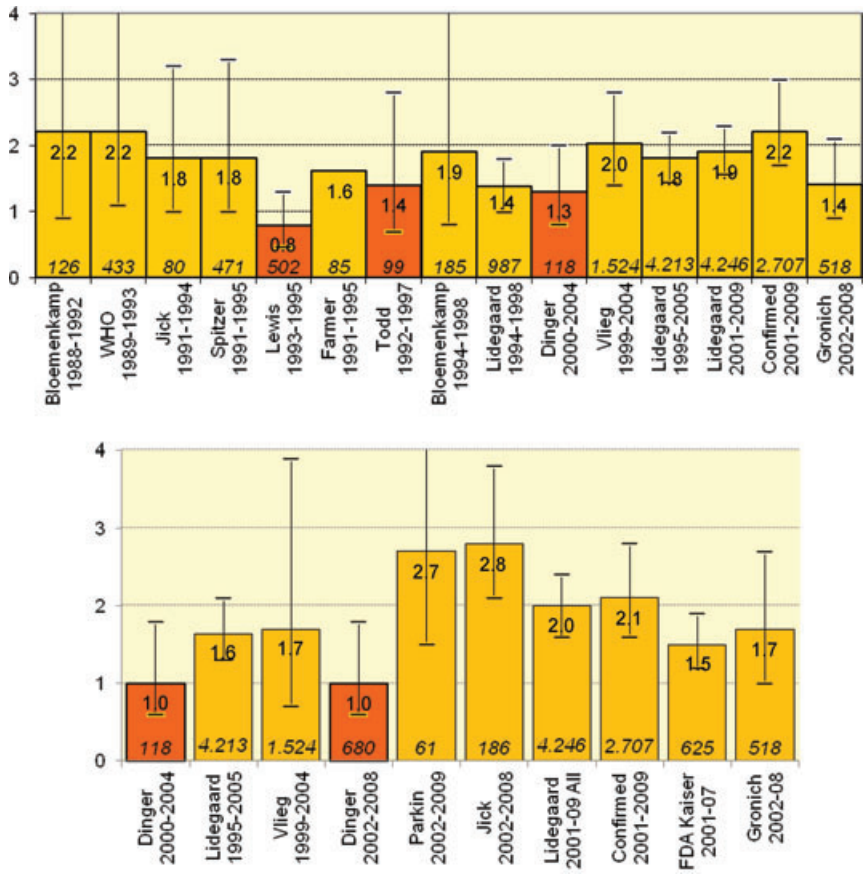

Figure 1. Relative risk of venous thrombosis in current users of combined oral contraceptives with desogestrel or gestodene (top panel) and drospirenone (bottom panel) vs. combined oral contraceptives with levonorgestrel. The 95% confidence interval is indicated. The total number of women with venous thrombosis in each study is indicated in italics in the bottom of each column.

Thus, a possible explanation for the observed differences in VTE risk between COCs containing different progestogens is the total estrogenicity of the combined product. The hypothesis proposed was that the greater is the estrogenicity of the OC, the greater the risk for VTE. The risk increase may be related to the dose of EE provided or due to the resultant estrogenicity of the COCs, which is also dependent on the progestogen used. Progestogens such as desogestrel, drosperinone and cyproteroneacetate in combination with the same dose of EE apparently have a greater estrogenicity as assessed by the change in SHBG compared with products containing the same amount EE combined with levonorgestrel. One possible mechanism by which a different estrogenicity might confer a differential risk of VTE is a differential influence on activated protein C, with more estrogenicity causing more resistance against activated protein C (30).

Clinical recommendations

Most studies find a doubled risk associated with the use of COCs with third- or fourth-generation progestogens compared with COCs with second-generation progestogens. In addition, clinicians need to consider risks related to age and body mass. Special care must therefore be exercised with obese women and those who are over the age of 35 years. While family history of venous thromboembolism is important, it has a relatively low predictive value. Screening women of a fertile age for abnormalities such as factor V Leiden mutations is, however, not warranted without a clear family disposition.

Nevertheless, it must not be forgotten that hormonal contraception is a mainstay of population and fertility control in modern society and, among all other drugs, hormonal contraception has an excellent safety record. We therefore advocate the following measures.

A low-dose pill with norethisterone, levonorgestrel or norgestimate is recommended as first choice. It is also the most affordable choice for many young women, who are the most frequent COC users. In the case of non-compliance, one can and should consider other combined pills if no other risk factors for venous thrombosis are present.

In women predisposed to VTE (adiposity, family disposition or genetic predisposition), one should primarily consider progestogen-only contraception, such as levonorgestrel-releasing intrauterine system.

In late reproductive age, arterial complications become more frequent. We have much less and, unfortunately, less

consistent information about the risk of arterial complications in users of COCs with different progestogens, but some studies suggest less risk of thrombotic stroke with third- than with second-generation pills (31,32), while another large study found the opposite (33). A new Danish study on thrombotic stroke did not demonstrate consistent differences in risk according to progestogen type (34). However, the risk of VTE increases in older fertile women. In women who are ≥35 years old without cardiovascular risk factors, second-generation pills or COCs with norethisterone should be used and not third- or fourth-generation COCs. Women over 35 years with cardiovascular risk factors such as smoking or diabetes, hypertension, migraine with aura or hyperlipidaemia should be advised to avoid COCs.

We recommend all prescribers to obtain information about family disposition for VTE, especially in young age, and to include previous experiences with hormonal contraception in order to optimize individual counselling and the achievement of an acceptable benefit/risk ratio.

Finally, we recommend that low-dose COCs with 20 μg EE combined with first- and second-generation progestogens should be launched in the Scandinavian countries.

Standard clinical information

All women being prescribed COCs should be informed about a threefold increase in the risk of VTE if the progestogen is norethisterone, levonorgestrel or norgestimate, and a sixfold increase if combined with third- or fourth-generation progestogens or cyproteroneacetate. They must at the same time also be informed that the absolute risk is low, especially in young women.

The women must know about symptoms of VTE, and remember to inform the clinician at any encounter about current use of COC in order to ensure early intervention in case of an event, thereby reducing the risk of more serious complications or even death.

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