HAUTE AUTORITÉ DE SANTÉ

BON USAGE DU MÉDICAMENT

Contraceptifs oraux estroprogestatifs : préférez les « pilules » de 1re ou 2e génération

- **Les contraceptifs oraux estroprogestatifs (COEP) sont parmi les moyens les plus efficaces (indice de Pearl < 1) pour la prévention des grossesses non désirées.**
- **L'efficacité des différents types de COEP est du même ordre.**
- **Tous les contraceptifs estroprogestatifs sont associés à une augmentation du risque d'accident thromboembolique artériel ou veineux. Avant leur prescription, il est indispensable de rechercher des facteurs de risque thromboembolique personnels ou familiaux. Chez les femmes ayant des facteurs de risque constituant une contre-indication, un autre mode de contraception devra être proposé.**
- **Les COEP dits de 3e génération (C3G, contenant du désogestrel, du gestodène ou du norgestimate) exposent les femmes à un surrisque d'accident thromboembolique veineux par rapport aux COEP dits de 1re ou 2e génération (C1G ou C2G).**
- **Aucune étude n'a démontré que les C3G apportaient un bénéfice supplémentaire par rapport aux C1G/C2G sur les effets indésirables comme l'acné, la prise de poids, les nausées, les mastodynies, la dysménorrhée, l'aménorrrhée et les méno-métrorragies.**
- **Du fait de leur moindre risque thromboembolique veineux pour une efficacité comparable, la HAS considère que les contraceptifs oraux de 1re ou de 2e génération doivent être préférés à ceux de 3e génération.**

1. Quels sont les différences entre les « générations » de contraceptifs oraux estroprogestatifs ?

- Selon le progestatif utilisé, la plupart des COEP ont été divisés en trois classes ou « générations », appellation qui laisse entendre que les plus récents sont préférables aux précédents, sans que ce soit avéré. Ces trois « générations » (C1G, C2G et C3G) utilisent le même estrogène, l'éthinyl-estradiol (EE) à des doses variées, associé à un progestatif norstéroïdien (*voir au verso les autres COEP*). Cette classification ne préjuge en rien des avantages ou inconvénients d'une « génération » par rapport aux autres.
- Tous les C1G/C2G sont remboursables. En revanche, seuls certains C3G ont été inscrits au remboursement. Les laboratoires concernés n'ayant pas demandé le remboursement des autres COEP de cette classe (*en italiques dans le tableau ci-dessous*), ceux-ci ne sont pas remboursables.

Classe	Estrogène	Progestatif	Spécialités	
C1G	EE (35 µg)	Noréthistérone	Triella®	
C2G	EE (20, 30 ou 40 µg)	Lévonorgestrel	Adepal®, Amarance®, Daily Gé®, Evanecia®, Leeloo®, Lovavulo®, Ludeal Gé®, Minidril®, Pacilia®, Trinordiol®, Zikiale®	
	EE (50 µg)	Norgestrel	Stediril®	
C3G	EE (20 ou 30 µg)	Désogestrel	Desobel®, Varnoline Continu® et EE/désogestrel Biogaran®	*Cycleane®, Mercilon®, Varnoline®*
	EE (15, 20, 30 ou 40 µg)	Gestodène	Carlin®, Efezial® et EE/gestodène Arrow®, Biogaran®, Ranbaxy®, Ratiopharm®, Sandoz®, Winthrop®	*Harmonet®, Meliane®, Melodia®, Minesse®, Minulet®, Moneva®, Phaeva®, Triminulet® et neuf génériques **
	EE(35 µg)	Norgestimate	–	*Cilest®, Effiprev®, Triafemi®, Tricilest®*

** : Edenelle®, Felixita®, Sylviane®, Perleane® et EE/gestodène Actavis®, Biogaran®, EG®, Teva®, Zydus®.*

2. Certains contraceptifs oraux estroprogestatifs sont-ils plus efficaces que d'autres ?

- Les COEP sont l'un des moyens contraceptifs les plus efficaces. Leurs indices de Pearl (nombre de grossesses pour 100 femmes prenant un COEP pendant un an) sont inférieurs à 1, à condition qu'il n'y ait pas d'oubli de prise.
- Il n'existe pas de différence d'efficacité entre les COEP : leurs indices de Pearl sont tous du même ordre.

Autres contraceptifs oraux estroprogestatifs

Les COEP plus récents utilisent des progestatifs de types différents. Les laboratoires concernés n'ayant pas demandé leur remboursement, la HAS n'a pas eu à se prononcer sur ce point.

Selon les données disponibles, il n'y a pas d'argument pour les préférer aux précédents. De plus, il est apparu que **les COEP contenant de la drospirénone présentent un surrisque thromboembolique par rapport aux C2G**.

Classe	Estrogène	Progestatif	Spécialités
Autres COEP	EE (30 µg)	Chlormadinone	Belara®
	EE (20 ou 30 µg)	Drospirénone	Belanette®, Convuline®, Drospibel®, Jasmine®, Jasminelle®, Jasminelle Continu®, Rimendia®, Yaz®, EE/drospirénone Biogaran® et Biogaran Continu®
	Estradiol (1,5 mg)	Nomégestrol	Zoely®
	Valérate d'estradiol (3/2/1 mg)	Diénogest	Qlaira®

3. Certains contraceptifs oraux estroprogestatifs sont-ils mieux tolérés que d'autres ?

- Aucune étude jusqu'à présent n'a démontré que les C3G avaient un intérêt clinique supplémentaire par rapport aux C1G/C2G sur les effets indésirables comme l'acné, la prise de poids, les nausées, les jambes lourdes, les mastodynies, la dysménorrhée, l'aménorrrhée ou les méno-métrorragies.

4. Comment réduire le risque de survenue d'un événement thromboembolique (veineux ou artériel) lié aux contraceptifs oraux estroprogestatifs ?

- Tous les COEP entraînent une augmentation du risque d'événement thromboembolique veineux, d'infarctus du myocarde et d'accident vasculaire cérébral (AVC) ischémique. C'est pourquoi toute prescription de COEP doit être précédée d'une recherche des facteurs de risque personnels ou familiaux de thrombose.
- En effet, si le risque cardiovasculaire lié aux COEP est faible dans l'absolu, il est accru en cas d'association à d'autres facteurs de risque, à réévaluer à chaque prescription, notamment :
  - tabagisme : l'arrêt du tabac doit être préconisé et accompagné ;
  - anomalies de la coagulation, d'origine génétique en particulier : il faut les rechercher en cas d'antécédents familiaux (et bien sûr personnels) d'accidents cardiovasculaires ;
  - âge : le risque thromboembolique augmentant avec l'âge, le rapport bénéfice/risque des COEP devra être réévalué individuellement et de façon régulière à partir de 35 ans.
- Par ailleurs, les utilisatrices de COEP doivent être informées des signes évocateurs d'accident vasculaire.

5. Quel est le risque thromboembolique veineux avec les C3G par rapport aux C1G/C2G ?

- De l'ensemble des travaux publiés, il ressort que le risque d'événement thromboembolique veineux est accru avec les C3G par rapport aux C1G/C2G.
  - Chez la femme en bonne santé sans autre facteur de risque, ce risque est d'environ 0,02 % par an avec les C1G/C2G ; avec les C3G, il passe à 0,04 % par an (soit 4 accidents par an au lieu de 2 pour 10 000 utilisatrices).
  - Le risque thromboembolique veineux lié aux COEP est maximal dans les 12 premiers mois. Il diminue avec la durée de prise de la contraception, mais le surrisque lié aux C3G par rapport aux C1G/C2G persiste.
- Lors de la prescription d'une contraception orale estroprogestative, il convient de préférer les C1G/C2G.
- Le surrisque thromboembolique veineux ne justifie pas un arrêt brutal d'une C3G jusque là bien supportée. À l'issue de la prescription en cours, le prescripteur envisagera avec la femme déjà sous C3G la méthode contraceptive la plus appropriée pour elle (autre contraceptif oral, dispositif intra-utérin, etc.).

Compte tenu des données scientifiques disponibles et au regard de l'existence d'alternatives (les C1G et C2G), le service médical rendu par les contraceptifs oraux estroprogestatifs dits de troisième génération est insuffisant pour leur prise en charge par la solidarité nationale.

HAS

Validé par la Commission de la Transparence de la HAS, ce document a été élaboré à partir des données de l'AMM, des études disponibles et de l'ensemble des avis de la Transparence.
Ces avis, comme l'ensemble des publications de la HAS, sont disponibles sur **www.has-sante.fr**

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CMAJ RESEARCH

Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-based cohort study

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Abstract

Background: Combined oral contraceptives are a common method of contraception, but they carry a risk of venous and arterial thrombosis. We assessed whether use of drospirenone was associated with an increase in thrombotic risk relative to third-generation combined oral contraceptives.

Methods: Using computerized records of the largest health care provider in Israel, we identified all women aged 12 to 50 years for whom combined oral contraceptives had been dispensed between Jan. 1, 2002, and Dec. 31, 2008. We followed the cohort until 2009. We used Poisson regression models to estimate the crude and adjusted rate ratios for risk factors for venous thrombotic events (specifically deep vein thrombosis and pulmonary embolism) and arterial thromboic events (specifically transient ischemic attack and cerebrovascular accident). We performed multivariable analyses to compare types of contraceptives, with adjustment for the various risk factors.

Results: We identified a total of 1017 (0.24%) venous and arterial thrombotic events among 431 223 use episodes during 819 749 woman-years of follow-up (6.33 venous events and 6.10 arterial events per 10 000 woman-years). In a multivariable model, use of drospirenone carried an increased risk of venous thrombotic events, relative to both third-generation combined oral contraceptives (rate ratio [RR] 1.43, 95% confidence interval [CI] 1.15–1.78) and second-generation combined oral contraceptives (RR 1.65, 95% CI 1.02–2.65). There was no increase in the risk of arterial thrombosis with drospirenone.

Interpretation: Use of drospirenone-containing oral contraceptives was associated with an increased risk of deep vein thrombosis and pulmonary embolism, but not transient ischemic attack or cerebrovascular attack, relative to second- and third-generation combined oral contraceptives.

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Oral hormonal therapy is the preferred method of contraception, especially among young women. In the United States in 2002, 12 million women were using "the pill."[1] In a survey of households in Great Britain conducted in 2005 and 2006, one-quarter of women aged 16 to 49 years of age were using this form of contraception.[2] A large variety of combined oral contraceptive preparations are available, differing in terms of estrogen dose and in terms of the dose and type of the progestin component. Among preparations currently in use, the estrogen dose ranges from 15 to 35 μg, and the progestins are second-generation, third-generation or newer. The second-generation progestins (levonorgestrel and norgestrel), which are derivatives of testosterone, have differing degrees of androgenic and estrogenic activities. The structure of these agents was modified to reduce the androgenic activity, thus producing the third-generation progestins (desogestrel, gestodene and norgestimate). Newer progestins are chlormadinone acetate, a derivative of progesterone, and drospirenone, an analogue of the aldosterone antagonist spironolactone having antimineralocorticoid and antiandrogenic activities. Drospirenone is promoted as causing less weight gain and edema than other forms of oral contraceptives, but few well-designed studies have compared the minor adverse effects of these drugs.[3]

The use of oral contraceptives has been reported to confer an increased risk of venous and arterial thrombotic events,[4–7] specifically an absolute risk of venous thrombosis of 6.29 per 10 000 woman-years, compared with 3.01 per 10 000 woman-years among nonusers.[8] It has

long been accepted that there is a dose–response relationship between estrogen and the risk of venous thrombotic events. Reducing the estrogen dose from 50 μg to 20–30 μg has reduced the risk.[9] Studies published since the mid-1990s have suggested a greater risk of venous thrombotic events with third-generation oral contraceptives than with second-generation formulations,[10–13] indicating that the risk is also progestin-dependent. The pathophysiological mechanism of the risk with different progestins is unknown. A twofold increase in the risk of arterial events (specifically ischemic stroke[6,14] and myocardial infarction[7]) has been observed in case–control studies for users of second-generation pills and possibly also third-generation preparations.[7,14]

Conflicting information is available regarding the risk of venous and arterial thrombotic events associated with drospirenone. An increased risk of venous thromboembolism, relative to second-generation pills, has been reported recently,[8,15,16] whereas two manufacturer-sponsored studies claimed no increase in risk.[17,18] In the study reported here, we investigated the risk of venous and arterial thrombotic events among users of various oral contraceptives in a large population-based cohort.

Methods

This population-based historical cohort study was based on automatically and routinely collected administrative and clinical data in a coded database. As such, approval was not sought from an ethics review board.

Data source

In Israel, medical care is provided by four not-for-profit health care providers. Every resident of the country may choose to receive his or her medical care from one of these four providers and can switch providers periodically with no penalty. The annual rate of changing providers is about 1%.[19] Clalit Health Services is the largest provider. Its enrolment accounts for more than half of the population, with a somewhat older age profile and lower socioeconomic status than the other three providers.[19] The Clalit clinical database[20,21] is a comprehensive database that was established in 1998. It has several components, including a medication database, a chronic diseases database, a primary care database of diagnoses by physician visit, a database of laboratory test results and a database of hospital admissions. The databases are based on a full accounting of relevant data achieved through the centralized and standardized computerization of all Clalit primary care physicians, laboratories, pharmacies, and admissions to and discharges from hospital for those insured. Full computerization of all Clalit providers was achieved in 2002, and our study period therefore started in that year. Among information that was not originally collected but that has been added gradually over time are data on health-related habits such as smoking and health-related markers such as body mass index (which are recorded in the markers database).

Study cohort

We searched the Clalit medication database for all women for whom at least one combined oral contraceptive prescription had been dispensed between Jan. 1, 2002, and Dec. 31, 2008, and who were between 12 and 50 years of age throughout the study period (i.e., the age range for contraception use and the age limit used in studies of the thromboembolic risk of contraceptives). Each type of combined oral contraceptive used by an individual woman was regarded as a separate use episode. All prescriptions for people insured by Clalit are filled in Clalit pharmacies, which have been centrally computerized since 2002. Variables in the database that were used for this study were the catalogue number of each medication, the date the prescription was first filled, the date it was last filled and the number of prescriptions filled.

We searched the Clalit primary care and hospital databases for diagnoses of deep vein thrombosis (International Classification of Diseases, ninth revision [ICD-9], codes 451.1, 451.83), pulmonary embolism (ICD-9 code 415.1), transient ischemic attack (ICD-9 code 435) and cerebrovascular accident (ICD-9 codes 430–432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 438) in the study cohort. We excluded women who had any of these diagnoses before starting contraceptive use.

Study outcomes

We identified first-time diagnoses of thrombotic events, specifically deep vein thrombosis, pulmonary embolism, transient ischemic attack and cerebrovascular accident. We followed the cohort until 2009. We attributed each such event to the last combined oral contraceptive used before the event. Most prescriptions were for a three-month period, and the thromboembolic risk has been reported to disappear within three months after a woman stops using oral contraceptives.[13,22] Therefore, if an event occurred more than six months since the last combined oral contraceptive was dispensed, we did not attribute it to any contraceptive. We classified deep vein thrombosis and pulmonary embolism diagnosed on the same day

as pulmonary embolism. We regarded an undetermined diagnosis of either transient ischemic attack or cerebrovascular accident as transient ischemic attack. We calculated the duration of oral contraceptive use from the number of one-month packages of combined oral contraceptives that were dispensed. The observation time for each woman was the sum of the number of months from beginning of use until six months after the last prescription was dispensed or until a thrombotic event, based on the dates of first and last prescriptions.

Study covariates

For all women in the study cohort, we searched the Clalit primary care, hospital admission and markers databases for diagnoses of clinical risk factors that are known from the literature to be related to venous and arterial thrombosis, specifically obesity (body mass index > 30), smoking and history of hypertension (ICD-9 401–405), hyperlipidemia (ICD-9 272.0–272.4), diabetes mellitus (ICD-9 250) or cancer (ICD-9 140–208). We documented a risk factor if it was diagnosed before the thrombotic event (for women with such an event) or at any time until the end of the study period (for women with no thrombotic event).

Statistical analysis

Combined oral contraceptives containing norgestrel and levonorgestrel were grouped together as second-generation agents. Formulations containing desogestrel, gestodene or norgestimate were grouped as third-generation products.[23,24] Combined oral contraceptives containing low-dose gestodene, drospirenone or chlormadinone were analyzed individually. We calculated the crude incidence of venous and arterial thrombotic events in relation to each of the following risk factors: age, diabetes, hyperlipidemia, hypertension, cancer, smoking, obesity and duration of contraceptive use (divided into four groups [quartiles]). We performed multiple imputations using all of the above-listed variables to impute missing data for smoking and obesity. We used Poisson regression analysis, with robust standard errors, to estimate the crude rate ratio (RR) for each risk factor and the adjusted RRs, with 95% confidence intervals [CIs], for venous and arterial thrombotic events for the contraceptive types. We also ran the model using the negative binomial distribution, for which the shape parameter is a convenient index of overdispersion. The results in these two models were similar. We performed multivariable analyses to compare types of treatment (drospirenone v. third-generation, drospirenone v. second-generation, third-generation v. second-generation), with adjustment for other risk factors.

We also performed a secondary analysis to determine if estrogen dosage affected the outcome. Specifically, we used the same model to compare third-generation oral contraceptives containing 20 μg ethinylestradiol (combined with desogestrel or gestodene, accounting for 44.4% of all use episodes in our cohort) with third-generation oral contraceptives containing 30–35 μg ethinylestradiol (combined with desogestrel, gestodene or norgestimate, accounting for 29.0% of all use episodes in our cohort).

Results

In our study population, a combined oral contraceptive was prescribed at least once to 14% of women 12–50 years of age and 20% of women 16–35 years of age. We noted a marked shift in prescribing patterns over the study period, with disappearance of the use of second-generation combined oral contraceptives and a marked

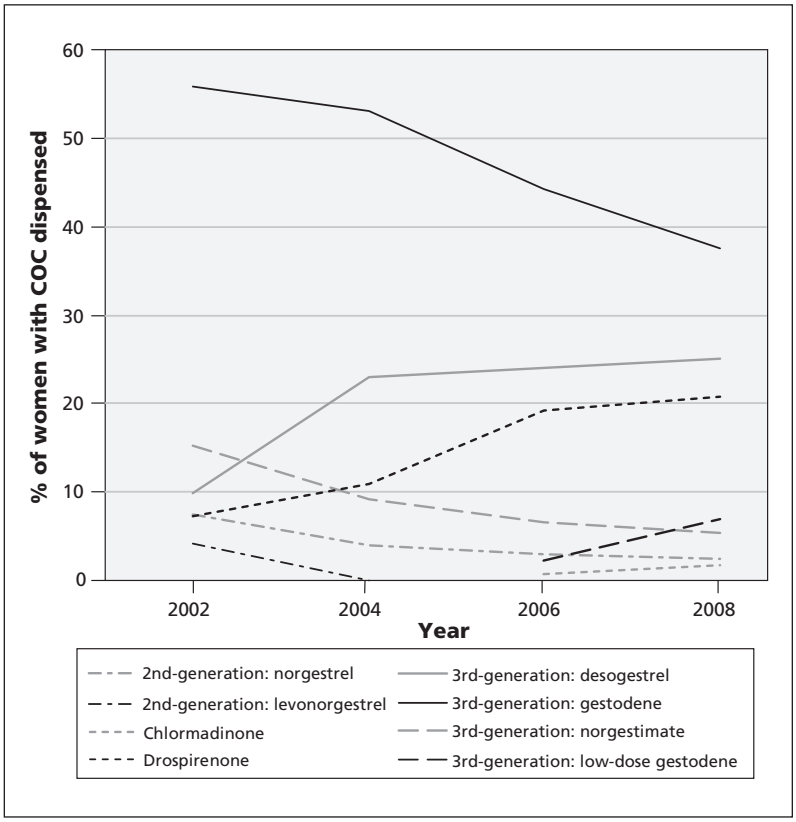

Figure 1: Time trends in the use of various combined oral contraceptives (COCs). In total, 5.0% of women in the study cohort used second-generation agents (4.1% norgestrel and 0.9% levonorgestrel), 73.4% used third-generation agents (22.7% desogestrel, 41.6% gestodene and 9.1% norgestimate), 3.6% used the low-dose gestodene-containing agent, 17.1% used a drospirenone-containing COC, and 0.9% used a COC containing chlormadinone acetate. All but one of the contraceptive agents contained 20–30 μg ethinylestradiol as the estrogenic component; the norgestimate-containing COC contained 35 μg ethinylestradiol.

increase in the use of drospirenone-containing combined oral contraceptives in recent years (Figure 1). The numbers of users of low-dose gestodene and chlormadinone were too small to allow their inclusion in the multivariable analysis.

Included in the cohort were 329 995 women 12–50 years of age, accounting for a total of 431 223 use episodes and 819 749 woman-years of follow-up. Characteristics of women using second- and third-generation combined oral contraceptives and drospirenone-containing agents are presented in Table 1. During the study period, 1017 venous and arterial thrombotic events were newly diagnosed (0.24% of all use episodes): 359 cases of deep vein thrombosis (35.3%), 159 cases of pulmonary embolism (15.6%), 194 cases of transient ischemic attack (19.1%) and 305 cases of cerebrovascular accident (30.0%), for overall rates of 6.33 venous events and 6.10 arterial events per 10 000 woman-years. In the univariable analysis, hyperlipidemia, hypertension, cancer, obesity and older age were found to be significant risk factors for venous thrombosis (Table 2). The risk of arterial thrombotic events was also influenced by diabetes. The risk was highest in the first months of use.

In the multivariable analysis, with adjustment for risk factors associated with thrombotic events, the risk of venous thrombotic events was significantly greater among drospirenone users than among users of third-generation combined oral contraceptives (RR 1.43, 95% CI 1.15–1.78) (Table 3). Drospirenone was also associated with increased risk of venous thrombotic events relative to second-generation combined oral contraceptives (RR 1.65, 1.02–2.65) (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110463/-/DC1). The difference in risk between second- and third-generation combined oral contraceptives was not statistically significant (RR 1.38, 95% CI 0.90–2.11) (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110463/-/DC1). Drospirenone was used by a greater proportion of women during the second half of the study period (Figure 1). The detection of disease improved over the study period because of technologic advancement, such as the use of computed tomography angiography for diagnosis of pulmonary embolism. We therefore performed a sensitivity analysis with calendar year as a variable. This modified analysis did not change the results, which implies that the increased risk associated with drospirenone was not a result of detection bias.

The use of drospirenone was not associated with an increased risk of arterial thrombotic events (transient ischemic attack or cerebrovascular accident), relative to use of second- or third-generation combined oral contraceptives, and use of a third-generation agent was not associated with an increased risk of an arterial event, relative to use of a second-generation agent (Table 3, Appendix 1, Appendix 2).

Restricting our analysis to first-time users (i.e., with data for only the first type of combined oral contraceptive used by each individual woman) yielded similar results but with weaker associations, probably because of smaller numbers of use episodes in each group. In this subgroup, the RR values for venous thrombotic events were 1.30 (95% CI 0.98–1.72) for the comparison of drospirenone with third-generation agents, 1.67 (95% CI 0.98–2.86) for the comparison of drospirenone with second-generation agents and 1.52 (95% CI 0.94–2.46) for the comparison of third-generation with second-generation agents. There was no increased risk for arterial events.

In the secondary analysis of estrogen dosage within third-generation pills, there was no difference between formulations with 20 μg estrogen and those with 30–35 μg estrogen in terms of venous thrombotic events (RR 0.95, 95% CI 0.77–1.16) or arterial thrombotic events (RR 1.10, 95% CI 0.90–1.34).

Table 1: Characteristics of women included in the study cohort, by type of combined oral contraceptive used

Characteristic	Type of oral contraceptive*; % of use episodes†		
	Second-generation *n = 21 546*	Third-generation *n = 316 371*	Drospirenone-containing *n = 73 629*
Age, yr, mean (SD)	33 (8.4)	27 (7.6)	26 (7.2)
Medical history			
Diabetes mellitus	1.78	0.71	0.64
Hyperlipidemia	5.66	5.07	6.11
Hypertension	3.30	1.40	1.10
Cancer	0.78	0.68	0.69
Smoking			
Yes	18.48	25.21	26.28
No	73.20	62.60	60.90
Unknown	8.40	12.20	12.80
Obesity			
Yes	26.44	15.32	13.41
No	53.20	59.20	61.60
Unknown	20.30	25.50	25.00

Note: SD = standard deviation.
*In addition to the use episodes for these three categories of combined oral contraceptives, there were an additional 19 677 use episodes for low-dose gestodene and chlormadinone, but the sample sizes were too small to allow analysis.
†Unless stated otherwise.

Interpretation

Use of drospirenone-containing combined oral contraceptives was associated with a significantly increased risk of venous thrombotic events (deep vein thrombosis and pulmonary embolism) but not arterial thrombotic events (transient ischemic attack and cerebrovascular accident), relative to use of second- or third-generation combined oral contraceptives. Independent risk factors for venous thrombotic events in drospirenone users included older age, obesity and history of cancer. The risk was highest in the first four months of use.

Venous thromboembolism is a well-documented adverse event occurring with use of oral contraceptives.[4,13] Following the publication of case studies of thrombotic events in drospirenone users, this risk was studied in two manufacturer-sponsored studies. The first of these was the European Active Surveillance Study,[17] which had 58 674 women and 142 475 woman-years of follow-up, with power sufficient to exclude only a twofold or higher risk of

Table 2: Risk factors associated with venous and arterial thrombotic events among users of combined oral contraceptives

Risk factor	Woman-years*	DVT and PE		TIA and CVA	
		No. (rate per 10 000 woman-years)	RR (95% CI)	No. (rate per 10 000 woman-years)	RR (95% CI)
Age, yr					
12–19	97 161	34 (3.50)	Reference	23 (2.37)	Reference
20–24	307 850	139 (4.52)	1.29 (0.89–1.88)	100 (3.25)	1.37 (1.06–1.78)
25–29	193 552	115 (5.94)	1.70 (1.16–2.49)	84 (4.34)	1.83 (1.41–2.39)
30–34	101 578	73 (7.19)	2.06 (1.37–3.09)	78 (7.68)	3.25 (2.48–4.25)
35–39	63 020	70 (11.11)	3.18 (2.11–4.79)	84 (13.33)	5.64 (4.32–7.36)
40–44	39 549	62 (15.68)	4.49 (2.96–6.83)	72 (18.21)	7.71 (5.88–10.10)
45–50	17 016	25 (14.69)	4.22 (2.52–7.07)	58 (34.09)	14.41 (10.91–19.05)
Diabetes mellitus					
No	812 103	513 (6.32)	Reference	482 (5.94)	Reference
Yes	7 646	5 (6.54)	1.04 (0.43–2.50)	17 (22.23)	3.75 (2.83–4.95)
Hyperlipidemia					
No	758 616	466 (6.14)	Reference	437 (5.76)	Reference
Yes	61 133	52 (8.51)	1.39 (1.04–1.85)	62 (10.14)	1.76 (1.51–2.06)
Hypertension					
No	804 878	498 (6.19)	Reference	453 (5.63)	Reference
Yes	14 871	20 (13.45)	2.19 (1.40–3.42)	46 (30.93)	5.50 (4.62–6.56)
Cancer					
No	813 367	501 (6.16)	Reference	491 (6.04)	Reference
Yes	6 382	17 (26.64)	4.33 (2.67–7.01)	8 (12.54)	2.09 (1.39–3.12)
Smoking					
No	583 511	379 (6.50)	Reference	353 (6.05)	Reference
Yes	236 238	139 (5.88)	0.91 (0.74–1.11)	146 (6.18)	1.02 (0.84–1.24)
Obesity					
No	666 334	347 (5.21)	Reference	331 (4.97)	Reference
Yes	153 415	171 (11.15)	2.15 (1.72–2.67)	168 (10.95)	2.21 (1.79–2.74)
Duration of use, mo					
≤ 2	75 224	103 (13.69)	Reference	97 (12.89)	Reference
3–4	68 795	75 (10.90)	0.80 (0.59–1.07)	83 (12.06)	0.94 (0.79–1.11)
5–13	211 942	141 (6.65)	0.49 (0.38–0.63)	154 (7.27)	0.56 (0.49–0.65)
≥ 14	463 788	199 (4.29)	0.31 (0.25–0.40)	165 (3.56)	0.28 (0.24–0.32)

Note: CI = confidence interval, CVA = cerebrovascular accident, DVT = deep vein thrombosis, PE = pulmonary embolism, RR = rate ratio, TIA = transient ischemic attack.
*Data on age were missing for 26 use episodes (23 woman-years of follow-up).

venous thromboembolism. This study showed noninferiority of drospirenone compared with levonorgestrel and other oral contraceptives. The second study[18] involved 22 429 women initiating drospirenone use (with 14 081 woman-years of follow-up) and 44 858 women initiating use of "other oral contraceptives" (with 22 575 woman-years of follow-up), but again the cohort was too small to observe a difference. In 2009, the Danish national follow-up study[8] and the MEGA (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) case–control study[25] showed that drospirenone and third-generation oral contraceptives carried increased risks of venous thromboembolism, when compared with second-generation oral contraceptives; however, drospirenone was not directly compared with the third-generation contraceptives. Two recent case–control studies identified an increased risk of venous thromboembolism with drospirenone, relative to second-generation levonorgestrel.[15,16] The exact mechanism by which drospirenone might increase the risk of venous thrombotic events is unknown. An increased prothrombotic effect was demonstrated for both drospirenone and third-generation pills, compared with second-generation pills.[26]

Table 3: Multivariable analysis of risk of venous and arterial thrombotic events among users of drospirenone-containing combined oral contraceptives relative to users of third-generation combined oral contraceptives

Variable	Type of event; adjusted RR* (95% CI)	
	DVT and PE	TIA and CVA
Third-generation oral contraceptive†	Reference	Reference
Drospirenone-containing oral contraceptive‡	1.43 (1.15–1.78)	0.97 (0.74–1.26)
Age, per year	1.05 (1.04–1.06)	1.08 (1.07–1.10)
Diabetes mellitus	0.40 (0.13–1.24)	1.42 (0.78–2.59)
Hyperlipidemia	1.26 (0.94-1.69)	1.20 (0.88-1.64)
Hypertension	1.42 (0.90–2.26)	2.16 (1.49–3.13)
Cancer	3.37 (2.01–5.67)	1.39 (0.65–2.94)
Smoking	0.99 (0.80–1.23)	1.19 (0.97–1.46)
Obesity	1.72 (1.39–2.12)	1.47 (1.19–1.83)
Duration of use, per month	0.98 (0.97–0.98)	0.97 (0.96–0.98)

Note: CI = confidence interval, CVA = cerebrovascular accident, DVT = deep vein thrombosis, PE = pulmonary embolism, RR = rate ratio, TIA = transient ischemic attack.
*For the overall comparison of drospirenone-containing oral contraceptives with third-generation oral contraceptives, RR was adjusted for all variables listed in the table. For each variable-specific comparison of drospirenone-containing oral contraceptives with third-generation oral contraceptives, RR was adjusted for all other variables listed.
†No. of thrombotic events among users of third-generation combined oral contraceptives: venous = 384 (no. of woman-years of follow-up = 651 455), arterial = 382 (no. of woman-years of follow-up = 651 376).
‡No. of thrombotic events among users of drospirenone-containing combined oral contraceptives: venous = 99 (no. of woman-years of follow-up = 114 797), arterial = 66 (no. of woman-years of follow-up = 114 755).

We did not observe any increased risk of arterial events with drospirenone relative to second- or third-generation combined oral contraceptives, and no such increased risk has been found in comparisons of third-generation pills with second-generation formulations.[7,14] Drospirenone, as an aldosterone antagonist, also decreases the blood pressure slightly,[27] which might balance other factors favouring arterial thrombosis. In case–control studies, smoking was found to be a risk factor for arterial events, but not for venous thrombotic events.[6,7,13,14,16]

We found that women were most vulnerable during the first months of using combined oral contraceptives. A similar pattern was previously demonstrated for venous events[25] but not for arterial events.[6] The reason for this temporal variation in risk has not been studied. Perhaps a relatively short period is enough to expose susceptible women and to facilitate the thrombotic process.

Limitations

Our study had several limitations. There was a possibility of confounding by indication if physicians preferred to prescribe drospirenone-containing contraceptives to women with a presumed higher risk of venous thromboembolism. We adjusted for most of the known clinical risk factors for venous thromboembolism that might have led to a change in prescription, but we did not have information about family history of this condition. Restricting our analysis to first-time users, to reduce indication bias (as was suggested by an earlier study[28]), did not change the results.

With the database system used for this study, we could not verify diagnoses by examining imaging data. Overdiagnosis might have occurred among users of oral contraceptives but presumably did not occur more often with certain types of pills. Another limitation was our inability to evaluate hospital admissions or acute illnesses as predisposing factors; again, however, a thrombotic event resulting from immobilization would probably not occur more often with a specific kind of combined oral contraceptive. Finally, we could not compare minor adverse effects or advantages between the preparations that we studied.

Conclusions

Most of the available information about the risks of venous and arterial thrombotic events in users of oral contraceptives comes from case–control studies. Venous and arterial events are typically described in separate cohorts. Our cohort of women from a large, unselected population, identified through computerized records, pro-

vides insight into risk factors for thrombotic events, as well as an opportunity to compare the risks of thrombotic events between different contraceptive preparations. With the increasing use of drospirenone-containing contraceptives, it is important to raise awareness of the increased, albeit small, risk of venous thromboembolism relative to third-generation pills, especially among those who are older or obese. Further research should explore the pathophysiologic mechanism of the risk of venous thromboembolism with drospirenone.

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REVIEW ARTICLE

Hormone therapies and venous thromboembolism: where are we now?

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Deep vein thrombosis is a common disease, with an incidence of one to three per 1000 individuals per year [1]. Numerous risk factors are known, which can be divided into genetic and acquired [2]. One of the most well-known acquired risk factors is the use of female hormones, i.e. oral contraceptive use or the use of hormone replacement therapy. Apart from the use of hormones orally, other routes of administration are also available, e.g. intrauterine devices, injectables, subcutaneous implants, or skin patches. While most research regarding the risk of venous thrombosis has been conducted on oral hormone use, an increasing number of studies are focusing on the thrombotic effect of these alternative routes of administration. Here, we will review the current knowledge on the risk of venous thrombosis associated with premenopausal hormone use for contraception and with postmenopausal hormone replacement therapy. The impact of hormone use for women who have an increased risk for venous thrombosis will be discussed. These include carriers of thrombophilia, women with a positive family history of venous thrombosis, and women who have experienced venous thrombosis.

Oral contraceptives

Combined oral contraceptives (containing an estrogen and a progestagen) were first approved in the USA in 1960. It is estimated that more than 100 million women worldwide use an oral contraceptive [3].

Soon after their introduction, it became apparent that the use of these female hormones was associated with an increased risk of thrombosis. The first report of an increased risk of venous thrombosis associated with oral contraceptive use appeared in 1961 [4]. Subsequently, numerous reports have been published on the increase in thrombotic risk, indicating a two-fold to six-fold increased risk of deep vein thrombosis associated with current oral contraceptive use [5–11].

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Most currently available oral contraceptives are combined preparations containing both an estrogen (i.e. ethinylestradiol [EE2]) and a progestagen. Numerous types of oral contraceptives are available, containing different doses of estrogen and different types of progestagen. The first available preparations contained a high dose of the estrogen EE2. However, after the reported increased thrombotic risk associated with combined oral contraceptive use was attributed to the amount of estrogen in the contraceptive pill, the dose of estrogen was reduced stepwise. The initial lowering of the estrogen dose from $>$ 50 μg to 30 μg was indeed shown to be associated with a clear decrease in the risk of venous thrombosis [12,13]. In two recently published studies, it was shown that a further decrease in the estrogen dose to 20 μg led to an additional lowering of the risk of venous thrombosis [10,11]. In the MEGA study, a large case–control study, we showed that, after adjustment for type of progestagen, oral contraceptives containing 20 μg of estrogen were associated with a slightly decreased risk of venous thrombosis as compared with oral contraceptives containing 30 μg of estrogen (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.5–1.2) [10]. The study by Lidegaard *et al.* [11] also showed that a reduction in estrogen dose from 30 or 40 to 20 μg was associated with an 18% reduction in the risk of venous thrombosis [11].

The progestagens in combined oral contraceptives appear to counter the prothrombotic effect of the estrogens. Numerous different types of progestagens with different chemical compositions are available. The oldest types of progestagens, i.e. the first-generation progestogens, were lynestrenol and norethisterone. Nowadays, these first-generation progestagens are not used very often. Second-generation oral contraceptives, which are widely used, contain the progestagens levonorgestrel or norgestrel. Newer types of oral contraceptives, i.e. the third-generation oral contraceptives, contain the progestagens gestodene or desogestrel. Norgestimate is categorized as a third-generation progestagen. However, as it is, in part, converted to levonorgestrel, it may metabolically belong more to the second-generation progestagens. Preparations containing cyproterone acetate are used for the treatment of acne vulgaris, seborrhea, or mild hirsutism, and have an antiovulatory action similar to that of a progestagen. Preparations

containing drospirenone, which is an antimineralcorticoid, also inhibit ovulation.

There is evidence that the different progestagens counter the prothrombotic effect of estrogens differently, and are therefore associated with different venous thrombotic risks [14]. The risk of venous thrombosis was reported to be increased for users of the third-generation oral contraceptives as compared with users of the second-generation oral contraceptives [15]. However, this finding was not confirmed in all studies. The difference in thrombotic risk between third-generation and second-generation oral contraceptives has been the subject of a long ongoing debate, with non-believers explaining the difference in risk by bias and confounding. However, a large meta-analysis countered most of these arguments of bias and confounding, and demonstrated an increased risk of thrombosis for third-generation as compared with second-generation oral contraceptives; subsequently, several other studies confirmed this finding [16]. Furthermore, the results of studies on the effects of different types of oral contraceptives on the hemostatic system were in line with these findings, i.e. showing that there was a more prothrombotic risk profile, including more activated protein C (APC) resistance, associated with third-generation oral contraceptives than with second-generation oral contraceptives [17–21].

Oral contraceptives containing cyproterone acetate have been associated with a highly increased risk of venous thrombosis or fatal pulmonary emboli; however, this was not confirmed by all studies [22–24]. Recent studies have indicated that these oral contraceptives are associated with an elevated thrombotic risk as compared with oral contraceptives containing levonorgestrel [10,11].

EE2 with drospirenone has been approved as an oral contraceptive in all European Union countries since 2000. Shortly after their introduction, several case reports indicated a highly increased risk of venous thrombosis associated with these oral contraceptives [25–28]. This high risk of thrombosis was confirmed by our large case–control study and a large follow-up study, which both reported a higher risk of thrombosis as compared with oral contraceptives containing levonorgestrel or gestodene [10,11].

The so-called mini-pill is an oral progestagen-only preparation. Whereas oral progestagen-only preparations are associated with an increased risk of venous thrombosis when used for therapeutic reasons (containing different progestagens or higher doses of the progestagens used in oral contraceptives) [29,30], oral progestagen-only preparations used for contraceptive reasons appeared to be, at most, associated with a mildly increased risk of thrombosis [30,31]. More recently, Lidegaard *et al.* [11] have shown that oral progestagen-only oral contraceptives do not appear to be associated with an increased risk of venous thrombosis, regardless of the type of progestagen: desogestrel-containing progestagen-only preparations, rate ratio (RR) 1.1, 95% CI 0.4–3.4; norethisterone-containing or levonorgestrel-containing preparations, RR 0.6, 95% CI 0.3–1.0.

Effect of oral contraceptive use on the coagulation system

Oral contraceptive use is associated with changes in the levels of coagulation factors, leading to a predisposition to venous thrombosis. Oral contraceptive use is associated with increased resistance to the natural anticoagulant activity of APC [32]. In line with the increased thrombotic risk associated with oral contraceptives containing desogestrel as compared with levonorgestrel, these third-generation pills induce more pronounced APC resistance than the second-generation preparations [17,18,33]. The highest APC resistance, resulting in the most thrombotic tendency of the coagulation system, was found in women using oral contraceptives containing cyproterone acetate [33]. Similar differences between these types of oral contraceptive were observed in levels of anticoagulant proteins, such as protein S and tissue factor pathway inhibitor (TFPI); that is, oral contraceptives associated with a higher risk had lower levels of both free protein S and free TFPI [20,34]. Furthermore, the changes induced in coagulation factors and fibrinolytic parameters differ between second-generation and third-generation oral contraceptives [19,21].

From the results of these studies, it is clear that the use of oral contraceptives is associated with a procoagulant risk profile. Still, one might question whether these intermediate endpoints, e.g. markers of hemostasis that have been related to the risk of venous thrombosis, indicate a true increased risk of venous thrombosis associated with hormone use. However, in line with observed differences in the risk of venous thrombosis associated with different progestagens, all studies using these intermediate endpoints point in the same direction, with a more thrombotic risk profile in users of the third-generation oral contraceptives containing desogestrel or gestodene, and in users of oral contraceptives containing cyproterone acetate or drospirenone, than in users of oral contraceptives containing levonorgestrel.

Non-oral contraceptives

Oral contraceptives are the most frequently used hormonal contraceptives. However, other routes of administration of hormonal contraceptives are also available, e.g. intrauterine devices, injectables, subcutaneous implants, or skin patches. The risk of venous thrombosis associated with these non-oral contraceptive methods has been studied to a much lesser extent than that associated with oral contraceptives.

In the following paragraphs, we provide an overview of the available information on the risk of venous thrombosis associated with depot medroxyprogesterone (DMPA) injectable progestagen-only contraceptives, the hormone-releasing intrauterine device, the hormonal contraceptive ring, the hormonal contraceptive patch, and the hormonal contraceptive implant.

Injectable DMPA progestagen-only contraceptives

DMPA is a long-acting injectable progestagen-only contraceptive. In 1998, the World Health Organization reported a small increase in thrombotic risk associated with the use of injectable

progestagen (medroxiprogesterone)-only contraceptives (OR 2.2; 95% CI 0.7–7.3) [31]. Although, also in the MEGA study, a small number of women used DMPA-only contraceptives, we found a clearly increased risk of venous thrombosis associated with these contraceptives as compared with non-use (OR 3.6; 95% CI 1.8–7.1) [35]. Other studies mainly investigated intermediate endpoints, e.g. coagulation factors and APC resistance. In contrast to these clinical findings, Walsh *et al*. reported a decrease in sex hormone-binding globulin (SHBG) level, a probable marker of the risk of venous thrombosis [36,37]. Several studies that assessed the effect of DMPA-only contraceptives on coagulation or inflammation markers reported little or no effect [36,38,39].

Levonorgestrel-releasing intrauterine device

The levonorgestrel-releasing intrauterine device or system is a T-shaped plastic contraceptive that is inserted into the uterine cavity [40]. After insertion of a levonorgestrel-releasing intrauterine device, plasma levels of levonorgestrel are 150–200 pg mL^{-1} in the peripheral blood [41], as compared with a maximal level of 800 pg mL^{-1} during the use of a 30-μg levonorgestrel-only pill. The use of the levonorgestrel-releasing intrauterine device was not associated with an increased risk of venous thrombosis in a large follow-up study on venous thrombosis (RR 0.9; 95% CI 0.6–1.3) or in the MEGA case–control study (OR 0.3; 95% CI 0.1–1.1) [11,35]. Furthermore, with the use of the thrombin generation-based APC resistance assay, higher sensitivity to APC in women 3 months after the insertion of the levonorgestrel-releasing intrauterine device than before the insertion was observed, suggesting a low thrombosis risk, whereas there was no change after insertion of a copper intrauterine device [42]. The decrease in APC resistance appeared to be most pronounced in women who switched from a combined oral contraceptive to the levonorgestrel-releasing intrauterine device.

Transdermal patches and hormone-releasing vaginal ring

New types of combined contraceptive are the transdermal patch and the hormone-releasing vaginal ring. The contraceptive patch was designed to deliver 20 μg of EE2 and the contraceptive vaginal ring 15 μg EE2 per day. Both types of contraceptive contain a third-generation progestagen. The transdermal patch contains norelgestromin, the primary active metabolite of norgestimate, and the vaginal ring contains etonogestrel, a metabolite of desogestrel [43].

So far, little information is available regarding the thrombotic risk associated with these contraceptive methods. As compared with oral contraceptives containing norgestimate, for users of the transdermal patch, the reported risks of venous thrombosis varied between no increase (OR 1.0; 95% CI 0.7–1.5) to a more than two-fold increase (incidence rate ratio 2.2; 95% CI 1.3–3.8) [44–46].

Further studies assessing the effect of these contraceptive methods on the risk of venous thrombosis mainly used intermediate endpoints. Again, findings were contradictory. In a randomized crossover trial, similar adverse effects on vascular risk markers with an oral contraceptive containing norgestimate and with the contraceptive patch were observed [47]. Other studies, however, reported more prothrombotic effects associated with the use of the hormonal patch than with different types of oral contraceptives [48–50].

Even less information is available on the risk of venous thrombosis associated with the vaginal ring. As compared with combined oral contraceptive use (mainly third-generation oral contraceptives), a beneficial effect associated with the use of the vaginal ring was reported [49], whereas in a different study, the vaginal ring was associated with more resistance to APC and a higher level of SHBG than the use of levonorgestrel-containing contraceptives [50,51].

Hormonal implants

The etonogestrel implant is a progestagen-only contraceptive that is implanted under the skin. Etonogestrel is an active metabolite of the third-generation progestagen desogestrel. The delivery dose of progestagen varies over time, from 60–70 μg d^{-1} in the first weeks of use to 25–30 μg d^{-1} after 3 years. Very little is known about the thrombogenicity of the etonogestrel implant. Lindqvist *et al*. [52] reported in 2003 that etonogestrel implant use was not related to hypercoagulable changes in the anticoagulant system or the prothrombotic factors V, VII, and VIII. In a study by Vieira *et al*. [53], it was reported that the etonogestrel-releasing implant was associated with a reduction in APC resistance and the levels of several prothrombotic factors (prothrombin, FVII, FX, and F_{1+2}), whereas plasminogen activator inhibitor-1 and FXI levels were increased. However, all factors remained within the normal range, suggesting that the use of an etonogestrel implant is not associated with a prothrombotic risk profile.

An overview of recent estimates of the thrombotic risks associated with the use of different types of hormonal contraceptives is shown in Table 1.

Hormone replacement therapy

Until the late 1990s, hormone replacement therapy was considered to be an effective measure to improve cardiovascular risk factors, in particular lipid profiles [54], and protect women against the postmenopausal rise in the incidence of arterial cardiovascular disease [55,56]. However, large, randomized controlled trials showed that hormone replacement therapy does not prevent arterial cardiovascular disease, and even has a detrimental effect in the first year of use [57–59]. Nowadays, the indication for hormone replacement therapy is limited to improving quality of life by alleviating perimenopausal complaints, and it should be given at the lowest possible dose for the shortest possible duration [60].

Like contraceptive hormones, hormone replacement therapy is available in various forms. It generally provides a low dose of estrogen, most often together with progesterone or a progestin.

Table 1 Recent estimates of relative risks associated with use of contraceptives

	MEGA case–control study [10,35], odds ratio (95% CI)	Danish National cohort study [11], rate ratio (95% CI)	WHO [31], odds ratio (95% CI)	Jick *et al.* [44], odds ratio (95% CI) Cole *et al.* [45], incidence rate ratio (95% CI)
Combined oral contraceptives				
Estrogen 30 μg and noresthisterone	3.9 (1.4–10.6)			
Estrogen 30 μg and levonorgestrel	3.6 (2.9–4.6)	2.02 (1.75–2.34)*		
Estrogen 37.5 μg and lynestrenol	5.6 (3.0–10.2)			
Estrogen 30 μg and norgestimate	5.9 (1.7–21.0)			
Estrogen 30 μg and desogestrel	7.3 (5.3–10.0)	3.55 (3.30–3.83)*		
Estrogen 30 μg and gestodene	5.6 (3.7–8.4)			
Estrogen 30 μg and drospirenone	6.3 (2.9–13.7)	4.00 (3.26–4.91)*		
Estrogen 35 μg and cyproterone acetate	6.8 (4.7–10.0)			
Progestagen-only				
Pills				
Levonorgestrel 30 μg or norethisterone 350 μg		0.59 (0.33–1.04)		
Desogestrel 75 μg		1.10 (0.35–3.41)		
Progestagen-only injectable	3.6 (1.8–7.1)		2.2 (0.7–7.3)	
Levonorgestrel-releasing intrauterine device	0.3 (0.1–1.1)	0.89 (0.64–1.26)		
Transdermal Patches†				1.0 (0.7–1.5) [44] to 2.2 (1.3–3.8) [45]

CI, confidence interval; WHO, World Health Organization.
All compared with non-use unless stated otherwise: *with 20–40 μg of estrogen; †as compared with oral contraceptives containing norgestimate. No risk estimates are available for the vaginal ring or hormonal implants.

Conjugated equine estrogens are derived from the urine of pregnant mares, contain several biologically active estrogen compounds, and are the most widely used components of hormone replacement therapy. Esterified estrogens are synthetic and fabricated from soybean and yam. Unopposed estrogen is restricted to women who have had a hysterectomy, because of the increased risk of endometrial cancer. Hormone replacement therapy can be taken by mouth, or delivered via patches, creams, gels or, more rarely, injection. Dosage can be varied cyclically, with estrogens being taken daily and progesterone or progestins taken for about 2 weeks every 1 or 2 months (sequentially combined hormone replacement therapy), or a constant dosage being used, with both types of hormones taken daily (continuous combined hormone replacement therapy).

Both observational studies and randomized controlled trials have consistently shown an approximately two-fold to three-fold increased risk of venous thrombosis in users of hormone replacement therapy [58,61–63]. Most early studies of venous thromboembolism in users of hormone replacement therapy were performed among women using conjugated equine estrogens alone or with medroxyprogesterone acetate. Although, in the Women's Health Initiative study, estrogen-only hormone replacement therapy in women without a uterus was associated with only a small increase in the risk of venous thrombosis in the first 2 years of use, and the risk was less than with the combination of estrogen plus progestin (hazard ratio (HR) 1.47; 95% CI 1.06–2.06) [64], this was not confirmed in a recent meta-analysis of both observational studies and randomized controlled trials [65]. Furthermore, a case–control study suggested that esterified estrogen is not associated with an increased risk of venous thrombosis [66,67].

Only a limited number of observational studies have assessed the risk of venous thrombosis associated with transdermal estrogen use, with inconsistent results, ranging from no increased risk to a point estimate of an approximately two-fold increased risk [61,68–71]. After meta-analysis, the pooled risk estimate for a first episode of venous thrombosis associated with transdermal estrogen was 1.2 (95% CI 0.9–1.7) [65]. Since this meta-analysis, other studies finding no increased risk of venous thrombosis in users of transdermal estrogen have been published [71,72]. An analysis in the UK's General Practice Research Database found no increased risk for venous thrombosis in users of transdermal estrogen with or without progestin (adjusted rate ratio 1.01 [95% CI 0.89–1.16], and 0.96 [95% CI 0.77–1.20], respectively) [71]. A recent large French epidemiological study showed that, although the overall risk of idiopathic venous thrombosis was not increased in users of transdermal hormone replacement therapy (HR 1.1; 95% CI 0.8–1.8), transdermal estrogen combined with norpregnane derivatives, in particular, increased the risk of idiopathic venous thrombosis as compared with other progestins [72].

Tibolone is a synthetic steroid whose metabolites have estrogenic, progestagenic and androgenic activities, and is also used as hormone replacement therapy. Trials that primarily assessed the effect of tibolone on osteoporotic fractures and breast cancer did not show an increased risk for venous thrombosis (HR 0.57, 95% CI 0.19–1.69) [73,74]. Both trials, however, showed other harmful effects, i.e. a higher risk of stroke [73] or an increased risk of recurrent breast cancer [74], in women treated with tibolone. The absence of an increased risk of venous thrombosis was also

observed in the UK's General Practice Research Database [71].

Effect of hormone replacement therapy on the coagulation system

Oral hormonal replacement therapy has very similar effects on coagulation and fibrinolysis variables as the use of oral contraceptives, all pointing towards a prothrombotic effect. In particular, oral estrogen-containing hormone replacement therapy decreases the levels of the natural coagulation inhibitors antithrombin, protein C, and protein S, and increases resistence to APC [75–77]. On the other hand, a systematic review of trials comparing the effects of transdermal hormone replacement therapy with oral hormone replacement therapy on markers concluded that these effects are absent or at least lower with transdermal hormone replacement therapy use [78]. The effects of tibolone on markers of thrombosis risk are also less than with oral hormone replacement therapy or absent [75–77].

Implications for prescribing in clinical practice – hormonal contraceptives

Baseline risk of venous thrombosis for women of fertile age

The absolute risk of venous thrombosis increases sharply with age, in particular after the age of 45 years [79,80]. Considering fertile women, the incidence rate of first venous thrombosis in a large Norwegian cohort study ranged from 0.36 per 1000 person-years in women aged 20–24 years to 0.37 and 0.82 per 1000 person-years in women aged 40–44 and 45–49 years, respectively [1]. If no valid observations on the absolute risk are available, the reported relative risk increases caused by the use of oral contraceptives should be multiplied by this baseline risk, which varies considerably with age. Even a small increase in the risk of venous thrombosis is relevant, given the huge number of women who use oral contraceptives worldwide, but these risks need to be balanced against the beneficial effects in terms of avoidance of unintended pregnancies [81].

Women with hereditary thrombophilia

The presence of hereditary thrombophilia strongly increases the risk of venous thrombosis associated with the use of oral contraceptives. For instance, as compared with women who do not use oral contraceptives and do not carry the FV Leiden mutation, the risk was found to be increased 35-fold in heterozygous women using oral contraceptives [6]. This risk increase has led to questions regarding the need to screen young women for FV Leiden prior to oral contraceptive use. However, in the absence of a clear family history of venous thrombosis, i.e. in the general population, where approximately 5% of women carry the mutation, the number needed to be tested to withhold oral contraceptives in carriers and to prevent a single death from pulmonary embolism would exceed half a million [82].

The situation may be different for women who have a positive family history of venous thrombosis. In clinical practice, the question often arises of whether oral contraceptives are contraindicated, and whether testing for thrombophilia would influence this decision [83]. It is important to note that selection bias is apparent in the observed risks of venous thrombosis in thrombophilia, meaning that thrombophilic individuals who are selected from families with a tendency to venous thrombosis have a higher risk than individuals with the same defect who have been identified through population testing [84]. Thus, when assessing the risk of venous thrombosis in an individual woman, it is important to clearly define the population to which she belongs; that is, does she have a personal or family history of venous thrombosis, or was she identified because of routine screening or other health problems (e.g. because of recurrent miscarriage)? Absolute risk estimates for asymptomatic family members of patients with venous thrombosis and known hereditary thrombophilia were obtained in several family studies. Carriers have a two-fold to 10-fold increased risk of venous thrombosis as compared with their female relatives who do not carry the defect, depending on the type of thrombophilia [85–94]. These kinds of family study have yielded useful risk estimates in this particular group of women while they are using oral contraceptives. In Table 2, the absolute risks per year of use of oral contraceptives and per type of thrombophilia are shown. Estimates obtained in well-sized retrospective studies are useful and valid, as the observations were made in women who were still unaware of their thrombophilic status and thus reflect a real-life situation.

For asymptomatic women with antithrombin, protein C or protein S deficiency and at least one first-degree or second-degree relative with venous thrombosis, the risk was found to be 4.3% (95% CI 1.4–9.7) per year of oral contraceptive use. This means that, within symptomatic families with these defects, approximately 25 (95% CI 10–66) women with thrombophilia need to refrain from oral contraceptive use to prevent one venous thrombosis event per year (assuming a population baseline risk of one in 10 000 in women not carrying a thrombophilic defect, which may not be completely realistic), and thus 50 (95% CI 20–132) women need to be

Table 2 Absolute risk of venous thrombosis in asymptomatic carriers of thrombophilia, estimated in retrospective family studies

	Oral contraceptive use (% per year of use, 95% CI)	Overall* (% per year, 95% CI)
Hereditary deficiencies of antithrombin, protein C, or protein S	4.3 (1.4–9.7) [85]	1.5 (0.7–2.8) [85]
Factor V Leiden	0.5 (0.1–1.4) [85,86]	0.5 (0.1–1.3) [85,86]
Prothrombin 20210A	0.2 (0.0–0.9) [88]	0.4 (0.1–1.1) [88]
Elevated FVIII:c	0.6 (0.2–1.5) [89]	1.3 (0.5–2.7) [89]
Mild hyperhomocysteinemia	0.1 (0.0–0.7) [90]	0.2 (0.1–0.3) [90]

CI, confidence interval.
*All carriers, including men and women of all ages, provoked and unprovoked venous thrombosis.

tested. For the milder thrombophilias, in particular those caused by FV Leiden and the prothrombin 20210A mutation, the risk estimates are more precise, because of the much higher prevalence of these mutations. For these gain-of-function mutations, approximately 200 (95% CI 77–1000) women need to refrain from oral contraceptive use to prevent one venous thrombosis event per year, and 400 (95% CI 152–2000) need to tested. Whether these numbers justify testing patients with venous thrombosis for thrombophilia and subsequent family testing is a matter of opinion rather than science [83,95,96].

Women with a positive family history of venous thrombosis

A family history of venous thrombosis is a reason for concern, but the sensitivity or predictive value appears to be very low. In a small study of 50 women who had an objectively diagnosed episode of venous thrombosis, only 16% had a positive family history [97]. In the large MEGA case–control study, 31% of 1605 patients with venous thrombosis had at least one first-degree relative who also had had venous thrombosis. A positive first-degree family history increased the risk of venous thrombosis from 2.2-fold (any relative) to 3.9-fold (more than one relative) [98]. As expected, also among carriers of thrombophilia, a positive family history increased the risk by 2.7-fold to 4.9-fold, thus interacting with the effect of the genetic risk factor alone.

Women with a personal history of venous thrombosis

According to our opinion, oral contraceptives should not be prescribed to women with a history of venous thrombosis [81]. The evidence for an adverse effect is indirect: venous thrombosis that occurred during oral contraceptive use was less likely to recur when the oral contraceptives were stopped [99]. In a prospective study of 272 women after a first episode of venous thrombosis, the recurrence rate was 1.3% per person-year in women who did not use oral contraceptives, as compared with approximately 3% per year in those who used oral contraceptives at some point during follow-up [100]. There was no apparent difference between women who used oral contraceptives at the time of their first venous thrombosis event and those who did not.

It is noteworthy that there is no indication to immediately discontinue oral contraceptives in women who are diagnosed with venous thrombosis. Anticoagulants effectively prevent the extension and recurrence of venous thrombosis [101], whereas effective contraception is crucial while women are using vitamin K antagonists, because these agents may lead to warfarin embryopathy [102]. Thus, oral contraceptives may be continued until shortly before discontinuation of anticoagulant therapy.

As effective contraception is vital for many women of fertile age, and hormonal methods are more effective than barrier methods and female tubal ligation, hormone-releasing intrauterine devices are often advised for women who have a history of venous thrombosis and have discontinued anticoagulant therapy. The results from the MEGA study and the large Danish cohort study suggest that this is, indeed, a safe contraceptive method with regard to the risk of venous thrombosis, although this study was limited to first thrombotic events, and the safety has not been tested in women with a history of venous thrombosis. Similarly, the risk for a first venous thrombosis is not clearly increased for progestagen-only pills, although the upper limit of the CI, particularly for the desogestrel-containing progestagen-only pill, does not exclude a significant 3.41-fold increase in risk.

Implications for prescribing in clinical practice – hormone replacement therapy

Given the much higher baseline risk of women who are exposed to hormone replacement therapy, because of their higher age, the impact of a relative risk increase on the absolute risk of venous thrombosis is markedly higher than in oral contraceptive users. In women aged 50–54 years, the incidence rate for a first venous thrombosis was 1.17 per 1000 person-years [1]. In the HERS trial, in which postmenopausal women younger than 80 years with confirmed coronary artery disease were included, the incidence rate for a first venous thrombosis was 6.3 per 1000 person-years in women on hormone replacement therapy, as compared with 2.2 per 1000 person-years in women using placebo (HR 2.89, 95% CI 1.50–5.58) [57]. In the WHI study, these rates were 3.4 and 1.6, respectively (HR 2.11, 95% CI 1.58–2.82) [59].

Women with hereditary thrombophilia or a positive family history

Risk estimates for thrombophilic women using hormone replacement therapy are less precise, because of the relatively small numbers of European women who used to take hormone replacement therapy and were included in the types of retrospective study that are informative for this situation. Thus, the known relative risks for the various thrombophilias should be multiplied by the baseline risk in the relevant age category. In general, women known to be carriers of thrombophilia, or with a positive first-degree family history of venous thrombosis, should be advised not to take hormone replacement therapy to relieve perimenopausal symptoms [65].

Guidelines recommend that hormone replacement therapy should be given at the lowest dose and for the shortest duration possible. On the basis of the current evidence, transdermal estrogen or tibolone should be preferred over combined hormone replacement therapy.

Women with a personal history of venous thrombosis

Hormone replacement therapy is contraindicated in women with a history of venous thrombosis. A randomized controlled trial of combined hormone replacement therapy in women with prior venous thrombosis was terminated early because of a marked difference in risk of recurrence between the women

who were given combined hormone replacement therapy and those given placebo (10.7% vs. 2.3%) [103]. To our knowledge, the effects of other routes of hormone replacement therapy have not been formerly tested in women who have a history of venous thrombosis.

Conclusions

All oral estrogen-containing hormonal regimens, used either for contraception or for hormone replacement postmenopausally, increase the risk of venous thrombosis. Therapeutic doses of progestagen-only preparations have a similar effect. Increases in venous thrombosis risk are modulated by dose of estrogen and type of progestagen. Although data are not abundant, current knowledge indicates that the risk of venous thrombosis is not clearly increased for the levonorgestrel-containing intrauterine device, transdermal estrogen, and tibolone. Hemostatic and fibrinolysis markers, most notably assays that measure resistance to APC, have shown effects of hormones that are in the same direction as epidemiologic data obtained with venous thrombosis as a clinical endpoint.

In order to minimize the risk of venous thrombosis associated with oral contraceptives, prudent prescribing in women who have an increased risk is the only option. However, solely having a risk factor may not be an absolute contraindication, but offers the possibility for women to make an informed decision about the use of this contraceptive method.

In our opinion, a personal history of venous thrombosis should be considered a contraindication for combined oral contraceptive use. Carriership of thrombophilia, in particular a deficiency of antithrombin, protein C or protein S, and, to a much lesser extent, FV Leiden or the prothrombin 20210A mutation, warrants counseling and balancing of benefits and risks, in which the family history of venous thrombosis should be taken into account. A strong family history in the absence of a known inherited thrombophilic defect warrants caution as well. A levonorgestrel-releasing intrauterine device does not increase the risk of a first venous thrombosis, an observation that may be extrapolated in clinical practice to offer women with a history of venous thrombosis a very effective contraceptive method. Similarly, progestagen-only pills could be considered, although risk estimates are less solid, particularly for desogestrel-containing progestagen-only pills. Hormone replacement therapy is contraindicated in women with a personal history of venous thrombosis, and should be discouraged in asymptomatic women with thrombophilia. If it is considered in exceptional cases, transdermal administration of estrogen or tibolone is preferred over oral hormone replacement preparations containing estrogen and progestin.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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RESEARCH

Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9

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Abstract

Objective To assess the risk of venous thromboembolism from use of combined oral contraceptives according to progestogen type and oestrogen dose.

Design National historical registry based cohort study.

Setting Four registries in Denmark.

Participants Non-pregnant Danish women aged 15-49 with no history of thrombotic disease and followed from January 2001 to December 2009.

Main outcome measures Relative and absolute risks of first time venous thromboembolism.

Results Within 8 010 290 women years of observation, 4307 first ever venous thromboembolic events were recorded and 4246 included, among which 2847 (67%) events were confirmed as certain. Compared with non-users of hormonal contraception, the relative risk of confirmed venous thromboembolism in users of oral contraceptives containing 30-40 µg ethinylestradiol with levonorgestrel was 2.9 (95% confidence interval 2.2 to 3.8), with desogestrel was 6.6 (5.6 to 7.8), with gestodene was 6.2 (5.6 to 7.0), and with drospirenone was 6.4 (5.4 to 7.5). With users of oral contraceptives with levonorgestrel as reference and after adjusting for length of use, the rate ratio of confirmed venous thromboembolism for users of oral contraceptives with desogestrel was 2.2 (1.7 to 3.0), with gestodene was 2.1 (1.6 to 2.8), and with drospirenone was 2.1 (1.6 to 2.8). The risk of confirmed venous thromboembolism was not increased with use of progestogen only pills or hormone releasing intrauterine devices. If oral contraceptives with desogestrel, gestodene, or drospirenone are anticipated to increase the risk of venous thromboembolism sixfold and those with levonorgestrel threefold, and the absolute risk of venous thromboembolism in current users of the former group is on average 10 per 10 000 women years, then 2000 women would need to shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel to prevent one event of venous thromboembolism in one year.

Conclusion After adjustment for length of use, users of oral contraceptives with desogestrel, gestodene, or drospirenone were at least at twice the risk of venous thromboembolism compared with users of oral contraceptives with levonorgestrel.

Introduction

The influence of specific types of combined oral contraceptives on the risk of thrombotic events remains the most important safety issue for these products. Several studies have investigated the relation between combined oral contraceptives and venous thromboembolism,[1-21] including newer large scale studies.[17-19] These new studies showed an increased risk of venous thromboembolism in current users of combined oral contraceptives and a decreasing risk by both time of use and decreasing oestrogen dose.

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International classification of diseases codes used in study
Codes for excluded diagnoses
Appendix 1: allocation rules applied in analysis
Appendix 2: rate ratios of venous thromboembolism with use of oral contraceptives with 3-40 µg ethinylestradiol; different exposure line formation
Appendix 3: rate ratios of venous thromboembolism with use of oral contraceptives with 3-40 µg ethinylestradiol; three sub-periods and during 2001-9
Appendix 4: rate ratios of venous thromboembolism with use of oral contraceptives with 3-40 µg ethinylestradiol; different user categories during 2001-9

Results on the significance of the type of progestogen differed. Ten studies reported an increased relative risk of venous thromboembolism among users of oral contraceptives with desogestrel or gestodene compared with those containing levonorgestrel,[1 2 4-7 9 13 17 18] a difference that was significant in eight of the studies,[1 2 4-6 13 17 18] whereas a further three studies found no difference.[8 14 19] In addition, four studies reported a higher relative risk of venous thromboembolism among users of combined oral contraceptives with drospirenone compared with those containing levonorgestrel,[17 18 20 21] whereas two other studies reported no difference.[14 19] Consequently, the European Medicines Agency asked our study team to revisit the Danish registry data for additional analyses, with a focus on differences in risk of venous thromboembolism between users of oral contraceptives with drospirenone and those with levonorgestrel in the period after the launch of drospirenone in 2001.

We assessed the relative and absolute risk of first time venous thromboembolism for users of oral contraceptives with different progestogens, different doses of oestrogen, and according to certainty of the diagnosis of venous thromboembolism. We also assessed the risk of venous thromboembolism in users of progestogen only pills and hormone releasing intrauterine devices.

Methods

We carried out a nationwide historical cohort study of all Danish women aged 15-49 during 1995-2009. The study focused on the period after the launch of combined oral contraceptives containing drospirenone in 2001. Information on the 1.2 million women of reproductive age in Denmark was collected from four sources of data: Statistics of Denmark, the national registry of patients, the national cause of death registry, and the national registry of medicinal products.

Statistics of Denmark: identification of women

Statistics of Denmark keeps records of all Danish citizens. A unique personal identification number is given to each citizen at birth or immigration. This number is used in public registries, enabling reliable linkage of data between registries. From Statistics of Denmark we identified Danish women in the age category 15-49 from 1 January 1995 to 31 December 2009. We also obtained data on length of schooling, ongoing or finished education, vital status, and emigration. Women were censored at death or emigration.

National registry of patients: end points

The national registry of patients has collected discharge diagnoses from all public and private hospitals in Denmark since 1977. From 1994 the registry has used diagnoses as coded in the ICD-10 (international classification of diseases, 10th revision). The web extra lists the codes used in this study.

To include first events only we excluded women with any type of venous or arterial thrombotic event before the study period (1977-2000). We also excluded women with malignant gynaecological disease, cancer of abdominal organs or breast, and lung or haematological cancer before the study period or we censored them at the time of diagnosis if any of these diseases occurred during the study period.

Surgery—the national registry of patients also records surgical codes from public and private hospitals. We excluded women at baseline who had undergone bilateral oophorectomy, unilateral oophorectomy on two occasions, hysterectomy, or sterilisation, or we censored them at the time of surgery.

Pregnancy—from the national patient registry we identified pregnancy outcomes and gestational age at termination (see web extra). We censored a woman's experience during pregnancy, as calculated from conception and three months after delivery (one month for abortions and ectopic pregnancies), from study follow-up.

Coagulation disturbances—we also excluded women with a coagulation disorder the first time such a diagnosis was recorded in the national patient registry, including Leiden factor V heterozygote or homozygote, prothrombin 20210 heterozygote or homozygote, protein C insufficiency, protein S insufficiency, and anti-thrombin III insufficiency.

National cause of death registry

As only those women admitted to hospitals would have been recorded in the national registry of patients, we also checked the national cause of death registry for lethal events from venous thromboembolism (see web extra table) during the study period (updated to 2008).

National registry of medicinal products: data on contraceptive usage

Since 1 January 1994 the national registry of medicinal products has collected information about filled prescriptions, including oral contraceptives. From this database we obtained daily updated information on redeemed prescriptions of oral contraceptives from 1995 to 2009. We categorised the products according to progestogen type, oestrogen dose, and length of use. Oral contraceptives with levonorgestrel and 30-40 µg ethinylestradiol were subcategorised as phasic preparations with 30-40 µg ethinylestradiol or combined pills with 30 µg ethinylestradiol.

A stepwise analysis was undertaken, including successively each of the following usage categories: starting use, defined as use of combined oral contraceptives with no history of hormonal contraception before the first prescription; new use, defined as starting use after a pause of at least 12 weeks for any prescription of a hormonal contraceptive; restarted use, defined as oral contraceptive use after a pause of 4-11 weeks; and switched use, defined as use of one preparation of oral contraceptive followed by use of a different preparation, within a pause of less than four weeks.

Duration of use

We estimated the duration of new use from the prescribed defined daily doses calculated from the date of prescription until the end date of defined daily doses of the last redeemed prescription or date of a study event. The duration of restarted use was defined as the period from the date of restart until the end date of defined daily doses of the last filled prescription or the date of a study event. Duration of switched use was calculated as the sum of use before switch and current use on the new preparation, until end date of defined daily doses of the last filled prescription or date of a study event. Thus the same woman could have several episodes of new, restarted, and switched use.

To account for use before the start of the study (left censoring bias), we assessed the use of oral contraceptives before the study period back to 1995. In doing this we allocated continuous users of hormonal contraceptives to the relevant category for duration of use on 1 January 2001.

Rules for allocation of person time to usage groups

We used four overall rules (see web extra for further details) to allocate products to each usage group:

Rule 1—a woman's time at risk for venous thromboembolism was allocated to the oral contraceptive preparation prescribed from the date it was redeemed until the end date calculated from defined daily doses. If no new prescription was redeemed by four weeks after this end date, then we changed the woman's usage status to previous user. However, if the woman got a new prescription for the same product within four weeks, we considered it continuous current use.

Rule 2—if a woman got a new prescription for the same product before the end date of the previous prescription, we summarised the prescribed defined daily doses as continuous current use.

Rule 3—if a woman cashed a new prescription for a different product before the end date of the previous prescription, we excluded the first four weeks after filling the new prescription in either oral contraceptive category, because it would be difficult to know which of the two products would account for venous thromboembolism. After four weeks we categorised such the woman as a switched user of the new preparation. In this case we estimated the duration of use from the first prescription of the previous preparation.

Rule 4—if a prescription ended and thereafter a woman redeemed a prescription for a new oral contraceptive after more than four weeks and less than 12 weeks, we estimated the episode of restarted use from the date when the new prescription was filled. The gap was considered as previous use.

Confounding

Social class

We used length of schooling and level of education as proxies for social class. Four strata were applied: women with elementary school education only (9-10 years of schooling), women with ongoing or completed high school education (2-3 years after elementary school), women with high school and ongoing or ended middle education (3-4 years after high school), and women with high school and ongoing or ended long education (5-6 years after high school). A fifth category included women lacking information on education, typically the youngest.

Body mass index

The type of oral contraceptive could be related to body mass index as a consequence of the secular increases in body mass index and use of recently launched combined oral contraceptives by time. We controlled for calendar year to deal with potential long term confounding by body mass index. In addition we carried out subanalyses for the periods 2001-5, 2006-May 2007, and June 2007-9. We chose these periods because of new data after 2005 and because of a "pill crisis" in Denmark in June 2007 after extensive media attention on one woman with venous thromboembolism who used oral contraceptives with drospirenone.

Smoking

Data on smoking were not available. Smoking is a weak risk factor for venous thromboembolism in young women.[13] We have no reason to believe in preferential prescribing of specific oral contraceptives among smokers. In Denmark the correlation between smoking and length of education is strong. Thus, controlling for years of schooling and length of education may have captured most confounding (if any) influenced by smoking.

Ovarian stimulation drugs

Women treated for infertility with ovarian stimulation drugs (Anatomical Therapeutic Chemical classification G03G) are anticipated to be at an increased risk for venous thromboembolism. Therefore we censored these women at first such treatment.

Recent surgery

From the national register of patients we identified women with venous thromboembolism who had undergone major surgery in the four weeks before admission. Major surgery was defined as a length of stay after surgery of more than one day, or orthopaedic surgery on the legs. We carried out sensitivity analyses with and without these women excluded.

Validity of the outcome diagnoses in the national register of patients

All events of venous thromboembolism during 2001-9 were cross checked with the national registry of medicinal products for anticoagulation therapy (defined as therapy with vitamin K antagonists or heparin). We defined women who were given anticoagulation therapy for at least four weeks as having confirmed venous thromboembolism. Thus we were able to restrict analyses to confirmed events only.

Furthermore, we validated the hospital charts of 200 randomly selected women with venous thromboembolism. Two independent skilled clinicians evaluated each chart and categorised each case as confirmed if two of three conditions were fulfilled: clinical signs of venous thromboembolism; diagnostic confirmation by ultrasound, phlebography, computed tomography, or scintigraphy (in case of pulmonary embolism); and at least four weeks of anticoagulation therapy after the diagnosis. The evaluation was done without knowledge of registry data on usage of oral contraceptives.

Statistical analysis

Data were analysed by multiple Poisson regression in five year age groups. We further stratified the estimates according to length of current use into: less than three months, 3-12 months, more than 12 months to four years, and more than four years.

We calculated absolute as well as relative risk estimates. Non-users of all types of hormonal contraception (never users plus former users) were used as the reference group for the relative risk estimates. Rate ratios were also calculated for the different product types. We adjusted the relative risk estimates for age, calendar year, length of schooling and education, and eventually for length of oral contraceptive use.

Sensitivity analyses were done for both different steps in exposure line formation and according to different categories of oral contraceptive use. We calculated three estimates of exposure lines: raw exposure analyses, in which no gap filling or extension of four weeks was realised; gap corrected exposure lines, in which gaps of less than four weeks were filled and (as a consequence of filling out gaps) exposures were prolonged with four weeks; and switch corrected exposure lines, in which we excluded the first four weeks after switch.

Four successive analyses were carried out for the exposure categories of starting oral contraceptives, adding new use, restarted use, and, finally, switched use.

Results

During 1995 to 2009 1 732 254 Danish women aged 15-49 were identified, corresponding to 17 329 718 women years of observation. The study period from January 2001 to December 2009 included 1 436 130 women and 9 954 925 observation years. Among these women 455 421 (31.7%) had never used hormonal contraception and 980 709 (68.3%) were ever users of some kind of hormonal contraception.

After exclusions and censoring owing to pregnancy (n=403 972 or 486 037 women years); ovarian stimulation (n=74 823 or 460 454 women years); previous cardiovascular disease including venous thromboembolism (n=31 252 or 135 828 women years); cancer (n=21 080 or 135 828 women years); coagulation disturbances (n=5122 or 19 258 women years); hysterectomy, bilateral oophorectomy, or sterilisation (n=146 019 or 760 449 women years); censoring after three years of using a hormone releasing intrauterine device (n=48 875 or 164 270 women years); and one month exclusions at switch of oral contraceptive use (n=252 968 or 32 598 women years), 1 296 120 women were included in the statistical analysis, contributing 8 010 290 women years of observation, with 4307 first time venous thromboembolic events recorded.

The venous thromboembolic events were distributed, with 82 (1.9%) women having cerebral venous thrombosis, 2738 (63.6%) deep venous thrombosis only, 1130 (26.2%) pulmonary embolism (with or without deep venous thrombosis), 55 (1.3%) portal thrombosis, 15 (0.4%) cava thrombosis, 4 (0.1%) thrombosis of a kidney vein, and 283 (6.6%) unspecified deep vein thrombosis.

Of the 4307 venous thromboembolic events, 61 occurred in women using hormonal contraceptives with so little exposure time and so few venous thromboembolic events that we did not calculate estimates.

The adjusted relative risk increased 6.8-fold from the youngest to the oldest women, and by 41% over the study period (5.1% per year), and was reduced by 51% with increasing length of education (table 1⇓).

Relative risk according to progestogen type and oestrogen dose

Table 2⇓ shows the absolute and relative risks of venous thromboembolism in current users of combined oral contraceptives with different types of progestogens and varying doses of oestrogen. The incidence rate of venous thromboembolism in non-users of combined oral contraceptives was 3.7 per 10 000 women years. Compared with non-users, the relative risk of venous thromboembolism in current users of oral contraceptives with levonorgestrel and 30 μg ethinylestradiol was 2.19 (95% confidence interval 1.74 to 2.75) and with levonorgestrel phasic 30-40 μg ethinylestradiol was 2.28 (1.85 to 2.83). The relative risk of venous thromboembolism in current users of oral contraceptives with 30 μg ethinylestradiol combined with desogestrel was 4.21 (3.63 to 4.87), with gestodene was 4.23 (3.87 to 4.63), and with drospirenone was 4.47 (3.91 to 5.11). The corresponding estimates for oral contraceptives with the same progestogens but 20 μg ethinylestradiol were 3.26 (2.88 to 3.69), 3.50 (3.09 to 3.97), and 4.84 (3.19 to 7.33). Progestogen only products conferred no increased risk of venous thromboembolism, whether taken as low dose norethisterone pills, as desogestrel only pills, or in the form of hormone releasing intrauterine devices.

The relative risk of venous thromboembolism from using oral contraceptives with norethisterone, levonorgestrel, desogestrel, or gestodene decreased with decreasing oestrogen dose, whereas no difference was apparent between oral contraceptives with drospirenone and either 30 μg ethinylestradiol or 20 μg ethinylestradiol. Oral contraceptives containing drospirenone and 20 μg ethinylestradiol were launched in Denmark in 2006.

Relative risk by validity of diagnosis

The venous thromboembolic events were stratified into confirmed (anticoagulation therapy recorded in the national registry of medicinal products) and unconfirmed (table 3⇓). Of the 4246 events diagnosed among non-users of hormonal contraception or among users of products included in this study, 2847 (67.1%) were confirmed and 1399 (32.9%) had no or less than four weeks' anticoagulation therapy recorded in the registry. The relative risks of venous thromboembolism were generally twofold to threefold higher in the confirmed group than the unconfirmed group. Thus in the confirmed group the relative risk of venous thrombolism with use of oral contraceptives with levonorgestrel increased to around 3, and for oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone and 30 μg ethinylestradiol increased to at least 6.

Progestogen only products had relative risk estimates below unity compared with non-users in both the confirmed and the unconfirmed groups.

The rate ratio between the estimates in the confirmed and unconfirmed groups was highest for oral contraceptives with desogestrel and lowest for those with norethisterone (table 3).

The proportion of confirmed events for specific oral contraceptives varied from 64% to 84%, and ranged from 72% to 78% for those with levonorgestrel, norgestimate, gestodene, and drospirenone and from 76% to 84% for those with desogestrel.

Table 4⇓ shows the rate ratio estimates between different product types. In the confirmed group, oral contraceptives with desogestrel, gestodene, or drospirenone conferred at least twice the risk of venous thromboembolism compared with oral contraceptives with levonorgestrel, and the rate ratio between oral contraceptives with drospirenone and those with desogestrel or gestodene was 1.01 (0.86 to 1.18). The corresponding rate ratios in the unconfirmed group were generally lower. The comparison between oral contraceptives with drospirenone and those with levonorgestrel was thus 1.78 (1.21 to 2.60), or 16% lower than the 2.12 (1.68 to 2.66) in the confirmed group. The rate ratio between these two product groups for all venous thromboembolic events was 2.00 (1.64 to 2.43), not far off the estimate in the confirmed group.

Relative risk adjusted for differences in length of use

To account for differences in the distribution of lengths of use between the groups, analyses were done in which the rate ratios with oral contraceptives containing levonorgestrel and 30 μg ethinylestradiol as reference were adjusted for differences in length of use and restricted to confirmed events (table 5⇓). The rate ratio estimates were slightly reduced for the newest products, reflecting a relatively higher proportion of short term users in these groups. The overall results, however, were unchanged, and the rate ratio between oral contraceptives with drospirenone compared with those containing levonorgestrel was still 2.09 (1.55 to 2.82). Table 6⇓ displays detailed results

according to length of use and specific combinations of progestogen types and oestrogen dose.

Sensitivity analyses

Relative risk through different steps in exposure line formation

In preliminary analyses, the influence of different steps in the exposure line formation was investigated. In the raw exposure lines no gap filling or prolongation of exposure was realised. The adjusted rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol and those with levonorgestrel and 30-40 μg ethinylestradiol was 2.2 (1.7 to 2.8), and between oral contraceptives with 30 μg ethinylestradiol and drospirenone versus oral contraceptives with 30 μg ethinylestradiol and desogestrel or gestodene the rate ratio was 1.1 (0.9 to 1.3).

In the gap corrected dataset these rate ratio estimates were unchanged, as they were in the dataset for switch corrected exposure lines. For this reason the analyses were done with all allocation rules applied (see web appendix 2).

Relative risk in different sub-periods

Another exploratory step in the analysis was to assess rate ratio estimates in three sub-periods. A non-significant tendency was for lower rate ratios for oral contraceptives with drospirenone compared with those containing levonorgestrel in the last period, but for the period 2001-9 the adjusted rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol compared with those containing levonorgestrel and 30-40 μg ethinylestradiol was 2.00 (1.64 to 2.43), and for the sub-period 2001-5 was 2.16 (1.65 to 2.83). Similar results were found when oral contraceptives with other progestogens were compared with those containing levonorgestrel (see web extra appendix 3). Consequently, subsequent analyses were done for the whole period 2001-9.

Results for different exposure categories

Sensitivity analyses were also done according to different user categories, including successively first starters only, then starters and new users, then including restarters, and finally including switchers. Starters had slightly higher rate ratios between users of oral contraceptives with drospirenone compared with those containing levonorgestrel of 2.69 (1.76 to 4.10) than estimates including the other categories, where the same rate ratios were between 1.96 (1.57 to 2.44) and 2.05 (1.56 to 2.70). See web extra appendix 4 for details.

Different reference groups

A third methodological issue was the oestrogen component in the levonorgestrel products used as reference. The rate ratio of venous thromboembolism between users of oral contraceptives with levonorgestrel and 30 μg ethinylestradiol and with levonorgestrel and 30-40 μg ethinylestradiol including phasic products did not differ significantly in any of the sub-periods. About half of women years using oral contraceptives with levonorgestrel contained 30 μg ethinylestradiol, the other half phasic products 30-40 μg ethinylestradiol. For the period 2001-9, the rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol and all levonorgestrel products with 30-40 μg ethinylestradiol was 2.00 (1.64 to 2.43) and with only levonorgestrel and 30 μg ethinylestradiol was 2.04 (1.58 to 2.63). Accordingly, all users of oral contraceptives with levonorgestrel and 30 μg or 30-40 μg ethinylestradiol were chosen as reference group. For rate ratio comparisons with specifically drospirenone, however, estimates with both 30 μg ethinylestradiol and all levonorgestrel users were calculated.

Recent surgery

Among women with confirmed venous thromboembolism, 33 (1.2%) had major surgery in the four weeks before the admission for venous thromboembolism. The results were similar with and without exclusion of women with recent surgery. Thus the rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol compared with those containing levonorgestrel was 2.18 (1.62 to 2.94) with these events included and 2.13 (1.58 to 2.87) without.

Chart evaluation of venous thromboembolism events

Of 200 evaluated hospital charts, 148 (74%) venous thromboembolic events were confirmed and 52 unconfirmed. Except for two women with distal limb thrombosis who were not offered anticoagulation therapy, the remaining 146 confirmed events were in women who had received anticoagulation therapy. However, two unconfirmed events were in women who had received anticoagulation therapy; one for a recent venous thromboembolism, which was not excluded because it was coded at the primary admission (before actual admission) with a superficial venous thrombosis diagnosis and therefore not excluded as previous venous thromboembolism. The other woman was treated for connective tissue disease. All 200 evaluated patients coded as having venous thromboembolism had clinical symptoms at admission.

Of the 200 validated events, 148 (74.0%) women had received anticoagulation therapy according to the medical charts. Of these, 133 (89.9%) were recorded in the national registry of medicinal products as having had anticoagulation therapy, suggesting that about 10% received treatment for free from the hospitals, and therefore were not recorded in the registry.

Among the 52 women without information on anticoagulation therapy in the medical charts, four (7.7%) were recorded in the registry as having received anticoagulation therapy. This can occur when treatment starts after discharge from the department to which the women were primarily admitted—that is, initiated from a coagulation laboratory just after discharge from the department. If these four events were added to the confirmed events in the sample of 200 women, the confirmed proportion increased to 152 of 200, or 76.0%.

Discussion

This study found that when compared with non-users of hormonal contraception, current users of oral contraceptives with levonorgestrel were at a threefold increased risk for confirmed venous thrombosis and users of oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone acetate a sixfold to sevenfold increased risk. This would give a rate ratio between the groups using oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone and those using oral contraceptives with levonorgestrel of at least 2.

Before interpreting the results of this analysis, the main differences in study design and analysis between the present and the primary publication[18] should be revisited. Potential biases in our primary publication were dealt with as follows: we eliminated left censoring bias by letting the new study period begin in 2001, with full exposure history for the previous six years; we defined length of use as duration of actual use rather

than the sum of all periods of use; we used four strata for duration of use, instead of three, ensuring a more detailed length of use allocation within the first year; we excluded the first exposure month after a switch, because of uncertainty as to which product group a woman should be allocated in case of venous thromboembolism in this period; analyses were stratified into confirmed and unconfirmed venous thromboembolic events; and a more effective exclusion of predisposed women including women with coagulation disorders was effected.

Results according to progestogen type and oestrogen dose

The addition of four more study years from 2006-9 and the restriction of the analyses to the period after 1 January 2001 did not change the overall results of our primary publication covering 1995-2005. With the additional data we reconfirmed and substantiated a differential risk of venous thromboembolism between users of combined oral contraceptives with different progestogens and (although to a less extent) with different oestrogen doses.

According to the present analysis, with the same dose of oestrogen, combined oral contraceptives containing the progestogens desogestrel, gestodene, cyproterone, or drospirenone confer about the same relative risk of venous thromboembolism, a risk that is about twice that from use of combined oral contraceptives with the same dose of oestrogen and levonorgestrel. Phasic combined oral contraceptives with levonorgestrel may confer a slightly but not significantly higher risk of venous thromboembolism than oral contraceptives with levonorgestrel and 30 µg ethinylestradiol, which could be due to the slightly higher total dose of oestrogen in the former group. Consequently the relative risk estimates are slightly smaller when the reference group was the whole group of oral contraceptives containing levonorgestrel than if compared with only oral contraceptives with levonorgestrel and 30 µg ethinylestradiol.

The oral contraceptives with desogestrel or gestodene and 20 µg ethinylestradiol implied a relative risk of venous thromboembolism that were 23% and 17% lower than the same progestogens with 30 µg ethinylestradiol. The missing trend for oral contraceptives with drospirenone according to oestrogen dose could be a consequence of fewer events (n=23) in the group using 20 µg ethinylestradiol, more active pill per cycle for one of the 20 µg products , or could also be influenced by the introduction of these oral contraceptives in 2006, on the assumption that attention to adverse effects is highest for new products. However, the 70% confirmed venous thromboembolism events in the new low dose drospirenone group was close to the proportion of confirmed events for the older oral contraceptives with drospirenone and 30 µg ethinylestradiol (74%), which does not support differential attention by women or their doctors.

Rate ratios and validity of diagnosis

More than two thirds of the included venous thromboembolic events were confirmed by a record of anticoagulation therapy in the national registry of medicinal products. Importantly, some women have treatment for free (owing to local policies in some hospitals when handing out these drugs) and consequently are not recorded in the registry. According to our random analysis of medical charts, an additional 10% are women with real events of venous thromboembolism, receiving anticoagulation treatment for free from the hospitals. A further small percentage of women start treatment after discharge, bringing the real proportion of confirmed events up to 152 of 200, or 76%.

In a previous case-control study during 1994-8, we got information from departments that 3.6% of cases were unconfirmed.[13] In addition, 95 of 1094 (8.7%) women who responded could not confirm their diagnosis, leaving what we considered to be 87.7% of valid cases. The stricter validation in the subsample in this study resulted in 76% with a valid diagnosis. The difference of about 10% may be explained by women who have clinical symptoms of venous thromboembolism at admission that could not be confirmed by radiography or ultrasonography. Such women could be told that they might have had venous thromboembolism that dissolved spontaneously or was too small to be confirmed by the available diagnostic equipment, and therefore did not require treatment. As a result of the lack of a more appropriate diagnosis such women might, nevertheless, be coded as having venous thromboembolism.

Compared with non-users of combined oral contraceptives, the relative risk of venous thromboembolism among current users of combined oral contraceptives was twofold to fourfold higher for confirmed than unconfirmed venous thromboembolism (table 3). The rate ratio estimates between different product groups were less sensitive, but nevertheless decreased by about 25% from the confirmed to the unconfirmed group (table 4).

Exposure line formation

Estimation of rate ratios through different steps in exposure line formation was necessary for at least two reasons. Firstly, we decided on the analytical strategy before the analyses started. Secondly, the relative risk for users of specific products compared with non-users increased slightly (not significantly) through the different steps, indicating a successively higher validity of exposure allocation—for example, the relative risk estimate of oral contraceptives with levonorgestrel and 30 µg ethinylestradiol increased from 1.9 (1.5 to 2.6) to 2.1 (1.6 to 2.8) and for those with drospirenone from 4.4 (3.7 to 5.1) to 4.7 (4.0 to 5.4) through the different exposure lines.

Owing to the high consistency in the rate ratio estimates in the different exposure lines, it is unlikely that different rules or other time intervals in the allocation rules would have changed the rate ratios substantially.

Analysis of different sub-periods

Overall, the rate ratio estimates were stable throughout the study periods. The slightly lower rate ratio estimates after June 2007 compared with the previous period could be a consequence of the media event in June 2007. Shortly after this the Danish Society of Obstetrics and Gynaecology published a press release in which they stated that oral contraceptives with drospirenone were unlikely to confer a higher risk of venous thromboembolism than the prevailing third generation oral contraceptives with desogestrel or gestodene, but that oral contraceptives with levonorgestrel were likely to confer a lower risk. Consequently, women at an anticipated increased risk of venous thromboembolism were recommended progestogen only contraception or alternatively oral contraceptives with levonorgestrel as first choice.

Thereby some women at an anticipated increased risk of venous thromboembolism could have been prescribed products containing levonorgestrel, increasing the estimates for oral contraceptives with levonorgestrel and decreasing the estimates for those with drospirenone. However, the relative risk estimates for oral contraceptives with levonorgestrel and 30 µg

ethinylestradiol with non-users of hormonal contraception as reference did not change: 2.3 (1.7 to 3.1) during 2001-5 and 2.4 (1.6 to 3.6) from June 2007-9. In contrast, the estimates for oral contraceptives with drospirenone and 30 μg ethinylestradiol decreased (non-significantly) from 4.7 (3.9 to 5.7) in 2001-5 to 4.1 (3.2 to 5.3) during 2007-9, which may explain the decreasing trend in the rate ratio estimates after June 2007.

Recent surgery

The exclusion of 33 women with confirmed venous thromboembolism who had major surgery within the previous four weeks did not change the results, primarily because of the low numbers. In addition, women undergoing surgery often receive anticoagulation therapy during their stay, and some may have stopped using oral contraceptives in the weeks around the surgery, circumstances for which we lacked information.

Strengths and limitations of the study

Expanding on our previous study by using four new years' worth of original data on exposure and end points confirmed our previously published results,[18] and therefore increased the validity of the present results. The inclusion of all Danish non-pregnant women over a nine year period ensured a high external validity.

The information on exposure was complete and gathered for purposes other than a scientific analysis, eliminating the recall bias that is common in case-control studies, and the problems of continuous updating data on exposure in cohort studies. Furthermore, we eliminated the problem of left censoring by measuring use of combined oral contraceptives over a six year period before our study started. We obtained consistent results from sensitivity analyses on exposure line formation, different sub-periods, and according to different user categories (for example, starters, restarters).

Finally, we were able to validate venous thromboembolic events by linking individual data on diagnosis to succeeding anticoagulation therapy. Restricting the analysis to only confirmed events provided a quantitative assessment of the consequence of misclassification of some diagnoses on risk estimates.

This study does, however, have some limitations. We could not control for family disposition and body mass index. Adiposity is a well documented risk factor for venous thromboembolism. It is unlikely that there should be any important preferential prescribing of specific types of oral contraceptives to obese women before June 2007. After that time, however, the public recommendations to women at an anticipated increased risk of venous thromboembolism to choose a progestogen only contraception or oral contraceptives with levonorgestrel could have overestimated the risk for oral contraceptives with levonorgestrel and underestimated that for oral contraceptives with desogestrel, gestodene, or drospirenone. Some could argue that obese women are more likely to choose oral contraceptives with drospirenone. The empirical support for such selective prescribing is weak, however, and does not explain the high relative risk estimates for the other three oral contraceptives with desogestrel, gestodene, and cyproterone. To date, no study has shown any confounding influence from body mass index, as adjustment for body mass index in studies with this information did not change the rate ratio between oral contraceptives with different progestogens.[14 17-19] Therefore, preferential prescribing of oral contraceptives with third generation progestogens or drospirenone to obese women is unlikely to explain the doubled risk for these products compared with oral contraceptives containing levonorgestrel, especially after 2006.

The same argument applies to family disposition. Although an important risk factor, family disposition has not been found to be an important confounder in studies over the past 10 years.

About a quarter of our included venous thromboembolic events could not be confirmed by review of the medical records. This would underestimate the influence of combined oral contraceptives on the risk of venous thromboembolism, as shown by comparing the risk estimates for confirmed events in this study with those in our primary publication,[18] whereas the rate ratio estimates were less sensitive to the inclusion of unconfirmed events.

The chart review confirmed a 99% positive predictive value of a diagnosis of venous thromboembolism with subsequent anticoagulation therapy, and that cross linkage with the national registry of medicinal products provided reliable validation of the events. However, we lost at least 10% of true events by excluding all events that were not recorded in the registry.

Table 7⇓ summarises studies that specifically assessed the risk of venous thromboembolism from use of oral contraceptives with levonorgestrel, desogestrel, gestodene, or drospirenone. We excluded those studies that did not specify the compounds used or that lacked a reference group. Our new estimates for specific products restricted to confirmed events of venous thromboembolism are close to those in a Dutch study,[17] whereas the rate ratio estimates between different product groups were slightly higher than in the Dutch study and slightly lower than in the two new studies from the United Kingdom[20] and the United States.[21] The UK and US studies included "idiopathic events" only, the risk estimates of which are expected to be slightly higher than those of studies that also include women with some other risk factors.

The two studies that did not find any difference in risk between oral contraceptives with drospirenone and those with levonorgestrel were two of the three studies that did not find any difference in risk between oral contraceptives with desogestrel or gestodene and those with levonorgestrel.

If we anticipate that oral contraceptives with desogestrel, gestodene, or drospirenone increase the risk of venous thromboembolism sixfold and that those with levonorgestrel increase the risk threefold, and that the absolute risk of venous thromboembolism in current users of the former group is on average 10 per 10 000 women years, then 2000 women would need to shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel to prevent one event of venous thromboembolism in one year.

Conclusion

Compared with non-users of hormonal contraception, current users of oral contraceptives with levonorgestrel had a threefold increased risk of venous thromboembolism and those using oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone a six to sevenfold increased risk.

This would give a rate ratio between the groups using oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone and those using oral contraceptive with levonorgestrel of at least 2. It is unlikely that these findings could be explained by bias or confounding.

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What is already known on this topic

Studies have shown an increased risk of venous thrombosis (VTE) with use of combined oral contraceptives

The risk was higher with oral contraceptives containing the progestogens desogestrel and gestodene than those containing levonorgestrel

Results on the risk from oral contraceptives with drospirenone have been conflicting

What this study adds

Women using oral contraceptives with drospirenone are at similar risk of VTE to those using oral contraceptives with desogestrel, gestodene, or cyproterone and higher than those using oral contraceptives with levonorgestrel

The risk of VTE was not reduced by using 20 µg oestrogen instead of 30 µg oestrogen in oral contraceptives with drospirenone

To prevent one event of VTE in one year about 2000 women should shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel

Contributors: ØL, EL, and FES planned the study, supervised the analysis, and interpreted the results. ØL wrote the manuscript. LHN did the statistical analyses and interpreted the results. CWS prepared the data from the national registry of patients and national death registry. All authors discussed and approved the final manuscript. ØL is guarantor of the study. The sponsor had no influence on the design, performance, or interpretation of the results or on the manuscript.

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Ethical approval: This study was approved by the Danish Data Protection Agency (Journal No 2010-41-4778). Ethical approval is not requested for registry based studies in Denmark.

Data sharing: No additional data available.

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Tables

Table 1| Characteristics of current users and non-users of combined oral contraceptives and adjusted relative risk of venous thromboembolism according to age, calendar year, and length of education

	Current users			Non-users				
Characteristics	Women years	No of events*	Incidence per 10 000 exposure years	Women years	No of events*	Incidence per 10 000 exposure years	Adjusted rate ratio† (95% CI)	P value
Age (years):								
15-19	571 333	239	4.2	670 766	49	0.7	1 (reference)	—
20-24	713 623	343	4.8	346 614	74	2.1	1.32 (1.13 to 1.54)	<0.001
25-29	549 862	375	6.8	463 810	134	2.9	1.99 (1.66 to 2.38)	<0.001
30-34	430 272	375	8.7	667 937	211	3.2	2.91 (2.40 to 3.55)	<0.001
35-39	369 859	447	12.1	861 442	304	3.5	4.01 (3.31 to 4.87)	<0.001
40-44	261 464	397	15.2	965 951	467	4.8	5.29 (4.36 to 6.41)	<0.001
45-49	153 147	319	20.8	984 209	573	5.8	6.58 (5.43 to 7.99)	<0.001
Year:								
2001	335 482	241	7.2	625 168	175	2.8	0.71 (0.62 to 0.81)	<0.001
2002	339 078	251	7.4	601 282	198	3.3	0.76 (0.66 to 0.86)	<0.001
2003	340 575	238	7.0	579 767	174	3.0	0.70 (0.61 to 0.80)	<0.001
2004	342 354	276	8.1	562 409	205	3.6	0.81 (0.72 to 0.93)	0.002
2005	341 273	275	8.1	544 028	217	4.0	0.86 (0.76 to 0.97)	0.02
2006	339 578	293	8.6	529 811	205	3.9	0.87 (0.77 to 0.99)	0.03
2007	337 072	311	9.2	516 775	245	4.7	1.01 (0.90 to 1.15)	0.82
2008	336 606	287	8.5	508 635	190	3.7	0.90 (0.79 to 1.02)	0.10
2009	337 542	323	9.6	492 855	203	4.1	1 (reference)	—
Level of education:								
Elementary school‡	695 339	762	11.0	1 194 278	748	6.3	1 (reference)	—
High school§	365 466	275	7.5	505 821	125	2.5	0.60 (0.54 to 0.67)	<0.001
High school and middle education¶	576 803	673	11.7	1 295 503	518	4.0	0.68 (0.63 to 0.73)	<0.001
High school and long education**	241 662	223	9.2	909 249	257	2.8	0.49 (0.44 to 0.55)	<0.001
No available information	1 170 290	562	4.8	1 055 878	164	1.6	0.78 (0.68 to 0.90)	0.0005

*Events are venous thromboembolisms.

†Age estimates adjusted for year, level of education, and use of oral contraceptives; year estimates adjusted for age, level of education, and use of combined oral contraceptives; and education estimates adjusted for age, year, and use of combined oral contraceptives.

‡9-10 years of education.

§2-3 years of education after elementary school.

¶3-4 years of education after high school.

**5-6 years of education after high school.

Table 2| Exposure time, number of events of venous thromboembolism, crude incidence per 10 000 user years, and adjusted relative risk of venous thromboembolism in current users of different oral contraceptives and hormone releasing intrauterine device with non-users as reference group

Group	Women years	No of events*	Crude incidence per 10 000 user years*	Adjusted relative risk† (95% CI)
Non-use	4 960 730	1812	3.7	1 (reference)
Progestogen with 50 µg ethinylestradiol:				
Norethisterone	6848	11	16.1	5.66 (3.12 to 10.3)
Levonorgestrel	23 691	31	13.1	3.54 (2.48 to 5.05)
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	10	3.7	1.57 (0.84 to 2.92)
Phasic levonorgestrel	105 970	89	8.4	2.28 (1.85 to 2.83)
Levonorgestrel combined	104 251	78	7.5	2.19 (1.74 to 2.75)
Norgestimate	267 664	165	6.2	2.56 (2.18 to 3.01)
Desogestrel	170 249	201	11.8	4.21 (3.63 to 4.87)
Gestodene	668 355	738	11.0	4.23 (3.87 to 4.63)
Drospirenone	286 859	266	9.3	4.47 (3.91 to 5.11)
Cyproterone	120 934	109	9.0	4.10 (3.37 to 4.99)
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	322	6.8	3.26 (2.88 to 3.69)
Gestodene	472 118	321	6.8	3.50 (3.09 to 3.97)
Drospirenone	23 055	23	10.0	4.84 (3.19 to 7.33)
Progestogen only:				
Norethisterone	44 168	9	2.0	0.56 (0.29 to 1.07)
Desogestrel	29 187	6	2.1	0.64 (0.29 to 1.42)
Levonorgestrel releasing intrauterine device	155 149	55	3.5	0.83 (0.63 to 1.08)

*Events are venous thromboembolisms.

†Adjusted for age, year, and level of education.

Table 3| Relative risk of venous thromboembolism among current users of oral contraceptives and hormone releasing intrauterine device according to certainty of diagnosis of venous thromboembolism, with non-users of hormonal contraception as reference group

		Anticoagulation (confirmed)		Not recorded		
Product type	Women years	No of events*	Adjusted relative risk† (95% CI)	No of events*	Adjusted relative risk† (95% CI)	% confirmed
Non-use	4 960 730	1004	1 (reference)	808	1 (reference)	55.4
Progestogen with 50 µg ethinylestradiol:						
Norethisterone	6848	7	6.24 (2.95 to 13.2)	4	5.10 (1.90 to 13.7)	63.6
Levonorgestrel	23 691	22	4.49 (2.94 to 6.85)	9	2.34 (1.21 to 4.52)	71.0
Progestogen with 30-40 µg ethinylestradiol:						
Norethisterone	27 355	8	2.24 (1.12 to 4.51)	2	0.73 (0.18 to 2.91)	80.0
Levonorgestrel phasic	105 970	66	3.09 (2.41 to 3.97)	23	1.31 (0.86 to 1.98)	74.2
Levonorgestrel combined	104 251	57	2.92 (2.23 to 3.81)	21	1.30 (0.84 to 2.00)	73.1
Norgestimate	267 664	119	3.52 (2.90 to 4.27)	46	1.44 (1.07 to 1.95)	72.1
Desogestrel	170 249	168	6.61 (5.60 to 7.80)	33	1.43 (1.01 to 2.04)	83.6
Gestodene	668 355	575	6.24 (5.61 to 6.95)	163	1.92 (1.61 to 2.28)	77.9
Drospirenone	286 859	196	6.37 (5.43 to 7.47)	70	2.32 (1.80 to 2.98)	73.7
Cyproterone	120 934	88	6.35 (5.09 to7.93)	21	1.58 (1.02 to 2.44)	80.7
Progestogen with 20 µg ethinylestradiol:						
Desogestrel	470 982	246	4.81 (4.15 to 5.56)	76	1.52 (1.19 to 1.94)	76.4
Gestodene	472 118	240	5.07 (4.37 to 5.88)	81	1.72 (1.36 to 2.19)	74.8
Drospirenone	23 055	16	6.95 (4.21 to 11.5)	7	2.58 (1.22 to 5.46)	69.6
Progestogen only:						
Norethisterone	44 168	6	0.68 (0.30 to 1.51)	3	0.41 (0.13 to 1.28)	66.7
Desogestrel	29 187	3	0.61 (0.20 to 1.90)	3	0.63 (0.20 to 1.97)	50.0
Levonorgestrel releasing intrauterine device	155 149	26	0.72 (0.49 to 1.06)	29	0.95 (0.65 to 1.38)	47.3

*Events are venous thromboembolisms.

†Adjusted for age, calendar year, and level of education.

Table 4| Rate ratios of venous thromboembolism between users of combined oral contraceptives with different progestogens according to certainty of diagnosis of venous thromboembolism

Comparison groups	No of events*	Rate ratio†		P value
		Partially adjusted	Fully adjusted‡ (95% CI)	
Confirmed events				
Drospirenone + 30 µg EE versus:				
Levonorgestrel + 30-40 µg EE (all)	196 *v* 123	2.03	2.12 (1.68 to 2.66)	<0.001
Levonorgestrel + 30 µg EE (without phasic preparations)	196 *v* 57	2.08	2.18 (1.62 to 2.94)	<0.001
Third generation progestogens§	196 *v* 743	0.98	1.01 (0.86 to 1.18)	0.9248
Desogestrel + 30 µg EE *v* levonorgestrel + 30-40 µg EE	168 *v* 123	2.18	2.20 (1.74 to 2.77)	<0.001
Gestodene + 30 µg EE *v* levonorgestrel + 30-40 µg EE	575 *v* 123	2.04	2.07 (1.70 to 2.52)	<0.001
Non-confirmed events				
Drospirenone + 30 µg EE versus:				
Levonorgestrel + 30-40 µg EE	70 *v* 44	1.71	1.78 (1.21 to 2.60)	0.0032
Levonorgestrel + 30 µg EE (without phasic preparations)	70 *v* 21	1.70	1.78 (1.09 to 2.91)	0.0213
Third generation progestogens§	70 *v* 196	1.25	1.27 (0.97 to 1.68)	0.0840
Desogestrel + 30 µg EE *v* levonorgestrel + 30-40 µg EE	33 *v* 44	1.10	1.10 (0.70 to 1.73)	0.6764
Gestodene + 30 µg EE *v* levonorgestrel + 30-40 µg EE	163 *v* 44	1.45	1.47 (1.05 to 2.06)	0.0236

EE=ethinylestradiol.

*Events are venous thromboembolisms.

†Adjusted for age and calendar year.

‡Adjusted for age, calendar year, and level of education.

§Desogestrel or gestodene.

Table 5| **Rate ratio of confirmed venous thromboembolism between different combined oral contraceptives with adjustment for length of use**

Product group	Women years	No of events*	Adjusted rate ratio† (95% CI)	P value
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	8	0.76 (0.36 to 1.60)	0.47
Levonorgestrel phasic	105 970	66	1.07 (0.75 to 1.52)	0.71
Levonorgestrel combined	104 251	57	1 (reference)	—
Norgestimate	267 664	119	1.18 (0.86 to 1.62)	0.30
Desogestrel	170 249	168	2.24 (1.65 to 3.02)	<0.001
Gestodene	668 355	575	2.12 (1.61 to 2.78)	<0.001
Drospirenone	286 859	196	2.09 (1.55 to 2.82)	<0.001
Cyproterone	120 934	88	2.11 (1.51 to 2.95)	<0.001
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	246	1.60 (1.20 to 2.14)	0.0015
Gestodene	472 118	240	1.70 (1.27 to 2.27)	0.0004
Drospirenone	23 055	16	2.22 (1.27 to 3.89)	0.005

*Events are venous thromboembolisms.

†Adjusted for age, calendar year, level of education, and length of use.

Table 6| **Relative risk of venous thromboembolism in current users of combined oral contraceptives according to length of use and with non-users of hormonal contraception as reference**

			Adjusted relative risk† (95% CI)			
Product type	**Women years**	**No of events***	**<3 months**	**3-12 months**	**>1-4 years**	**>4 years**
Non-use	4 960 730	1812	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Progestogen with 30-40 µg ethinylestradiol:						
Levonorgestel (all)	210 221	167	4.07 (2.70 to 6.15)	2.54 (1.80 to 3.59)	2.12 (1.61 to 2.80)	1.88 (1.45 to 2.43)
Norgestimate	267 664	165	3.81 (2.60 to 5.58)	2.98 (2.22 to 4.00)	2.47 (1.91 to 3.20)	1.82 (1.27 to 2.59)
Desogestrel	170 249	201	4.59 (3.01 to 7.00)	4.20 (3.11 to 5.67)	3.77 (2.95 to 4.81)	4.64 (3.64 to 5.92)
Gestodene	668 355	738	4.83 (3.85 to 6.05)	4.65 (3.96 to 5.45)	4.12 (3.61 to 4.70)	3.94 (3.43 to 4.54)
Drospirenone	286 859	266	4.70 (3.45 to 6.40)	5.95 (4.88 to 7.24)	3.38 (2.69 to 4.24)	4.34 (3.10 to 6.08)
Cyproterone	120 934	109	4.23 (2.50 to 7.17)	4.21 (2.95 to 6.01)	4.90 (3.70 to 6.49)	2.43 (1.41 to 4.19)
Progestogen with 20 µg ethinylestradiol:						
Desogestrel	470 982	322	3.18 (2.31 to 4.38)	3.18 (2.55 to 3.98)	3.49 (2.91 to 4.17)	3.09 (2.42 to 3.96)
Gestodene	472 118	321	3.46 (2.49 to 4.81)	4.51 (3.69 to 5.52)	3.38 (2.81 to 4.06)	2.65 (2.00 to 3.51)
Drospirenone	23 055	23	6.16 (2.76 to 13.77)	7.25 (4.19 to 12.56)	2.58 (0.96 to 6.89)	—

*Events are venous thromboembolisms.

†Adjusted for age, calendar year, and level of education.

Table 7| **Relative risk of venous thromboembolism in current users of different combined oral contraceptives according to study. Non-users of hormonal contraception as reference group unless specified otherwise**

			Relative risk (95% CI)		
Study	**Sampling period**	**No of events***	**COC with levonorgestrel**	**COC with third generation progestogens†**	**COC with drospirenone**
Bloemenkamp[1]	1988-92	126	3.8 (1.7 to 8.4)	8.7 (3.9 to 19.3)	NA
WHO[4]	1989-93	433	3.6 (2.5 to 5.1)	7.4 (4.2 to 12.9)	NA
Jick[2]	1991-4	80	1 (Reference)	1.8 (1.0 to 3.2)	NA
Spitzer[5]	1991-5	471	3.7 (2.2 to 6.2)	6.7 (3.4 to 13)	NA
Farmer[6]	1991-5	85	3.1‡ (2.1 to 4.5)	5.0‡ (3.7 to 6.5)	NA
Lewis[8]	1993-5	502	2.9 (1.9 to 4.2)	2.3 (1.5 to 3.5)	NA
Todd[9]	1992-7	99	1 (Reference)	1.4 (0.7 to 2.8)	NA
Bloemenkamp[7]	1994-8	185	3.7 (1.9 to 7.2)	5.6 (NA)	NA
Lidegaard[13]	1994-8	987	2.9 (2.2 to 3.8)	4.0 (3.2 to 4.9)	NA
Dinger[14]	2000-4	118	1 (Reference)	1.3 (NS)	1.0 (0.6 to 1.8)
Vlieg[17]	1999-2004	1524	3.6 (2.9 to 4.6)	7.3 (5.3 to 10.0)	6.3 (2.9 to 13.7)
Lidegaard[18]	1995-2005	4213	2.0 (1.8 to 2.3)	3.6 (3.3 to 3.8)	4.0 (3.3 to 4.9)
Dinger[19]	2002-8	680	1 (Reference)	NA	1.0 (0.6 to 1.8)
Parkin[20]	2002-9	61	1 (Reference)	NA	2.7 (1.5 to 4.7)
Jick[21]	2002-8	186	1 (Reference)	NA	2.8 (2.1 to 3.8)
Present study:					
All reported events*	2001-9	4246	2.2 (1.7 to 2.8)	4.2 (3.6 to 4.9)	4.5 (3.9 to 5.1)
Confirmed events only*	2001-9	2707	2.9 (2.2 to 3.8)	6.8 (5.7 to 8.1)	6.3 (5.4 to 7.5)

COC=combined oral contraceptives; NA=not available; NS=non-significant.

*Events are venous thromboembolisms.

†Desogestrel or gestodene.

‡Absolute risk per 10 000 women years.

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ORIGINAL ARTICLE

Sex hormone-binding globulin as a marker for the thrombotic risk of hormonal contraceptives

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Summary. *Background:* It takes many years to obtain reliable values for the risk of venous thrombosis of hormonal contraceptive users from clinical data. Measurement of activated protein C (APC) resistance via thrombin generation is a validated test for determining the thrombogenicity of hormonal contraceptives. Sex hormone-binding globulin (SHBG) might serve as a marker for the risk of venous thrombosis, and can be easily and rapidly measured in routine laboratories. *Objective:* To determine whether SHBG is a useful marker for the thrombotic risk of hormonal contraceptive users by comparing plasma SHBG levels with normalized APC sensitivity ratio (nAPCsr) values and thrombosis risks reported in the recent literature. *Methods:* We conducted an observational study in 262 users of different contraceptives, and measured nAPCsr and SHBG levels. *Results:* Users of contraceptives with a higher risk of causing venous thrombosis, i.e. combined hormonal contraceptives containing desogestrel, cyproterone acetate or drospirenone, and the transdermal patch, had higher SHBG levels than users of combined hormonal contraceptives containing levonorgestrel, which carry a lower thrombosis risk. Users of the patch had the highest SHBG levels, with a mean difference of 246 nmol L^{-1} (95% confidence interval 179–349) from that in users of levonorgestrel-containing combined hormonal contraceptives. SHBG levels were positively associated with both the nAPCsr and the risks of venous thrombosis reported in the recent literature. *Conclusion:* SHBG is a useful marker with which to estimate the thrombotic safety of a preparation.

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Introduction

The use of combined oral contraceptives is associated with a three-fold to six-fold increased risk of venous thrombosis [1]. This increased risk depends on both the estrogen dose and the progestogen type of combined oral contraceptives [1]. So-called 'high-dose' combined oral contraceptives containing 50 μg or more ethinylestradiol (EE) are associated with a two-fold higher risk of thrombosis than 'low-dose' combined oral contraceptives containing 20–30 μg of EE [2,3]. Furthermore, combined oral contraceptives containing the progestogens gestodene (GTD), desogestrel (DSG), cyproterone acetate (CPA) or drospirenone (DRSP) increase the risk of venous thrombosis by a factor of two as compared with combined oral contraceptives containing levonorgestrel (LNG) [1–13].

The differences in the risk of venous thrombosis can be at least partially explained by the association of various combined oral contraceptives with differences in resistance to activated protein C (APC) as measured with the thrombin generation-based APC resistance test and quantified via a normalized APC sensitivity ratio (nAPCsr) [14–16]. High nAPCsr indicates increased APC resistance, which is a risk factor for venous thrombosis. Thrombin generation-based APC resistance has been validated in a case–control study by Tans *et al.* [17], and predicts the risk of venous thrombosis in users of combined oral contraceptives, as well as in non-users and men, with or without the factor V Leiden mutation. The highest odds ratio (OR) of venous thrombosis in the absence of the FV Leiden mutation was observed in premenopausal women using combined oral contraceptives, lending support to the hypothesis that the prothrombotic effect of combined oral contraceptives is the result of acquired APC resistance in a thrombin generation-based test [17]. Users of combined oral contraceptives with a higher risk of causing venous thrombosis, e.g. those containing DSG, CPA or DRSP, have been found to be more

resistant to the anticoagulant action of APC than users of combined oral contraceptives with a lower risk of causing venous thrombosis, i.e. those containing LNG [3,6,9,10,14–16].

As the absolute risk of venous thrombosis in women using combined oral contraceptives is low, i.e. three to four per 10 000 woman-years [1], the assessment of differences in risk between an existing and a new preparation requires hundreds of thousands of users. This sample size makes a clinical study of a new hormonal contraceptive before market authorization almost impossible.

In a search for other markers that can predict the risk of venous thrombosis in users of hormonal contraceptives, Odlind *et al*. [18] postulated sex hormone-binding globulin (SHBG) as a marker for estrogenicity of a contraceptive preparation and possibly for the risk of venous thrombosis. SHBG is a carrier protein that is produced in the liver and binds estrogen and testosterone [19]. The hypothesis is that estrogens cause a dose-related increase in SHBG levels, whereas progestogens induce a decrease in SHBG levels, dependent on both the dose and the type of progestogen [20–22]. The type-related differences in the progestogen-induced decrease in SHBG levels can be interpreted as differences in the antiestrogenic properties of progestogens. Thus, the effect of a hormonal contraceptive on SHBG is the combined result of the estrogenic effect of EE and the antiestrogenic effect of the progestogen, yielding the total estrogenicity of that hormonal contraceptive. This estrogenicity might serve as a marker for venous thrombosis. Several studies have shown an association between the risk of causing venous thrombosis of combined oral contraceptives, APC resistance, and SHBG levels [1–3,15,23].

To investigate whether SHBG is a useful marker for the risk of venous thrombosis of combined oral contraceptives, we determined SHBG levels in non-users and in users of different contraceptives, both hormonal and non-hormonal, and compared the SHBG levels with nAPCsr as determined via thrombin generation and with the risks of venous thrombosis as reported in the literature.

Materials and methods

Study design and participants

We conducted an observational study. In a series of four different studies, we included users of various hormonal and non-hormonal contraceptives [15,24–26]. Users of different combined hormonal contraceptives, including oral, transdermal and vaginal combined hormonal contraceptives, users of LNG-releasing intrauterine devices (IUDs) (LNG-IUDs), users of copper-releasing IUDs (Cu-IUDs) and healthy female non-users with regular, ovulatory menstrual cycles were studied.

The inclusion criterion for all participants was as follows: healthy women using a hormonal contraceptive for at least three cycles. Exclusion criteria were age < 18 years, and contraindications for combined hormonal contraceptive use as stated by the World Health Organization [27]. A more detailed description can be found in the original articles [15,24–26].

Participants who were carriers of the FV Leiden mutation were excluded from the analysis, because this mutation causes resistance to APC without affecting SHBG levels ($n = 30$). The following data were not used because of a small sample size: users of a combined oral contraceptive containing GTD, norgestimate and norethisterone ($n = 3$ for GTD, $n = 1$ for norgestimate, and $n = 2$ for norethisterone). Furthermore, we only used data from users of combined oral contraceptives containing 30–35 μg of EE; users of preparations with other amounts of EE were excluded ($n = 24$). For 26 participants, data were not complete, so they were excluded. In total, we excluded 86 participants.

In our final analysis, we used the samples of 262 participants: 159 users of a combined oral contraceptive (containing 30–35 μg of EE and LNG, DSG, CPA, or DRSP), 60 users of the LNG-IUD, 17 users of the Cu-IUD, seven users of the transdermal patch (containing EE and norelgestromine [NGM]), six users of the vaginal ring (containing EE and etonogestrel [ENG]), and 13 non-users (mid-cycle).

Written informed consent was given by all participants, and the studies were all approved by the Medical Ethics Committee of the Leiden University Medical Center, The Netherlands.

Laboratory methods

The plasma samples from the studies were taken, processed and stored identically. Blood samples were taken from the antecubital vein in the morning in a fasting state, and collected in 0.106 mol L^{-1} sodium citrate (pH 5.8). Cell-free, citrated plasma was prepared by centrifuging blood at $2100 \times g$ for 10 min at 18 °C, coded, and centrally stored at − 80 °C.

SHBG (nmol L^{-1}) was measured with an immunometric assay (Immulite 2000 XPi; Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The sensitivity is 0.2 nmol L^{-1}, and has a long-term variation of 6%, at levels of both 5 and 80 nmol L^{-1}. The within-assay variation is 3–4%, and the between-assay variation is 3.5–6%. APC resistance was measured with the thrombin generation-based APC resistance test, as described previously [14].

nAPCsr values of plasma samples from women using an LNG-IUD or a Cu-IUD were originally measured with a variant of the thrombin generation-based APC resistance assay, by the use of using calibrated automated thrombinography [24,28]. As nAPCsr values determined with calibrated automated thrombinography are higher than those determined with the classical endpoint method [16,29], the plasma samples from IUD users were reanalyzed with the endpoint method.

SHBG levels and APC resistance in non-users during mid-cycle were used in the analysis. The different phases in the menstrual cycle were defined by repeated measurements of progesterone and estradiol levels; mid-cycle is defined as the time when estradiol levels are high and progesterone levels are low.

Table 1 Body mass index (BMI) and age of the research population

		BMI (kg m^{-2})		Age (years)	
Contraceptive	*N*	Mean	Range	Mean	Range
None	13	21.7	19–29	29.0	20–48
LNG-IUD	60	24.5	18–47	32.6	17–52
Cu-IUD	17	24.2	18–32	32.4	20–45
LNG/EE	72	22.2	17–38	25.7	18–51
DSG/EE	18	24.0	20–32	30.2	18–49
DRSP/EE	47	23.8	18–34	28.4	18–47
CPA/EE	22	22.1	19–26	27.5	19–44
ENG/EE (ring)	6	24.2	21–28	26.4	20–36
NGM/EE (patch)	7	22.4	20–26	31.1	25–43
All	262	23.5	18–47	28.8	17–52

CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; EE, ethinylestradiol; ENG, etonogestrel; DRSP, drospirenone; DSG, desogestrel; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

Statistical analysis

We used means, mean differences, 95% confidence intervals (CIs) and ranges to describe variables. We constructed a scatterplot to describe the association between SHBG levels and nAPCsr; in this figure, SHBG data were logarithmically transformed to create normality, and a histogram analysis of the residuals was performed to check whether this assumption is valid. A regression analysis was performed to describe the association.

Results

There were no significant differences in body mass index or age between the women using different kinds of hormonal contraceptive (Table 1).

SHBG levels during contraceptive use

SHBG levels in users of the studied contraceptives were compared with those in non-users and in users of the most used combined oral contraceptive containing LNG/EE. Users of contraceptives containing EE plus CPA, DRSP or DSG, and users of the transdermal patch or vaginal ring, had higher SHBG levels than users of the LNG/EE-containing combined oral contraceptive. Users of the LNG-IUD or Cu-IUD had SHBG levels lower than or similar to those in non-users (Fig. 1; Table 2).

Association between SHBG and APC resistance

SHBG plasma levels were positively associated with nAPCsr in users of different kinds of hormonal contraceptive (i.e. combined oral contraceptives and LNG-IUD) and non-users. An exponential association was observed according to the equation: $\log_{10}(\text{SHBG}) = 1.525 + (0.160 \times \text{nAPCsr})$. Thus, when the nAPCsr increases by 1 unit, SHBG levels increase by 45% ($10^{0.160} = 1.45$) (Fig. 2).

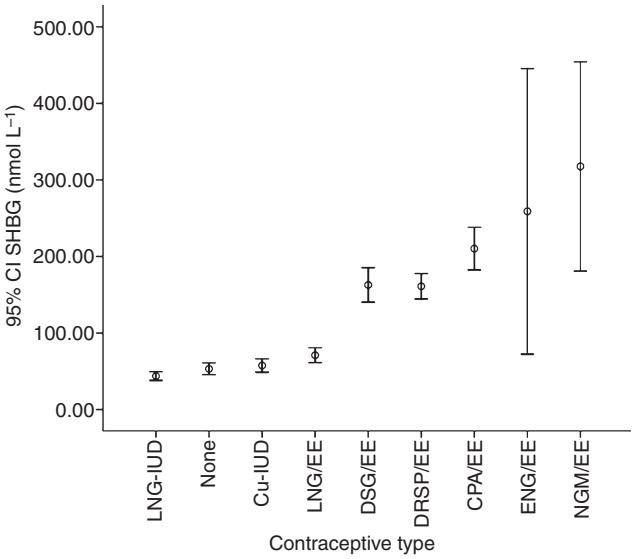

Fig. 1. Sex hormone-binding globulin (SHBG) levels and their 95% confidence intervals (CIs) by contraceptive type. CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; ENG, etonogestrel; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

Risk ranking per contraceptive

For risk ranking, we used recent publications by van Hylckama Vlieg *et al*. [3] and Jick *et al*. [30] (Table 3). The observed OR for venous thrombosis during use of the LNG-IUD as compared with non-users was 0.3 (95% CI 0.1–1.1) [3], and the observed OR during use of the transdermal patch as compared with use of the LNG-containing combined oral contraceptives was variable, and reported to be between 1.3 and 2.0 [30]. The risk of venous thrombosis during use of a Cu-IUD is unknown, but is not expected to be increased as compared with non-users. There are no data on the contraceptive vaginal ring as compared with non-users, but a study on the risk of venous thrombosis of the contraceptive ring showed a 1.56-fold increased risk as compared with a group of combined oral contraceptives with low estrogen [13].

The SHBG levels measured in this study are associated with the ORs reported in the recent literature: higher SHBG levels are present in users of contraceptives with a higher risk of venous thrombosis (Table 3; Fig. 3).

Discussion

In this study, we observed positive associations between the effects of hormonal contraceptives on SHBG levels, the nAPCsr and the thrombotic risk reported in the recent literature. A high nAPCsr in the thrombin generation-based test indicate an increased resistance to APC, and is reported to be a risk factor for venous thrombosis [11]. Together, these observations support the hypothesis that both the APCsr and SHBG levels are markers for the risk of venous thrombosis during the use of hormonal contraceptives.

Table 2 Mean sex hormone-binding globulin (SHBG) and activated protein C (APC) resistance levels, mean differences (MDs) and 95% confidence intervals (CIs) for non-users as compared with levonorgestrel (LNG)/ethinylestradiol (EE) users

		SHBG (nmol L^{-1})					APC resistance (ratio)		
			Compared with non-use		Compared with LNG/EE		Compared with non-use		
Contraceptive	*N*	Mean	MD	95% CI	MD	95% CI	Mean	MD	95% CI
None	13	53.22	Ref.				1.54	Ref.	
LNG-IUD	60	43.77	− 9.45	− 22.08 to 3.17	− 27.23	− 39.03 to − 15.44	0.85	− 0.69	− 1.03 to − 0.36
Cu-IUD	17	57.52	4.29	− 7.26 to 15.85	− 13.48	− 34.00 to 7.03	1.03	− 0.51	−0.93 to − 0.09
LNG/EE	72	71.00	17.78	− 5.46 to 41.02	Ref.		2.66	1.12	0.69 to 1.54
DSG/EE	18	162.78	109.55	82.98 to 136.13	91.78	69.60 to 113.96	3.94	2.40	1.93 to 2.86
DRSP/EE	47	161.04	107.82	7.10 to 139.54	90.04	72.23 to 107.85	3.53	1.98	1.49 to 2.48
CPA/EE	22	210.27	157.05	121.03 to 193.07	139.27	116.41 to 162.13	4.00	2.46	2.07 to 2.84
ENG/EE (ring)	6	258.93	205.71	104.77 to 306.65	187.93	136.51 to 239.36	3.02	1.47	0.94 to 2.02
NGM/EE (patch)	7	317.57	264.35	179.63 to 349.06	246.57	201.29 to 291.85	3.12	1.57	0.87 to 2.28

CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; DSG, desogestrel; DRSP, drospirenone; ENG, etonogestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

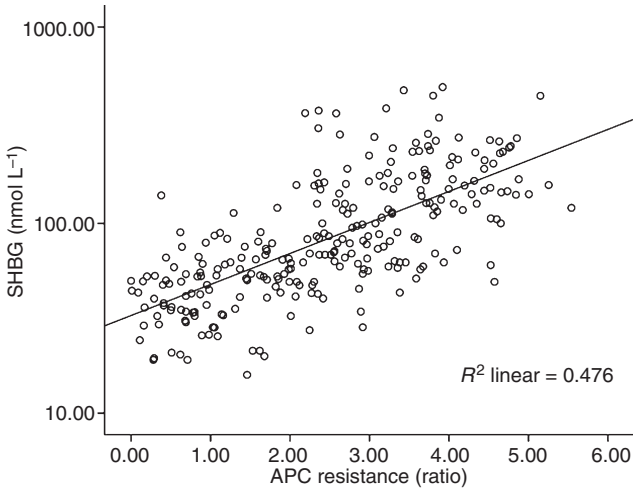

Fig. 2. The association between sex hormone-binding globulin (SHBG) and activated protein C (APC) resistance. Equation: $\log_{10}(\text{SHBG}) = 1.525 + (0.160 \times \text{nAPCsr})$.

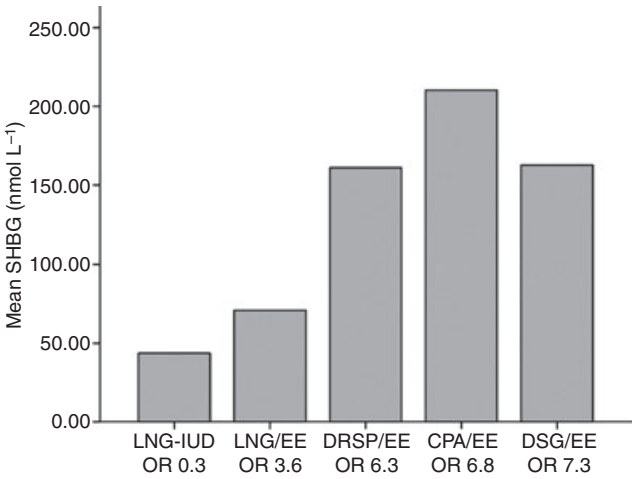

Fig. 3. The association between odds ratios (ORs) of the risk of venous thrombosis of various contraceptives as published in the recent literature [3,31,32] and sex hormone-binding globulin (SHBG) levels of hormonal contraceptives. CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device.

Table 3 The odds ratios (ORs) of venous thrombosis during the use of different types of hormonal contraceptive as compared with non-users, according to the recent literature [3,31,32]

	Risk		
Contraceptive	OR	95% CI	Reference
None	Ref.		
LNG-IUD	0.3	0.1–1.1	[31]
Cu-IUD	–	–	
LNG/EE	3.6	2.9–4.6	[3]
DSG/EE	7.3	5.3–10.0	[3]
DRSP/EE	6.3	2.9–13.7	[3]
CPA/EE	6.8	4.6–10.0	[3]
ENG/EE (ring)	–	–	
NGM/EE (patch)	1.3–2.0	–	[32]

CI, confidence interval; CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; ENG, etonogestrel; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

The use of the LNG-IUD did not increase SHBG levels, which is in concordance with recent clinical data. In a national cohort study by Lidegaard *et al.* [12], users of the LNG-IUD had no increased risk of thrombosis as compared with non-users (relative risk 0.83; 95% CI 0.63–1.08). This was confirmed by van Hylckama Vlieg *et al.* [31], who also did not find an increased risk in a recent case–control study (OR 0.3%; 95% CI 0.1–1.1).

Limited data are available on the thrombotic risk of the contraceptive transdermal patch and vaginal ring. Conflicting results have been reported on the thrombotic safety of the contraceptive patch, with estimates of the thrombotic risk varying between 0.9 (95% CI 0.5–1.6) [32] and 2.4 (95% CI 1.1–5.5) [33] as compared with oral contraceptives containing norgestimate and EE [29,30,34].

Recently, the first study on the risk of venous thrombosis of the contraceptive ring has been published by the FDA [13]. Use of the vaginal ring was associated with a 1.56-fold (95% CI 1.02–2.37) higher risk of thrombosis than in a group of users of combined oral contraceptives with low estrogen. The study also observed a 1.55-fold (95% CI 1.02–2.37) higher thrombotic risk during use of the transdermal patch. In our study, users of the vaginal ring and the transdermal patch had the highest SHBG levels of all contraceptive users. These results are in agreement with earlier studies reporting increases in SHBG of $\sim$ 260% for transdermal patch users and $\sim$ 150% for vaginal ring users as compared with pretreatment levels [18,26]. The increased SHBG levels in women using the patch and ring as compared with women using combined oral contraceptives containing LNG suggest an increased thrombotic risk.

The increased risk of the vaginal ring might be explained by the fact that ENG is the active metabolite of DSG. According to the recent literature, the use of combined hormonal contraceptives containing DSG is associated with a 1.82-fold (95% CI 1.49–2.22) higher risk of venous thrombosis than the use of combined oral contraceptives containing LNG/EE [6]. However, peak serum concentrations of EE and DSG are significantly lower in women using the contraceptive ring than in women using a combined oral contraceptive containing DSG and EE [35].

The increased risk of the transdermal patch might be explained by the 60% higher exposure to EE, as measured by the area under the curve and steady-state concentration, during use of the contraceptive patch than use of an oral contraceptive composed of NGM and EE. NGM exposure is similar during use of the contraceptive patch and pill [36,37]. As the increased SHBG levels in users of the patch and ring in our study are based on a small number of participants, further studies are indicated to confirm these results and to allow definite conclusions to be drawn.

The difference in SHBG levels between the hormone preparations was not the result of differences between women, but was rather the result of differences between contraceptive methods, as shown by the women who switched from one contraceptive type to another in the original studies. For example, switching from a combined hormonal contraceptive containing CPA to a combined hormonal contraceptive containing LNG resulted in a mean decrease of SHBG level of 150 nmol L^{-1} (95% CI -206 to -94) [6,19,20].

Currently, a biological explanation for the association between the changes in SHBG level and APC resistance induced by hormonal contraceptives is lacking. It is known that estrogen increases the risk of venous thrombosis, and that a higher dose is associated with a higher risk. We propose that SHBG reflects the overall estrogenicity of a hormonal contraceptive, and thereby the risk of venous thrombosis. SHBG and several coagulation factors and anticoagulant proteins are synthesized in the liver, and hormonal contraceptives, which are metabolized in the liver, might interfere with the synthesis of both SHBG and coagulation factors. There are now different studies demonstrating an association between SHBG and the risk of venous thrombosis. However, the mechanism is still not known, and further research is needed to unravel the association, changes in other proteins produced in the liver, changes of hemostatic parameters, and the increased risk of venous thrombosis.

We acknowledge that caution is required when surrogate markers are used, as they can be severely misleading [38]. Preferably, a surrogate marker should be validated in a prospective trial in which both the surrogate marker and the clinical endpoint are assessed. However, for very rare events, such as venous thrombosis during combined hormonal contraceptive use, a clinical study is almost impossible, owing to the required number of participants. In order to prospectively demonstrate a doubling of the risk of venous thrombosis between two different combined hormonal contraceptives with a power of 80% and a significance level of 5%, a cohort of approximately 500 000 women must be followed for 1 year [27]. Case–control studies only become possible postmarketing [27,39]. Such a large sample size makes it almost impossible for a pharmaceutical company to evaluate the risk of venous thrombosis of a new preparation before market authorization.

There are now reasonably reliable data on the risk of venous thrombosis from several epidemiological studies, showing that the combination of EE and LNG carries the lowest risk of venous thrombosis of all combined hormonal contraceptives [1,3,5,6]. Comparison of the SHBG levels in users of a new preparation with that in users of EE plus LNG could give an estimation of the magnitude of the risk of venous thrombosis before a new preparation is launched, and should be included in the general benefit–risk analysis of the new preparation. SHBG measurement is already recommended in guidelines applying to the clinical development of a new combined hormonal contraceptive by the European Medicines Agency.

In conclusion, our data support the idea that SHBG could be a useful marker for estimating the risk of venous thrombosis of a new hormonal contraceptive. Preferably, the effect of a new hormonal contraceptive on SHBG should be compared with the effect of the combined hormonal contraceptive with the lowest reported risk of venous thrombosis, i.e. an oral preparation containing EE plus LNG.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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ORIGINAL ARTICLE

Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

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ABSTRACT

BACKGROUND

Although several studies have assessed the risk of venous thromboembolism with newer hormonal contraception, few have examined thrombotic stroke and myocardial infarction, and results have been conflicting.

METHODS

In this 15-year Danish historical cohort study, we followed nonpregnant women, 15 to 49 years old, with no history of cardiovascular disease or cancer. Data on use of hormonal contraception, clinical end points, and potential confounders were obtained from four national registries.

RESULTS

A total of 1,626,158 women contributed 14,251,063 person-years of observation, during which 3311 thrombotic strokes (21.4 per 100,000 person-years) and 1725 myocardial infarctions (10.1 per 100,000 person-years) occurred. As compared with nonuse, current use of oral contraceptives that included ethinyl estradiol at a dose of 30 to 40 μg was associated with the following relative risks (and 95% confidence intervals) for thrombotic stroke and myocardial infarction, according to progestin type: norethindrone, 2.2 (1.5 to 3.2) and 2.3 (1.3 to 3.9); levonorgestrel, 1.7 (1.4 to 2.0) and 2.0 (1.6 to 2.5); norgestimate, 1.5 (1.2 to 1.9) and 1.3 (0.9 to 1.9); desogestrel, 2.2 (1.8 to 2.7) and 2.1 (1.5 to 2.8); gestodene, 1.8 (1.6 to 2.0) and 1.9 (1.6 to 2.3); and drospirenone, 1.6 (1.2 to 2.2) and 1.7 (1.0 to 2.6), respectively. With ethinyl estradiol at a dose of 20 μg, the corresponding relative risks according to progestin type were as follows: desogestrel, 1.5 (1.3 to 1.9) and 1.6 (1.1 to 2.1); gestodene, 1.7 (1.4 to 2.1) and 1.2 (0.8 to 1.9); and drospirenone, 0.9 (0.2 to 3.5) and 0.0. For transdermal patches, the corresponding relative risks were 3.2 (0.8 to 12.6) and 0.0, and for a vaginal ring, 2.5 (1.4 to 4.4) and 2.1 (0.7 to 6.5).

CONCLUSIONS

Although the absolute risks of thrombotic stroke and myocardial infarction associated with the use of hormonal contraception were low, the risk was increased by a factor of 0.9 to 1.7 with oral contraceptives that included ethinyl estradiol at a dose of 20 μg and by a factor of 1.3 to 2.3 with those that included ethinyl estradiol at a dose of 30 to 40 μg, with relatively small differences in risk according to progestin type. (Funded by the Danish Heart Association.)

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The risk of thromboembolic complications with the use of hormonal contraception is an important issue scientifically and is relevant for counseling women about contraceptive options. Several studies have assessed the risk of venous thromboembolism associated with the use of newer hormonal contraceptive products, (i.e., those from the past 10 years)[1-8] but few studies have examined thrombotic stroke and myocardial infarction, and the results of available studies have been conflicting.[7-20] Although arterial complications are less frequent than venous complications among young women, the short-term and long-term consequences of arterial complications are often more serious.

In addition to oral contraceptive pills and intramuscular injections of depot medroxyprogesterone acetate, the options for hormonal contraception currently include a vaginal ring, transdermal patches, subcutaneous implants, and the levonorgestrel-releasing intrauterine device (IUD; known in Europe as the levonorgestrel intrauterine system). The aim of this study was to assess the risks of thrombotic stroke and myocardial infarction associated with the use of various types of hormonal contraception, according to estrogen dose, progestin type, and route of administration.

Methods

Study Population

We followed an open historical cohort of Danish women, 15 to 49 years old, for a 15-year period, from January 1995 through December 2009. The population was identified on the basis of data from Statistics Denmark. A unique personal identification number that is given to all Danish citizens at birth and to people who have immigrated to Denmark is used in all public registries, allowing reliable linkage of data among different registries. Statistics Denmark also provided data on length of schooling, status of education (ongoing or finished), vital status, and emigration. Data were censored at the time of death or emigration.

Approval for the study was obtained from the Danish Data Protection Agency. Because this was a registry study, the requirement for written informed consent was waived.

End Points

Data on clinical end points were obtained from the National Registry of Patients, which has collected discharge diagnoses from public and private Danish hospitals since 1977, and the Register of Causes of Death. The relevant diagnostic codes are listed in Table 1S in the Supplementary Appendix, available with the full text of this article at NEJM.org. We identified thrombotic stroke using the diagnostic code for cerebral infarction (which is used for both cerebral thrombosis and cerebral embolism) and the less-specific diagnostic code for "cerebral apoplexy"; thrombotic events have been found to constitute 80 to 90% of the events in young women that are classified as cerebral apoplexy.[21-23] Transient cerebral ischemic attack was not included.

To restrict the analysis to first-ever events, we excluded data from all women who had received a diagnosis of any type of venous or arterial thrombotic event before the study period (i.e., from 1977 through 1994). In addition, data from women who had gynecologic, abdominal, breast, lung, or hematologic cancer before the study period were excluded or, if any of these diseases occurred during the study period, were censored at the time of diagnosis (Table 1S in the Supplementary Appendix).

The National Registry of Patients also records surgical codes from public and private hospitals. Data from women who had undergone bilateral oophorectomy, unilateral oophorectomy two times, hysterectomy, or a sterilization procedure were either excluded at baseline or censored at the time of surgery (Table 1S in the Supplementary Appendix).

Pregnancy outcomes and gestational ages at termination were identified according to the codes specified in Table 1S in the Supplementary Appendix. Data from women were temporarily censored during pregnancy, which was defined as the period from conception through 3 months after delivery (or 1 month after abortion or termination of ectopic pregnancy). Data from women with a coagulation disorder were censored at the recorded date of the initial diagnosis (Table 1S in the Supplementary Appendix).

Finally, information about smoking habits was obtained from the National Registry of Patients. Information about whether a woman smoked was available for 480,223 women, covering 5.2 million person-years of observation (37% of risk time).

Prescription Data

The Register of Medicinal Products Statistics provided information, updated daily, about filled

prescriptions for oral contraceptives and other types of hormonal contraception from 1995 through 2009. We categorized the products in use according to estrogen dose, progestin type, and route of administration.

Duration of use was estimated to be the period from the date of the prescription until the end date of the last filled prescription or the date of a study event. Further details regarding the assessment of duration of use are given in a previous report.[6] From the prescription registry, we also obtained updated information about medication for the treatment of diabetes, heart arrhythmia, hypertension, and hyperlipidemia. Data from women with prescriptions for ovarian stimulants were censored at the time that such a prescription was first filled.

STATISTICAL ANALYSIS

Using Poisson regression, we calculated the estimated risks of thrombotic events, with stratification according to estrogen dose (50 μg, 30 to 40 μg, or 20 μg of ethinyl estradiol or progestin-only contraceptive), progestin type, route of administration, and duration of use (<1 year, 1 to 4 years, or >4 years). The reference group comprised nonusers (women who had never used hormonal contraception as well as former users), and the estimates of relative risk were adjusted for age, calendar year, length of schooling, educational level (ongoing or completed), and status with respect to hypertension, heart disease, diabetes, and hyperlipidemia (defined by the use or nonuse of medications for these conditions). Imputed values for missing data on smoking status were calculated with the use of standard procedures of imputation,[24] and sensitivity analyses that included imputation for smoking status were conducted (Table 2S in the Supplementary Appendix).

Tests for interactions of the different types of hormonal contraception with age and with predisposing diseases were conducted. Sensitivity analyses in which only the specific code for cerebral infarction, DI63, was included were performed for all product types. Finally, sensitivity tests were conducted for the three periods of 1995 through 1999, 2000 through 2004, and 2005 through 2009.

RESULTS

THROMBOTIC EVENTS IN THE STUDY COHORT

After the exclusion and censoring of data as specified in Figure 1, the study cohort included 1,626,158 women, with 14,251,063 person-years of observation. During this period, 3311 women had a first thrombotic stroke (1633 events [49.3%] were coded as cerebral infarction, and 1678 [50.7%] as cerebral apoplexy), and 1725 had a first myocardial infarction. The case fatality rate during the primary event or subsequent hospital stay was 1.0% for thrombotic stroke (34 of 3311 women) and 10.8% for myocardial infarction (186 of 1725).

After adjustment for calendar year, educational level, status with respect to predisposing diseases,

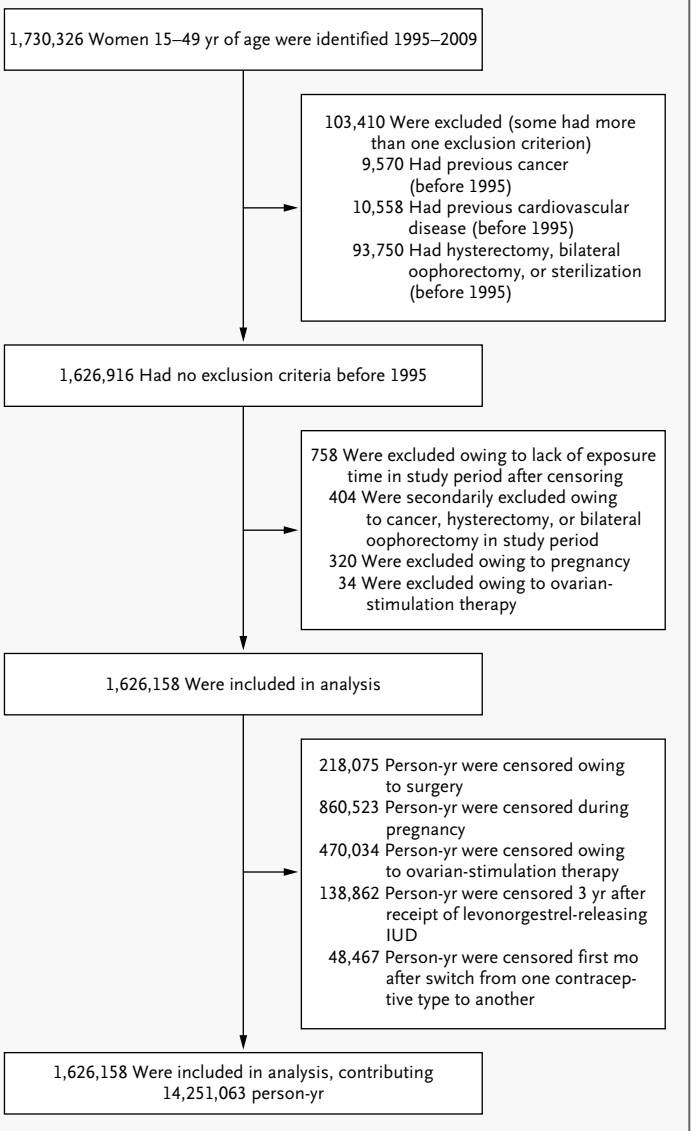

Figure 1. Screening, Exclusions, and Data Censoring.
Shown are the numbers of women who met the various exclusion criteria and those for whom data were censored. IUD denotes intrauterine device.

and use or nonuse of hormonal contraception, the incidence rates of thrombotic stroke and myocardial infarction were increased by factors of 20 and 100, respectively, in the oldest age group (45 to 49 years) as compared with the youngest age group (15 to 19 years) (Table 1).

Women with the highest level of education had about half as many thrombotic strokes and about one third as many myocardial infarctions as women with the lowest level of education (Table 1). The relative risks of thrombotic stroke and myocardial infarction, respectively, among women who filled prescriptions for medications to treat predisposing disorders, as compared with women who did not fill prescriptions for these medications, were as follows: for diabetes, 2.73 (95% confidence interval [CI], 2.32 to 3.22) and 4.66 (95% CI, 3.88 to 5.61); for hypertension, 2.32 (95% CI, 2.14 to 2.50) and 2.17 (95% CI, 1.95 to 2.42); and for hyperlipidemia, 2.11 (95% CI, 1.74 to 2.56) and 1.88 (95% CI, 1.46 to 2.41) (Table 1).

HORMONAL CONTRACEPTION AND ARTERIAL THROMBOSIS

In 4.9 million person-years of use of hormonal contraception, 1051 women had a thrombotic

Table 1. Incidence Rates and Adjusted Relative Risks of Thrombotic Stroke and Myocardial Infarction among Nonpregnant Danish Women, According to Age, Calendar Year, Educational Level, and Predisposing Risk Factors, 1995–2009.

Variable	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
Age							
15–19 yr	2,075,087	70	3.4	0.05 (0.04–0.06)	9	0.4	0.01 (0.01–0.02)
20–24 yr	1,961,761	110	5.6	0.07 (0.06–0.09)	13	0.7	0.02 (0.01–0.03)
25–29 yr	1,906,954	201	10.5	0.16 (0.13–0.18)	41	2.2	0.06 (0.04–0.08)
30–34 yr	2,053,357	317	15.4	0.26 (0.23–0.30)	102	5.0	0.15 (0.12–0.18)
35–39 yr	2,149,752	501	23.3	0.40 (0.36–0.44)	262	12.2	0.36 (0.31–0.41)
40–44 yr	2,104,119	825	39.2	0.65 (0.59–0.71)	534	25.4	0.71 (0.64–0.80)
45–49 yr	2,000,033	1287	64.4	1.00	764	38.2	1.00
Year							
1995	1,110,157	183	16.5	1.00	108	9.7	1.00
1996	1,082,648	172	15.9	0.91 (0.74–1.12)	105	9.7	0.94 (0.72–1.23)
1997	1,052,178	192	18.3	1.02 (0.83–1.25)	104	9.9	0.94 (0.72–1.23)
1998	1,026,757	168	16.4	0.89 (0.72–1.10)	100	9.7	0.90 (0.69–1.19)
1999	1,001,828	219	21.9	1.16 (0.95–1.41)	109	10.9	0.98 (0.75–1.28)
2000	981,241	211	21.5	1.11 (0.91–1.36)	125	12.7	1.12 (0.87–1.45)
2001	959,246	218	22.7	1.15 (0.94–1.40)	133	13.9	1.19 (0.92–1.53)
2002	938,943	224	23.9	1.18 (0.97–1.44)	143	15.2	1.27 (0.99–1.64)
2003	918,924	236	25.7	1.25 (1.03–1.51)	148	16.1	1.32 (1.03–1.70)
2004	903,351	232	25.7	1.22 (1.00–1.48)	126	14.0	1.12 (0.87–1.45)
2005	883,911	243	27.5	1.28 (1.06–1.56)	117	13.2	1.05 (0.80–1.36)
2006	867,957	273	31.5	1.45 (1.20–1.75)	102	11.8	0.91 (0.69–1.20)
2007	852,227	251	29.5	1.34 (1.10–1.62)	121	14.2	1.09 (0.84–1.42)
2008	843,664	232	27.5	1.24 (1.02–1.51)	87	10.3	0.78 (0.59–1.04)
2009	828,032	257	31.0	1.39 (1.15–1.69)	97	11.7	0.89 (0.67–1.18)

Table 1. (Continued.)

Variable	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
Educational level†							
Elementary school completed	3,808,238	1355	35.6	2.06 (1.85–2.29)	816	21.4	3.08 (2.63–3.61)
High school ongoing or completed	1,638,840	198	12.1	1.1 (0.93–1.31)	72	4.4	1.31 (0.99–1.72)
High school and middle education ongoing or completed	3,778,853	1080	28.6	1.4 (1.26–1.56)	587	15.5	1.87 (1.59–2.20)
High school and long education ongoing or completed	2,383,029	470	19.7	1.00	194	8.1	1.00
Unknown	2,642,102	208	7.9	1.88 (1.54–2.28)	56	2.1	2.36 (1.72–3.24)
Risk factor							
Diabetes‡	123,264	186	150.9	2.73 (2.32–3.22)	159	129.0	4.66 (3.88–5.61)
Hypertension‡	1,343,081	1039	77.4	2.32 (2.14–2.50)	581	43.3	2.17 (1.95–2.42)
Hyperlipidemia‡	63,111	139	220.3	2.11 (1.74–2.56)	85	134.7	1.88 (1.46–2.41)
Arrhythmia‡	69,752	68	97.5	1.80 (1.41–2.29)	54	77.4	2.56 (1.95–3.37)
Smoking§	1,195,490	204	17.1	1.57 (1.31–1.87)	112	9.37	3.62 (2.69–4.87)

* Relative risks were adjusted for hormonal contraception and the other variables included in the table.
† In Denmark, middle education is defined as 4 years of education after high school, and long education as 5 to 6 years of education after high school.
‡ Risk factors were identified on the basis of the use of medications that are used to treat these conditions.
§ Data on smoking are for the subpopulation with available information (480,223 women, covering 5.2 million person-years of observation and including about 1.2 million person-years among smokers).

stroke and 497 had a myocardial infarction; the crude incidence rates were 21.4 and 10.1 per 100,000 person-years, respectively. The corresponding incidence rates in 9,336,662 person-years of nonuse, during which 2260 women had a thrombotic stroke and 1228 had a myocardial infarction, were 24.2 and 13.2 per 100,000 person-years, with the higher rates primarily due to older age and a higher frequency of predisposing conditions among nonusers (Table 2).

The risk among previous users was similar to the risk among women who had never used hormonal contraception. The rate ratio for thrombotic stroke among previous users, as compared with women who had never used hormonal contraception, was 1.04 (95% CI, 0.95 to 1.15), and for myocardial infarction, 0.99 (95% CI, 0.86 to 1.13).

After stratifying the data for current users of hormonal contraception according to estrogen dose, progestin type, and route of administration, we estimated the crude incidence rates and adjusted relative risks of thrombotic events for users as compared with nonusers (Table 2). The estimated relative risks of thrombotic stroke and myocardial infarction among users of combined oral contraceptive pills that included ethinyl estradiol at a dose of 30 to 40 μg did not differ significantly according to the type of progestin, ranging from 1.40 to 2.20 for stroke and from 1.33 to 2.28 for myocardial infarction. For both end points, the risk estimates were lowest with contraceptive pills that included norgestimate or cyproterone acetate and were highest with those that included norethindrone or desogestrel (Table 2).

For women who used desogestrel with a reduced dose of ethinyl estradiol (20 μg), as compared with nonusers, the relative risks of thrombotic stroke and myocardial infarction were 1.53 (95% CI, 1.26 to 1.87) and 1.55 (95% CI, 1.13 to 2.13), respectively. For women who used drospirenone with ethinyl estradiol at a dose of 20 μg, the relative risk of thrombotic stroke was 0.88

Table 2. Incidence Rates and Adjusted Relative Risks of Thrombotic Stroke and Myocardial Infarction among Users of Different Types of Hormonal Contraception, as Compared with Nonusers.*

Type of Hormonal Contraception	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)†	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)†
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
None	9,336,662	2260	24.2	1.00	1228	13.2	1.00
Ethinyl estradiol, 50 μg							
Norethindrone	43,234	9	20.8	1.27 (0.66–2.45)	11	25.4	2.74 (1.51–4.97)
Levonorgestrel	54,474	32	58.7	2.26 (1.59–3.20)	36	66.1	4.31 (3.09–6.00)
Ethinyl estradiol, 30 to 40 μg							
Norethindrone	126,984	28	22.1	2.17 (1.49–3.15)	14	11.0	2.28 (1.34–3.87)
Levonorgestrel	460,559	144	31.3	1.65 (1.39–1.95)	91	19.8	2.02 (1.63–2.50)
Norgestimate	453,536	78	17.2	1.52 (1.21–1.91)	28	6.2	1.33 (0.91–1.94)
Desogestrel	313,560	99	31.6	2.20 (1.79–2.69)	43	13.7	2.09 (1.54–2.84)
Gestodene	1,318,962	285	21.6	1.80 (1.58–2.04)	133	10.1	1.94 (1.62–2.33)
Drospirenone	286,770	52	18.1	1.64 (1.24–2.18)	18	6.3	1.65 (1.03–2.63)
Cyproterone acetate	187,145	29	15.5	1.40 (0.97–2.03)	12	6.4	1.47 (0.83–2.61)
Ethinyl estradiol, 20 μg							
Desogestrel	695,603	105	15.1	1.53 (1.26–1.87)	40	5.8	1.55 (1.13–2.13)
Gestodene	564,268	88	15.6	1.70 (1.37–2.12)	21	3.7	1.20 (0.77–1.85)
Drospirenone	23,056	2	8.7	0.88 (0.22–3.53)	0	0	0 (0.00–12.99)
Progestin only							
Norethindrone	85,874	28	32.6	1.35 (0.93–1.96)	9	10.5	0.81 (0.42–1.56)
Levonorgestrel	8,556	1	11.7	0.44 (0.06–3.12)	0	0	0 (0.00–35.01)
Desogestrel	29,185	9	30.8	1.37 (0.71–2.63)	4	13.7	1.46 (0.55–3.90)
Levonorgestrel IUD	184,875	45	24.3	0.73 (0.54–0.98)	31	16.8	1.02 (0.71–1.46)
Implant	24,954	3	12.0	0.88 (0.28–2.72)	3	12.0	2.14 (0.69–6.65)
Other							
Patch	4,748	2	42.1	3.15 (0.79–12.60)	0	0	0 (0.00–63.10)
Vaginal ring	38,246	12	31.4	2.49 (1.41–4.41)	3	7.8	2.08 (0.67–6.48)

* IUD denotes intrauterine device.
† Relative risks were adjusted for age, educational level, calendar year, and risk factors.

(95% CI, 0.22 to 3.53); there were no myocardial infarctions in this group.

None of the progestin-only products, including the levonorgestrel-releasing IUD and the subcutaneous implants, significantly increased the risk of thrombotic stroke or myocardial infarction (Table 2), but the numbers were small for several of these groups. In contrast, the relative risk of thrombotic stroke was 3.15 (95% CI, 0.79 to 12.6) among women who used contraceptive patches and 2.49 (95% CI, 1.41 to 4.41) among those who used a vaginal ring. Numbers of myocardial infarctions were too low to provide reliable estimates.

An analysis adjusted for differences in progestin type, age, and calendar year showed that combined oral contraceptives with doses of ethinyl estradiol of 20 μg, 30 to 40 μg, and 50 μg were associated with a relative risk of thrombotic

stroke of 1.60 (95% CI, 1.37 to 1.86), 1.75 (95% CI, 1.61 to 1.92), and 1.97 (95% CI, 1.45 to 2.66), respectively (P=0.24 for trend). The corresponding relative risks for myocardial infarction were 1.40 (95% CI, 1.07 to 1.81), 1.88 (95% CI, 1.66 to 2.13), and 3.73 (95% CI, 2.78 to 5.00), respectively (P<0.001 for trend).

SMOKING

Information about whether a woman smoked was available for 480,223 women, covering 5.2 million person-years of observation and including 1.2 million person-years among smokers. Smoking status was known for 582 women who had a thrombotic stroke and for 193 women who had a myocardial infarction. For women who smoked as compared with those who did not, the relative risks of thrombotic stroke and myocardial infarction were 1.57 (95% CI, 1.31 to 1.87) and 3.62 (95% CI, 2.69 to 4.87), respectively. However, smoking had no confounding influence on the relative risk of arterial thrombosis among users of different types of hormonal contraception, after adjustment for age and predisposing conditions, and the results of an analysis in which smoking status was imputed were similar to the results with no imputation of smoking status (Table 2S in the Supplementary Appendix).

SENSITIVITY ANALYSES

There was no consistent interaction between the use of oral contraceptives and the relative risk of thrombotic stroke or myocardial infarction in different age groups, and there were no trends according to duration of use for either end point (Table 3). The sensitivity analysis, which included only women with the diagnostic code for cerebral infarction, provided slightly higher risk estimates than our primary analysis of thrombotic stroke (Table 3S in the Supplementary Appendix). Although the incidence rate of thrombotic stroke increased over time, we could not detect any consistent change in the estimated relative risks of the two end points for four different product groups during the three periods of 1995 through 1999, 2000 through 2004, and 2005 through 2009 (data not shown). We found no interaction between the use of hormonal contraception and predisposing disease for the risk of thrombotic stroke or myocardial infarction. The age distribution according to product group is shown in Figure 2S in the Supplementary Appendix.

DISCUSSION

The rates of thrombotic stroke and myocardial infarction increased by factors of 20 and 100, respectively, with increasing age. Only small differences in risk were observed between women who took combination pills containing intermediate-dose ethinyl estradiol (30 to 40 μg) and those who took low-dose ethinyl estradiol (20 μg), and only minor variations in risk were associated with different progestin types.

The increased incidence of thrombotic stroke over the 15-year study period probably reflects improvements in the diagnostic equipment, allowing the detection of small cerebral infarctions, rather than a real increase in incidence. The steep increase in incidence with older age has been shown in several previous studies.[9-11,25] This information has clinical implications, given that arterial thrombosis after the age of 30 years is more frequent and has more serious consequences than venous thrombosis.[6] The risk of arterial thrombosis should therefore be considered together with the risk of venous thrombosis when hormonal contraception is prescribed.

The relative risk of thrombotic stroke of 1.4 to 2.2 among current users of oral contraceptives containing ethinyl estradiol at a dose of 30 to 40 μg is slightly lower than previously reported (Table 4S in the Supplementary Appendix). In a multicenter World Health Organization study, Poulter et al. found that women who used second-generation oral contraceptive pills with levonorgestrel, as compared with nonusers, had a relative risk of thrombotic stroke of 2.7 (95% CI, 1.8 to 4.1) and users of third-generation pills had a relative risk of 1.8 (95% CI, 0.6 to 5.2).[9] Among women who had their blood pressure measured before obtaining a prescription, these risk estimates were reduced to 2.0 (95% CI, 1.1 to 3.6) and 1.6 (95% CI, 0.4 to 6.6), respectively.[9] These estimates are closer to ours, perhaps because a majority of Danish women have their blood pressure checked before obtaining prescriptions for oral contraceptives.

In our secondary analysis, which included only the code for cerebral infarction, we observed a slightly higher relative risk of stroke associated with hormonal contraception, as compared with our primary analysis. This difference may have been due to the inclusion of 15 to 20% of hemorrhagic strokes in the primary analysis that were

Table 3. Relative Risk of Thrombotic Stroke and Myocardial Infarction among Users of Selected Types of Combined Oral Contraception with Ethinyl Estradiol at a Dose of 30 to 40 μg, as Compared with Nonusers, According to Duration of Use.

Type of Hormonal Contraception	No. of Person-yr	Thrombotic Stroke		Myocardial Infarction	
		No. of Events	Relative Risk (95% CI)	No. of Events	Relative Risk (95% CI)
Nonuse	9,336,662	2260	1.00	1228	1.00
Levonorgestrel					
<1 yr	175,205	45	1.72 (1.28–2.32)	24	1.91 (1.27–2.87)
1–4 yr	190,598	49	1.50 (1.13–1.99)	32	1.95 (1.37–2.77)
>4 yr	94,756	50	1.74 (1.31–2.30)	35	2.26 (1.61–3.17)
Desogestrel					
<1 yr	131,061	31	1.91 (1.34–2.73)	10	1.45 (0.78–2.71)
1–4 yr	130,633	38	2.13 (1.54–2.94)	21	2.67 (1.73–4.12)
>4 yr	51,866	30	2.48 (1.73–3.56)	12	2.09 (1.18–3.69)
Gestodene					
<1 yr	541,756	107	1.91 (1.57–2.33)	44	1.97 (1.45–2.67)
1–4 yr	554,721	96	1.53 (1.24–1.88)	47	1.83 (1.36–2.46)
>4 yr	222,485	82	1.86 (1.49–2.33)	42	2.08 (1.52–2.84)
Drospirenone					
<1 yr	139,543	30	2.00 (1.38–2.88)	8	1.64 (0.81–3.30)
1–4 yr	116,873	11	0.84 (0.46–1.52)	8	1.91 (0.95–3.84)
>4 yr	30,353	11	2.20 (1.21–3.98)	2	1.12 (0.28–4.50)
All above types					
<1 yr	987,564	213	1.90 (1.64–2.20)	86	1.85 (1.48–2.31)
1–4 yr	992,825	194	1.55 (1.33–1.80)	108	1.99 (1.63–2.43)
>4 yr	399,461	173	1.93 (1.65–2.26)	91	2.11 (1.70–2.62)

coded as cerebral apoplexy, supporting the finding that oral contraception is associated with a lower risk of cerebral hemorrhage than of cerebral infarction.[26-28]

Heinemann et al. reported a case–control study showing that women who used second-generation oral contraceptive pills with levonorgestrel or norgestimate had a risk of thrombotic stroke that was 2.7 times (95% CI, 1.5 to 4.6) as high as the risk among nonusers and those who used third-generation pills had a risk that was 3.4 times (95% CI, 1.9 to 6.4) as high.[10] These estimates are higher than those reported in the present study.

In a previous Danish case–control study that covered the period from 1994 through 1998, we found that users of second-generation oral contraceptive pills had a risk of cerebral thromboembolism that was 2.2 times (95% CI, 1.6 to 3.0) as high as the risk among nonusers.[11] The odds ratio for cerebral thromboembolism among users of third-generation pills was 1.4 (95% CI, 1.0 to 1.9). These results are in accordance with our current findings.

Gronich et al. recently found that oral contraceptives with drospirenone and ethinyl estradiol at a dose of 30 μg were associated with the same magnitude of risk as second-generation and third-generation pills with the same dose of estrogen[8] — results that are in agreement with ours. Our data suggest a relatively high risk of thrombotic stroke with the use of a vaginal ring and possibly with the use of transdermal patches. Until further evidence emerges, one might expect a higher risk of thrombotic stroke with parenteral administra-

tion than with oral administration (estrogen combined with progestin).

There was a relatively high correlation in risk estimates for thrombotic stroke and myocardial infarction among the different product groups — a finding that increases the likelihood that the observed differences in risk were real rather than random variations. One previous study showed a tendency toward a higher relative risk of myocardial infarction with the use of third-generation, as compared with second-generation, oral contraceptives,[16] three showed the opposite result,[13,14,19] and one showed no difference[18] (Table 4S in the Supplementary Appendix). We found no consistent difference according to progestin type, but the risk decreased with lower doses of estrogen. We also found that low-dose pills were associated with approximately a 50% increase in the risk of myocardial infarction and intermediate-dose pills with up to a 100% increase in risk.

A crucial point in all registry-based studies is the validity of the diagnostic codes. In our 2002 study, we excluded 5.0% of women with a diagnosis of thrombotic stroke because of an absence of confirmation from the patient or the treating department.[11] The diagnosis of myocardial infarction has been found to be valid in 93.6% of patients of all ages,[29] and the percentage is probably higher among young patients. Any diagnostic misclassification may have led to an underestimation of the relative risks among current users. Another limitation is that, for some women, there may have been a time lag between the date of the prescription and the date the medication was actually started.

We had detailed and valid exposure information because the prescriptions were transferred electronically from the pharmacies by bar codes linked to the personal identification number. We were thus free of recall bias, an issue of concern in all retrospective case–control studies. The national cohort design ensured a large sample and allowed the calculation of risk estimates for specific product groups according to estrogen dose, progestin type, and route of administration — the majority with an acceptable precision. The design also avoided the problem of sample reduction due to nonresponse in survey studies, ensuring a high external validity.

For the levonorgestrel-releasing IUD, we had information only about the dates that the women received the IUD. Although this IUD has a valid period of 5 years, many women have it removed before the expiration date. Because of this uncertainty, we censored data for women with a levonorgestrel-releasing IUD after 3 years, unless another prescription for hormonal contraception was filled before that date. This approach reduced our exposure time for this specific product but increased the probability that the women who were classified as having a levonorgestrel-releasing IUD actually did have it.

Data on body-mass index were not available, but body-mass index was not a confounder in our previous study.[11] Smoking, although an important risk factor for arterial thrombosis, had no confounding influence in either this study or our previous one, in which we had more comprehensive information about this potential confounder. Therefore, it is not likely that our results were strongly influenced by incomplete data on these two potential confounders. However, in the absence of definitive data, we cannot be sure whether there would be an interaction with smoking.

In conclusion, women who used oral contraceptives with ethinyl estradiol at a dose of 30 to 40 μg had a risk of arterial thrombosis that was 1.3 to 2.3 times as high as the risk among nonusers, and women who used pills with ethinyl estradiol at a dose of 20 μg had a risk that was 0.9 to 1.7 times as high, with only small differences according to progestin type. We estimate that among 10,000 women who use desogestrel with ethinyl estradiol at a dose of 20 μg for 1 year, 2 will have arterial thrombosis and 6.8 women taking the same product will have venous thrombosis. Although venous thrombosis is three to four times as frequent as arterial thrombosis among young women, the latter is associated with higher mortality and more serious consequences for the survivors. Therefore, these figures should be taken into account when prescribing hormonal contraception.

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CMAJ RESEARCH

Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-based cohort study

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See related commentary by Solymoss at www.cmaj.ca/lookup/doi/10.1503/cmaj.111614

Abstract

Background: Combined oral contraceptives are a common method of contraception, but they carry a risk of venous and arterial thrombosis. We assessed whether use of drospirenone was associated with an increase in thrombotic risk relative to third-generation combined oral contraceptives.

Methods: Using computerized records of the largest health care provider in Israel, we identified all women aged 12 to 50 years for whom combined oral contraceptives had been dispensed between Jan. 1, 2002, and Dec. 31, 2008. We followed the cohort until 2009. We used Poisson regression models to estimate the crude and adjusted rate ratios for risk factors for venous thrombotic events (specifically deep vein thrombosis and pulmonary embolism) and arterial thromboic events (specifically transient ischemic attack and cerebrovascular accident). We performed multivariable analyses to compare types of contraceptives, with adjustment for the various risk factors.

Results: We identified a total of 1017 (0.24%) venous and arterial thrombotic events among 431 223 use episodes during 819 749 woman-years of follow-up (6.33 venous events and 6.10 arterial events per 10 000 woman-years). In a multivariable model, use of drospirenone carried an increased risk of venous thrombotic events, relative to both third-generation combined oral contraceptives (rate ratio [RR] 1.43, 95% confidence interval [CI] 1.15–1.78) and second-generation combined oral contraceptives (RR 1.65, 95% CI 1.02–2.65). There was no increase in the risk of arterial thrombosis with drospirenone.

Interpretation: Use of drospirenone-containing oral contraceptives was associated with an increased risk of deep vein thrombosis and pulmonary embolism, but not transient ischemic attack or cerebrovascular attack, relative to second- and third-generation combined oral contraceptives.

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Oral hormonal therapy is the preferred method of contraception, especially among young women. In the United States in 2002, 12 million women were using "the pill."[1] In a survey of households in Great Britain conducted in 2005 and 2006, one-quarter of women aged 16 to 49 years of age were using this form of contraception.[2] A large variety of combined oral contraceptive preparations are available, differing in terms of estrogen dose and in terms of the dose and type of the progestin component. Among preparations currently in use, the estrogen dose ranges from 15 to 35 μg, and the progestins are second-generation, third-generation or newer. The second-generation progestins (levonorgestrel and norgestrel), which are derivatives of testosterone, have differing degrees of androgenic and estrogenic activities. The structure of these agents was modified to reduce the androgenic activity, thus producing the third-generation progestins (desogestrel, gestodene and norgestimate). Newer progestins are chlormadinone acetate, a derivative of progesterone, and drospirenone, an analogue of the aldosterone antagonist spironolactone having antimineralocorticoid and antiandrogenic activities. Drospirenone is promoted as causing less weight gain and edema than other forms of oral contraceptives, but few well-designed studies have compared the minor adverse effects of these drugs.[3]

The use of oral contraceptives has been reported to confer an increased risk of venous and arterial thrombotic events,[4–7] specifically an absolute risk of venous thrombosis of 6.29 per 10 000 woman-years, compared with 3.01 per 10 000 woman-years among nonusers.[8] It has

long been accepted that there is a dose–response relationship between estrogen and the risk of venous thrombotic events. Reducing the estrogen dose from 50 μg to 20–30 μg has reduced the risk.[9] Studies published since the mid-1990s have suggested a greater risk of venous thrombotic events with third-generation oral contraceptives than with second-generation formulations,[10–13] indicating that the risk is also progestin-dependent. The pathophysiological mechanism of the risk with different progestins is unknown. A twofold increase in the risk of arterial events (specifically ischemic stroke[6,14] and myocardial infarction[7]) has been observed in case–control studies for users of second-generation pills and possibly also third-generation preparations.[7,14]

Conflicting information is available regarding the risk of venous and arterial thrombotic events associated with drospirenone. An increased risk of venous thromboembolism, relative to second-generation pills, has been reported recently,[8,15,16] whereas two manufacturer-sponsored studies claimed no increase in risk.[17,18] In the study reported here, we investigated the risk of venous and arterial thrombotic events among users of various oral contraceptives in a large population-based cohort.

Methods

This population-based historical cohort study was based on automatically and routinely collected administrative and clinical data in a coded database. As such, approval was not sought from an ethics review board.

Data source

In Israel, medical care is provided by four not-for-profit health care providers. Every resident of the country may choose to receive his or her medical care from one of these four providers and can switch providers periodically with no penalty. The annual rate of changing providers is about 1%.[19] Clalit Health Services is the largest provider. Its enrolment accounts for more than half of the population, with a somewhat older age profile and lower socioeconomic status than the other three providers.[19] The Clalit clinical database[20,21] is a comprehensive database that was established in 1998. It has several components, including a medication database, a chronic diseases database, a primary care database of diagnoses by physician visit, a database of laboratory test results and a database of hospital admissions. The databases are based on a full accounting of relevant data achieved through the centralized and standardized computerization of all Clalit primary care physicians, laboratories, pharmacies, and admissions to and discharges from hospital for those insured. Full computerization of all Clalit providers was achieved in 2002, and our study period therefore started in that year. Among information that was not originally collected but that has been added gradually over time are data on health-related habits such as smoking and health-related markers such as body mass index (which are recorded in the markers database).

Study cohort

We searched the Clalit medication database for all women for whom at least one combined oral contraceptive prescription had been dispensed between Jan. 1, 2002, and Dec. 31, 2008, and who were between 12 and 50 years of age throughout the study period (i.e., the age range for contraception use and the age limit used in studies of the thromboembolic risk of contraceptives). Each type of combined oral contraceptive used by an individual woman was regarded as a separate use episode. All prescriptions for people insured by Clalit are filled in Clalit pharmacies, which have been centrally computerized since 2002. Variables in the database that were used for this study were the catalogue number of each medication, the date the prescription was first filled, the date it was last filled and the number of prescriptions filled.

We searched the Clalit primary care and hospital databases for diagnoses of deep vein thrombosis (International Classification of Diseases, ninth revision [ICD-9], codes 451.1, 451.83), pulmonary embolism (ICD-9 code 415.1), transient ischemic attack (ICD-9 code 435) and cerebrovascular accident (ICD-9 codes 430–432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 438) in the study cohort. We excluded women who had any of these diagnoses before starting contraceptive use.

Study outcomes

We identified first-time diagnoses of thrombotic events, specifically deep vein thrombosis, pulmonary embolism, transient ischemic attack and cerebrovascular accident. We followed the cohort until 2009. We attributed each such event to the last combined oral contraceptive used before the event. Most prescriptions were for a three-month period, and the thromboembolic risk has been reported to disappear within three months after a woman stops using oral contraceptives.[13,22] Therefore, if an event occurred more than six months since the last combined oral contraceptive was dispensed, we did not attribute it to any contraceptive. We classified deep vein thrombosis and pulmonary embolism diagnosed on the same day

as pulmonary embolism. We regarded an undetermined diagnosis of either transient ischemic attack or cerebrovascular accident as transient ischemic attack. We calculated the duration of oral contraceptive use from the number of one-month packages of combined oral contraceptives that were dispensed. The observation time for each woman was the sum of the number of months from beginning of use until six months after the last prescription was dispensed or until a thrombotic event, based on the dates of first and last prescriptions.

Study covariates

For all women in the study cohort, we searched the Clalit primary care, hospital admission and markers databases for diagnoses of clinical risk factors that are known from the literature to be related to venous and arterial thrombosis, specifically obesity (body mass index > 30), smoking and history of hypertension (ICD-9 401–405), hyperlipidemia (ICD-9 272.0–272.4), diabetes mellitus (ICD-9 250) or cancer (ICD-9 140–208). We documented a risk factor if it was diagnosed before the thrombotic event (for women with such an event) or at any time until the end of the study period (for women with no thrombotic event).

Statistical analysis

Combined oral contraceptives containing norgestrel and levonorgestrel were grouped together as second-generation agents. Formulations containing desogestrel, gestodene or norgestimate were grouped as third-generation products.[23,24] Combined oral contraceptives containing low-dose gestodene, drospirenone or chlormadinone were analyzed individually. We calculated the crude incidence of venous and arterial thrombotic events in relation to each of the following risk factors: age, diabetes, hyperlipidemia, hypertension, cancer, smoking, obesity and duration of contraceptive use (divided into four groups [quartiles]). We performed multiple imputations using all of the above-listed variables to impute missing data for smoking and obesity. We used Poisson regression analysis, with robust standard errors, to estimate the crude rate ratio (RR) for each risk factor and the adjusted RRs, with 95% confidence intervals [CIs], for venous and arterial thrombotic events for the contraceptive types. We also ran the model using the negative binomial distribution, for which the shape parameter is a convenient index of overdispersion. The results in these two models were similar. We performed multivariable analyses to compare types of treatment (drospirenone v. third-generation, drospirenone v. second-generation, third-generation v. second-generation), with adjustment for other risk factors.

We also performed a secondary analysis to determine if estrogen dosage affected the outcome. Specifically, we used the same model to compare third-generation oral contraceptives containing 20 μg ethinylestradiol (combined with desogestrel or gestodene, accounting for 44.4% of all use episodes in our cohort) with third-generation oral contraceptives containing 30–35 μg ethinylestradiol (combined with desogestrel, gestodene or norgestimate, accounting for 29.0% of all use episodes in our cohort).

Results

In our study population, a combined oral contraceptive was prescribed at least once to 14% of women 12–50 years of age and 20% of women 16–35 years of age. We noted a marked shift in prescribing patterns over the study period, with disappearance of the use of second-generation combined oral contraceptives and a marked

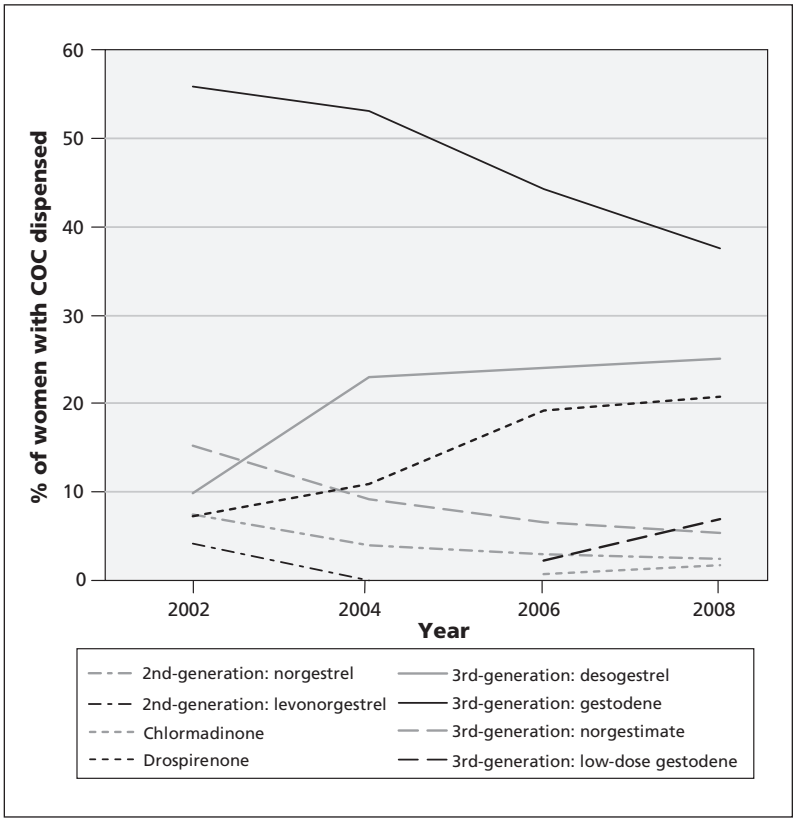

Figure 1: Time trends in the use of various combined oral contraceptives (COCs). In total, 5.0% of women in the study cohort used second-generation agents (4.1% norgestrel and 0.9% levonorgestrel), 73.4% used third-generation agents (22.7% desogestrel, 41.6% gestodene and 9.1% norgestimate), 3.6% used the low-dose gestodene-containing agent, 17.1% used a drospirenone-containing COC, and 0.9% used a COC containing chlormadinone acetate. All but one of the contraceptive agents contained 20–30 μg ethinylestradiol as the estrogenic component; the norgestimate-containing COC contained 35 μg ethinylestradiol.

increase in the use of drospirenone-containing combined oral contraceptives in recent years (Figure 1). The numbers of users of low-dose gestodene and chlormadinone were too small to allow their inclusion in the multivariable analysis.

Included in the cohort were 329 995 women 12–50 years of age, accounting for a total of 431 223 use episodes and 819 749 woman-years of follow-up. Characteristics of women using second- and third-generation combined oral contraceptives and drospirenone-containing agents are presented in Table 1. During the study period, 1017 venous and arterial thrombotic events were newly diagnosed (0.24% of all use episodes): 359 cases of deep vein thrombosis (35.3%), 159 cases of pulmonary embolism (15.6%), 194 cases of transient ischemic attack (19.1%) and 305 cases of cerebrovascular accident (30.0%), for overall rates of 6.33 venous events and 6.10 arterial events per 10 000 woman-years. In the univariable analysis, hyperlipidemia, hypertension, cancer, obesity and older age were found to be significant risk factors for venous thrombosis (Table 2). The risk of arterial thrombotic events was also influenced by diabetes. The risk was highest in the first months of use.

In the multivariable analysis, with adjustment for risk factors associated with thrombotic events, the risk of venous thrombotic events was significantly greater among drospirenone users than among users of third-generation combined oral contraceptives (RR 1.43, 95% CI 1.15–1.78) (Table 3). Drospirenone was also associated with increased risk of venous thrombotic events relative to second-generation combined oral contraceptives (RR 1.65, 1.02–2.65) (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110463/-/DC1). The difference in risk between second- and third-generation combined oral contraceptives was not statistically significant (RR 1.38, 95% CI 0.90–2.11) (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110463/-/DC1). Drospirenone was used by a greater proportion of women during the second half of the study period (Figure 1). The detection of disease improved over the study period because of technologic advancement, such as the use of computed tomography angiography for diagnosis of pulmonary embolism. We therefore performed a sensitivity analysis with calendar year as a variable. This modified analysis did not change the results, which implies that the increased risk associated with drospirenone was not a result of detection bias.

The use of drospirenone was not associated with an increased risk of arterial thrombotic events (transient ischemic attack or cerebrovascular accident), relative to use of second- or third-generation combined oral contraceptives, and use of a third-generation agent was not associated with an increased risk of an arterial event, relative to use of a second-generation agent (Table 3, Appendix 1, Appendix 2).

Restricting our analysis to first-time users (i.e., with data for only the first type of combined oral contraceptive used by each individual woman) yielded similar results but with weaker associations, probably because of smaller numbers of use episodes in each group. In this subgroup, the RR values for venous thrombotic events were 1.30 (95% CI 0.98–1.72) for the comparison of drospirenone with third-generation agents, 1.67 (95% CI 0.98–2.86) for the comparison of drospirenone with second-generation agents and 1.52 (95% CI 0.94–2.46) for the comparison of third-generation with second-generation agents. There was no increased risk for arterial events.

In the secondary analysis of estrogen dosage within third-generation pills, there was no difference between formulations with 20 μg estrogen and those with 30–35 μg estrogen in terms of venous thrombotic events (RR 0.95, 95% CI 0.77–1.16) or arterial thrombotic events (RR 1.10, 95% CI 0.90–1.34).

Table 1: Characteristics of women included in the study cohort, by type of combined oral contraceptive used

Characteristic	Type of oral contraceptive*; % of use episodes†		
	Second-generation *n = 21 546*	Third-generation *n = 316 371*	Drospirenone-containing *n = 73 629*
Age, yr, mean (SD)	33 (8.4)	27 (7.6)	26 (7.2)
Medical history			
Diabetes mellitus	1.78	0.71	0.64
Hyperlipidemia	5.66	5.07	6.11
Hypertension	3.30	1.40	1.10
Cancer	0.78	0.68	0.69
Smoking			
Yes	18.48	25.21	26.28
No	73.20	62.60	60.90
Unknown	8.40	12.20	12.80
Obesity			
Yes	26.44	15.32	13.41
No	53.20	59.20	61.60
Unknown	20.30	25.50	25.00

Note: SD = standard deviation.
*In addition to the use episodes for these three categories of combined oral contraceptives, there were an additional 19 677 use episodes for low-dose gestodene and chlormadinone, but the sample sizes were too small to allow analysis.
†Unless stated otherwise.

Interpretation

Use of drospirenone-containing combined oral contraceptives was associated with a significantly increased risk of venous thrombotic events (deep vein thrombosis and pulmonary embolism) but not arterial thrombotic events (transient ischemic attack and cerebrovascular accident), relative to use of second- or third-generation combined oral contraceptives. Independent risk factors for venous thrombotic events in drospirenone users included older age, obesity and history of cancer. The risk was highest in the first four months of use.

Venous thromboembolism is a well-documented adverse event occurring with use of oral contraceptives.[4,13] Following the publication of case studies of thrombotic events in drospirenone users, this risk was studied in two manufacturer-sponsored studies. The first of these was the European Active Surveillance Study,[17] which had 58 674 women and 142 475 woman-years of follow-up, with power sufficient to exclude only a twofold or higher risk of

Table 2: Risk factors associated with venous and arterial thrombotic events among users of combined oral contraceptives

Risk factor	Woman-years*	DVT and PE		TIA and CVA	
		No. (rate per 10 000 woman-years)	RR (95% CI)	No. (rate per 10 000 woman-years)	RR (95% CI)
Age, yr					
12–19	97 161	34 (3.50)	Reference	23 (2.37)	Reference
20–24	307 850	139 (4.52)	1.29 (0.89–1.88)	100 (3.25)	1.37 (1.06–1.78)
25–29	193 552	115 (5.94)	1.70 (1.16–2.49)	84 (4.34)	1.83 (1.41–2.39)
30–34	101 578	73 (7.19)	2.06 (1.37–3.09)	78 (7.68)	3.25 (2.48–4.25)
35–39	63 020	70 (11.11)	3.18 (2.11–4.79)	84 (13.33)	5.64 (4.32–7.36)
40–44	39 549	62 (15.68)	4.49 (2.96–6.83)	72 (18.21)	7.71 (5.88–10.10)
45–50	17 016	25 (14.69)	4.22 (2.52–7.07)	58 (34.09)	14.41 (10.91–19.05)
Diabetes mellitus					
No	812 103	513 (6.32)	Reference	482 (5.94)	Reference
Yes	7 646	5 (6.54)	1.04 (0.43–2.50)	17 (22.23)	3.75 (2.83–4.95)
Hyperlipidemia					
No	758 616	466 (6.14)	Reference	437 (5.76)	Reference
Yes	61 133	52 (8.51)	1.39 (1.04–1.85)	62 (10.14)	1.76 (1.51–2.06)
Hypertension					
No	804 878	498 (6.19)	Reference	453 (5.63)	Reference
Yes	14 871	20 (13.45)	2.19 (1.40–3.42)	46 (30.93)	5.50 (4.62–6.56)
Cancer					
No	813 367	501 (6.16)	Reference	491 (6.04)	Reference
Yes	6 382	17 (26.64)	4.33 (2.67–7.01)	8 (12.54)	2.09 (1.39–3.12)
Smoking					
No	583 511	379 (6.50)	Reference	353 (6.05)	Reference
Yes	236 238	139 (5.88)	0.91 (0.74–1.11)	146 (6.18)	1.02 (0.84–1.24)
Obesity					
No	666 334	347 (5.21)	Reference	331 (4.97)	Reference
Yes	153 415	171 (11.15)	2.15 (1.72–2.67)	168 (10.95)	2.21 (1.79–2.74)
Duration of use, mo					
≤ 2	75 224	103 (13.69)	Reference	97 (12.89)	Reference
3–4	68 795	75 (10.90)	0.80 (0.59–1.07)	83 (12.06)	0.94 (0.79–1.11)
5–13	211 942	141 (6.65)	0.49 (0.38–0.63)	154 (7.27)	0.56 (0.49–0.65)
≥ 14	463 788	199 (4.29)	0.31 (0.25–0.40)	165 (3.56)	0.28 (0.24–0.32)

Note: CI = confidence interval, CVA = cerebrovascular accident, DVT = deep vein thrombosis, PE = pulmonary embolism, RR = rate ratio, TIA = transient ischemic attack.
*Data on age were missing for 26 use episodes (23 woman-years of follow-up).

venous thromboembolism. This study showed noninferiority of drospirenone compared with levonorgestrel and other oral contraceptives. The second study[18] involved 22 429 women initiating drospirenone use (with 14 081 woman-years of follow-up) and 44 858 women initiating use of "other oral contraceptives" (with 22 575 woman-years of follow-up), but again the cohort was too small to observe a difference. In 2009, the Danish national follow-up study[8] and the MEGA (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) case–control study[25] showed that drospirenone and third-generation oral contraceptives carried increased risks of venous thromboembolism, when compared with second-generation oral contraceptives; however, drospirenone was not directly compared with the third-generation contraceptives. Two recent case–control studies identified an increased risk of venous thromboembolism with drospirenone, relative to second-generation levonorgestrel.[15,16] The exact mechanism by which drospirenone might increase the risk of venous thrombotic events is unknown. An increased prothrombotic effect was demonstrated for both drospirenone and third-generation pills, compared with second-generation pills.[26]

Table 3: Multivariable analysis of risk of venous and arterial thrombotic events among users of drospirenone-containing combined oral contraceptives relative to users of third-generation combined oral contraceptives

Variable	Type of event; adjusted RR* (95% CI)	
	DVT and PE	TIA and CVA
Third-generation oral contraceptive†	Reference	Reference
Drospirenone-containing oral contraceptive‡	1.43 (1.15–1.78)	0.97 (0.74–1.26)
Age, per year	1.05 (1.04–1.06)	1.08 (1.07–1.10)
Diabetes mellitus	0.40 (0.13–1.24)	1.42 (0.78–2.59)
Hyperlipidemia	1.26 (0.94-1.69)	1.20 (0.88-1.64)
Hypertension	1.42 (0.90–2.26)	2.16 (1.49–3.13)
Cancer	3.37 (2.01–5.67)	1.39 (0.65–2.94)
Smoking	0.99 (0.80–1.23)	1.19 (0.97–1.46)
Obesity	1.72 (1.39–2.12)	1.47 (1.19–1.83)
Duration of use, per month	0.98 (0.97–0.98)	0.97 (0.96–0.98)

Note: CI = confidence interval, CVA = cerebrovascular accident, DVT = deep vein thrombosis, PE = pulmonary embolism, RR = rate ratio, TIA = transient ischemic attack.
*For the overall comparison of drospirenone-containing oral contraceptives with third-generation oral contraceptives, RR was adjusted for all variables listed in the table. For each variable-specific comparison of drospirenone-containing oral contraceptives with third-generation oral contraceptives, RR was adjusted for all other variables listed.
†No. of thrombotic events among users of third-generation combined oral contraceptives: venous = 384 (no. of woman-years of follow-up = 651 455), arterial = 382 (no. of woman-years of follow-up = 651 376).
‡No. of thrombotic events among users of drospirenone-containing combined oral contraceptives: venous = 99 (no. of woman-years of follow-up = 114 797), arterial = 66 (no. of woman-years of follow-up = 114 755).

We did not observe any increased risk of arterial events with drospirenone relative to second- or third-generation combined oral contraceptives, and no such increased risk has been found in comparisons of third-generation pills with second-generation formulations.[7,14] Drospirenone, as an aldosterone antagonist, also decreases the blood pressure slightly,[27] which might balance other factors favouring arterial thrombosis. In case–control studies, smoking was found to be a risk factor for arterial events, but not for venous thrombotic events.[6,7,13,14,16]

We found that women were most vulnerable during the first months of using combined oral contraceptives. A similar pattern was previously demonstrated for venous events[25] but not for arterial events.[6] The reason for this temporal variation in risk has not been studied. Perhaps a relatively short period is enough to expose susceptible women and to facilitate the thrombotic process.

Limitations

Our study had several limitations. There was a possibility of confounding by indication if physicians preferred to prescribe drospirenone-containing contraceptives to women with a presumed higher risk of venous thromboembolism. We adjusted for most of the known clinical risk factors for venous thromboembolism that might have led to a change in prescription, but we did not have information about family history of this condition. Restricting our analysis to first-time users, to reduce indication bias (as was suggested by an earlier study[28]), did not change the results.

With the database system used for this study, we could not verify diagnoses by examining imaging data. Overdiagnosis might have occurred among users of oral contraceptives but presumably did not occur more often with certain types of pills. Another limitation was our inability to evaluate hospital admissions or acute illnesses as predisposing factors; again, however, a thrombotic event resulting from immobilization would probably not occur more often with a specific kind of combined oral contraceptive. Finally, we could not compare minor adverse effects or advantages between the preparations that we studied.

Conclusions

Most of the available information about the risks of venous and arterial thrombotic events in users of oral contraceptives comes from case–control studies. Venous and arterial events are typically described in separate cohorts. Our cohort of women from a large, unselected population, identified through computerized records, pro-

vides insight into risk factors for thrombotic events, as well as an opportunity to compare the risks of thrombotic events between different contraceptive preparations. With the increasing use of drospirenone-containing contraceptives, it is important to raise awareness of the increased, albeit small, risk of venous thromboembolism relative to third-generation pills, especially among those who are older or obese. Further research should explore the pathophysiologic mechanism of the risk of venous thromboembolism with drospirenone.

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REVIEW ARTICLE

Hormone therapies and venous thromboembolism: where are we now?

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Deep vein thrombosis is a common disease, with an incidence of one to three per 1000 individuals per year [1]. Numerous risk factors are known, which can be divided into genetic and acquired [2]. One of the most well-known acquired risk factors is the use of female hormones, i.e. oral contraceptive use or the use of hormone replacement therapy. Apart from the use of hormones orally, other routes of administration are also available, e.g. intrauterine devices, injectables, subcutaneous implants, or skin patches. While most research regarding the risk of venous thrombosis has been conducted on oral hormone use, an increasing number of studies are focusing on the thrombotic effect of these alternative routes of administration. Here, we will review the current knowledge on the risk of venous thrombosis associated with premenopausal hormone use for contraception and with postmenopausal hormone replacement therapy. The impact of hormone use for women who have an increased risk for venous thrombosis will be discussed. These include carriers of thrombophilia, women with a positive family history of venous thrombosis, and women who have experienced venous thrombosis.

Oral contraceptives

Combined oral contraceptives (containing an estrogen and a progestagen) were first approved in the USA in 1960. It is estimated that more than 100 million women worldwide use an oral contraceptive [3].

Soon after their introduction, it became apparent that the use of these female hormones was associated with an increased risk of thrombosis. The first report of an increased risk of venous thrombosis associated with oral contraceptive use appeared in 1961 [4]. Subsequently, numerous reports have been published on the increase in thrombotic risk, indicating a two-fold to six-fold increased risk of deep vein thrombosis associated with current oral contraceptive use [5–11].

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Most currently available oral contraceptives are combined preparations containing both an estrogen (i.e. ethinylestradiol [EE2]) and a progestagen. Numerous types of oral contraceptives are available, containing different doses of estrogen and different types of progestagen. The first available preparations contained a high dose of the estrogen EE2. However, after the reported increased thrombotic risk associated with combined oral contraceptive use was attributed to the amount of estrogen in the contraceptive pill, the dose of estrogen was reduced stepwise. The initial lowering of the estrogen dose from $>$ 50 μg to 30 μg was indeed shown to be associated with a clear decrease in the risk of venous thrombosis [12,13]. In two recently published studies, it was shown that a further decrease in the estrogen dose to 20 μg led to an additional lowering of the risk of venous thrombosis [10,11]. In the MEGA study, a large case–control study, we showed that, after adjustment for type of progestagen, oral contraceptives containing 20 μg of estrogen were associated with a slightly decreased risk of venous thrombosis as compared with oral contraceptives containing 30 μg of estrogen (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.5–1.2) [10]. The study by Lidegaard *et al.* [11] also showed that a reduction in estrogen dose from 30 or 40 to 20 μg was associated with an 18% reduction in the risk of venous thrombosis [11].

The progestagens in combined oral contraceptives appear to counter the prothrombotic effect of the estrogens. Numerous different types of progestagens with different chemical compositions are available. The oldest types of progestagens, i.e. the first-generation progestogens, were lynestrenol and norethisterone. Nowadays, these first-generation progestagens are not used very often. Second-generation oral contraceptives, which are widely used, contain the progestagens levonorgestrel or norgestrel. Newer types of oral contraceptives, i.e. the third-generation oral contraceptives, contain the progestagens gestodene or desogestrel. Norgestimate is categorized as a third-generation progestagen. However, as it is, in part, converted to levonorgestrel, it may metabolically belong more to the second-generation progestagens. Preparations containing cyproterone acetate are used for the treatment of acne vulgaris, seborrhea, or mild hirsutism, and have an antiovulatory action similar to that of a progestagen. Preparations

containing drospirenone, which is an antimineralcorticoid, also inhibit ovulation.

There is evidence that the different progestagens counter the prothrombotic effect of estrogens differently, and are therefore associated with different venous thrombotic risks [14]. The risk of venous thrombosis was reported to be increased for users of the third-generation oral contraceptives as compared with users of the second-generation oral contraceptives [15]. However, this finding was not confirmed in all studies. The difference in thrombotic risk between third-generation and second-generation oral contraceptives has been the subject of a long ongoing debate, with non-believers explaining the difference in risk by bias and confounding. However, a large meta-analysis countered most of these arguments of bias and confounding, and demonstrated an increased risk of thrombosis for third-generation as compared with second-generation oral contraceptives; subsequently, several other studies confirmed this finding [16]. Furthermore, the results of studies on the effects of different types of oral contraceptives on the hemostatic system were in line with these findings, i.e. showing that there was a more prothrombotic risk profile, including more activated protein C (APC) resistance, associated with third-generation oral contraceptives than with second-generation oral contraceptives [17–21].

Oral contraceptives containing cyproterone acetate have been associated with a highly increased risk of venous thrombosis or fatal pulmonary emboli; however, this was not confirmed by all studies [22–24]. Recent studies have indicated that these oral contraceptives are associated with an elevated thrombotic risk as compared with oral contraceptives containing levonorgestrel [10,11].

EE2 with drospirenone has been approved as an oral contraceptive in all European Union countries since 2000. Shortly after their introduction, several case reports indicated a highly increased risk of venous thrombosis associated with these oral contraceptives [25–28]. This high risk of thrombosis was confirmed by our large case–control study and a large follow-up study, which both reported a higher risk of thrombosis as compared with oral contraceptives containing levonorgestrel or gestodene [10,11].

The so-called mini-pill is an oral progestagen-only preparation. Whereas oral progestagen-only preparations are associated with an increased risk of venous thrombosis when used for therapeutic reasons (containing different progestagens or higher doses of the progestagens used in oral contraceptives) [29,30], oral progestagen-only preparations used for contraceptive reasons appeared to be, at most, associated with a mildly increased risk of thrombosis [30,31]. More recently, Lidegaard *et al.* [11] have shown that oral progestagen-only oral contraceptives do not appear to be associated with an increased risk of venous thrombosis, regardless of the type of progestagen: desogestrel-containing progestagen-only preparations, rate ratio (RR) 1.1, 95% CI 0.4–3.4; norethisterone-containing or levonorgestrel-containing preparations, RR 0.6, 95% CI 0.3–1.0.

Effect of oral contraceptive use on the coagulation system

Oral contraceptive use is associated with changes in the levels of coagulation factors, leading to a predisposition to venous thrombosis. Oral contraceptive use is associated with increased resistance to the natural anticoagulant activity of APC [32]. In line with the increased thrombotic risk associated with oral contraceptives containing desogestrel as compared with levonorgestrel, these third-generation pills induce more pronounced APC resistance than the second-generation preparations [17,18,33]. The highest APC resistance, resulting in the most thrombotic tendency of the coagulation system, was found in women using oral contraceptives containing cyproterone acetate [33]. Similar differences between these types of oral contraceptive were observed in levels of anticoagulant proteins, such as protein S and tissue factor pathway inhibitor (TFPI); that is, oral contraceptives associated with a higher risk had lower levels of both free protein S and free TFPI [20,34]. Furthermore, the changes induced in coagulation factors and fibrinolytic parameters differ between second-generation and third-generation oral contraceptives [19,21].

From the results of these studies, it is clear that the use of oral contraceptives is associated with a procoagulant risk profile. Still, one might question whether these intermediate endpoints, e.g. markers of hemostasis that have been related to the risk of venous thrombosis, indicate a true increased risk of venous thrombosis associated with hormone use. However, in line with observed differences in the risk of venous thrombosis associated with different progestagens, all studies using these intermediate endpoints point in the same direction, with a more thrombotic risk profile in users of the third-generation oral contraceptives containing desogestrel or gestodene, and in users of oral contraceptives containing cyproterone acetate or drospirenone, than in users of oral contraceptives containing levonorgestrel.

Non-oral contraceptives

Oral contraceptives are the most frequently used hormonal contraceptives. However, other routes of administration of hormonal contraceptives are also available, e.g. intrauterine devices, injectables, subcutaneous implants, or skin patches. The risk of venous thrombosis associated with these non-oral contraceptive methods has been studied to a much lesser extent than that associated with oral contraceptives.

In the following paragraphs, we provide an overview of the available information on the risk of venous thrombosis associated with depot medroxyprogesterone (DMPA) injectable progestagen-only contraceptives, the hormone-releasing intrauterine device, the hormonal contraceptive ring, the hormonal contraceptive patch, and the hormonal contraceptive implant.

Injectable DMPA progestagen-only contraceptives

DMPA is a long-acting injectable progestagen-only contraceptive. In 1998, the World Health Organization reported a small increase in thrombotic risk associated with the use of injectable

progestagen (medroxiprogesterone)-only contraceptives (OR 2.2; 95% CI 0.7–7.3) [31]. Although, also in the MEGA study, a small number of women used DMPA-only contraceptives, we found a clearly increased risk of venous thrombosis associated with these contraceptives as compared with non-use (OR 3.6; 95% CI 1.8–7.1) [35]. Other studies mainly investigated intermediate endpoints, e.g. coagulation factors and APC resistance. In contrast to these clinical findings, Walsh *et al*. reported a decrease in sex hormone-binding globulin (SHBG) level, a probable marker of the risk of venous thrombosis [36,37]. Several studies that assessed the effect of DMPA-only contraceptives on coagulation or inflammation markers reported little or no effect [36,38,39].

Levonorgestrel-releasing intrauterine device

The levonorgestrel-releasing intrauterine device or system is a T-shaped plastic contraceptive that is inserted into the uterine cavity [40]. After insertion of a levonorgestrel-releasing intrauterine device, plasma levels of levonorgestrel are 150–200 pg mL^{-1} in the peripheral blood [41], as compared with a maximal level of 800 pg mL^{-1} during the use of a 30-μg levonorgestrel-only pill. The use of the levonorgestrel-releasing intrauterine device was not associated with an increased risk of venous thrombosis in a large follow-up study on venous thrombosis (RR 0.9; 95% CI 0.6–1.3) or in the MEGA case–control study (OR 0.3; 95% CI 0.1–1.1) [11,35]. Furthermore, with the use of the thrombin generation-based APC resistance assay, higher sensitivity to APC in women 3 months after the insertion of the levonorgestrel-releasing intrauterine device than before the insertion was observed, suggesting a low thrombosis risk, whereas there was no change after insertion of a copper intrauterine device [42]. The decrease in APC resistance appeared to be most pronounced in women who switched from a combined oral contraceptive to the levonorgestrel-releasing intrauterine device.

Transdermal patches and hormone-releasing vaginal ring

New types of combined contraceptive are the transdermal patch and the hormone-releasing vaginal ring. The contraceptive patch was designed to deliver 20 μg of EE2 and the contraceptive vaginal ring 15 μg EE2 per day. Both types of contraceptive contain a third-generation progestagen. The transdermal patch contains norelgestromin, the primary active metabolite of norgestimate, and the vaginal ring contains etonogestrel, a metabolite of desogestrel [43].

So far, little information is available regarding the thrombotic risk associated with these contraceptive methods. As compared with oral contraceptives containing norgestimate, for users of the transdermal patch, the reported risks of venous thrombosis varied between no increase (OR 1.0; 95% CI 0.7–1.5) to a more than two-fold increase (incidence rate ratio 2.2; 95% CI 1.3–3.8) [44–46].

Further studies assessing the effect of these contraceptive methods on the risk of venous thrombosis mainly used intermediate endpoints. Again, findings were contradictory. In a randomized crossover trial, similar adverse effects on vascular risk markers with an oral contraceptive containing norgestimate and with the contraceptive patch were observed [47]. Other studies, however, reported more prothrombotic effects associated with the use of the hormonal patch than with different types of oral contraceptives [48–50].

Even less information is available on the risk of venous thrombosis associated with the vaginal ring. As compared with combined oral contraceptive use (mainly third-generation oral contraceptives), a beneficial effect associated with the use of the vaginal ring was reported [49], whereas in a different study, the vaginal ring was associated with more resistance to APC and a higher level of SHBG than the use of levonorgestrel-containing contraceptives [50,51].

Hormonal implants

The etonogestrel implant is a progestagen-only contraceptive that is implanted under the skin. Etonogestrel is an active metabolite of the third-generation progestagen desogestrel. The delivery dose of progestagen varies over time, from 60–70 μg d^{-1} in the first weeks of use to 25–30 μg d^{-1} after 3 years. Very little is known about the thrombogenicity of the etonogestrel implant. Lindqvist *et al*. [52] reported in 2003 that etonogestrel implant use was not related to hypercoagulable changes in the anticoagulant system or the prothrombotic factors V, VII, and VIII. In a study by Vieira *et al*. [53], it was reported that the etonogestrel-releasing implant was associated with a reduction in APC resistance and the levels of several prothrombotic factors (prothrombin, FVII, FX, and F_{1+2}), whereas plasminogen activator inhibitor-1 and FXI levels were increased. However, all factors remained within the normal range, suggesting that the use of an etonogestrel implant is not associated with a prothrombotic risk profile.

An overview of recent estimates of the thrombotic risks associated with the use of different types of hormonal contraceptives is shown in Table 1.

Hormone replacement therapy

Until the late 1990s, hormone replacement therapy was considered to be an effective measure to improve cardiovascular risk factors, in particular lipid profiles [54], and protect women against the postmenopausal rise in the incidence of arterial cardiovascular disease [55,56]. However, large, randomized controlled trials showed that hormone replacement therapy does not prevent arterial cardiovascular disease, and even has a detrimental effect in the first year of use [57–59]. Nowadays, the indication for hormone replacement therapy is limited to improving quality of life by alleviating perimenopausal complaints, and it should be given at the lowest possible dose for the shortest possible duration [60].

Like contraceptive hormones, hormone replacement therapy is available in various forms. It generally provides a low dose of estrogen, most often together with progesterone or a progestin.

Table 1 Recent estimates of relative risks associated with use of contraceptives

	MEGA case–control study [10,35], odds ratio (95% CI)	Danish National cohort study [11], rate ratio (95% CI)	WHO [31], odds ratio (95% CI)	Jick *et al.* [44], odds ratio (95% CI) Cole *et al.* [45], incidence rate ratio (95% CI)
Combined oral contraceptives				
Estrogen 30 μg and noresthisterone	3.9 (1.4–10.6)			
Estrogen 30 μg and levonorgestrel	3.6 (2.9–4.6)	2.02 (1.75–2.34)*		
Estrogen 37.5 μg and lynestrenol	5.6 (3.0–10.2)			
Estrogen 30 μg and norgestimate	5.9 (1.7–21.0)			
Estrogen 30 μg and desogestrel	7.3 (5.3–10.0)	3.55 (3.30–3.83)*		
Estrogen 30 μg and gestodene	5.6 (3.7–8.4)			
Estrogen 30 μg and drospirenone	6.3 (2.9–13.7)	4.00 (3.26–4.91)*		
Estrogen 35 μg and cyproterone acetate	6.8 (4.7–10.0)			
Progestagen-only				
Pills				
Levonorgestrel 30 μg or norethisterone 350 μg		0.59 (0.33–1.04)		
Desogestrel 75 μg		1.10 (0.35–3.41)		
Progestagen-only injectable	3.6 (1.8–7.1)		2.2 (0.7–7.3)	
Levonorgestrel-releasing intrauterine device	0.3 (0.1–1.1)	0.89 (0.64–1.26)		
Transdermal Patches†				1.0 (0.7–1.5) [44] to 2.2 (1.3–3.8) [45]

CI, confidence interval; WHO, World Health Organization.
All compared with non-use unless stated otherwise: *with 20–40 μg of estrogen; †as compared with oral contraceptives containing norgestimate. No risk estimates are available for the vaginal ring or hormonal implants.

Conjugated equine estrogens are derived from the urine of pregnant mares, contain several biologically active estrogen compounds, and are the most widely used components of hormone replacement therapy. Esterified estrogens are synthetic and fabricated from soybean and yam. Unopposed estrogen is restricted to women who have had a hysterectomy, because of the increased risk of endometrial cancer. Hormone replacement therapy can be taken by mouth, or delivered via patches, creams, gels or, more rarely, injection. Dosage can be varied cyclically, with estrogens being taken daily and progesterone or progestins taken for about 2 weeks every 1 or 2 months (sequentially combined hormone replacement therapy), or a constant dosage being used, with both types of hormones taken daily (continuous combined hormone replacement therapy).

Both observational studies and randomized controlled trials have consistently shown an approximately two-fold to three-fold increased risk of venous thrombosis in users of hormone replacement therapy [58,61–63]. Most early studies of venous thromboembolism in users of hormone replacement therapy were performed among women using conjugated equine estrogens alone or with medroxyprogesterone acetate. Although, in the Women's Health Initiative study, estrogen-only hormone replacement therapy in women without a uterus was associated with only a small increase in the risk of venous thrombosis in the first 2 years of use, and the risk was less than with the combination of estrogen plus progestin (hazard ratio (HR) 1.47; 95% CI 1.06–2.06) [64], this was not confirmed in a recent meta-analysis of both observational studies and randomized controlled trials [65]. Furthermore, a case–control study suggested that esterified estrogen is not associated with an increased risk of venous thrombosis [66,67].

Only a limited number of observational studies have assessed the risk of venous thrombosis associated with transdermal estrogen use, with inconsistent results, ranging from no increased risk to a point estimate of an approximately two-fold increased risk [61,68–71]. After meta-analysis, the pooled risk estimate for a first episode of venous thrombosis associated with transdermal estrogen was 1.2 (95% CI 0.9–1.7) [65]. Since this meta-analysis, other studies finding no increased risk of venous thrombosis in users of transdermal estrogen have been published [71,72]. An analysis in the UK's General Practice Research Database found no increased risk for venous thrombosis in users of transdermal estrogen with or without progestin (adjusted rate ratio 1.01 [95% CI 0.89–1.16], and 0.96 [95% CI 0.77–1.20], respectively) [71]. A recent large French epidemiological study showed that, although the overall risk of idiopathic venous thrombosis was not increased in users of transdermal hormone replacement therapy (HR 1.1; 95% CI 0.8–1.8), transdermal estrogen combined with norpregnane derivatives, in particular, increased the risk of idiopathic venous thrombosis as compared with other progestins [72].

Tibolone is a synthetic steroid whose metabolites have estrogenic, progestagenic and androgenic activities, and is also used as hormone replacement therapy. Trials that primarily assessed the effect of tibolone on osteoporotic fractures and breast cancer did not show an increased risk for venous thrombosis (HR 0.57, 95% CI 0.19–1.69) [73,74]. Both trials, however, showed other harmful effects, i.e. a higher risk of stroke [73] or an increased risk of recurrent breast cancer [74], in women treated with tibolone. The absence of an increased risk of venous thrombosis was also

observed in the UK's General Practice Research Database [71].

Effect of hormone replacement therapy on the coagulation system

Oral hormonal replacement therapy has very similar effects on coagulation and fibrinolysis variables as the use of oral contraceptives, all pointing towards a prothrombotic effect. In particular, oral estrogen-containing hormone replacement therapy decreases the levels of the natural coagulation inhibitors antithrombin, protein C, and protein S, and increases resistence to APC [75–77]. On the other hand, a systematic review of trials comparing the effects of transdermal hormone replacement therapy with oral hormone replacement therapy on markers concluded that these effects are absent or at least lower with transdermal hormone replacement therapy use [78]. The effects of tibolone on markers of thrombosis risk are also less than with oral hormone replacement therapy or absent [75–77].

Implications for prescribing in clinical practice – hormonal contraceptives

Baseline risk of venous thrombosis for women of fertile age

The absolute risk of venous thrombosis increases sharply with age, in particular after the age of 45 years [79,80]. Considering fertile women, the incidence rate of first venous thrombosis in a large Norwegian cohort study ranged from 0.36 per 1000 person-years in women aged 20–24 years to 0.37 and 0.82 per 1000 person-years in women aged 40–44 and 45–49 years, respectively [1]. If no valid observations on the absolute risk are available, the reported relative risk increases caused by the use of oral contraceptives should be multiplied by this baseline risk, which varies considerably with age. Even a small increase in the risk of venous thrombosis is relevant, given the huge number of women who use oral contraceptives worldwide, but these risks need to be balanced against the beneficial effects in terms of avoidance of unintended pregnancies [81].

Women with hereditary thrombophilia

The presence of hereditary thrombophilia strongly increases the risk of venous thrombosis associated with the use of oral contraceptives. For instance, as compared with women who do not use oral contraceptives and do not carry the FV Leiden mutation, the risk was found to be increased 35-fold in heterozygous women using oral contraceptives [6]. This risk increase has led to questions regarding the need to screen young women for FV Leiden prior to oral contraceptive use. However, in the absence of a clear family history of venous thrombosis, i.e. in the general population, where approximately 5% of women carry the mutation, the number needed to be tested to withhold oral contraceptives in carriers and to prevent a single death from pulmonary embolism would exceed half a million [82].

The situation may be different for women who have a positive family history of venous thrombosis. In clinical practice, the question often arises of whether oral contraceptives are contraindicated, and whether testing for thrombophilia would influence this decision [83]. It is important to note that selection bias is apparent in the observed risks of venous thrombosis in thrombophilia, meaning that thrombophilic individuals who are selected from families with a tendency to venous thrombosis have a higher risk than individuals with the same defect who have been identified through population testing [84]. Thus, when assessing the risk of venous thrombosis in an individual woman, it is important to clearly define the population to which she belongs; that is, does she have a personal or family history of venous thrombosis, or was she identified because of routine screening or other health problems (e.g. because of recurrent miscarriage)? Absolute risk estimates for asymptomatic family members of patients with venous thrombosis and known hereditary thrombophilia were obtained in several family studies. Carriers have a two-fold to 10-fold increased risk of venous thrombosis as compared with their female relatives who do not carry the defect, depending on the type of thrombophilia [85–94]. These kinds of family study have yielded useful risk estimates in this particular group of women while they are using oral contraceptives. In Table 2, the absolute risks per year of use of oral contraceptives and per type of thrombophilia are shown. Estimates obtained in well-sized retrospective studies are useful and valid, as the observations were made in women who were still unaware of their thrombophilic status and thus reflect a real-life situation.

For asymptomatic women with antithrombin, protein C or protein S deficiency and at least one first-degree or second-degree relative with venous thrombosis, the risk was found to be 4.3% (95% CI 1.4–9.7) per year of oral contraceptive use. This means that, within symptomatic families with these defects, approximately 25 (95% CI 10–66) women with thrombophilia need to refrain from oral contraceptive use to prevent one venous thrombosis event per year (assuming a population baseline risk of one in 10 000 in women not carrying a thrombophilic defect, which may not be completely realistic), and thus 50 (95% CI 20–132) women need to be

Table 2 Absolute risk of venous thrombosis in asymptomatic carriers of thrombophilia, estimated in retrospective family studies

	Oral contraceptive use (% per year of use, 95% CI)	Overall* (% per year, 95% CI)
Hereditary deficiencies of antithrombin, protein C, or protein S	4.3 (1.4–9.7) [85]	1.5 (0.7–2.8) [85]
Factor V Leiden	0.5 (0.1–1.4) [85,86]	0.5 (0.1–1.3) [85,86]
Prothrombin 20210A	0.2 (0.0–0.9) [88]	0.4 (0.1–1.1) [88]
Elevated FVIII:c	0.6 (0.2–1.5) [89]	1.3 (0.5–2.7) [89]
Mild hyperhomocysteinemia	0.1 (0.0–0.7) [90]	0.2 (0.1–0.3) [90]

CI, confidence interval.
*All carriers, including men and women of all ages, provoked and unprovoked venous thrombosis.

tested. For the milder thrombophilias, in particular those caused by FV Leiden and the prothrombin 20210A mutation, the risk estimates are more precise, because of the much higher prevalence of these mutations. For these gain-of-function mutations, approximately 200 (95% CI 77–1000) women need to refrain from oral contraceptive use to prevent one venous thrombosis event per year, and 400 (95% CI 152–2000) need to tested. Whether these numbers justify testing patients with venous thrombosis for thrombophilia and subsequent family testing is a matter of opinion rather than science [83,95,96].

Women with a positive family history of venous thrombosis

A family history of venous thrombosis is a reason for concern, but the sensitivity or predictive value appears to be very low. In a small study of 50 women who had an objectively diagnosed episode of venous thrombosis, only 16% had a positive family history [97]. In the large MEGA case–control study, 31% of 1605 patients with venous thrombosis had at least one first-degree relative who also had had venous thrombosis. A positive first-degree family history increased the risk of venous thrombosis from 2.2-fold (any relative) to 3.9-fold (more than one relative) [98]. As expected, also among carriers of thrombophilia, a positive family history increased the risk by 2.7-fold to 4.9-fold, thus interacting with the effect of the genetic risk factor alone.

Women with a personal history of venous thrombosis

According to our opinion, oral contraceptives should not be prescribed to women with a history of venous thrombosis [81]. The evidence for an adverse effect is indirect: venous thrombosis that occurred during oral contraceptive use was less likely to recur when the oral contraceptives were stopped [99]. In a prospective study of 272 women after a first episode of venous thrombosis, the recurrence rate was 1.3% per person-year in women who did not use oral contraceptives, as compared with approximately 3% per year in those who used oral contraceptives at some point during follow-up [100]. There was no apparent difference between women who used oral contraceptives at the time of their first venous thrombosis event and those who did not.

It is noteworthy that there is no indication to immediately discontinue oral contraceptives in women who are diagnosed with venous thrombosis. Anticoagulants effectively prevent the extension and recurrence of venous thrombosis [101], whereas effective contraception is crucial while women are using vitamin K antagonists, because these agents may lead to warfarin embryopathy [102]. Thus, oral contraceptives may be continued until shortly before discontinuation of anticoagulant therapy.

As effective contraception is vital for many women of fertile age, and hormonal methods are more effective than barrier methods and female tubal ligation, hormone-releasing intrauterine devices are often advised for women who have a history of venous thrombosis and have discontinued anticoagulant therapy. The results from the MEGA study and the large Danish cohort study suggest that this is, indeed, a safe contraceptive method with regard to the risk of venous thrombosis, although this study was limited to first thrombotic events, and the safety has not been tested in women with a history of venous thrombosis. Similarly, the risk for a first venous thrombosis is not clearly increased for progestagen-only pills, although the upper limit of the CI, particularly for the desogestrel-containing progestagen-only pill, does not exclude a significant 3.41-fold increase in risk.

Implications for prescribing in clinical practice – hormone replacement therapy

Given the much higher baseline risk of women who are exposed to hormone replacement therapy, because of their higher age, the impact of a relative risk increase on the absolute risk of venous thrombosis is markedly higher than in oral contraceptive users. In women aged 50–54 years, the incidence rate for a first venous thrombosis was 1.17 per 1000 person-years [1]. In the HERS trial, in which postmenopausal women younger than 80 years with confirmed coronary artery disease were included, the incidence rate for a first venous thrombosis was 6.3 per 1000 person-years in women on hormone replacement therapy, as compared with 2.2 per 1000 person-years in women using placebo (HR 2.89, 95% CI 1.50–5.58) [57]. In the WHI study, these rates were 3.4 and 1.6, respectively (HR 2.11, 95% CI 1.58–2.82) [59].

Women with hereditary thrombophilia or a positive family history

Risk estimates for thrombophilic women using hormone replacement therapy are less precise, because of the relatively small numbers of European women who used to take hormone replacement therapy and were included in the types of retrospective study that are informative for this situation. Thus, the known relative risks for the various thrombophilias should be multiplied by the baseline risk in the relevant age category. In general, women known to be carriers of thrombophilia, or with a positive first-degree family history of venous thrombosis, should be advised not to take hormone replacement therapy to relieve perimenopausal symptoms [65].

Guidelines recommend that hormone replacement therapy should be given at the lowest dose and for the shortest duration possible. On the basis of the current evidence, transdermal estrogen or tibolone should be preferred over combined hormone replacement therapy.

Women with a personal history of venous thrombosis

Hormone replacement therapy is contraindicated in women with a history of venous thrombosis. A randomized controlled trial of combined hormone replacement therapy in women with prior venous thrombosis was terminated early because of a marked difference in risk of recurrence between the women

who were given combined hormone replacement therapy and those given placebo (10.7% vs. 2.3%) [103]. To our knowledge, the effects of other routes of hormone replacement therapy have not been formerly tested in women who have a history of venous thrombosis.

Conclusions

All oral estrogen-containing hormonal regimens, used either for contraception or for hormone replacement postmenopausally, increase the risk of venous thrombosis. Therapeutic doses of progestagen-only preparations have a similar effect. Increases in venous thrombosis risk are modulated by dose of estrogen and type of progestagen. Although data are not abundant, current knowledge indicates that the risk of venous thrombosis is not clearly increased for the levonorgestrel-containing intrauterine device, transdermal estrogen, and tibolone. Hemostatic and fibrinolysis markers, most notably assays that measure resistance to APC, have shown effects of hormones that are in the same direction as epidemiologic data obtained with venous thrombosis as a clinical endpoint.

In order to minimize the risk of venous thrombosis associated with oral contraceptives, prudent prescribing in women who have an increased risk is the only option. However, solely having a risk factor may not be an absolute contraindication, but offers the possibility for women to make an informed decision about the use of this contraceptive method.

In our opinion, a personal history of venous thrombosis should be considered a contraindication for combined oral contraceptive use. Carriership of thrombophilia, in particular a deficiency of antithrombin, protein C or protein S, and, to a much lesser extent, FV Leiden or the prothrombin 20210A mutation, warrants counseling and balancing of benefits and risks, in which the family history of venous thrombosis should be taken into account. A strong family history in the absence of a known inherited thrombophilic defect warrants caution as well. A levonorgestrel-releasing intrauterine device does not increase the risk of a first venous thrombosis, an observation that may be extrapolated in clinical practice to offer women with a history of venous thrombosis a very effective contraceptive method. Similarly, progestagen-only pills could be considered, although risk estimates are less solid, particularly for desogestrel-containing progestagen-only pills. Hormone replacement therapy is contraindicated in women with a personal history of venous thrombosis, and should be discouraged in asymptomatic women with thrombophilia. If it is considered in exceptional cases, transdermal administration of estrogen or tibolone is preferred over oral hormone replacement preparations containing estrogen and progestin.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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RESEARCH

Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9

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Abstract

Objective To assess the risk of venous thromboembolism from use of combined oral contraceptives according to progestogen type and oestrogen dose.

Design National historical registry based cohort study.

Setting Four registries in Denmark.

Participants Non-pregnant Danish women aged 15-49 with no history of thrombotic disease and followed from January 2001 to December 2009.

Main outcome measures Relative and absolute risks of first time venous thromboembolism.

Results Within 8 010 290 women years of observation, 4307 first ever venous thromboembolic events were recorded and 4246 included, among which 2847 (67%) events were confirmed as certain. Compared with non-users of hormonal contraception, the relative risk of confirmed venous thromboembolism in users of oral contraceptives containing 30-40 µg ethinylestradiol with levonorgestrel was 2.9 (95% confidence interval 2.2 to 3.8), with desogestrel was 6.6 (5.6 to 7.8), with gestodene was 6.2 (5.6 to 7.0), and with drospirenone was 6.4 (5.4 to 7.5). With users of oral contraceptives with levonorgestrel as reference and after adjusting for length of use, the rate ratio of confirmed venous thromboembolism for users of oral contraceptives with desogestrel was 2.2 (1.7 to 3.0), with gestodene was 2.1 (1.6 to 2.8), and with drospirenone was 2.1 (1.6 to 2.8). The risk of confirmed venous thromboembolism was not increased with use of progestogen only pills or hormone releasing intrauterine devices. If oral contraceptives with desogestrel, gestodene, or drospirenone are anticipated to increase the risk of venous thromboembolism sixfold and those with levonorgestrel threefold, and the absolute risk of venous thromboembolism in current users of the former group is on average 10 per 10 000 women years, then 2000 women would need to shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel to prevent one event of venous thromboembolism in one year.

Conclusion After adjustment for length of use, users of oral contraceptives with desogestrel, gestodene, or drospirenone were at least at twice the risk of venous thromboembolism compared with users of oral contraceptives with levonorgestrel.

Introduction

The influence of specific types of combined oral contraceptives on the risk of thrombotic events remains the most important safety issue for these products. Several studies have investigated the relation between combined oral contraceptives and venous thromboembolism,[1-21] including newer large scale studies.[17-19] These new studies showed an increased risk of venous thromboembolism in current users of combined oral contraceptives and a decreasing risk by both time of use and decreasing oestrogen dose.

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International classification of diseases codes used in study
Codes for excluded diagnoses
Appendix 1: allocation rules applied in analysis
Appendix 2: rate ratios of venous thromboembolism with use of oral contraceptives with 3-40 µg ethinylestradiol; different exposure line formation
Appendix 3: rate ratios of venous thromboembolism with use of oral contraceptives with 3-40 µg ethinylestradiol; three sub-periods and during 2001-9
Appendix 4: rate ratios of venous thromboembolism with use of oral contraceptives with 3-40 µg ethinylestradiol; different user categories during 2001-9

Results on the significance of the type of progestogen differed. Ten studies reported an increased relative risk of venous thromboembolism among users of oral contraceptives with desogestrel or gestodene compared with those containing levonorgestrel,[1 2 4-7 9 13 17 18] a difference that was significant in eight of the studies,[1 2 4-6 13 17 18] whereas a further three studies found no difference.[8 14 19] In addition, four studies reported a higher relative risk of venous thromboembolism among users of combined oral contraceptives with drospirenone compared with those containing levonorgestrel,[17 18 20 21] whereas two other studies reported no difference.[14 19] Consequently, the European Medicines Agency asked our study team to revisit the Danish registry data for additional analyses, with a focus on differences in risk of venous thromboembolism between users of oral contraceptives with drospirenone and those with levonorgestrel in the period after the launch of drospirenone in 2001.

We assessed the relative and absolute risk of first time venous thromboembolism for users of oral contraceptives with different progestogens, different doses of oestrogen, and according to certainty of the diagnosis of venous thromboembolism. We also assessed the risk of venous thromboembolism in users of progestogen only pills and hormone releasing intrauterine devices.

Methods

We carried out a nationwide historical cohort study of all Danish women aged 15-49 during 1995-2009. The study focused on the period after the launch of combined oral contraceptives containing drospirenone in 2001. Information on the 1.2 million women of reproductive age in Denmark was collected from four sources of data: Statistics of Denmark, the national registry of patients, the national cause of death registry, and the national registry of medicinal products.

Statistics of Denmark: identification of women

Statistics of Denmark keeps records of all Danish citizens. A unique personal identification number is given to each citizen at birth or immigration. This number is used in public registries, enabling reliable linkage of data between registries. From Statistics of Denmark we identified Danish women in the age category 15-49 from 1 January 1995 to 31 December 2009. We also obtained data on length of schooling, ongoing or finished education, vital status, and emigration. Women were censored at death or emigration.

National registry of patients: end points

The national registry of patients has collected discharge diagnoses from all public and private hospitals in Denmark since 1977. From 1994 the registry has used diagnoses as coded in the ICD-10 (international classification of diseases, 10th revision). The web extra lists the codes used in this study.

To include first events only we excluded women with any type of venous or arterial thrombotic event before the study period (1977-2000). We also excluded women with malignant gynaecological disease, cancer of abdominal organs or breast, and lung or haematological cancer before the study period or we censored them at the time of diagnosis if any of these diseases occurred during the study period.

Surgery—the national registry of patients also records surgical codes from public and private hospitals. We excluded women at baseline who had undergone bilateral oophorectomy, unilateral oophorectomy on two occasions, hysterectomy, or sterilisation, or we censored them at the time of surgery.

Pregnancy—from the national patient registry we identified pregnancy outcomes and gestational age at termination (see web extra). We censored a woman's experience during pregnancy, as calculated from conception and three months after delivery (one month for abortions and ectopic pregnancies), from study follow-up.

Coagulation disturbances—we also excluded women with a coagulation disorder the first time such a diagnosis was recorded in the national patient registry, including Leiden factor V heterozygote or homozygote, prothrombin 20210 heterozygote or homozygote, protein C insufficiency, protein S insufficiency, and anti-thrombin III insufficiency.

National cause of death registry

As only those women admitted to hospitals would have been recorded in the national registry of patients, we also checked the national cause of death registry for lethal events from venous thromboembolism (see web extra table) during the study period (updated to 2008).

National registry of medicinal products: data on contraceptive usage

Since 1 January 1994 the national registry of medicinal products has collected information about filled prescriptions, including oral contraceptives. From this database we obtained daily updated information on redeemed prescriptions of oral contraceptives from 1995 to 2009. We categorised the products according to progestogen type, oestrogen dose, and length of use. Oral contraceptives with levonorgestrel and 30-40 µg ethinylestradiol were subcategorised as phasic preparations with 30-40 µg ethinylestradiol or combined pills with 30 µg ethinylestradiol.

A stepwise analysis was undertaken, including successively each of the following usage categories: starting use, defined as use of combined oral contraceptives with no history of hormonal contraception before the first prescription; new use, defined as starting use after a pause of at least 12 weeks for any prescription of a hormonal contraceptive; restarted use, defined as oral contraceptive use after a pause of 4-11 weeks; and switched use, defined as use of one preparation of oral contraceptive followed by use of a different preparation, within a pause of less than four weeks.

Duration of use

We estimated the duration of new use from the prescribed defined daily doses calculated from the date of prescription until the end date of defined daily doses of the last redeemed prescription or date of a study event. The duration of restarted use was defined as the period from the date of restart until the end date of defined daily doses of the last filled prescription or the date of a study event. Duration of switched use was calculated as the sum of use before switch and current use on the new preparation, until end date of defined daily doses of the last filled prescription or date of a study event. Thus the same woman could have several episodes of new, restarted, and switched use.

To account for use before the start of the study (left censoring bias), we assessed the use of oral contraceptives before the study period back to 1995. In doing this we allocated continuous users of hormonal contraceptives to the relevant category for duration of use on 1 January 2001.

Rules for allocation of person time to usage groups

We used four overall rules (see web extra for further details) to allocate products to each usage group:

Rule 1—a woman's time at risk for venous thromboembolism was allocated to the oral contraceptive preparation prescribed from the date it was redeemed until the end date calculated from defined daily doses. If no new prescription was redeemed by four weeks after this end date, then we changed the woman's usage status to previous user. However, if the woman got a new prescription for the same product within four weeks, we considered it continuous current use.

Rule 2—if a woman got a new prescription for the same product before the end date of the previous prescription, we summarised the prescribed defined daily doses as continuous current use.

Rule 3—if a woman cashed a new prescription for a different product before the end date of the previous prescription, we excluded the first four weeks after filling the new prescription in either oral contraceptive category, because it would be difficult to know which of the two products would account for venous thromboembolism. After four weeks we categorised such the woman as a switched user of the new preparation. In this case we estimated the duration of use from the first prescription of the previous preparation.

Rule 4—if a prescription ended and thereafter a woman redeemed a prescription for a new oral contraceptive after more than four weeks and less than 12 weeks, we estimated the episode of restarted use from the date when the new prescription was filled. The gap was considered as previous use.

Confounding

Social class

We used length of schooling and level of education as proxies for social class. Four strata were applied: women with elementary school education only (9-10 years of schooling), women with ongoing or completed high school education (2-3 years after elementary school), women with high school and ongoing or ended middle education (3-4 years after high school), and women with high school and ongoing or ended long education (5-6 years after high school). A fifth category included women lacking information on education, typically the youngest.

Body mass index

The type of oral contraceptive could be related to body mass index as a consequence of the secular increases in body mass index and use of recently launched combined oral contraceptives by time. We controlled for calendar year to deal with potential long term confounding by body mass index. In addition we carried out subanalyses for the periods 2001-5, 2006-May 2007, and June 2007-9. We chose these periods because of new data after 2005 and because of a "pill crisis" in Denmark in June 2007 after extensive media attention on one woman with venous thromboembolism who used oral contraceptives with drospirenone.

Smoking

Data on smoking were not available. Smoking is a weak risk factor for venous thromboembolism in young women.[13] We have no reason to believe in preferential prescribing of specific oral contraceptives among smokers. In Denmark the correlation between smoking and length of education is strong. Thus, controlling for years of schooling and length of education may have captured most confounding (if any) influenced by smoking.

Ovarian stimulation drugs

Women treated for infertility with ovarian stimulation drugs (Anatomical Therapeutic Chemical classification G03G) are anticipated to be at an increased risk for venous thromboembolism. Therefore we censored these women at first such treatment.

Recent surgery

From the national register of patients we identified women with venous thromboembolism who had undergone major surgery in the four weeks before admission. Major surgery was defined as a length of stay after surgery of more than one day, or orthopaedic surgery on the legs. We carried out sensitivity analyses with and without these women excluded.

Validity of the outcome diagnoses in the national register of patients

All events of venous thromboembolism during 2001-9 were cross checked with the national registry of medicinal products for anticoagulation therapy (defined as therapy with vitamin K antagonists or heparin). We defined women who were given anticoagulation therapy for at least four weeks as having confirmed venous thromboembolism. Thus we were able to restrict analyses to confirmed events only.

Furthermore, we validated the hospital charts of 200 randomly selected women with venous thromboembolism. Two independent skilled clinicians evaluated each chart and categorised each case as confirmed if two of three conditions were fulfilled: clinical signs of venous thromboembolism; diagnostic confirmation by ultrasound, phlebography, computed tomography, or scintigraphy (in case of pulmonary embolism); and at least four weeks of anticoagulation therapy after the diagnosis. The evaluation was done without knowledge of registry data on usage of oral contraceptives.

Statistical analysis

Data were analysed by multiple Poisson regression in five year age groups. We further stratified the estimates according to length of current use into: less than three months, 3-12 months, more than 12 months to four years, and more than four years.

We calculated absolute as well as relative risk estimates. Non-users of all types of hormonal contraception (never users plus former users) were used as the reference group for the relative risk estimates. Rate ratios were also calculated for the different product types. We adjusted the relative risk estimates for age, calendar year, length of schooling and education, and eventually for length of oral contraceptive use.

Sensitivity analyses were done for both different steps in exposure line formation and according to different categories of oral contraceptive use. We calculated three estimates of exposure lines: raw exposure analyses, in which no gap filling or extension of four weeks was realised; gap corrected exposure lines, in which gaps of less than four weeks were filled and (as a consequence of filling out gaps) exposures were prolonged with four weeks; and switch corrected exposure lines, in which we excluded the first four weeks after switch.

Four successive analyses were carried out for the exposure categories of starting oral contraceptives, adding new use, restarted use, and, finally, switched use.

Results

During 1995 to 2009 1 732 254 Danish women aged 15-49 were identified, corresponding to 17 329 718 women years of observation. The study period from January 2001 to December 2009 included 1 436 130 women and 9 954 925 observation years. Among these women 455 421 (31.7%) had never used hormonal contraception and 980 709 (68.3%) were ever users of some kind of hormonal contraception.

After exclusions and censoring owing to pregnancy (n=403 972 or 486 037 women years); ovarian stimulation (n=74 823 or 460 454 women years); previous cardiovascular disease including venous thromboembolism (n=31 252 or 135 828 women years); cancer (n=21 080 or 135 828 women years); coagulation disturbances (n=5122 or 19 258 women years); hysterectomy, bilateral oophorectomy, or sterilisation (n=146 019 or 760 449 women years); censoring after three years of using a hormone releasing intrauterine device (n=48 875 or 164 270 women years); and one month exclusions at switch of oral contraceptive use (n=252 968 or 32 598 women years), 1 296 120 women were included in the statistical analysis, contributing 8 010 290 women years of observation, with 4307 first time venous thromboembolic events recorded.

The venous thromboembolic events were distributed, with 82 (1.9%) women having cerebral venous thrombosis, 2738 (63.6%) deep venous thrombosis only, 1130 (26.2%) pulmonary embolism (with or without deep venous thrombosis), 55 (1.3%) portal thrombosis, 15 (0.4%) cava thrombosis, 4 (0.1%) thrombosis of a kidney vein, and 283 (6.6%) unspecified deep vein thrombosis.

Of the 4307 venous thromboembolic events, 61 occurred in women using hormonal contraceptives with so little exposure time and so few venous thromboembolic events that we did not calculate estimates.

The adjusted relative risk increased 6.8-fold from the youngest to the oldest women, and by 41% over the study period (5.1% per year), and was reduced by 51% with increasing length of education (table 1⇓).

Relative risk according to progestogen type and oestrogen dose

Table 2⇓ shows the absolute and relative risks of venous thromboembolism in current users of combined oral contraceptives with different types of progestogens and varying doses of oestrogen. The incidence rate of venous thromboembolism in non-users of combined oral contraceptives was 3.7 per 10 000 women years. Compared with non-users, the relative risk of venous thromboembolism in current users of oral contraceptives with levonorgestrel and 30 μg ethinylestradiol was 2.19 (95% confidence interval 1.74 to 2.75) and with levonorgestrel phasic 30-40 μg ethinylestradiol was 2.28 (1.85 to 2.83). The relative risk of venous thromboembolism in current users of oral contraceptives with 30 μg ethinylestradiol combined with desogestrel was 4.21 (3.63 to 4.87), with gestodene was 4.23 (3.87 to 4.63), and with drospirenone was 4.47 (3.91 to 5.11). The corresponding estimates for oral contraceptives with the same progestogens but 20 μg ethinylestradiol were 3.26 (2.88 to 3.69), 3.50 (3.09 to 3.97), and 4.84 (3.19 to 7.33). Progestogen only products conferred no increased risk of venous thromboembolism, whether taken as low dose norethisterone pills, as desogestrel only pills, or in the form of hormone releasing intrauterine devices.

The relative risk of venous thromboembolism from using oral contraceptives with norethisterone, levonorgestrel, desogestrel, or gestodene decreased with decreasing oestrogen dose, whereas no difference was apparent between oral contraceptives with drospirenone and either 30 μg ethinylestradiol or 20 μg ethinylestradiol. Oral contraceptives containing drospirenone and 20 μg ethinylestradiol were launched in Denmark in 2006.

Relative risk by validity of diagnosis

The venous thromboembolic events were stratified into confirmed (anticoagulation therapy recorded in the national registry of medicinal products) and unconfirmed (table 3⇓). Of the 4246 events diagnosed among non-users of hormonal contraception or among users of products included in this study, 2847 (67.1%) were confirmed and 1399 (32.9%) had no or less than four weeks' anticoagulation therapy recorded in the registry. The relative risks of venous thromboembolism were generally twofold to threefold higher in the confirmed group than the unconfirmed group. Thus in the confirmed group the relative risk of venous thrombolism with use of oral contraceptives with levonorgestrel increased to around 3, and for oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone and 30 μg ethinylestradiol increased to at least 6.

Progestogen only products had relative risk estimates below unity compared with non-users in both the confirmed and the unconfirmed groups.

The rate ratio between the estimates in the confirmed and unconfirmed groups was highest for oral contraceptives with desogestrel and lowest for those with norethisterone (table 3).

The proportion of confirmed events for specific oral contraceptives varied from 64% to 84%, and ranged from 72% to 78% for those with levonorgestrel, norgestimate, gestodene, and drospirenone and from 76% to 84% for those with desogestrel.

Table 4⇓ shows the rate ratio estimates between different product types. In the confirmed group, oral contraceptives with desogestrel, gestodene, or drospirenone conferred at least twice the risk of venous thromboembolism compared with oral contraceptives with levonorgestrel, and the rate ratio between oral contraceptives with drospirenone and those with desogestrel or gestodene was 1.01 (0.86 to 1.18). The corresponding rate ratios in the unconfirmed group were generally lower. The comparison between oral contraceptives with drospirenone and those with levonorgestrel was thus 1.78 (1.21 to 2.60), or 16% lower than the 2.12 (1.68 to 2.66) in the confirmed group. The rate ratio between these two product groups for all venous thromboembolic events was 2.00 (1.64 to 2.43), not far off the estimate in the confirmed group.

Relative risk adjusted for differences in length of use

To account for differences in the distribution of lengths of use between the groups, analyses were done in which the rate ratios with oral contraceptives containing levonorgestrel and 30 μg ethinylestradiol as reference were adjusted for differences in length of use and restricted to confirmed events (table 5⇓). The rate ratio estimates were slightly reduced for the newest products, reflecting a relatively higher proportion of short term users in these groups. The overall results, however, were unchanged, and the rate ratio between oral contraceptives with drospirenone compared with those containing levonorgestrel was still 2.09 (1.55 to 2.82). Table 6⇓ displays detailed results

according to length of use and specific combinations of progestogen types and oestrogen dose.

Sensitivity analyses

Relative risk through different steps in exposure line formation

In preliminary analyses, the influence of different steps in the exposure line formation was investigated. In the raw exposure lines no gap filling or prolongation of exposure was realised. The adjusted rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol and those with levonorgestrel and 30-40 μg ethinylestradiol was 2.2 (1.7 to 2.8), and between oral contraceptives with 30 μg ethinylestradiol and drospirenone versus oral contraceptives with 30 μg ethinylestradiol and desogestrel or gestodene the rate ratio was 1.1 (0.9 to 1.3).

In the gap corrected dataset these rate ratio estimates were unchanged, as they were in the dataset for switch corrected exposure lines. For this reason the analyses were done with all allocation rules applied (see web appendix 2).

Relative risk in different sub-periods

Another exploratory step in the analysis was to assess rate ratio estimates in three sub-periods. A non-significant tendency was for lower rate ratios for oral contraceptives with drospirenone compared with those containing levonorgestrel in the last period, but for the period 2001-9 the adjusted rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol compared with those containing levonorgestrel and 30-40 μg ethinylestradiol was 2.00 (1.64 to 2.43), and for the sub-period 2001-5 was 2.16 (1.65 to 2.83). Similar results were found when oral contraceptives with other progestogens were compared with those containing levonorgestrel (see web extra appendix 3). Consequently, subsequent analyses were done for the whole period 2001-9.

Results for different exposure categories

Sensitivity analyses were also done according to different user categories, including successively first starters only, then starters and new users, then including restarters, and finally including switchers. Starters had slightly higher rate ratios between users of oral contraceptives with drospirenone compared with those containing levonorgestrel of 2.69 (1.76 to 4.10) than estimates including the other categories, where the same rate ratios were between 1.96 (1.57 to 2.44) and 2.05 (1.56 to 2.70). See web extra appendix 4 for details.

Different reference groups

A third methodological issue was the oestrogen component in the levonorgestrel products used as reference. The rate ratio of venous thromboembolism between users of oral contraceptives with levonorgestrel and 30 μg ethinylestradiol and with levonorgestrel and 30-40 μg ethinylestradiol including phasic products did not differ significantly in any of the sub-periods. About half of women years using oral contraceptives with levonorgestrel contained 30 μg ethinylestradiol, the other half phasic products 30-40 μg ethinylestradiol. For the period 2001-9, the rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol and all levonorgestrel products with 30-40 μg ethinylestradiol was 2.00 (1.64 to 2.43) and with only levonorgestrel and 30 μg ethinylestradiol was 2.04 (1.58 to 2.63). Accordingly, all users of oral contraceptives with levonorgestrel and 30 μg or 30-40 μg ethinylestradiol were chosen as reference group. For rate ratio comparisons with specifically drospirenone, however, estimates with both 30 μg ethinylestradiol and all levonorgestrel users were calculated.

Recent surgery

Among women with confirmed venous thromboembolism, 33 (1.2%) had major surgery in the four weeks before the admission for venous thromboembolism. The results were similar with and without exclusion of women with recent surgery. Thus the rate ratio between oral contraceptives with drospirenone and 30 μg ethinylestradiol compared with those containing levonorgestrel was 2.18 (1.62 to 2.94) with these events included and 2.13 (1.58 to 2.87) without.

Chart evaluation of venous thromboembolism events

Of 200 evaluated hospital charts, 148 (74%) venous thromboembolic events were confirmed and 52 unconfirmed. Except for two women with distal limb thrombosis who were not offered anticoagulation therapy, the remaining 146 confirmed events were in women who had received anticoagulation therapy. However, two unconfirmed events were in women who had received anticoagulation therapy; one for a recent venous thromboembolism, which was not excluded because it was coded at the primary admission (before actual admission) with a superficial venous thrombosis diagnosis and therefore not excluded as previous venous thromboembolism. The other woman was treated for connective tissue disease. All 200 evaluated patients coded as having venous thromboembolism had clinical symptoms at admission.

Of the 200 validated events, 148 (74.0%) women had received anticoagulation therapy according to the medical charts. Of these, 133 (89.9%) were recorded in the national registry of medicinal products as having had anticoagulation therapy, suggesting that about 10% received treatment for free from the hospitals, and therefore were not recorded in the registry.

Among the 52 women without information on anticoagulation therapy in the medical charts, four (7.7%) were recorded in the registry as having received anticoagulation therapy. This can occur when treatment starts after discharge from the department to which the women were primarily admitted—that is, initiated from a coagulation laboratory just after discharge from the department. If these four events were added to the confirmed events in the sample of 200 women, the confirmed proportion increased to 152 of 200, or 76.0%.

Discussion

This study found that when compared with non-users of hormonal contraception, current users of oral contraceptives with levonorgestrel were at a threefold increased risk for confirmed venous thrombosis and users of oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone acetate a sixfold to sevenfold increased risk. This would give a rate ratio between the groups using oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone and those using oral contraceptives with levonorgestrel of at least 2.

Before interpreting the results of this analysis, the main differences in study design and analysis between the present and the primary publication[18] should be revisited. Potential biases in our primary publication were dealt with as follows: we eliminated left censoring bias by letting the new study period begin in 2001, with full exposure history for the previous six years; we defined length of use as duration of actual use rather

than the sum of all periods of use; we used four strata for duration of use, instead of three, ensuring a more detailed length of use allocation within the first year; we excluded the first exposure month after a switch, because of uncertainty as to which product group a woman should be allocated in case of venous thromboembolism in this period; analyses were stratified into confirmed and unconfirmed venous thromboembolic events; and a more effective exclusion of predisposed women including women with coagulation disorders was effected.

Results according to progestogen type and oestrogen dose

The addition of four more study years from 2006-9 and the restriction of the analyses to the period after 1 January 2001 did not change the overall results of our primary publication covering 1995-2005. With the additional data we reconfirmed and substantiated a differential risk of venous thromboembolism between users of combined oral contraceptives with different progestogens and (although to a less extent) with different oestrogen doses.

According to the present analysis, with the same dose of oestrogen, combined oral contraceptives containing the progestogens desogestrel, gestodene, cyproterone, or drospirenone confer about the same relative risk of venous thromboembolism, a risk that is about twice that from use of combined oral contraceptives with the same dose of oestrogen and levonorgestrel. Phasic combined oral contraceptives with levonorgestrel may confer a slightly but not significantly higher risk of venous thromboembolism than oral contraceptives with levonorgestrel and 30 µg ethinylestradiol, which could be due to the slightly higher total dose of oestrogen in the former group. Consequently the relative risk estimates are slightly smaller when the reference group was the whole group of oral contraceptives containing levonorgestrel than if compared with only oral contraceptives with levonorgestrel and 30 µg ethinylestradiol.

The oral contraceptives with desogestrel or gestodene and 20 µg ethinylestradiol implied a relative risk of venous thromboembolism that were 23% and 17% lower than the same progestogens with 30 µg ethinylestradiol. The missing trend for oral contraceptives with drospirenone according to oestrogen dose could be a consequence of fewer events (n=23) in the group using 20 µg ethinylestradiol, more active pill per cycle for one of the 20 µg products , or could also be influenced by the introduction of these oral contraceptives in 2006, on the assumption that attention to adverse effects is highest for new products. However, the 70% confirmed venous thromboembolism events in the new low dose drospirenone group was close to the proportion of confirmed events for the older oral contraceptives with drospirenone and 30 µg ethinylestradiol (74%), which does not support differential attention by women or their doctors.

Rate ratios and validity of diagnosis

More than two thirds of the included venous thromboembolic events were confirmed by a record of anticoagulation therapy in the national registry of medicinal products. Importantly, some women have treatment for free (owing to local policies in some hospitals when handing out these drugs) and consequently are not recorded in the registry. According to our random analysis of medical charts, an additional 10% are women with real events of venous thromboembolism, receiving anticoagulation treatment for free from the hospitals. A further small percentage of women start treatment after discharge, bringing the real proportion of confirmed events up to 152 of 200, or 76%.

In a previous case-control study during 1994-8, we got information from departments that 3.6% of cases were unconfirmed.[13] In addition, 95 of 1094 (8.7%) women who responded could not confirm their diagnosis, leaving what we considered to be 87.7% of valid cases. The stricter validation in the subsample in this study resulted in 76% with a valid diagnosis. The difference of about 10% may be explained by women who have clinical symptoms of venous thromboembolism at admission that could not be confirmed by radiography or ultrasonography. Such women could be told that they might have had venous thromboembolism that dissolved spontaneously or was too small to be confirmed by the available diagnostic equipment, and therefore did not require treatment. As a result of the lack of a more appropriate diagnosis such women might, nevertheless, be coded as having venous thromboembolism.

Compared with non-users of combined oral contraceptives, the relative risk of venous thromboembolism among current users of combined oral contraceptives was twofold to fourfold higher for confirmed than unconfirmed venous thromboembolism (table 3). The rate ratio estimates between different product groups were less sensitive, but nevertheless decreased by about 25% from the confirmed to the unconfirmed group (table 4).

Exposure line formation

Estimation of rate ratios through different steps in exposure line formation was necessary for at least two reasons. Firstly, we decided on the analytical strategy before the analyses started. Secondly, the relative risk for users of specific products compared with non-users increased slightly (not significantly) through the different steps, indicating a successively higher validity of exposure allocation—for example, the relative risk estimate of oral contraceptives with levonorgestrel and 30 µg ethinylestradiol increased from 1.9 (1.5 to 2.6) to 2.1 (1.6 to 2.8) and for those with drospirenone from 4.4 (3.7 to 5.1) to 4.7 (4.0 to 5.4) through the different exposure lines.

Owing to the high consistency in the rate ratio estimates in the different exposure lines, it is unlikely that different rules or other time intervals in the allocation rules would have changed the rate ratios substantially.

Analysis of different sub-periods

Overall, the rate ratio estimates were stable throughout the study periods. The slightly lower rate ratio estimates after June 2007 compared with the previous period could be a consequence of the media event in June 2007. Shortly after this the Danish Society of Obstetrics and Gynaecology published a press release in which they stated that oral contraceptives with drospirenone were unlikely to confer a higher risk of venous thromboembolism than the prevailing third generation oral contraceptives with desogestrel or gestodene, but that oral contraceptives with levonorgestrel were likely to confer a lower risk. Consequently, women at an anticipated increased risk of venous thromboembolism were recommended progestogen only contraception or alternatively oral contraceptives with levonorgestrel as first choice.

Thereby some women at an anticipated increased risk of venous thromboembolism could have been prescribed products containing levonorgestrel, increasing the estimates for oral contraceptives with levonorgestrel and decreasing the estimates for those with drospirenone. However, the relative risk estimates for oral contraceptives with levonorgestrel and 30 µg

ethinylestradiol with non-users of hormonal contraception as reference did not change: 2.3 (1.7 to 3.1) during 2001-5 and 2.4 (1.6 to 3.6) from June 2007-9. In contrast, the estimates for oral contraceptives with drospirenone and 30 μg ethinylestradiol decreased (non-significantly) from 4.7 (3.9 to 5.7) in 2001-5 to 4.1 (3.2 to 5.3) during 2007-9, which may explain the decreasing trend in the rate ratio estimates after June 2007.

Recent surgery

The exclusion of 33 women with confirmed venous thromboembolism who had major surgery within the previous four weeks did not change the results, primarily because of the low numbers. In addition, women undergoing surgery often receive anticoagulation therapy during their stay, and some may have stopped using oral contraceptives in the weeks around the surgery, circumstances for which we lacked information.

Strengths and limitations of the study

Expanding on our previous study by using four new years' worth of original data on exposure and end points confirmed our previously published results,[18] and therefore increased the validity of the present results. The inclusion of all Danish non-pregnant women over a nine year period ensured a high external validity.

The information on exposure was complete and gathered for purposes other than a scientific analysis, eliminating the recall bias that is common in case-control studies, and the problems of continuous updating data on exposure in cohort studies. Furthermore, we eliminated the problem of left censoring by measuring use of combined oral contraceptives over a six year period before our study started. We obtained consistent results from sensitivity analyses on exposure line formation, different sub-periods, and according to different user categories (for example, starters, restarters).

Finally, we were able to validate venous thromboembolic events by linking individual data on diagnosis to succeeding anticoagulation therapy. Restricting the analysis to only confirmed events provided a quantitative assessment of the consequence of misclassification of some diagnoses on risk estimates.

This study does, however, have some limitations. We could not control for family disposition and body mass index. Adiposity is a well documented risk factor for venous thromboembolism. It is unlikely that there should be any important preferential prescribing of specific types of oral contraceptives to obese women before June 2007. After that time, however, the public recommendations to women at an anticipated increased risk of venous thromboembolism to choose a progestogen only contraception or oral contraceptives with levonorgestrel could have overestimated the risk for oral contraceptives with levonorgestrel and underestimated that for oral contraceptives with desogestrel, gestodene, or drospirenone. Some could argue that obese women are more likely to choose oral contraceptives with drospirenone. The empirical support for such selective prescribing is weak, however, and does not explain the high relative risk estimates for the other three oral contraceptives with desogestrel, gestodene, and cyproterone. To date, no study has shown any confounding influence from body mass index, as adjustment for body mass index in studies with this information did not change the rate ratio between oral contraceptives with different progestogens.[14 17-19] Therefore, preferential prescribing of oral contraceptives with third generation progestogens or drospirenone to obese women is unlikely to explain the doubled risk for these products compared with oral contraceptives containing levonorgestrel, especially after 2006.

The same argument applies to family disposition. Although an important risk factor, family disposition has not been found to be an important confounder in studies over the past 10 years.

About a quarter of our included venous thromboembolic events could not be confirmed by review of the medical records. This would underestimate the influence of combined oral contraceptives on the risk of venous thromboembolism, as shown by comparing the risk estimates for confirmed events in this study with those in our primary publication,[18] whereas the rate ratio estimates were less sensitive to the inclusion of unconfirmed events.

The chart review confirmed a 99% positive predictive value of a diagnosis of venous thromboembolism with subsequent anticoagulation therapy, and that cross linkage with the national registry of medicinal products provided reliable validation of the events. However, we lost at least 10% of true events by excluding all events that were not recorded in the registry.

Table 7⇓ summarises studies that specifically assessed the risk of venous thromboembolism from use of oral contraceptives with levonorgestrel, desogestrel, gestodene, or drospirenone. We excluded those studies that did not specify the compounds used or that lacked a reference group. Our new estimates for specific products restricted to confirmed events of venous thromboembolism are close to those in a Dutch study,[17] whereas the rate ratio estimates between different product groups were slightly higher than in the Dutch study and slightly lower than in the two new studies from the United Kingdom[20] and the United States.[21] The UK and US studies included "idiopathic events" only, the risk estimates of which are expected to be slightly higher than those of studies that also include women with some other risk factors.

The two studies that did not find any difference in risk between oral contraceptives with drospirenone and those with levonorgestrel were two of the three studies that did not find any difference in risk between oral contraceptives with desogestrel or gestodene and those with levonorgestrel.

If we anticipate that oral contraceptives with desogestrel, gestodene, or drospirenone increase the risk of venous thromboembolism sixfold and that those with levonorgestrel increase the risk threefold, and that the absolute risk of venous thromboembolism in current users of the former group is on average 10 per 10 000 women years, then 2000 women would need to shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel to prevent one event of venous thromboembolism in one year.

Conclusion

Compared with non-users of hormonal contraception, current users of oral contraceptives with levonorgestrel had a threefold increased risk of venous thromboembolism and those using oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone a six to sevenfold increased risk.

This would give a rate ratio between the groups using oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone and those using oral contraceptive with levonorgestrel of at least 2. It is unlikely that these findings could be explained by bias or confounding.

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What is already known on this topic

Studies have shown an increased risk of venous thrombosis (VTE) with use of combined oral contraceptives

The risk was higher with oral contraceptives containing the progestogens desogestrel and gestodene than those containing levonorgestrel

Results on the risk from oral contraceptives with drospirenone have been conflicting

What this study adds

Women using oral contraceptives with drospirenone are at similar risk of VTE to those using oral contraceptives with desogestrel, gestodene, or cyproterone and higher than those using oral contraceptives with levonorgestrel

The risk of VTE was not reduced by using 20 µg oestrogen instead of 30 µg oestrogen in oral contraceptives with drospirenone

To prevent one event of VTE in one year about 2000 women should shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel

Contributors: ØL, EL, and FES planned the study, supervised the analysis, and interpreted the results. ØL wrote the manuscript. LHN did the statistical analyses and interpreted the results. CWS prepared the data from the national registry of patients and national death registry. All authors discussed and approved the final manuscript. ØL is guarantor of the study. The sponsor had no influence on the design, performance, or interpretation of the results or on the manuscript.

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Ethical approval: This study was approved by the Danish Data Protection Agency (Journal No 2010-41-4778). Ethical approval is not requested for registry based studies in Denmark.

Data sharing: No additional data available.

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Tables

Table 1| Characteristics of current users and non-users of combined oral contraceptives and adjusted relative risk of venous thromboembolism according to age, calendar year, and length of education

	Current users			Non-users				
Characteristics	Women years	No of events*	Incidence per 10 000 exposure years	Women years	No of events*	Incidence per 10 000 exposure years	Adjusted rate ratio† (95% CI)	P value
Age (years):								
15-19	571 333	239	4.2	670 766	49	0.7	1 (reference)	—
20-24	713 623	343	4.8	346 614	74	2.1	1.32 (1.13 to 1.54)	<0.001
25-29	549 862	375	6.8	463 810	134	2.9	1.99 (1.66 to 2.38)	<0.001
30-34	430 272	375	8.7	667 937	211	3.2	2.91 (2.40 to 3.55)	<0.001
35-39	369 859	447	12.1	861 442	304	3.5	4.01 (3.31 to 4.87)	<0.001
40-44	261 464	397	15.2	965 951	467	4.8	5.29 (4.36 to 6.41)	<0.001
45-49	153 147	319	20.8	984 209	573	5.8	6.58 (5.43 to 7.99)	<0.001
Year:								
2001	335 482	241	7.2	625 168	175	2.8	0.71 (0.62 to 0.81)	<0.001
2002	339 078	251	7.4	601 282	198	3.3	0.76 (0.66 to 0.86)	<0.001
2003	340 575	238	7.0	579 767	174	3.0	0.70 (0.61 to 0.80)	<0.001
2004	342 354	276	8.1	562 409	205	3.6	0.81 (0.72 to 0.93)	0.002
2005	341 273	275	8.1	544 028	217	4.0	0.86 (0.76 to 0.97)	0.02
2006	339 578	293	8.6	529 811	205	3.9	0.87 (0.77 to 0.99)	0.03
2007	337 072	311	9.2	516 775	245	4.7	1.01 (0.90 to 1.15)	0.82
2008	336 606	287	8.5	508 635	190	3.7	0.90 (0.79 to 1.02)	0.10
2009	337 542	323	9.6	492 855	203	4.1	1 (reference)	—
Level of education:								
Elementary school‡	695 339	762	11.0	1 194 278	748	6.3	1 (reference)	—
High school§	365 466	275	7.5	505 821	125	2.5	0.60 (0.54 to 0.67)	<0.001
High school and middle education¶	576 803	673	11.7	1 295 503	518	4.0	0.68 (0.63 to 0.73)	<0.001
High school and long education**	241 662	223	9.2	909 249	257	2.8	0.49 (0.44 to 0.55)	<0.001
No available information	1 170 290	562	4.8	1 055 878	164	1.6	0.78 (0.68 to 0.90)	0.0005

*Events are venous thromboembolisms.

†Age estimates adjusted for year, level of education, and use of oral contraceptives; year estimates adjusted for age, level of education, and use of combined oral contraceptives; and education estimates adjusted for age, year, and use of combined oral contraceptives.

‡9-10 years of education.

§2-3 years of education after elementary school.

¶3-4 years of education after high school.

**5-6 years of education after high school.

Table 2| Exposure time, number of events of venous thromboembolism, crude incidence per 10 000 user years, and adjusted relative risk of venous thromboembolism in current users of different oral contraceptives and hormone releasing intrauterine device with non-users as reference group

Group	Women years	No of events*	Crude incidence per 10 000 user years*	Adjusted relative risk† (95% CI)
Non-use	4 960 730	1812	3.7	1 (reference)
Progestogen with 50 µg ethinylestradiol:				
Norethisterone	6848	11	16.1	5.66 (3.12 to 10.3)
Levonorgestrel	23 691	31	13.1	3.54 (2.48 to 5.05)
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	10	3.7	1.57 (0.84 to 2.92)
Phasic levonorgestrel	105 970	89	8.4	2.28 (1.85 to 2.83)
Levonorgestrel combined	104 251	78	7.5	2.19 (1.74 to 2.75)
Norgestimate	267 664	165	6.2	2.56 (2.18 to 3.01)
Desogestrel	170 249	201	11.8	4.21 (3.63 to 4.87)
Gestodene	668 355	738	11.0	4.23 (3.87 to 4.63)
Drospirenone	286 859	266	9.3	4.47 (3.91 to 5.11)
Cyproterone	120 934	109	9.0	4.10 (3.37 to 4.99)
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	322	6.8	3.26 (2.88 to 3.69)
Gestodene	472 118	321	6.8	3.50 (3.09 to 3.97)
Drospirenone	23 055	23	10.0	4.84 (3.19 to 7.33)
Progestogen only:				
Norethisterone	44 168	9	2.0	0.56 (0.29 to 1.07)
Desogestrel	29 187	6	2.1	0.64 (0.29 to 1.42)
Levonorgestrel releasing intrauterine device	155 149	55	3.5	0.83 (0.63 to 1.08)

*Events are venous thromboembolisms.

†Adjusted for age, year, and level of education.

Table 3| Relative risk of venous thromboembolism among current users of oral contraceptives and hormone releasing intrauterine device according to certainty of diagnosis of venous thromboembolism, with non-users of hormonal contraception as reference group

		Anticoagulation (confirmed)		Not recorded		
Product type	Women years	No of events*	Adjusted relative risk† (95% CI)	No of events*	Adjusted relative risk† (95% CI)	% confirmed
Non-use	4 960 730	1004	1 (reference)	808	1 (reference)	55.4
Progestogen with 50 µg ethinylestradiol:						
Norethisterone	6848	7	6.24 (2.95 to 13.2)	4	5.10 (1.90 to 13.7)	63.6
Levonorgestrel	23 691	22	4.49 (2.94 to 6.85)	9	2.34 (1.21 to 4.52)	71.0
Progestogen with 30-40 µg ethinylestradiol:						
Norethisterone	27 355	8	2.24 (1.12 to 4.51)	2	0.73 (0.18 to 2.91)	80.0
Levonorgestrel phasic	105 970	66	3.09 (2.41 to 3.97)	23	1.31 (0.86 to 1.98)	74.2
Levonorgestrel combined	104 251	57	2.92 (2.23 to 3.81)	21	1.30 (0.84 to 2.00)	73.1
Norgestimate	267 664	119	3.52 (2.90 to 4.27)	46	1.44 (1.07 to 1.95)	72.1
Desogestrel	170 249	168	6.61 (5.60 to 7.80)	33	1.43 (1.01 to 2.04)	83.6
Gestodene	668 355	575	6.24 (5.61 to 6.95)	163	1.92 (1.61 to 2.28)	77.9
Drospirenone	286 859	196	6.37 (5.43 to 7.47)	70	2.32 (1.80 to 2.98)	73.7
Cyproterone	120 934	88	6.35 (5.09 to7.93)	21	1.58 (1.02 to 2.44)	80.7
Progestogen with 20 µg ethinylestradiol:						
Desogestrel	470 982	246	4.81 (4.15 to 5.56)	76	1.52 (1.19 to 1.94)	76.4
Gestodene	472 118	240	5.07 (4.37 to 5.88)	81	1.72 (1.36 to 2.19)	74.8
Drospirenone	23 055	16	6.95 (4.21 to 11.5)	7	2.58 (1.22 to 5.46)	69.6
Progestogen only:						
Norethisterone	44 168	6	0.68 (0.30 to 1.51)	3	0.41 (0.13 to 1.28)	66.7
Desogestrel	29 187	3	0.61 (0.20 to 1.90)	3	0.63 (0.20 to 1.97)	50.0
Levonorgestrel releasing intrauterine device	155 149	26	0.72 (0.49 to 1.06)	29	0.95 (0.65 to 1.38)	47.3

*Events are venous thromboembolisms.

†Adjusted for age, calendar year, and level of education.

Table 4| Rate ratios of venous thromboembolism between users of combined oral contraceptives with different progestogens according to certainty of diagnosis of venous thromboembolism

Comparison groups	No of events*	Rate ratio†		P value
		Partially adjusted	Fully adjusted‡ (95% CI)	
Confirmed events				
Drospirenone + 30 µg EE versus:				
Levonorgestrel + 30-40 µg EE (all)	196 *v* 123	2.03	2.12 (1.68 to 2.66)	<0.001
Levonorgestrel + 30 µg EE (without phasic preparations)	196 *v* 57	2.08	2.18 (1.62 to 2.94)	<0.001
Third generation progestogens§	196 *v* 743	0.98	1.01 (0.86 to 1.18)	0.9248
Desogestrel + 30 µg EE *v* levonorgestrel + 30-40 µg EE	168 *v* 123	2.18	2.20 (1.74 to 2.77)	<0.001
Gestodene + 30 µg EE *v* levonorgestrel + 30-40 µg EE	575 *v* 123	2.04	2.07 (1.70 to 2.52)	<0.001
Non-confirmed events				
Drospirenone + 30 µg EE versus:				
Levonorgestrel + 30-40 µg EE	70 *v* 44	1.71	1.78 (1.21 to 2.60)	0.0032
Levonorgestrel + 30 µg EE (without phasic preparations)	70 *v* 21	1.70	1.78 (1.09 to 2.91)	0.0213
Third generation progestogens§	70 *v* 196	1.25	1.27 (0.97 to 1.68)	0.0840
Desogestrel + 30 µg EE *v* levonorgestrel + 30-40 µg EE	33 *v* 44	1.10	1.10 (0.70 to 1.73)	0.6764
Gestodene + 30 µg EE *v* levonorgestrel + 30-40 µg EE	163 *v* 44	1.45	1.47 (1.05 to 2.06)	0.0236

EE=ethinylestradiol.

*Events are venous thromboembolisms.

†Adjusted for age and calendar year.

‡Adjusted for age, calendar year, and level of education.

§Desogestrel or gestodene.

Table 5| **Rate ratio of confirmed venous thromboembolism between different combined oral contraceptives with adjustment for length of use**

Product group	Women years	No of events*	Adjusted rate ratio† (95% CI)	P value
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	8	0.76 (0.36 to 1.60)	0.47
Levonorgestrel phasic	105 970	66	1.07 (0.75 to 1.52)	0.71
Levonorgestrel combined	104 251	57	1 (reference)	—
Norgestimate	267 664	119	1.18 (0.86 to 1.62)	0.30
Desogestrel	170 249	168	2.24 (1.65 to 3.02)	<0.001
Gestodene	668 355	575	2.12 (1.61 to 2.78)	<0.001
Drospirenone	286 859	196	2.09 (1.55 to 2.82)	<0.001
Cyproterone	120 934	88	2.11 (1.51 to 2.95)	<0.001
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	246	1.60 (1.20 to 2.14)	0.0015
Gestodene	472 118	240	1.70 (1.27 to 2.27)	0.0004
Drospirenone	23 055	16	2.22 (1.27 to 3.89)	0.005

*Events are venous thromboembolisms.

†Adjusted for age, calendar year, level of education, and length of use.

Table 6| **Relative risk of venous thromboembolism in current users of combined oral contraceptives according to length of use and with non-users of hormonal contraception as reference**

			Adjusted relative risk† (95% CI)			
Product type	**Women years**	**No of events***	**<3 months**	**3-12 months**	**>1-4 years**	**>4 years**
Non-use	4 960 730	1812	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Progestogen with 30-40 µg ethinylestradiol:						
Levonorgestel (all)	210 221	167	4.07 (2.70 to 6.15)	2.54 (1.80 to 3.59)	2.12 (1.61 to 2.80)	1.88 (1.45 to 2.43)
Norgestimate	267 664	165	3.81 (2.60 to 5.58)	2.98 (2.22 to 4.00)	2.47 (1.91 to 3.20)	1.82 (1.27 to 2.59)
Desogestrel	170 249	201	4.59 (3.01 to 7.00)	4.20 (3.11 to 5.67)	3.77 (2.95 to 4.81)	4.64 (3.64 to 5.92)
Gestodene	668 355	738	4.83 (3.85 to 6.05)	4.65 (3.96 to 5.45)	4.12 (3.61 to 4.70)	3.94 (3.43 to 4.54)
Drospirenone	286 859	266	4.70 (3.45 to 6.40)	5.95 (4.88 to 7.24)	3.38 (2.69 to 4.24)	4.34 (3.10 to 6.08)
Cyproterone	120 934	109	4.23 (2.50 to 7.17)	4.21 (2.95 to 6.01)	4.90 (3.70 to 6.49)	2.43 (1.41 to 4.19)
Progestogen with 20 µg ethinylestradiol:						
Desogestrel	470 982	322	3.18 (2.31 to 4.38)	3.18 (2.55 to 3.98)	3.49 (2.91 to 4.17)	3.09 (2.42 to 3.96)
Gestodene	472 118	321	3.46 (2.49 to 4.81)	4.51 (3.69 to 5.52)	3.38 (2.81 to 4.06)	2.65 (2.00 to 3.51)
Drospirenone	23 055	23	6.16 (2.76 to 13.77)	7.25 (4.19 to 12.56)	2.58 (0.96 to 6.89)	—

*Events are venous thromboembolisms.

†Adjusted for age, calendar year, and level of education.

Table 7| **Relative risk of venous thromboembolism in current users of different combined oral contraceptives according to study. Non-users of hormonal contraception as reference group unless specified otherwise**

			Relative risk (95% CI)		
Study	**Sampling period**	**No of events***	**COC with levonorgestrel**	**COC with third generation progestogens†**	**COC with drospirenone**
Bloemenkamp[1]	1988-92	126	3.8 (1.7 to 8.4)	8.7 (3.9 to 19.3)	NA
WHO[4]	1989-93	433	3.6 (2.5 to 5.1)	7.4 (4.2 to 12.9)	NA
Jick[2]	1991-4	80	1 (Reference)	1.8 (1.0 to 3.2)	NA
Spitzer[5]	1991-5	471	3.7 (2.2 to 6.2)	6.7 (3.4 to 13)	NA
Farmer[6]	1991-5	85	3.1‡ (2.1 to 4.5)	5.0‡ (3.7 to 6.5)	NA
Lewis[8]	1993-5	502	2.9 (1.9 to 4.2)	2.3 (1.5 to 3.5)	NA
Todd[9]	1992-7	99	1 (Reference)	1.4 (0.7 to 2.8)	NA
Bloemenkamp[7]	1994-8	185	3.7 (1.9 to 7.2)	5.6 (NA)	NA
Lidegaard[13]	1994-8	987	2.9 (2.2 to 3.8)	4.0 (3.2 to 4.9)	NA
Dinger[14]	2000-4	118	1 (Reference)	1.3 (NS)	1.0 (0.6 to 1.8)
Vlieg[17]	1999-2004	1524	3.6 (2.9 to 4.6)	7.3 (5.3 to 10.0)	6.3 (2.9 to 13.7)
Lidegaard[18]	1995-2005	4213	2.0 (1.8 to 2.3)	3.6 (3.3 to 3.8)	4.0 (3.3 to 4.9)
Dinger[19]	2002-8	680	1 (Reference)	NA	1.0 (0.6 to 1.8)
Parkin[20]	2002-9	61	1 (Reference)	NA	2.7 (1.5 to 4.7)
Jick[21]	2002-8	186	1 (Reference)	NA	2.8 (2.1 to 3.8)
Present study:					
All reported events*	2001-9	4246	2.2 (1.7 to 2.8)	4.2 (3.6 to 4.9)	4.5 (3.9 to 5.1)
Confirmed events only*	2001-9	2707	2.9 (2.2 to 3.8)	6.8 (5.7 to 8.1)	6.3 (5.4 to 7.5)

COC=combined oral contraceptives; NA=not available; NS=non-significant.

*Events are venous thromboembolisms.

†Desogestrel or gestodene.

‡Absolute risk per 10 000 women years.

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ORIGINAL ARTICLE

Sex hormone-binding globulin as a marker for the thrombotic risk of hormonal contraceptives

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Summary. *Background:* It takes many years to obtain reliable values for the risk of venous thrombosis of hormonal contraceptive users from clinical data. Measurement of activated protein C (APC) resistance via thrombin generation is a validated test for determining the thrombogenicity of hormonal contraceptives. Sex hormone-binding globulin (SHBG) might serve as a marker for the risk of venous thrombosis, and can be easily and rapidly measured in routine laboratories. *Objective:* To determine whether SHBG is a useful marker for the thrombotic risk of hormonal contraceptive users by comparing plasma SHBG levels with normalized APC sensitivity ratio (nAPCsr) values and thrombosis risks reported in the recent literature. *Methods:* We conducted an observational study in 262 users of different contraceptives, and measured nAPCsr and SHBG levels. *Results:* Users of contraceptives with a higher risk of causing venous thrombosis, i.e. combined hormonal contraceptives containing desogestrel, cyproterone acetate or drospirenone, and the transdermal patch, had higher SHBG levels than users of combined hormonal contraceptives containing levonorgestrel, which carry a lower thrombosis risk. Users of the patch had the highest SHBG levels, with a mean difference of 246 nmol L^{-1} (95% confidence interval 179–349) from that in users of levonorgestrel-containing combined hormonal contraceptives. SHBG levels were positively associated with both the nAPCsr and the risks of venous thrombosis reported in the recent literature. *Conclusion:* SHBG is a useful marker with which to estimate the thrombotic safety of a preparation.

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Introduction

The use of combined oral contraceptives is associated with a three-fold to six-fold increased risk of venous thrombosis [1]. This increased risk depends on both the estrogen dose and the progestogen type of combined oral contraceptives [1]. So-called 'high-dose' combined oral contraceptives containing 50 μg or more ethinylestradiol (EE) are associated with a two-fold higher risk of thrombosis than 'low-dose' combined oral contraceptives containing 20–30 μg of EE [2,3]. Furthermore, combined oral contraceptives containing the progestogens gestodene (GTD), desogestrel (DSG), cyproterone acetate (CPA) or drospirenone (DRSP) increase the risk of venous thrombosis by a factor of two as compared with combined oral contraceptives containing levonorgestrel (LNG) [1–13].

The differences in the risk of venous thrombosis can be at least partially explained by the association of various combined oral contraceptives with differences in resistance to activated protein C (APC) as measured with the thrombin generation-based APC resistance test and quantified via a normalized APC sensitivity ratio (nAPCsr) [14–16]. High nAPCsr indicates increased APC resistance, which is a risk factor for venous thrombosis. Thrombin generation-based APC resistance has been validated in a case–control study by Tans *et al.* [17], and predicts the risk of venous thrombosis in users of combined oral contraceptives, as well as in non-users and men, with or without the factor V Leiden mutation. The highest odds ratio (OR) of venous thrombosis in the absence of the FV Leiden mutation was observed in premenopausal women using combined oral contraceptives, lending support to the hypothesis that the prothrombotic effect of combined oral contraceptives is the result of acquired APC resistance in a thrombin generation-based test [17]. Users of combined oral contraceptives with a higher risk of causing venous thrombosis, e.g. those containing DSG, CPA or DRSP, have been found to be more

resistant to the anticoagulant action of APC than users of combined oral contraceptives with a lower risk of causing venous thrombosis, i.e. those containing LNG [3,6,9,10,14–16].

As the absolute risk of venous thrombosis in women using combined oral contraceptives is low, i.e. three to four per 10 000 woman-years [1], the assessment of differences in risk between an existing and a new preparation requires hundreds of thousands of users. This sample size makes a clinical study of a new hormonal contraceptive before market authorization almost impossible.

In a search for other markers that can predict the risk of venous thrombosis in users of hormonal contraceptives, Odlind *et al*. [18] postulated sex hormone-binding globulin (SHBG) as a marker for estrogenicity of a contraceptive preparation and possibly for the risk of venous thrombosis. SHBG is a carrier protein that is produced in the liver and binds estrogen and testosterone [19]. The hypothesis is that estrogens cause a dose-related increase in SHBG levels, whereas progestogens induce a decrease in SHBG levels, dependent on both the dose and the type of progestogen [20–22]. The type-related differences in the progestogen-induced decrease in SHBG levels can be interpreted as differences in the antiestrogenic properties of progestogens. Thus, the effect of a hormonal contraceptive on SHBG is the combined result of the estrogenic effect of EE and the antiestrogenic effect of the progestogen, yielding the total estrogenicity of that hormonal contraceptive. This estrogenicity might serve as a marker for venous thrombosis. Several studies have shown an association between the risk of causing venous thrombosis of combined oral contraceptives, APC resistance, and SHBG levels [1–3,15,23].

To investigate whether SHBG is a useful marker for the risk of venous thrombosis of combined oral contraceptives, we determined SHBG levels in non-users and in users of different contraceptives, both hormonal and non-hormonal, and compared the SHBG levels with nAPCsr as determined via thrombin generation and with the risks of venous thrombosis as reported in the literature.

Materials and methods

Study design and participants

We conducted an observational study. In a series of four different studies, we included users of various hormonal and non-hormonal contraceptives [15,24–26]. Users of different combined hormonal contraceptives, including oral, transdermal and vaginal combined hormonal contraceptives, users of LNG-releasing intrauterine devices (IUDs) (LNG-IUDs), users of copper-releasing IUDs (Cu-IUDs) and healthy female non-users with regular, ovulatory menstrual cycles were studied.

The inclusion criterion for all participants was as follows: healthy women using a hormonal contraceptive for at least three cycles. Exclusion criteria were age < 18 years, and contraindications for combined hormonal contraceptive use as stated by the World Health Organization [27]. A more detailed description can be found in the original articles [15,24–26].

Participants who were carriers of the FV Leiden mutation were excluded from the analysis, because this mutation causes resistance to APC without affecting SHBG levels ($n = 30$). The following data were not used because of a small sample size: users of a combined oral contraceptive containing GTD, norgestimate and norethisterone ($n = 3$ for GTD, $n = 1$ for norgestimate, and $n = 2$ for norethisterone). Furthermore, we only used data from users of combined oral contraceptives containing 30–35 μg of EE; users of preparations with other amounts of EE were excluded ($n = 24$). For 26 participants, data were not complete, so they were excluded. In total, we excluded 86 participants.

In our final analysis, we used the samples of 262 participants: 159 users of a combined oral contraceptive (containing 30–35 μg of EE and LNG, DSG, CPA, or DRSP), 60 users of the LNG-IUD, 17 users of the Cu-IUD, seven users of the transdermal patch (containing EE and norelgestromine [NGM]), six users of the vaginal ring (containing EE and etonogestrel [ENG]), and 13 non-users (mid-cycle).

Written informed consent was given by all participants, and the studies were all approved by the Medical Ethics Committee of the Leiden University Medical Center, The Netherlands.

Laboratory methods

The plasma samples from the studies were taken, processed and stored identically. Blood samples were taken from the antecubital vein in the morning in a fasting state, and collected in 0.106 mol L^{-1} sodium citrate (pH 5.8). Cell-free, citrated plasma was prepared by centrifuging blood at $2100 \times g$ for 10 min at 18 °C, coded, and centrally stored at − 80 °C.

SHBG (nmol L^{-1}) was measured with an immunometric assay (Immulite 2000 XPi; Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The sensitivity is 0.2 nmol L^{-1}, and has a long-term variation of 6%, at levels of both 5 and 80 nmol L^{-1}. The within-assay variation is 3–4%, and the between-assay variation is 3.5–6%. APC resistance was measured with the thrombin generation-based APC resistance test, as described previously [14].

nAPCsr values of plasma samples from women using an LNG-IUD or a Cu-IUD were originally measured with a variant of the thrombin generation-based APC resistance assay, by the use of using calibrated automated thrombinography [24,28]. As nAPCsr values determined with calibrated automated thrombinography are higher than those determined with the classical endpoint method [16,29], the plasma samples from IUD users were reanalyzed with the endpoint method.

SHBG levels and APC resistance in non-users during mid-cycle were used in the analysis. The different phases in the menstrual cycle were defined by repeated measurements of progesterone and estradiol levels; mid-cycle is defined as the time when estradiol levels are high and progesterone levels are low.

Table 1 Body mass index (BMI) and age of the research population

		BMI (kg m^{-2})		Age (years)	
Contraceptive	*N*	Mean	Range	Mean	Range
None	13	21.7	19–29	29.0	20–48
LNG-IUD	60	24.5	18–47	32.6	17–52
Cu-IUD	17	24.2	18–32	32.4	20–45
LNG/EE	72	22.2	17–38	25.7	18–51
DSG/EE	18	24.0	20–32	30.2	18–49
DRSP/EE	47	23.8	18–34	28.4	18–47
CPA/EE	22	22.1	19–26	27.5	19–44
ENG/EE (ring)	6	24.2	21–28	26.4	20–36
NGM/EE (patch)	7	22.4	20–26	31.1	25–43
All	262	23.5	18–47	28.8	17–52

CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; EE, ethinylestradiol; ENG, etonogestrel; DRSP, drospirenone; DSG, desogestrel; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

Statistical analysis

We used means, mean differences, 95% confidence intervals (CIs) and ranges to describe variables. We constructed a scatterplot to describe the association between SHBG levels and nAPCsr; in this figure, SHBG data were logarithmically transformed to create normality, and a histogram analysis of the residuals was performed to check whether this assumption is valid. A regression analysis was performed to describe the association.

Results

There were no significant differences in body mass index or age between the women using different kinds of hormonal contraceptive (Table 1).

SHBG levels during contraceptive use

SHBG levels in users of the studied contraceptives were compared with those in non-users and in users of the most used combined oral contraceptive containing LNG/EE. Users of contraceptives containing EE plus CPA, DRSP or DSG, and users of the transdermal patch or vaginal ring, had higher SHBG levels than users of the LNG/EE-containing combined oral contraceptive. Users of the LNG-IUD or Cu-IUD had SHBG levels lower than or similar to those in non-users (Fig. 1; Table 2).

Association between SHBG and APC resistance

SHBG plasma levels were positively associated with nAPCsr in users of different kinds of hormonal contraceptive (i.e. combined oral contraceptives and LNG-IUD) and non-users. An exponential association was observed according to the equation: $\log_{10}(\text{SHBG}) = 1.525 + (0.160 \times \text{nAPCsr})$. Thus, when the nAPCsr increases by 1 unit, SHBG levels increase by 45% ($10^{0.160} = 1.45$) (Fig. 2).

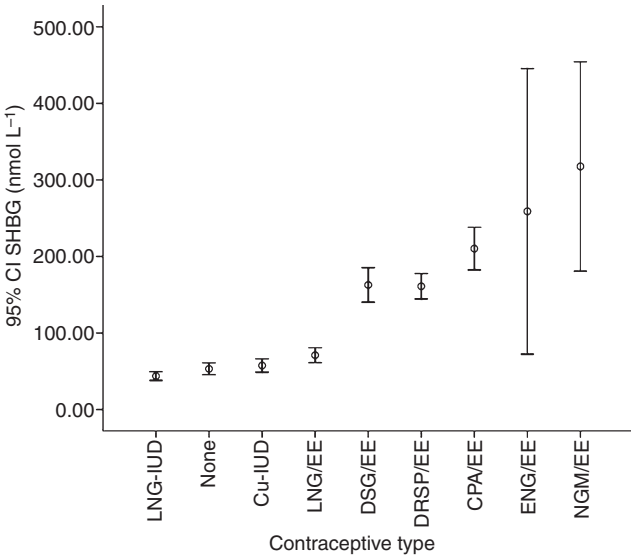

Fig. 1. Sex hormone-binding globulin (SHBG) levels and their 95% confidence intervals (CIs) by contraceptive type. CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; ENG, etonogestrel; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

Risk ranking per contraceptive

For risk ranking, we used recent publications by van Hylckama Vlieg *et al*. [3] and Jick *et al*. [30] (Table 3). The observed OR for venous thrombosis during use of the LNG-IUD as compared with non-users was 0.3 (95% CI 0.1–1.1) [3], and the observed OR during use of the transdermal patch as compared with use of the LNG-containing combined oral contraceptives was variable, and reported to be between 1.3 and 2.0 [30]. The risk of venous thrombosis during use of a Cu-IUD is unknown, but is not expected to be increased as compared with non-users. There are no data on the contraceptive vaginal ring as compared with non-users, but a study on the risk of venous thrombosis of the contraceptive ring showed a 1.56-fold increased risk as compared with a group of combined oral contraceptives with low estrogen [13].

The SHBG levels measured in this study are associated with the ORs reported in the recent literature: higher SHBG levels are present in users of contraceptives with a higher risk of venous thrombosis (Table 3; Fig. 3).

Discussion

In this study, we observed positive associations between the effects of hormonal contraceptives on SHBG levels, the nAPCsr and the thrombotic risk reported in the recent literature. A high nAPCsr in the thrombin generation-based test indicate an increased resistance to APC, and is reported to be a risk factor for venous thrombosis [11]. Together, these observations support the hypothesis that both the APCsr and SHBG levels are markers for the risk of venous thrombosis during the use of hormonal contraceptives.

Table 2 Mean sex hormone-binding globulin (SHBG) and activated protein C (APC) resistance levels, mean differences (MDs) and 95% confidence intervals (CIs) for non-users as compared with levonorgestrel (LNG)/ethinylestradiol (EE) users

		SHBG (nmol L^{-1})					APC resistance (ratio)		
			Compared with non-use		Compared with LNG/EE		Compared with non-use		
Contraceptive	*N*	Mean	MD	95% CI	MD	95% CI	Mean	MD	95% CI
None	13	53.22	Ref.				1.54	Ref.	
LNG-IUD	60	43.77	− 9.45	− 22.08 to 3.17	− 27.23	− 39.03 to − 15.44	0.85	− 0.69	− 1.03 to − 0.36
Cu-IUD	17	57.52	4.29	− 7.26 to 15.85	− 13.48	− 34.00 to 7.03	1.03	− 0.51	−0.93 to − 0.09
LNG/EE	72	71.00	17.78	− 5.46 to 41.02	Ref.		2.66	1.12	0.69 to 1.54
DSG/EE	18	162.78	109.55	82.98 to 136.13	91.78	69.60 to 113.96	3.94	2.40	1.93 to 2.86
DRSP/EE	47	161.04	107.82	7.10 to 139.54	90.04	72.23 to 107.85	3.53	1.98	1.49 to 2.48
CPA/EE	22	210.27	157.05	121.03 to 193.07	139.27	116.41 to 162.13	4.00	2.46	2.07 to 2.84
ENG/EE (ring)	6	258.93	205.71	104.77 to 306.65	187.93	136.51 to 239.36	3.02	1.47	0.94 to 2.02
NGM/EE (patch)	7	317.57	264.35	179.63 to 349.06	246.57	201.29 to 291.85	3.12	1.57	0.87 to 2.28

CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; DSG, desogestrel; DRSP, drospirenone; ENG, etonogestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

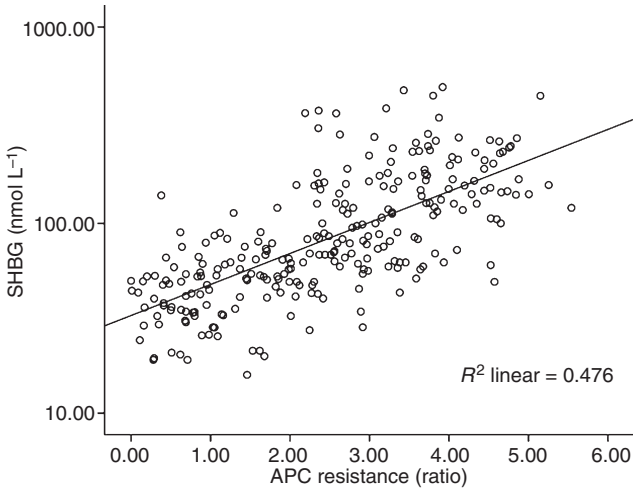

Fig. 2. The association between sex hormone-binding globulin (SHBG) and activated protein C (APC) resistance. Equation: $\log_{10}(\text{SHBG}) = 1.525 + (0.160 \times \text{nAPCsr})$.

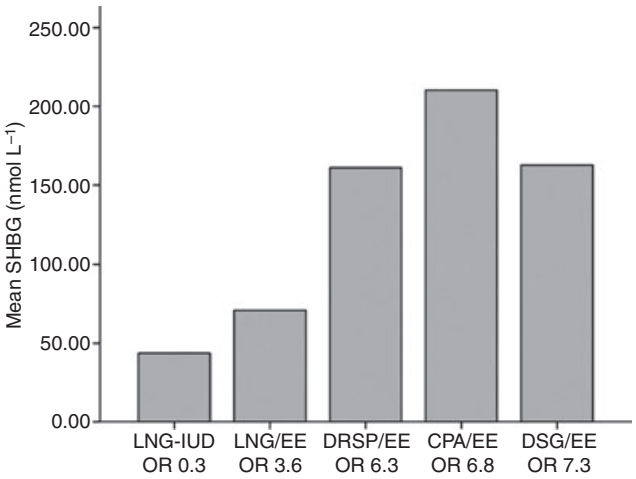

Fig. 3. The association between odds ratios (ORs) of the risk of venous thrombosis of various contraceptives as published in the recent literature [3,31,32] and sex hormone-binding globulin (SHBG) levels of hormonal contraceptives. CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device.

Table 3 The odds ratios (ORs) of venous thrombosis during the use of different types of hormonal contraceptive as compared with non-users, according to the recent literature [3,31,32]

	Risk		
Contraceptive	OR	95% CI	Reference
None	Ref.		
LNG-IUD	0.3	0.1–1.1	[31]
Cu-IUD	–	–	
LNG/EE	3.6	2.9–4.6	[3]
DSG/EE	7.3	5.3–10.0	[3]
DRSP/EE	6.3	2.9–13.7	[3]
CPA/EE	6.8	4.6–10.0	[3]
ENG/EE (ring)	–	–	
NGM/EE (patch)	1.3–2.0	–	[32]

CI, confidence interval; CPA, cyproterone acetate; Cu-IUD, copper-releasing intrauterine device; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; ENG, etonogestrel; LNG, levonorgestrel; LNG-IUD, levonorgestrel-releasing intrauterine device; NGM, norelgestromine.

The use of the LNG-IUD did not increase SHBG levels, which is in concordance with recent clinical data. In a national cohort study by Lidegaard *et al.* [12], users of the LNG-IUD had no increased risk of thrombosis as compared with non-users (relative risk 0.83; 95% CI 0.63–1.08). This was confirmed by van Hylckama Vlieg *et al.* [31], who also did not find an increased risk in a recent case–control study (OR 0.3%; 95% CI 0.1–1.1).

Limited data are available on the thrombotic risk of the contraceptive transdermal patch and vaginal ring. Conflicting results have been reported on the thrombotic safety of the contraceptive patch, with estimates of the thrombotic risk varying between 0.9 (95% CI 0.5–1.6) [32] and 2.4 (95% CI 1.1–5.5) [33] as compared with oral contraceptives containing norgestimate and EE [29,30,34].

Recently, the first study on the risk of venous thrombosis of the contraceptive ring has been published by the FDA [13]. Use of the vaginal ring was associated with a 1.56-fold (95% CI 1.02–2.37) higher risk of thrombosis than in a group of users of combined oral contraceptives with low estrogen. The study also observed a 1.55-fold (95% CI 1.02–2.37) higher thrombotic risk during use of the transdermal patch. In our study, users of the vaginal ring and the transdermal patch had the highest SHBG levels of all contraceptive users. These results are in agreement with earlier studies reporting increases in SHBG of $\sim$ 260% for transdermal patch users and $\sim$ 150% for vaginal ring users as compared with pretreatment levels [18,26]. The increased SHBG levels in women using the patch and ring as compared with women using combined oral contraceptives containing LNG suggest an increased thrombotic risk.

The increased risk of the vaginal ring might be explained by the fact that ENG is the active metabolite of DSG. According to the recent literature, the use of combined hormonal contraceptives containing DSG is associated with a 1.82-fold (95% CI 1.49–2.22) higher risk of venous thrombosis than the use of combined oral contraceptives containing LNG/EE [6]. However, peak serum concentrations of EE and DSG are significantly lower in women using the contraceptive ring than in women using a combined oral contraceptive containing DSG and EE [35].

The increased risk of the transdermal patch might be explained by the 60% higher exposure to EE, as measured by the area under the curve and steady-state concentration, during use of the contraceptive patch than use of an oral contraceptive composed of NGM and EE. NGM exposure is similar during use of the contraceptive patch and pill [36,37]. As the increased SHBG levels in users of the patch and ring in our study are based on a small number of participants, further studies are indicated to confirm these results and to allow definite conclusions to be drawn.

The difference in SHBG levels between the hormone preparations was not the result of differences between women, but was rather the result of differences between contraceptive methods, as shown by the women who switched from one contraceptive type to another in the original studies. For example, switching from a combined hormonal contraceptive containing CPA to a combined hormonal contraceptive containing LNG resulted in a mean decrease of SHBG level of 150 nmol L^{-1} (95% CI -206 to -94) [6,19,20].

Currently, a biological explanation for the association between the changes in SHBG level and APC resistance induced by hormonal contraceptives is lacking. It is known that estrogen increases the risk of venous thrombosis, and that a higher dose is associated with a higher risk. We propose that SHBG reflects the overall estrogenicity of a hormonal contraceptive, and thereby the risk of venous thrombosis. SHBG and several coagulation factors and anticoagulant proteins are synthesized in the liver, and hormonal contraceptives, which are metabolized in the liver, might interfere with the synthesis of both SHBG and coagulation factors. There are now different studies demonstrating an association between SHBG and the risk of venous thrombosis. However, the mechanism is still not known, and further research is needed to unravel the association, changes in other proteins produced in the liver, changes of hemostatic parameters, and the increased risk of venous thrombosis.

We acknowledge that caution is required when surrogate markers are used, as they can be severely misleading [38]. Preferably, a surrogate marker should be validated in a prospective trial in which both the surrogate marker and the clinical endpoint are assessed. However, for very rare events, such as venous thrombosis during combined hormonal contraceptive use, a clinical study is almost impossible, owing to the required number of participants. In order to prospectively demonstrate a doubling of the risk of venous thrombosis between two different combined hormonal contraceptives with a power of 80% and a significance level of 5%, a cohort of approximately 500 000 women must be followed for 1 year [27]. Case–control studies only become possible postmarketing [27,39]. Such a large sample size makes it almost impossible for a pharmaceutical company to evaluate the risk of venous thrombosis of a new preparation before market authorization.

There are now reasonably reliable data on the risk of venous thrombosis from several epidemiological studies, showing that the combination of EE and LNG carries the lowest risk of venous thrombosis of all combined hormonal contraceptives [1,3,5,6]. Comparison of the SHBG levels in users of a new preparation with that in users of EE plus LNG could give an estimation of the magnitude of the risk of venous thrombosis before a new preparation is launched, and should be included in the general benefit–risk analysis of the new preparation. SHBG measurement is already recommended in guidelines applying to the clinical development of a new combined hormonal contraceptive by the European Medicines Agency.

In conclusion, our data support the idea that SHBG could be a useful marker for estimating the risk of venous thrombosis of a new hormonal contraceptive. Preferably, the effect of a new hormonal contraceptive on SHBG should be compared with the effect of the combined hormonal contraceptive with the lowest reported risk of venous thrombosis, i.e. an oral preparation containing EE plus LNG.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Importance of Family History as a Risk Factor for Venous Thromboembolism

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Editorial

Importance of Family History as a Risk Factor for Venous Thromboembolism

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Venous thromboembolism (VTE) is a multifactorial disease with many known genetic and acquired risk factors.[1] A positive family history is an independent risk factor for VTE that may reflect the presence of a hereditary thrombophilic disorder. However, the predictive value of a positive family history for detection of known heritable causes of VTE is low,[2,3] suggesting that there are as-yet undiscovered genetic or environmental risk factors that account for the familial clustering of this disorder.

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In the current edition of *Circulation*, Zöller and colleagues[4] present the results of their database linkage study that explored the role of family history as a risk factor for VTE. Using unique individual national identifiers to link data from the national Swedish Multigenerational Registry (a family data set that links second-generation Swedes born since 1932 with their siblings) with information from the Swedish Hospital Discharge Register (which contains complete data on all hospital discharge diagnoses since 1986), they identified 45 362 patients hospitalized for deep vein thrombosis, pulmonary embolism, thrombophlebitis (including superficial phlebitis), or thrombosis in unusual sites over a 21-year period. On the basis of results from other population-based epidemiological studies, the reported VTE incidence rates of 32.5 per 100 000 in male and 36.2 per 100 000 in female individuals are somewhat lower than expected,[5,6] likely reflecting the high rate of out-of-hospital VTE management in Sweden.[7] However, the exponential rise in incidence rates with increasing age is consistent with prior work. As previously reported,[5] there is a spike in incidence rates among female individuals 10 to 40 years of age, reflecting the reproductive period; a male predominance then emerges after 50 years of age.

The most striking findings of the study by Zöller and colleagues were the increased incidence rates and standardized incidence ratios for VTE in patients with a history of VTE in ≥1 siblings and the effect of age on the standardized incidence ratios. The overall standardized incidence ratios ranged from 2 to 3, which is consistent with prior reports,[3] but the ratios were >20-fold higher among those with ≥2 affected proband siblings than those with a single affected proband sibling, making this one of the strongest risk factors for VTE identified to date (the Table).[8] The highest incidence rates among patients with a familial sibling history were observed in those ≥70 years of age (386.5 per 100 000 in male and 374.3 per 100 000 in female individuals), whereas the highest familial standardized incidence ratios occurred at much younger ages (ratio of 4.34 among male individuals 20 to 29 years of age and 5.49 among female individuals 10 to 19 years of age). Familial standardized incidence ratios declined with increasing age, reflecting the diminishing impact of family history as a risk factor for VTE at older ages. Environmental sharing appeared to have little effect on the risk of VTE, a finding that suggests that genetic factors explain most of the increased familial risk.

The study by Zöller et al was rigorously conducted and is the largest population-based study to date that explores the importance of family history as a risk factor for VTE. The study provides robust evidence of the strength of the association and the influence of age and sex on this association. A potential limitation of the study is that it was restricted to hospitalized cases of VTE, thereby excluding information on siblings who were treated as outpatients. One method to explore the impact of excluding outpatients would be to examine the consistency of the results over the 21-year study period because the shift from inpatient to outpatient management of VTE gained increasing popularity over the years. Although this was not done, outpatient management of VTE is unlikely to have had much impact on the standardized incidence ratios because there is no reason to suspect that patients with a familial sibling VTE history would be affected differently by outpatient treatment than those without such a history. Another potential limitation of this study is the lack of information about known risk factors for VTE. The absence of this information precludes exploration into the extent to which genetic and environmental VTE risk factors contribute to the familial clustering of cases.

The findings of this study have implications for clinical practice. Family history is a powerful risk factor for VTE, particularly in those who have >1 sibling with a history of VTE. Known genetic thrombophilic disorders account for only a fraction of the risk conferred by a positive family history,[3] indicating that testing family members does little to improve risk prediction. In families in which >1 sibling has a history of VTE, the high risk of VTE mandates vigilance for early detection of recurrent disease, avoidance of recognized environmental risk factors such as estrogen-containing compounds, and vigorous thromboprophylaxis during periods of

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Table. Risk Factors for Venous Thromboembolism

Weak Risk Factors (Odds Ratio <2)	Moderate Risk Factors (Odds Ratio 2 to 9)	Strong Risk Factors (Odds Ratio >10)
Increasing age	Previous VTE	Family history of VTE affecting ≥ 2 siblings
Obesity	Family history of VTE affecting 1 sibling	Hip fracture
Bed rest >3 d	Central venous line	Hip or knee replacement
Immobility owing to sitting (eg, prolonged car or air travel)	Congestive heart failure/respiratory failure	Major general surgery
Laparoscopic surgery	Arthroscopic knee surgery	Major trauma
Varicose veins	Oral contraceptive pill or hormone replacement therapy	Spinal cord injury
Pregnancy, antepartum	Malignancy Paralytic stroke Pregnancy, postpartum	

VTE indicates venous thromboembolism. Adapted from Reference 8.

risk such as surgery or immobilization for medical illness. For young women with a strong family history of VTE, thromboprophylaxis during pregnancy and the puerperium may also be a consideration.

What are the implications of this study for further research? Although thrombophilic disorders are found in 30% to 50% of young patients with VTE, many patients have none of the known defects. The study by Zöller and colleagues suggests that searches for new genetic determinants of VTE should focus on young patients with >1 sibling with a history of VTE.

The pathogenesis of VTE reflects a complex interplay between inherited and acquired risk factors.[9] The study by Zöller et al highlights the importance of a family history of VTE over the life cycle. For younger patients, a positive family history is a major risk factor for VTE that trumps known thrombophilic disorders. What are the genetic defects responsible for this association? This is an area that deserves further study.

Disclosures

None.

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ORIGINAL ARTICLE

Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

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ABSTRACT

BACKGROUND

Although several studies have assessed the risk of venous thromboembolism with newer hormonal contraception, few have examined thrombotic stroke and myocardial infarction, and results have been conflicting.

METHODS

In this 15-year Danish historical cohort study, we followed nonpregnant women, 15 to 49 years old, with no history of cardiovascular disease or cancer. Data on use of hormonal contraception, clinical end points, and potential confounders were obtained from four national registries.

RESULTS

A total of 1,626,158 women contributed 14,251,063 person-years of observation, during which 3311 thrombotic strokes (21.4 per 100,000 person-years) and 1725 myocardial infarctions (10.1 per 100,000 person-years) occurred. As compared with nonuse, current use of oral contraceptives that included ethinyl estradiol at a dose of 30 to 40 μg was associated with the following relative risks (and 95% confidence intervals) for thrombotic stroke and myocardial infarction, according to progestin type: norethindrone, 2.2 (1.5 to 3.2) and 2.3 (1.3 to 3.9); levonorgestrel, 1.7 (1.4 to 2.0) and 2.0 (1.6 to 2.5); norgestimate, 1.5 (1.2 to 1.9) and 1.3 (0.9 to 1.9); desogestrel, 2.2 (1.8 to 2.7) and 2.1 (1.5 to 2.8); gestodene, 1.8 (1.6 to 2.0) and 1.9 (1.6 to 2.3); and drospirenone, 1.6 (1.2 to 2.2) and 1.7 (1.0 to 2.6), respectively. With ethinyl estradiol at a dose of 20 μg, the corresponding relative risks according to progestin type were as follows: desogestrel, 1.5 (1.3 to 1.9) and 1.6 (1.1 to 2.1); gestodene, 1.7 (1.4 to 2.1) and 1.2 (0.8 to 1.9); and drospirenone, 0.9 (0.2 to 3.5) and 0.0. For transdermal patches, the corresponding relative risks were 3.2 (0.8 to 12.6) and 0.0, and for a vaginal ring, 2.5 (1.4 to 4.4) and 2.1 (0.7 to 6.5).

CONCLUSIONS

Although the absolute risks of thrombotic stroke and myocardial infarction associated with the use of hormonal contraception were low, the risk was increased by a factor of 0.9 to 1.7 with oral contraceptives that included ethinyl estradiol at a dose of 20 μg and by a factor of 1.3 to 2.3 with those that included ethinyl estradiol at a dose of 30 to 40 μg, with relatively small differences in risk according to progestin type. (Funded by the Danish Heart Association.)

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The risk of thromboembolic complications with the use of hormonal contraception is an important issue scientifically and is relevant for counseling women about contraceptive options. Several studies have assessed the risk of venous thromboembolism associated with the use of newer hormonal contraceptive products, (i.e., those from the past 10 years)[1-8] but few studies have examined thrombotic stroke and myocardial infarction, and the results of available studies have been conflicting.[7-20] Although arterial complications are less frequent than venous complications among young women, the short-term and long-term consequences of arterial complications are often more serious.

In addition to oral contraceptive pills and intramuscular injections of depot medroxyprogesterone acetate, the options for hormonal contraception currently include a vaginal ring, transdermal patches, subcutaneous implants, and the levonorgestrel-releasing intrauterine device (IUD; known in Europe as the levonorgestrel intrauterine system). The aim of this study was to assess the risks of thrombotic stroke and myocardial infarction associated with the use of various types of hormonal contraception, according to estrogen dose, progestin type, and route of administration.

Methods

Study Population

We followed an open historical cohort of Danish women, 15 to 49 years old, for a 15-year period, from January 1995 through December 2009. The population was identified on the basis of data from Statistics Denmark. A unique personal identification number that is given to all Danish citizens at birth and to people who have immigrated to Denmark is used in all public registries, allowing reliable linkage of data among different registries. Statistics Denmark also provided data on length of schooling, status of education (ongoing or finished), vital status, and emigration. Data were censored at the time of death or emigration.

Approval for the study was obtained from the Danish Data Protection Agency. Because this was a registry study, the requirement for written informed consent was waived.

End Points

Data on clinical end points were obtained from the National Registry of Patients, which has collected discharge diagnoses from public and private Danish hospitals since 1977, and the Register of Causes of Death. The relevant diagnostic codes are listed in Table 1S in the Supplementary Appendix, available with the full text of this article at NEJM.org. We identified thrombotic stroke using the diagnostic code for cerebral infarction (which is used for both cerebral thrombosis and cerebral embolism) and the less-specific diagnostic code for "cerebral apoplexy"; thrombotic events have been found to constitute 80 to 90% of the events in young women that are classified as cerebral apoplexy.[21-23] Transient cerebral ischemic attack was not included.

To restrict the analysis to first-ever events, we excluded data from all women who had received a diagnosis of any type of venous or arterial thrombotic event before the study period (i.e., from 1977 through 1994). In addition, data from women who had gynecologic, abdominal, breast, lung, or hematologic cancer before the study period were excluded or, if any of these diseases occurred during the study period, were censored at the time of diagnosis (Table 1S in the Supplementary Appendix).

The National Registry of Patients also records surgical codes from public and private hospitals. Data from women who had undergone bilateral oophorectomy, unilateral oophorectomy two times, hysterectomy, or a sterilization procedure were either excluded at baseline or censored at the time of surgery (Table 1S in the Supplementary Appendix).

Pregnancy outcomes and gestational ages at termination were identified according to the codes specified in Table 1S in the Supplementary Appendix. Data from women were temporarily censored during pregnancy, which was defined as the period from conception through 3 months after delivery (or 1 month after abortion or termination of ectopic pregnancy). Data from women with a coagulation disorder were censored at the recorded date of the initial diagnosis (Table 1S in the Supplementary Appendix).

Finally, information about smoking habits was obtained from the National Registry of Patients. Information about whether a woman smoked was available for 480,223 women, covering 5.2 million person-years of observation (37% of risk time).

Prescription Data

The Register of Medicinal Products Statistics provided information, updated daily, about filled

prescriptions for oral contraceptives and other types of hormonal contraception from 1995 through 2009. We categorized the products in use according to estrogen dose, progestin type, and route of administration.

Duration of use was estimated to be the period from the date of the prescription until the end date of the last filled prescription or the date of a study event. Further details regarding the assessment of duration of use are given in a previous report.[6] From the prescription registry, we also obtained updated information about medication for the treatment of diabetes, heart arrhythmia, hypertension, and hyperlipidemia. Data from women with prescriptions for ovarian stimulants were censored at the time that such a prescription was first filled.

STATISTICAL ANALYSIS

Using Poisson regression, we calculated the estimated risks of thrombotic events, with stratification according to estrogen dose (50 μg, 30 to 40 μg, or 20 μg of ethinyl estradiol or progestin-only contraceptive), progestin type, route of administration, and duration of use (<1 year, 1 to 4 years, or >4 years). The reference group comprised nonusers (women who had never used hormonal contraception as well as former users), and the estimates of relative risk were adjusted for age, calendar year, length of schooling, educational level (ongoing or completed), and status with respect to hypertension, heart disease, diabetes, and hyperlipidemia (defined by the use or nonuse of medications for these conditions). Imputed values for missing data on smoking status were calculated with the use of standard procedures of imputation,[24] and sensitivity analyses that included imputation for smoking status were conducted (Table 2S in the Supplementary Appendix).

Tests for interactions of the different types of hormonal contraception with age and with predisposing diseases were conducted. Sensitivity analyses in which only the specific code for cerebral infarction, DI63, was included were performed for all product types. Finally, sensitivity tests were conducted for the three periods of 1995 through 1999, 2000 through 2004, and 2005 through 2009.

RESULTS

THROMBOTIC EVENTS IN THE STUDY COHORT

After the exclusion and censoring of data as specified in Figure 1, the study cohort included 1,626,158 women, with 14,251,063 person-years of observation. During this period, 3311 women had a first thrombotic stroke (1633 events [49.3%] were coded as cerebral infarction, and 1678 [50.7%] as cerebral apoplexy), and 1725 had a first myocardial infarction. The case fatality rate during the primary event or subsequent hospital stay was 1.0% for thrombotic stroke (34 of 3311 women) and 10.8% for myocardial infarction (186 of 1725).

After adjustment for calendar year, educational level, status with respect to predisposing diseases,

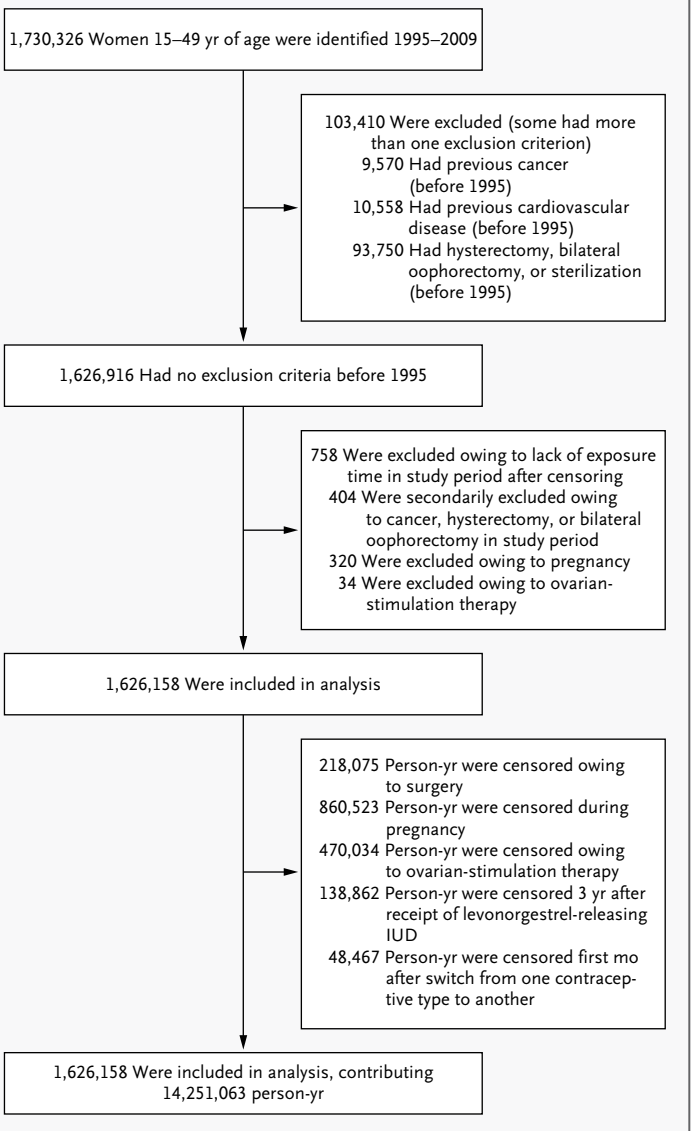

Figure 1. Screening, Exclusions, and Data Censoring.
Shown are the numbers of women who met the various exclusion criteria and those for whom data were censored. IUD denotes intrauterine device.

and use or nonuse of hormonal contraception, the incidence rates of thrombotic stroke and myocardial infarction were increased by factors of 20 and 100, respectively, in the oldest age group (45 to 49 years) as compared with the youngest age group (15 to 19 years) (Table 1).

Women with the highest level of education had about half as many thrombotic strokes and about one third as many myocardial infarctions as women with the lowest level of education (Table 1). The relative risks of thrombotic stroke and myocardial infarction, respectively, among women who filled prescriptions for medications to treat predisposing disorders, as compared with women who did not fill prescriptions for these medications, were as follows: for diabetes, 2.73 (95% confidence interval [CI], 2.32 to 3.22) and 4.66 (95% CI, 3.88 to 5.61); for hypertension, 2.32 (95% CI, 2.14 to 2.50) and 2.17 (95% CI, 1.95 to 2.42); and for hyperlipidemia, 2.11 (95% CI, 1.74 to 2.56) and 1.88 (95% CI, 1.46 to 2.41) (Table 1).

HORMONAL CONTRACEPTION AND ARTERIAL THROMBOSIS

In 4.9 million person-years of use of hormonal contraception, 1051 women had a thrombotic

Table 1. Incidence Rates and Adjusted Relative Risks of Thrombotic Stroke and Myocardial Infarction among Nonpregnant Danish Women, According to Age, Calendar Year, Educational Level, and Predisposing Risk Factors, 1995–2009.

Variable	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
Age							
15–19 yr	2,075,087	70	3.4	0.05 (0.04–0.06)	9	0.4	0.01 (0.01–0.02)
20–24 yr	1,961,761	110	5.6	0.07 (0.06–0.09)	13	0.7	0.02 (0.01–0.03)
25–29 yr	1,906,954	201	10.5	0.16 (0.13–0.18)	41	2.2	0.06 (0.04–0.08)
30–34 yr	2,053,357	317	15.4	0.26 (0.23–0.30)	102	5.0	0.15 (0.12–0.18)
35–39 yr	2,149,752	501	23.3	0.40 (0.36–0.44)	262	12.2	0.36 (0.31–0.41)
40–44 yr	2,104,119	825	39.2	0.65 (0.59–0.71)	534	25.4	0.71 (0.64–0.80)
45–49 yr	2,000,033	1287	64.4	1.00	764	38.2	1.00
Year							
1995	1,110,157	183	16.5	1.00	108	9.7	1.00
1996	1,082,648	172	15.9	0.91 (0.74–1.12)	105	9.7	0.94 (0.72–1.23)
1997	1,052,178	192	18.3	1.02 (0.83–1.25)	104	9.9	0.94 (0.72–1.23)
1998	1,026,757	168	16.4	0.89 (0.72–1.10)	100	9.7	0.90 (0.69–1.19)
1999	1,001,828	219	21.9	1.16 (0.95–1.41)	109	10.9	0.98 (0.75–1.28)
2000	981,241	211	21.5	1.11 (0.91–1.36)	125	12.7	1.12 (0.87–1.45)
2001	959,246	218	22.7	1.15 (0.94–1.40)	133	13.9	1.19 (0.92–1.53)
2002	938,943	224	23.9	1.18 (0.97–1.44)	143	15.2	1.27 (0.99–1.64)
2003	918,924	236	25.7	1.25 (1.03–1.51)	148	16.1	1.32 (1.03–1.70)
2004	903,351	232	25.7	1.22 (1.00–1.48)	126	14.0	1.12 (0.87–1.45)
2005	883,911	243	27.5	1.28 (1.06–1.56)	117	13.2	1.05 (0.80–1.36)
2006	867,957	273	31.5	1.45 (1.20–1.75)	102	11.8	0.91 (0.69–1.20)
2007	852,227	251	29.5	1.34 (1.10–1.62)	121	14.2	1.09 (0.84–1.42)
2008	843,664	232	27.5	1.24 (1.02–1.51)	87	10.3	0.78 (0.59–1.04)
2009	828,032	257	31.0	1.39 (1.15–1.69)	97	11.7	0.89 (0.67–1.18)

Table 1. (Continued.)

Variable	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
Educational level†							
Elementary school completed	3,808,238	1355	35.6	2.06 (1.85–2.29)	816	21.4	3.08 (2.63–3.61)
High school ongoing or completed	1,638,840	198	12.1	1.1 (0.93–1.31)	72	4.4	1.31 (0.99–1.72)
High school and middle education ongoing or completed	3,778,853	1080	28.6	1.4 (1.26–1.56)	587	15.5	1.87 (1.59–2.20)
High school and long education ongoing or completed	2,383,029	470	19.7	1.00	194	8.1	1.00
Unknown	2,642,102	208	7.9	1.88 (1.54–2.28)	56	2.1	2.36 (1.72–3.24)
Risk factor							
Diabetes‡	123,264	186	150.9	2.73 (2.32–3.22)	159	129.0	4.66 (3.88–5.61)
Hypertension‡	1,343,081	1039	77.4	2.32 (2.14–2.50)	581	43.3	2.17 (1.95–2.42)
Hyperlipidemia‡	63,111	139	220.3	2.11 (1.74–2.56)	85	134.7	1.88 (1.46–2.41)
Arrhythmia‡	69,752	68	97.5	1.80 (1.41–2.29)	54	77.4	2.56 (1.95–3.37)
Smoking§	1,195,490	204	17.1	1.57 (1.31–1.87)	112	9.37	3.62 (2.69–4.87)

* Relative risks were adjusted for hormonal contraception and the other variables included in the table.
† In Denmark, middle education is defined as 4 years of education after high school, and long education as 5 to 6 years of education after high school.
‡ Risk factors were identified on the basis of the use of medications that are used to treat these conditions.
§ Data on smoking are for the subpopulation with available information (480,223 women, covering 5.2 million person-years of observation and including about 1.2 million person-years among smokers).

stroke and 497 had a myocardial infarction; the crude incidence rates were 21.4 and 10.1 per 100,000 person-years, respectively. The corresponding incidence rates in 9,336,662 person-years of nonuse, during which 2260 women had a thrombotic stroke and 1228 had a myocardial infarction, were 24.2 and 13.2 per 100,000 person-years, with the higher rates primarily due to older age and a higher frequency of predisposing conditions among nonusers (Table 2).

The risk among previous users was similar to the risk among women who had never used hormonal contraception. The rate ratio for thrombotic stroke among previous users, as compared with women who had never used hormonal contraception, was 1.04 (95% CI, 0.95 to 1.15), and for myocardial infarction, 0.99 (95% CI, 0.86 to 1.13).

After stratifying the data for current users of hormonal contraception according to estrogen dose, progestin type, and route of administration, we estimated the crude incidence rates and adjusted relative risks of thrombotic events for users as compared with nonusers (Table 2). The estimated relative risks of thrombotic stroke and myocardial infarction among users of combined oral contraceptive pills that included ethinyl estradiol at a dose of 30 to 40 μg did not differ significantly according to the type of progestin, ranging from 1.40 to 2.20 for stroke and from 1.33 to 2.28 for myocardial infarction. For both end points, the risk estimates were lowest with contraceptive pills that included norgestimate or cyproterone acetate and were highest with those that included norethindrone or desogestrel (Table 2).

For women who used desogestrel with a reduced dose of ethinyl estradiol (20 μg), as compared with nonusers, the relative risks of thrombotic stroke and myocardial infarction were 1.53 (95% CI, 1.26 to 1.87) and 1.55 (95% CI, 1.13 to 2.13), respectively. For women who used drospirenone with ethinyl estradiol at a dose of 20 μg, the relative risk of thrombotic stroke was 0.88

Table 2. Incidence Rates and Adjusted Relative Risks of Thrombotic Stroke and Myocardial Infarction among Users of Different Types of Hormonal Contraception, as Compared with Nonusers.*

Type of Hormonal Contraception	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)†	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)†
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
None	9,336,662	2260	24.2	1.00	1228	13.2	1.00
Ethinyl estradiol, 50 μg							
Norethindrone	43,234	9	20.8	1.27 (0.66–2.45)	11	25.4	2.74 (1.51–4.97)
Levonorgestrel	54,474	32	58.7	2.26 (1.59–3.20)	36	66.1	4.31 (3.09–6.00)
Ethinyl estradiol, 30 to 40 μg							
Norethindrone	126,984	28	22.1	2.17 (1.49–3.15)	14	11.0	2.28 (1.34–3.87)
Levonorgestrel	460,559	144	31.3	1.65 (1.39–1.95)	91	19.8	2.02 (1.63–2.50)
Norgestimate	453,536	78	17.2	1.52 (1.21–1.91)	28	6.2	1.33 (0.91–1.94)
Desogestrel	313,560	99	31.6	2.20 (1.79–2.69)	43	13.7	2.09 (1.54–2.84)
Gestodene	1,318,962	285	21.6	1.80 (1.58–2.04)	133	10.1	1.94 (1.62–2.33)
Drospirenone	286,770	52	18.1	1.64 (1.24–2.18)	18	6.3	1.65 (1.03–2.63)
Cyproterone acetate	187,145	29	15.5	1.40 (0.97–2.03)	12	6.4	1.47 (0.83–2.61)
Ethinyl estradiol, 20 μg							
Desogestrel	695,603	105	15.1	1.53 (1.26–1.87)	40	5.8	1.55 (1.13–2.13)
Gestodene	564,268	88	15.6	1.70 (1.37–2.12)	21	3.7	1.20 (0.77–1.85)
Drospirenone	23,056	2	8.7	0.88 (0.22–3.53)	0	0	0 (0.00–12.99)
Progestin only							
Norethindrone	85,874	28	32.6	1.35 (0.93–1.96)	9	10.5	0.81 (0.42–1.56)
Levonorgestrel	8,556	1	11.7	0.44 (0.06–3.12)	0	0	0 (0.00–35.01)
Desogestrel	29,185	9	30.8	1.37 (0.71–2.63)	4	13.7	1.46 (0.55–3.90)
Levonorgestrel IUD	184,875	45	24.3	0.73 (0.54–0.98)	31	16.8	1.02 (0.71–1.46)
Implant	24,954	3	12.0	0.88 (0.28–2.72)	3	12.0	2.14 (0.69–6.65)
Other							
Patch	4,748	2	42.1	3.15 (0.79–12.60)	0	0	0 (0.00–63.10)
Vaginal ring	38,246	12	31.4	2.49 (1.41–4.41)	3	7.8	2.08 (0.67–6.48)

* IUD denotes intrauterine device.
† Relative risks were adjusted for age, educational level, calendar year, and risk factors.

(95% CI, 0.22 to 3.53); there were no myocardial infarctions in this group.

None of the progestin-only products, including the levonorgestrel-releasing IUD and the subcutaneous implants, significantly increased the risk of thrombotic stroke or myocardial infarction (Table 2), but the numbers were small for several of these groups. In contrast, the relative risk of thrombotic stroke was 3.15 (95% CI, 0.79 to 12.6) among women who used contraceptive patches and 2.49 (95% CI, 1.41 to 4.41) among those who used a vaginal ring. Numbers of myocardial infarctions were too low to provide reliable estimates.

An analysis adjusted for differences in progestin type, age, and calendar year showed that combined oral contraceptives with doses of ethinyl estradiol of 20 μg, 30 to 40 μg, and 50 μg were associated with a relative risk of thrombotic

stroke of 1.60 (95% CI, 1.37 to 1.86), 1.75 (95% CI, 1.61 to 1.92), and 1.97 (95% CI, 1.45 to 2.66), respectively (P=0.24 for trend). The corresponding relative risks for myocardial infarction were 1.40 (95% CI, 1.07 to 1.81), 1.88 (95% CI, 1.66 to 2.13), and 3.73 (95% CI, 2.78 to 5.00), respectively (P<0.001 for trend).

SMOKING

Information about whether a woman smoked was available for 480,223 women, covering 5.2 million person-years of observation and including 1.2 million person-years among smokers. Smoking status was known for 582 women who had a thrombotic stroke and for 193 women who had a myocardial infarction. For women who smoked as compared with those who did not, the relative risks of thrombotic stroke and myocardial infarction were 1.57 (95% CI, 1.31 to 1.87) and 3.62 (95% CI, 2.69 to 4.87), respectively. However, smoking had no confounding influence on the relative risk of arterial thrombosis among users of different types of hormonal contraception, after adjustment for age and predisposing conditions, and the results of an analysis in which smoking status was imputed were similar to the results with no imputation of smoking status (Table 2S in the Supplementary Appendix).

SENSITIVITY ANALYSES

There was no consistent interaction between the use of oral contraceptives and the relative risk of thrombotic stroke or myocardial infarction in different age groups, and there were no trends according to duration of use for either end point (Table 3). The sensitivity analysis, which included only women with the diagnostic code for cerebral infarction, provided slightly higher risk estimates than our primary analysis of thrombotic stroke (Table 3S in the Supplementary Appendix). Although the incidence rate of thrombotic stroke increased over time, we could not detect any consistent change in the estimated relative risks of the two end points for four different product groups during the three periods of 1995 through 1999, 2000 through 2004, and 2005 through 2009 (data not shown). We found no interaction between the use of hormonal contraception and predisposing disease for the risk of thrombotic stroke or myocardial infarction. The age distribution according to product group is shown in Figure 2S in the Supplementary Appendix.

DISCUSSION

The rates of thrombotic stroke and myocardial infarction increased by factors of 20 and 100, respectively, with increasing age. Only small differences in risk were observed between women who took combination pills containing intermediate-dose ethinyl estradiol (30 to 40 μg) and those who took low-dose ethinyl estradiol (20 μg), and only minor variations in risk were associated with different progestin types.

The increased incidence of thrombotic stroke over the 15-year study period probably reflects improvements in the diagnostic equipment, allowing the detection of small cerebral infarctions, rather than a real increase in incidence. The steep increase in incidence with older age has been shown in several previous studies.[9-11,25] This information has clinical implications, given that arterial thrombosis after the age of 30 years is more frequent and has more serious consequences than venous thrombosis.[6] The risk of arterial thrombosis should therefore be considered together with the risk of venous thrombosis when hormonal contraception is prescribed.

The relative risk of thrombotic stroke of 1.4 to 2.2 among current users of oral contraceptives containing ethinyl estradiol at a dose of 30 to 40 μg is slightly lower than previously reported (Table 4S in the Supplementary Appendix). In a multicenter World Health Organization study, Poulter et al. found that women who used second-generation oral contraceptive pills with levonorgestrel, as compared with nonusers, had a relative risk of thrombotic stroke of 2.7 (95% CI, 1.8 to 4.1) and users of third-generation pills had a relative risk of 1.8 (95% CI, 0.6 to 5.2).[9] Among women who had their blood pressure measured before obtaining a prescription, these risk estimates were reduced to 2.0 (95% CI, 1.1 to 3.6) and 1.6 (95% CI, 0.4 to 6.6), respectively.[9] These estimates are closer to ours, perhaps because a majority of Danish women have their blood pressure checked before obtaining prescriptions for oral contraceptives.

In our secondary analysis, which included only the code for cerebral infarction, we observed a slightly higher relative risk of stroke associated with hormonal contraception, as compared with our primary analysis. This difference may have been due to the inclusion of 15 to 20% of hemorrhagic strokes in the primary analysis that were

Table 3. Relative Risk of Thrombotic Stroke and Myocardial Infarction among Users of Selected Types of Combined Oral Contraception with Ethinyl Estradiol at a Dose of 30 to 40 μg, as Compared with Nonusers, According to Duration of Use.

Type of Hormonal Contraception	No. of Person-yr	Thrombotic Stroke		Myocardial Infarction	
		No. of Events	Relative Risk (95% CI)	No. of Events	Relative Risk (95% CI)
Nonuse	9,336,662	2260	1.00	1228	1.00
Levonorgestrel					
<1 yr	175,205	45	1.72 (1.28–2.32)	24	1.91 (1.27–2.87)
1–4 yr	190,598	49	1.50 (1.13–1.99)	32	1.95 (1.37–2.77)
>4 yr	94,756	50	1.74 (1.31–2.30)	35	2.26 (1.61–3.17)
Desogestrel					
<1 yr	131,061	31	1.91 (1.34–2.73)	10	1.45 (0.78–2.71)
1–4 yr	130,633	38	2.13 (1.54–2.94)	21	2.67 (1.73–4.12)
>4 yr	51,866	30	2.48 (1.73–3.56)	12	2.09 (1.18–3.69)
Gestodene					
<1 yr	541,756	107	1.91 (1.57–2.33)	44	1.97 (1.45–2.67)
1–4 yr	554,721	96	1.53 (1.24–1.88)	47	1.83 (1.36–2.46)
>4 yr	222,485	82	1.86 (1.49–2.33)	42	2.08 (1.52–2.84)
Drospirenone					
<1 yr	139,543	30	2.00 (1.38–2.88)	8	1.64 (0.81–3.30)
1–4 yr	116,873	11	0.84 (0.46–1.52)	8	1.91 (0.95–3.84)
>4 yr	30,353	11	2.20 (1.21–3.98)	2	1.12 (0.28–4.50)
All above types					
<1 yr	987,564	213	1.90 (1.64–2.20)	86	1.85 (1.48–2.31)
1–4 yr	992,825	194	1.55 (1.33–1.80)	108	1.99 (1.63–2.43)
>4 yr	399,461	173	1.93 (1.65–2.26)	91	2.11 (1.70–2.62)

coded as cerebral apoplexy, supporting the finding that oral contraception is associated with a lower risk of cerebral hemorrhage than of cerebral infarction.[26-28]

Heinemann et al. reported a case–control study showing that women who used second-generation oral contraceptive pills with levonorgestrel or norgestimate had a risk of thrombotic stroke that was 2.7 times (95% CI, 1.5 to 4.6) as high as the risk among nonusers and those who used third-generation pills had a risk that was 3.4 times (95% CI, 1.9 to 6.4) as high.[10] These estimates are higher than those reported in the present study.

In a previous Danish case–control study that covered the period from 1994 through 1998, we found that users of second-generation oral contraceptive pills had a risk of cerebral thromboembolism that was 2.2 times (95% CI, 1.6 to 3.0) as high as the risk among nonusers.[11] The odds ratio for cerebral thromboembolism among users of third-generation pills was 1.4 (95% CI, 1.0 to 1.9). These results are in accordance with our current findings.

Gronich et al. recently found that oral contraceptives with drospirenone and ethinyl estradiol at a dose of 30 μg were associated with the same magnitude of risk as second-generation and third-generation pills with the same dose of estrogen[8] — results that are in agreement with ours. Our data suggest a relatively high risk of thrombotic stroke with the use of a vaginal ring and possibly with the use of transdermal patches. Until further evidence emerges, one might expect a higher risk of thrombotic stroke with parenteral administra-

tion than with oral administration (estrogen combined with progestin).

There was a relatively high correlation in risk estimates for thrombotic stroke and myocardial infarction among the different product groups — a finding that increases the likelihood that the observed differences in risk were real rather than random variations. One previous study showed a tendency toward a higher relative risk of myocardial infarction with the use of third-generation, as compared with second-generation, oral contraceptives,[16] three showed the opposite result,[13,14,19] and one showed no difference[18] (Table 4S in the Supplementary Appendix). We found no consistent difference according to progestin type, but the risk decreased with lower doses of estrogen. We also found that low-dose pills were associated with approximately a 50% increase in the risk of myocardial infarction and intermediate-dose pills with up to a 100% increase in risk.

A crucial point in all registry-based studies is the validity of the diagnostic codes. In our 2002 study, we excluded 5.0% of women with a diagnosis of thrombotic stroke because of an absence of confirmation from the patient or the treating department.[11] The diagnosis of myocardial infarction has been found to be valid in 93.6% of patients of all ages,[29] and the percentage is probably higher among young patients. Any diagnostic misclassification may have led to an underestimation of the relative risks among current users. Another limitation is that, for some women, there may have been a time lag between the date of the prescription and the date the medication was actually started.

We had detailed and valid exposure information because the prescriptions were transferred electronically from the pharmacies by bar codes linked to the personal identification number. We were thus free of recall bias, an issue of concern in all retrospective case–control studies. The national cohort design ensured a large sample and allowed the calculation of risk estimates for specific product groups according to estrogen dose, progestin type, and route of administration — the majority with an acceptable precision. The design also avoided the problem of sample reduction due to nonresponse in survey studies, ensuring a high external validity.

For the levonorgestrel-releasing IUD, we had information only about the dates that the women received the IUD. Although this IUD has a valid period of 5 years, many women have it removed before the expiration date. Because of this uncertainty, we censored data for women with a levonorgestrel-releasing IUD after 3 years, unless another prescription for hormonal contraception was filled before that date. This approach reduced our exposure time for this specific product but increased the probability that the women who were classified as having a levonorgestrel-releasing IUD actually did have it.

Data on body-mass index were not available, but body-mass index was not a confounder in our previous study.[11] Smoking, although an important risk factor for arterial thrombosis, had no confounding influence in either this study or our previous one, in which we had more comprehensive information about this potential confounder. Therefore, it is not likely that our results were strongly influenced by incomplete data on these two potential confounders. However, in the absence of definitive data, we cannot be sure whether there would be an interaction with smoking.

In conclusion, women who used oral contraceptives with ethinyl estradiol at a dose of 30 to 40 μg had a risk of arterial thrombosis that was 1.3 to 2.3 times as high as the risk among nonusers, and women who used pills with ethinyl estradiol at a dose of 20 μg had a risk that was 0.9 to 1.7 times as high, with only small differences according to progestin type. We estimate that among 10,000 women who use desogestrel with ethinyl estradiol at a dose of 20 μg for 1 year, 2 will have arterial thrombosis and 6.8 women taking the same product will have venous thrombosis. Although venous thrombosis is three to four times as frequent as arterial thrombosis among young women, the latter is associated with higher mortality and more serious consequences for the survivors. Therefore, these figures should be taken into account when prescribing hormonal contraception.

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RESEARCH

Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10

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Abstract

Objective To assess the risk of venous thrombosis in current users of non-oral hormonal contraception.

Design Historical national registry based cohort study.

Setting Four national registries in Denmark.

Participants All Danish non-pregnant women aged 15-49 (n=1 626 158), free of previous thrombotic disease or cancer, were followed from 2001 to 2010.

Main outcome measures Incidence rate of venous thrombosis in users of transdermal, vaginal, intrauterine, or subcutaneous hormonal contraception, relative risk of venous thrombosis compared with non-users, and rate ratios of venous thrombosis in current users of non-oral products compared with the standard reference oral contraceptive with levonorgestrel and 30-40 µg oestrogen. Diagnoses were confirmed by at least four weeks of anticoagulation therapy after the diagnosis.

Results Within 9 429 128 woman years of observation, 5287 first ever venous thrombosis events were recorded, of which 3434 were confirmed. In non-users of hormonal contraception the incidence rate of confirmed events was 2.1 per 10 000 woman years. Compared with non-users of hormonal contraception, and after adjustment for age, calendar year, and education, the relative risk of confirmed venous thrombosis in users of transdermal combined contraceptive patches was 7.9 (95% confidence interval 3.5 to 17.7) and of the vaginal ring was 6.5 (4.7 to 8.9). The corresponding incidences per 10 000 exposure years were 9.7 and 7.8 events. The relative risk was increased in women who used subcutaneous implants (1.4, 0.6 to 3.4) but not in those who used the levonorgestrel intrauterine system (0.6, 0.4 to 0.8). Compared with users of combined oral contraceptives containing levonorgestrel, the adjusted relative risk of venous thrombosis in users of transdermal patches was 2.3 (1.0 to 5.2) and of the vaginal ring was 1.9 (1.3 to 2.7).

Conclusion Women who use transdermal patches or vaginal rings for contraception have a 7.9 and 6.5 times increased risk of confirmed venous thrombosis compared with non-users of hormonal contraception of the same age, corresponding to 9.7 and 7.8 events per 10 000 exposure years. The risk was slightly increased in women using subcutaneous implants but not in those using the levonorgestrel intrauterine system.

Introduction

Several studies have assessed the risk of venous thrombosis in women using oral contraceptives.[1-10] However, none has assessed the risk in women using subcutaneous hormonal implants. A recent study reported a 48% higher risk of venous thrombosis in women using a vaginal ring compared with those using combined oral contraceptives containing levonorgestrel,[11] and a few studies have reported the risk in women using a transdermal combined contraceptive patch, although the results were conflicting.[12-16]

Using a historical national registry based cohort study design, we assessed the absolute and relative risk of venous thrombosis in Danish women using non-oral hormonal contraception.

Methods

Information on the four national data sources that provided information for the study is provided in detail elsewhere.[10] Briefly, from Statistics Denmark we obtained data on length of schooling, ongoing or finished education, vital status, and emigration of all Danish women aged 15-49 from 1 January 2001 to 31 December 2010. We censored women in cases of death or emigration.

Since 1977 the national registry of patients has collected discharge diagnoses from all public and private hospitals in Denmark (see appendix for a list of the relevant diagnoses and

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Disease codes (international classification of diseases, 10th revision)

codes used in this study). To include only first ever events, we excluded women with any type of venous or arterial thrombotic event before the study period (1977-2000), those with cancer, those who had undergone bilateral oophorectomy or hysterectomy, and those who had been sterilised. From study follow-up we censored a woman's risk time during pregnancy, calculated from conception to three months after delivery, and women with a coagulation disorder from the first time such a diagnosis was recorded (appendix). The registry records only women admitted alive to hospital. Lethal events from venous thrombosis were captured in the national cause of death registry.

A diagnosis of venous thrombosis was confirmed through prescribed anticoagulation therapy recorded in the national registry of medicinal products for at least four weeks after the diagnosis. Since 1 January 1994, and validated from 1995, information on filled prescriptions, including hormonal contraception, collected by the national registry of medicinal products has been complete. From this database we obtained information that had been updated daily on redeemed prescriptions of hormonal contraception from 1995 to 2010. We categorised the products in use according to progestogen type, oestrogen dose, and route of being administered. Duration of use was estimated from the prescribed defined daily doses from the date of prescription until the end date of defined daily doses of the last redeemed prescription or date of a study event. When hormonal contraception was switched without pause, we calculated duration as the sum of use before switch and current use of the new preparation. If a pause lasted for more than four weeks, we reset the length of use. To account for use before study start (left censoring bias), we allocated continuous users of hormonal contraception to the relevant duration of use category on 1 January 2001 by assessing use before the study period back to 1995.

Women who used the levonorgestrel intrauterine system were censored after three years and included again when a new prescription of a hormonal contraceptive product was recorded. This was done owing to missing information on removal of these devices.

Length of schooling and level of education were used as proxies for social class. Four strata were applied: elementary school education only, ongoing or completed high school education, high school and ongoing or ended middle length education, and high school and ongoing or ended long education. A fifth category included women without information on education, typically the youngest women.

We controlled for calendar year to deal with potential secular confounding of increasing adiposity by time.

Data on smoking were not available. Smoking is a weak risk factor for venous thrombosis in young women. However, we have no reason to believe in preferential prescribing of specific types of hormonal contraception among smokers. In Denmark the correlation between smoking and length of education is strong. Thus, controlling for years of schooling and length of education may have captured most confounding (if any) influenced by smoking.

As women treated for infertility with ovarian stimulation drugs (Anatomical Therapeutic Chemical code G03G) are anticipated to be at an increased risk of venous thrombosis, we censored these women during such treatment.

Statistical analysis

Using multiple Poisson regression we analysed data in five year age groups: 15-19, 20-24, and 45-49 years. The non-oral contraceptive products included transdermal patches containing norelgestromin (the active metabolite of norgestimate) and ethinylestradiol, a vaginal ring with etonogestrel (third generation progestogen) and ethinylestradiol, subcutaneous implants containing etonogestrel only, and the levonorgestrel intrauterine system (hormone intrauterine device). Two reference oral contraceptives with levonorgestrel and norgestimate, respectively, were assessed for comparison.

We stratified the estimates into three categories according to length of contraceptive use (<1 year, 1-4 years, >4 years). Absolute as well as relative risk estimates were calculated. The reference group for the relative risk estimates was non-users of all types of hormonal contraception (never users+former users). We calculated rate ratios for the different product types, with users of oral contraceptives containing 30-40 µg oestrogen and levonorgestrel as reference. Tests for interaction with age and year were carried out.

Relative risk estimates were adjusted for age, calendar year, length of schooling and education, and eventually for length of contraceptive use. For all relative risk estimates and incidence rate ratios we calculated 95% confidence limits. We set the level of significance at $P<0.05$.

Results

After exclusions and censoring, 1 626 158 non-pregnant women free of previous thrombotic diseases or cancer contributed 9 429 128 woman years of observation. During this time 5287 diagnoses of first ever venous thrombosis events were recorded, corresponding to 8.1 per 10 000 woman years. Current users of hormonal contraception contributed 3 536 946 woman years and of these, 325 849 concerned non-oral products. Non-users of hormonal contraception contributed 5 892 182 woman years, with an overall incidence of confirmed venous thrombosis of 2.1 per 10 000 woman years. The incidence of venous thrombosis increased by 42.9% during the 10 year study period, or by 4.3% per year (table 1⇓). After adjustment for calendar year and use of hormonal contraception, the incidence increased by 6.3-fold with increasing age and decreased by 51.2% with increasing length of education.

Hormonal contraception and venous thrombosis

Current use of combined oral contraceptives with 30-40 µg oestrogen and levonorgestrel increased the risk of confirmed venous thrombosis by 3.2 (2.7 to 3.8), corresponding to an incidence of 6.2 events per 10 000 exposure years (table 2⇓).

During 6178 woman years, six confirmed events of venous thrombosis were observed in association with transdermal combined contraceptive patches, corresponding to an incidence of 9.7 per 10 000 exposure years. Compared with non-users of hormonal contraception, the adjusted relative risk was 7.9 (3.5 to 17.7) and compared with users of oral contraceptives containing levonorgestrel the rate ratio was 2.5 (1.1 to 5.6, tables 2 and 3⇓). After adjustment for length of use, the rate ratio was reduced to 2.3 (1.0 to 5.2). When compared with oral contraceptives containing the corresponding progestogen (norgestimate), the adjusted rate ratio was 2.2 (1.0 to 5.0).

During 50 334 woman years, 39 confirmed venous thrombosis events were observed with the combined contraceptive vaginal ring, corresponding to an incidence of 7.8 per 10 000 exposure years and an adjusted relative risk of 6.5 (4.7 to 8.9) compared with non-users of hormonal contraception. Compared with users of combined oral contraceptives with levonorgestrel, the rate

ratio was 2.0 (1.4 to 2.9), which after adjustment for length of use was reduced to 1.9 (1.3 to 2.7, tables 2 and 3).

During 29 497 woman years, five confirmed venous thrombosis events were observed with progestogen only subcutaneous implants, corresponding to an incidence rate of 1.7 per 10 000 exposure years and an adjusted relative risk of 1.4 (0.6 to 3.4, table 2) compared with non-users of hormonal contraception. Compared with users of combined oral contraceptives with levonorgestrel, the rate ratio was 0.4 (0.2 to 1.1, table 3).

The adjusted relative risk of confirmed venous thrombosis with the levonorgestrel intrauterine system was 0.6 (0.4 to 0.8, table 2). Compared with users of combined oral contraceptives with levonorgestrel, the rate ratio was 0.2 (0.1 to 0.3, table 3).

After stratification according to length of use, the relative risk of venous thrombosis in women using combined oral contraceptives was reduced with increasing length of use (table 4⇓). No reduction by time was seen in users of transdermal combined contraceptive patches or progestogen only contraception, and no consistent changes were seen for women who used the vaginal ring.

Discussion

Women who use combined hormonal transdermal patches or vaginal rings for contraception have a 7.9 or 6.5 times increased risk of venous thrombosis compared with non-users of hormonal contraception of the same age, corresponding to 9.7 and 7.8 events per 10 000 exposure years. The risk was slightly increased in women using subcutaneous implants but not in those using the levonorgestrel intrauterine system.

An incidence rate of confirmed venous thrombosis in users of transdermal patches of 1 in 1000 exposure years was found in a recent American study,[11] and a relative risk of 7.9 compared with non-users of hormonal contraception or twice the risk with use of the corresponding combined oral contraceptive containing norgestimate in several previous studies[11 14-16] although not all[12 13] (table 5⇓). These results are supported by pharmacokinetic studies showing 60% higher plasma levels of oestrogen in women who use transdermal patches compared with those using the corresponding combined oral contraceptive.[17]

With an incidence of 7.8 confirmed events per 10 000 exposure years, the vaginal ring conferred a 90% higher risk of venous thrombosis than did combined oral contraceptives containing levonorgestrel, bringing the risk to the same level as that of combined oral contraceptives with third and fourth generation progestogens, and compatible with the Food and Drug Administration study.[11] Supporting our and the FDA results is the three[18] and five times[19] increase in sex hormone binding globulin in users of vaginal ring contraception compared with users of combined oral contraceptives containing levonorgestrel, and the activated protein C sensitivity ratio 3.75 times higher than with oral contraceptives,[19] both considered as surrogate markers for the risk of venous thrombosis.

The modest non-significant 40% increased relative risk of venous thrombosis in women using subcutaneous implants is not surprising, as other types of progestogen only contraception do not confer an increased risk,[10] and it is less than half the risk found in users of combined oral contraceptives containing levonorgestrel.

The low risk of venous thrombosis in users of the levonorgestrel intrauterine system has been shown in previous studies.[7 10] In the present study this product actually significantly decreased the risk of venous thrombosis, suggesting that the influence of progestogen only contraception on risk of venous thrombosis may depend on dose.

The inconsistent changes with length of use for the non-oral products could be influenced by the low power in some of the length of use categories. Another possibility, however, is that the non-oral route influences the coagulation system and liver differentially compared with the oral route. Nor did the FDA report show any consistent change in risk with length of use of either the patch or the vaginal ring.

The clinical implications of the findings can be expressed in terms of the number of women who should change their hormonal contraceptive from the transdermal patch or the vaginal ring to combined oral contraceptives containing levonorgestrel to prevent one event of venous thrombosis in a year. If the incidence rate of venous thrombosis in women using combined oral contraceptives containing levonorgestrel is 6 per 10 000 exposure years, the vaginal ring is 11 per 10 exposure years, and the transdermal patch is 14 per 10 000 exposure years, then 2000 women using the vaginal ring and 1250 using the transdermal patch should shift to combined oral contraceptives with levonorgestrel to prevent one event of venous thrombosis in one year. A risk of 10 per 10 000 woman years implies a risk of venous thrombosis of more than 1% over a 10 year user period. Therefore women are generally advised to use combined oral contraceptives with levonorgestrel or norgestimate, rather than to use transdermal patches or vaginal rings.

Strengths and limitations of the study

The inclusion of all Danish non-pregnant women over a decade ensures outstanding external validity. Information on use of hormonal contraception from a prescription database is the most reliable data on exposure available today for four reasons. Firstly, each pharmacy transfers data electronically by bar codes, eliminating typing errors. Secondly, the collection of these data in a central national database is done primarily for reimbursement purposes and therefore should not be biased by the pursuit of pharmacoepidemiological studies. Thirdly, the continued daily update of information on use eliminates recall bias, as we know from case-control studies, and the problems of continuous updating of data on exposure in cohort studies. Fourthly, we eliminated the problem of left censoring bias by assessing exposure to hormonal contraception over a six year period before our study started. And we were able to validate each venous thrombosis event by linking individual data on diagnosis to succeeding anticoagulation therapy.

We could not control for family disposition or for body mass index. Adiposity is a well documented risk factor for venous thrombosis. So far no study has shown any confounding influence from adiposity, as the rate ratio between hormonal contraception with different progestogens was not changed in studies adjusting for this information.[6 8 20]

Conclusion

Use of transdermal patches and vaginal rings conferred incidence rates of 9.7 and 7.8 confirmed venous thromboses per 10 000 exposure years, and relative risks of 7.9 and 6.5 compared with non-use of hormonal contraception, respectively. A subcutaneous progestogen only implant may increase the risk by 40%, whereas the levonorgestrel intrauterine system did not confer any increased risk, but perhaps even protection.

This study was approved by the Danish Data Protection Agency (J No 2010-41-4778).

What is already known on this topic

Combined oral contraceptives with levonorgestrel or norgestimate confer half the risk of venous thrombosis than oral contraceptives containing desogestrel, gestodene, or drospirenone

Progestogen only pills do not confer an increased risk of venous thrombosis

What this study adds

Women who use combined contraceptive transdermal patches are at an increased risk of venous thrombosis about eight times that of non-users of hormonal contraception, corresponding to 9.7 events per 10 000 exposure years

Vaginal rings increased the risk of venous thrombosis 6.5 times compared with non-use of hormonal contraception, corresponding to 7.8 events per 10 000 exposure years

The risk of venous thrombosis was not significantly increased with use of subcutaneous implants or the levonorgestrel intrauterine system compared with non-use of hormonal contraception

Contributors: ØL planned the study, supervised the analysis, interpreted the results, and wrote the manuscript. He is guarantor of the study. EL planned the study, interpreted the results, and revised the manuscript. LHN made the statistical analyses and interpreted the results. CWS prepared all data from the national registry of patients and national death registry. All authors discussed and approved the final manuscript. ØL decided when and where to attempt publication.

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Ethical approval: Ethical approval is not requested for registry based studies in Denmark, and consent from participating patients is not required.

Data sharing: No additional data available.

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Tables

Table 1| Crude incidence rate and adjusted relative risk of confirmed venous thrombosis according to age, calendar year, and length of education

		Venous thrombosis				
Variables	**Woman years**	**All**	**Confirmed**	**Incidence per 10 000 woman years**	**Adjusted relative risk* (95% CI)**	**P value**
Age:						
15-19	1 403 925	365	251	1.79	0.16 (0.13 to 0.19)	<0.001
20-24	1 198 098	479	326	2.72	0.19 (0.16 to 0.22)	<0.001
25-29	1 145 729	594	387	3.38	0.30 (0.27 to 0.33)	<0.001
30-34	1 299 645	715	448	3.45	0.44 (0.40 to 0.48)	<0.001
35-39	1 509 447	930	601	3.98	0.60 (0.55 to 0.66)	<0.001
40-44	1 510 042	1105	705	4.67	0.82 (0.75 to 0.89)	<0.001
45-49	1 362 242	1099	716	5.26	1.00 (reference)	—
Year:						
2001	994 095	444	315	3.17	0.70 (0.61 to 0.79)	<0.001
2002	979 715	466	331	3.38	0.72 (0.64 to 0.82)	<0.001
2003	963 470	438	304	3.16	0.68 (0.60 to 0.77)	<0.001
2004	953 604	512	319	3.35	0.79 (0.70 to 0.89)	<0.001
2005	939 935	525	362	3.85	0.81 (0.72 to 0.91)	0.0005
2006	929 975	537	363	3.90	0.84 (0.74 to 0.94)	0.0028
2007	921 713	615	391	4.24	0.97 (0.87 to 1.09)	0.6531
2008	918 349	538	347	3.78	0.87 (0.77 to 0.98)	0.0171
2009	911 825	599	365	4.00	0.98 (0.87 to 1.09)	0.6597
2010	916 449	613	337	3.68	1.00 (reference)	—
Education:						
1 (low)	2 164 635	1819	1159	5.35	1.25 (1.11 to 1.42)	0.0004
2	1 026 525	475	314	3.06	0.72 (0.62 to 0.83)	<0.001
3	2 236 972	1456	974	4.35	0.83 (0.73 to 0.95)	0.0087
4 (high)	1 385 214	602	382	2.76	0.61 (0.53 to 0.71)	<0.001
Not available	2 615 782	935	605	2.31	1.00 (reference)	—

*Adjusted for age, calendar year, education, and use of hormonal contraception.

Table 2| Crude incidence rate and adjusted relative risk of venous thrombosis in current users of non-oral hormonal contraception and combined oral contraceptives (COC) with non-users as reference

Outcome, contraception type	Woman years	No with venous thrombosis	Incidence per 10 000 exposure years	Adjusted relative risk* (95% CI)	P value
All venous thromboses:					
Non-use	5 892 182	2262	3.84	1.00 (reference)	—
COC with levonorgestrel and 30-40 µg oestrogen	231 675	201	8.68	2.37 (2.05 to 2.74)	<0.001
COC with norgestimate	298 566	198	6.63	2.63 (2.27 to 3.05)	<0.001
Patch	6178	7	11.33	4.40 (2.09 to 9.24)	<0.001
Vaginal ring	50 334	55	10.93	4.29 (3.27 to 5.62)	<0.001
Implant	29 497	15	5.09	2.08 (1.25 to 3.46)	0.005
Levonorgestrel IUS	239 841	88	3.67	0.80 (0.65 to 0.99)	0.040
Confirmed events:					
Non-use	5 892 182	1209	2.05	1.00 (reference)	—
COC with levonorgestrel and 30-40 µg oestrogen	231 675	144	6.22	3.21 (2.70 to 3.81)	<0.001
COC with norgestimate	298 566	135	4.52	3.57 (2.98 to 4.27)	<0.001
Patch	6178	6	9.71	7.90 (3.54 to 17.65)	<0.001
Vaginal ring	50 334	39	7.75	6.48 (4.69 to 8.94)	<0.001
Implant	29 497	5	1.70	1.40 (0.58 to 3.38)	0.450
Levonorgestrel IUS	239 841	33	1.38	0.57 (0.41 to 0.81)	0.002

Patch=transdermal contraceptive patch (EVRA; Johnson & Johnson, NJ, USA); implant=subcutaneous implant (Implanon; MSD; NJ, USA); vaginal ring=combined hormonal vaginal ring (NuvaRing; MSD, NJ, USA); levonorgestrel IUS=levonorgestrel intrauterine system (Mirena: Bayer Pharma, Berlin, Germany).
*Adjusted for age, calendar year, and education.

Table 3| Rate ratio estimates of venous thrombosis between users of different types of non-oral hormonal contraception and users of combined oral contraceptives (COC) with levonorgestrel and 30-40 µg oestrogen (reference group)

Outcome, contraception type	Woman years	No with venous thrombosis	Adjusted rate ratio (95% CI)*	P value
All venous thrombosis:				
COC with levonorgestrel and 30-40 µg oestrogen	231 675	201	1.00 (reference)	—
COC with norgestimate	298 566	198	1.11 (0.91 to 1.35)	0.305
Patch	6178	7	1.85 (0.87 to 3.94)	0.109
Vaginal ring	50 334	55	1.81 (1.34 to 2.44)	0.0001
Implant	29 497	15	0.88 (0.52 to 1.48)	0.623
Levonorgestrel IUS	239 841	88	0.34 (0.26 to 0.43)	<0.001
Confirmed events:				
COC with levonorgestrel and 30-40 µg oestrogen	231 675	144	1.00 (reference)	—
COC with norgestimate	298 566	135	1.11 (0.88 to 1.41)	0.378
Patch	6178	6	2.46 (1.09 to 5.58)	0.031
Vaginal ring	50 334	39	2.02 (1.41 to 2.89)	0.0001
Implant	29 497	5	0.44 (0.18 to 1.07)	0.070
Levonorgestrel IUS	239 841	33	0.18 (0.12 to 0.26)	<0.001
Confirmed events adjusted for length of use:				
COC with levonorgestrel and 30-40 µg oestrogen	231 675	144	1.00 (reference)	—
COC with norgestimate	298 566	135	1.09 (0.86 to 1.38)	0.465
Patch	6178	6	2.31 (1.02 to 5.23)	0.045
Vaginal ring	50 334	39	1.90 (1.33 to 2.71)	0.001
Implant	29 497	5	0.43 (0.18 to 1.05)	0.064
Levonorgestrel IUS	239 841	33	0.18 (0.12 to 0.26)	<0.001

Patch=transdermal contraceptive patch (EVRA; Johnson & Johnson, NJ, USA); implant=subcutaneous implant (Implanon; MSD; NJ, USA); vaginal ring=combined hormonal vaginal ring (NuvaRing; MSD, NJ, USA); levonorgestrel IUS=levonorgestrel intrauterine system (Mirena; Bayer Pharma, Berlin, Germany).
*Adjusted for age, calendar year, and education.

Table 4| Relative risk of confirmed venous thrombosis in current users of different types of hormonal contraception according to length of use

Hormonal contraception	No with confirmed venous thrombosis	Adjusted relative risk (95% CI)*		
		<1 year	1-4 years	>4 years
Non-use	1209	1 (reference)	1 (reference)	1 (reference)
COC with levonorgestrel and 30-40 µg oestrogen	144	4.25 (3.17 to 5.69)	3.07 (2.28 to 4.13)	2.71 (2.06 to 3.58)
COC with norgestimate	135	4.97 (3.86 to 6.39)	2.97 (2.19 to 4.03)	2.67 (1.82 to 3.92)
Patch	6	6.89 (2.22 to 21.4)	11.9 (3.82 to 36.9)	NA
Vaginal ring	39	8.36 (5.73 to 12.2)	3.83 (1.91 to 7.69)	5.37 (1.73 to 16.7)
Implant	5	1.63 (0.41 to 6.52)	1.43 (0.46 to 4.45)	NA
Levonorgestrel IUS	33	0.59 (0.34 to 1.05)	0.61 (0.39 to 0.94)	NA

COC=combined oral contraceptive; patch=transdermal contraceptive patch (EVRA; Johnson & Johnson, NJ, USA); implant=subcutaneous implant (Implanon; MSD, NJ, USA); vaginal ring=combined hormonal vaginal ring (NuvaRing; MSD; NJ, USA); levonorgestrel IUS=levonorgestrel intrauterine system (Mirena; Bayer Pharma, Berlin, Germany); NA=not available.

*Adjusted for age, calendar year, and education.

Table 5| Incidence of venous thrombosis in users of transdermal contraceptive patch and corresponding combined oral contraceptive (COC) with norgestimate, and rate ratio of venous thrombosis in users of patch versus users of combined oral contraceptives with norgestimate

			Incidence per 10 000 exposure years		
Study	**Sampling period**	**No with venous thrombosis**	**Patch**	**COC with norgestimate**	**Rate ratio (95% CI)**
Jick 2006[12]	2002-05	68	5.3	4.2	1.1 (0.7 to 1.8)
Jick 2007[13]	2002-06	56	NA	NA	1.1 (0.6 to 2.1)
Jick 2010[14]	2002-07	38	NA	NA	2.4 (1.2 to 5.0)
Cole 2007[15]	2002-04	57	4.1	1.8	2.2 (1.3 to 3.8)
Dore 2010[16]	2002-06	201	NA	NA	2.0 (1.2 to 3.3)
FDA 2011[11]	2001-07	625	9.6	6.6*	1.3* (0.9 to 1.7)
Lidegaard 2011[10]	2001-10	3434	9.7	4.5	2.2 (1.0 to 5.0)

NA=not available; FDA=Food and Drug Administration.

*Reference group was users of combined oral contraceptives with levonorgestrel and 30-40 µg oestrogen.

UNAFORMEC

Des données pour décider en médecine générale

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Mots clés : contraception, interruption volontaire de grossesse, médecine de l'adolescent

La contraception pose chez les adolescent(e)s des questions complexes et un paradoxe : selon les premières données du Baromètre Santé 2010, plus de 91 % des Françaises sexuellement actives âgées de 15 à 24 ans déclarent employer une méthode contraceptive [1] ; malgré cet usage fortement généralisé de la contraception, le nombre d'interruptions volontaires de grossesse (IVG) chez les adolescentes reste très élevé : 18 000 mineures enceintes en France en 2010, 13 500 ayant recours à l'IVG, 2 grossesses non prévues sur 3 survenant sous contraception. Une double approche semble indispensable pour tenter de résoudre ce paradoxe. Faciliter l'information et la mise à disposition de la contraception est la première : accès, modalités de prescription, coût, confidentialité, choix éclairé du mode contraceptif[1] ; « éduquer » les adolescents à la sexualité la seconde (éducation sexuelle à l'école, campagnes de communication, information sur les dangers de la pornographie) où parents et professionnels ont des rôles complémentaires. La combinaison de ces deux approches semble indispensable si l'on veut éviter que l'IVG ne soit un mode de contraception banalisé…

Abstract: Emergency contraception and medical abortion in adolescent women
The number of medical abortions remained stable in France, around 200,000 per year per 750,000 pregnancies, despite a massive distribution of contraceptives. After steadily increasing until 2006, the number of medical abortions now seems to decrease among adolescents, but it remains high.
One of the key for this problem is the access to emergency contraception. Its effectiveness depends on many parameters. Its delivery must be accompanied by the necessary information : one should not trivialize the unexpected, but inform on all possible preventive measures. The basic issue is that of knowledge about sexuality and reproduction. Pharmacists, school nurses, social workers and doctors are all concerned, and the practitioners in particular who should speak about emergency contraception (and prescribe it) during a consultation for contraception…
The access of under eighteens to medical abortion was made easier in texts and in facts, and the question of professional responsibility was anticipated in case of the absence of parental consent, improving the management of difficult situations when there are family conflicts.
Key words: Abortion, Legal; Adolescent Medicine; Contraception

Contraception d'urgence et IVG chez l'adolescente

Ces dossiers sont issus de textes publiés chaque semaine depuis quelques années dans *Bibliomed*. Actualisés si nécessaire en fonction des données les plus récentes, ils ne résultent pas d'une revue systématique de la littérature, mais d'une veille documentaire en continu des principales revues médicales publiant des études fondées sur les preuves, ou des recommandations en résultant. Ils ont pour ambition de fournir au médecin généraliste une actualisation des données sur les questions pertinentes pour leur pratique retenues par le comité de rédaction.

Les questions auxquelles répond ce dossier ont fait l'objet de 4 publications de *Bibliomed* : 390 du 16 juin 2005, 391 du 23 juin 2005 (mise à jour février 2012), 637 du 6 octobre 2011, 639 du 20 octobre 2011.

1. Cf. notre dossier « Des données pour décider en médecine générale » de mars : Contraception de l'adolescente.

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Les pays d'Europe du nord et la Suisse ont mis en œuvre des campagnes ambitieuses d'information et de communication sur la sexualité, les pays anglo-saxons plutôt facilité l'accès à la contraception. On peut observer que chacune de ces stratégies ne suffit pas à elle seule pour faire diminuer les taux des grossesses adolescentes. Cela ne peut passer que par une stratégie d'action complète en agissant sur ces deux registres, comme le souligne le rapport Nisand 2012 [2], complétant celui de 2006 qui insistait surtout sur les causes des fréquents échecs de la contraception [3]. Les questions concernant la contraception de rattrapage et l'IVG, gratuites et anonymes contrairement à la contraception, payante et passant par l'autorisation parentale, sont l'objet de ce dossier. La proposition d'accès gratuit et anonyme à tous les moyens de contraception fait aujourd'hui l'objet d'un débat politique qui semble agité... La question de fond, celle de l'accompagnement des adolescents dans leurs interrogations autour de la sexualité, reste posée : peut-on prétendre éduquer en matière de sexualité ? Qui doit faire cette éducation ? Comment tenir un discours positif sur la contraception ?

Faciliter l'accès à la contraception d'urgence

Les jeunes Françaises avaient peu recours (moins de $15^0/_{00}$) à la contraception d'urgence avant 2000, cependant que leur recours à l'IVG augmentait régulièrement, de 8 000 IVG en 1990 à 11 000 en 2002 (plus de $25^0/_{00}$ des 20-24 ans) comme au Canada (en 2001, 20 000 IVG chez des femmes de moins de 20 ans) [4]. Même si le nombre d'IVG chez les adolescentes semble maintenant stabilisé, il reste cependant élevé [5]. Une diffusion plus large de la contraception d'urgence pourrait-elle inverser ces données ? Depuis 1999, le pharmacien d'officine français peut dispenser du lévonorgestrel sans ordonnance[2]. Il le peut également, à titre anonyme et gratuit, pour les mineures depuis 2002[3], de même que les infirmières et infirmiers scolaires dans certains cas particuliers. La vente de médicaments de contraception d'urgence a augmenté d'un tiers entre 2000 et 2003. Une étude observationnelle canadienne [6] et un rapport ministériel français [7] ont alors montré que la possibilité de dispensation anonyme et gratuite avait augmenté le nombre de jeunes utilisatrices.

Canada : la dispensation hors prescription a favorisé la contraception d'urgence

L'étude canadienne concerne la contraception d'urgence entre début 1996 et fin 2002 en Colombie britannique. Les pharmaciens ont la possibilité de dispensation de lévonorgestrel sans prescription depuis décembre 2000 [6]. Il y a eu 8 900 prescriptions annuelles entre 1996 et 2000, 16 000 en 2001, 18 000 en 2002. **Le nombre d'utilisatrices a augmenté en 2002, à la fois chez les pharmaciens (+ 64 %) et les médecins (+ 32 %).** Ce sont les femmes, surtout en milieu urbain, surtout âgées de 20 à 24 ans, qui ont eu le plus recours à la contraception d'urgence, suivies des 15-19 ans et 25-29 ans, dans plus de la moitié des cas à cause d'un échec de la contraception usuelle (dont 9 fois sur 10 une rupture de préservatif). Le recours répété restait peu fréquent (2 %). Le pharmacien était sollicité 1 fois sur 2 dans les 24 heures ; les femmes en difficultés financières consultaient plutôt leur médecin. Le collège des pharmaciens de Colombie britannique a proposé à ses adhérents une formation de 4 heures pour qu'ils puissent assurer aux femmes qui le souhaitent un entretien confidentiel de 10 à 15 mn (rémunéré 25 $).

France : après le décret de 2002

La vente de lévonorgestrel, avec ou sans ordonnance, est passée de 570 000 boîtes en 2000 à 625 000 en 2001 et à près de 660 000 en 2002 [7]. **Environ 90 % des boîtes ont été délivrées en dehors d'une prescription médicale.** La contraception d'urgence hors prescription médicale obligatoire répondait bien à une réelle demande des femmes, en rapide progression. De janvier au 31 août 2002, où le dispositif de délivrance aux mineures a été mis en œuvre, l'Assurance-Maladie faisait état de la prise en charge de plus de 25 000 boîtes, chiffre qui ne tient pas compte de la délivrance du médicament hors dispositif : il s'agirait plutôt au total d'**un minimum de 35 000 jeunes femmes** pour les 8 premiers mois de la seule année 2002. Le rapport ministériel [7] ajoutait qu'il faudrait maintenant intégrer au dispositif tous les autres professionnels de santé concernés, dont les médecins généralistes, pour améliorer l'information des adolescent(e)s sur les questions relatives à la fécondité, la contraception, la sexualité et la prévention des infections sexuellement transmissibles.

Huit ans plus tard, les premiers résultats du *Baromètre Santé 2010* [1] confirment que plus de 91 % des Françaises sexuellement actives âgées de 15 à 24 ans déclarent employer une méthode contraceptive. Cependant, les deux tiers des grossesses non prévues ont lieu sous contraception. Il reste donc, en France, du chemin à parcourir...

Que conclure pour notre pratique ?

Le nombre d'IVG reste stable en France, autour de 200 000 par an pour 750 000 grossesses, malgré une diffusion massive des méthodes contraceptives. Cet apparent paradoxe s'explique en partie par une augmentation de la demande d'IVG en cas de grossesse non prévue [8]. Dans cette hypothèse, **une plus grande accessibilité à la contraception d'urgence est indispensable**.

L'efficacité de la contraception d'urgence dépend de nombreux paramètres, dont la date probable de l'ovulation, le délai entre le rapport non protégé et la prise médicamenteuse. La délivrance de la contraception d'urgence doit être accompagnée des informations nécessaires, ce qui pose de nombreuses questions : contenu de l'information, délais, lieux, professionnels en cause, comme le redisent les auteurs du récent Baromètre santé 2010 [1].

2. Arrêté du 27 mai 1999. JO 30/5/99 : 7982.
3. Décret n° 2002-39. JO 10/1/02 : 590.

Contraception d'urgence et IVG

La contraception d'urgence après un rapport sexuel non ou mal protégé est une contraception de « rattrapage ». Son but affirmé est de réduire le nombre de grossesses non désirées, donc le recours à l'IVG pour ce motif, en particulier chez les adolescentes et les très jeunes femmes : on observe à cet âge une plus grande fréquence d'absence totale de contraception que chez les adultes (9,4 % contre 3,6 %) et une proportion d'échec du préservatif significativement plus élevée (17,8 % contre 11,5 %) [9]. En facilitant en 2002 l'accès des mineures à la contraception d'urgence en France (gratuité, anonymat, hors prescription médicale), accompagné du conseil nécessaire, le législateur espérait modifier la situation. Il y a pourtant eu encore en 2009 15,6 IVG pour 1 000 jeunes femmes âgées de 15 à 19 ans [1]. Le rapport 2004 de l'ANAES rappelait – c'est toujours d'actualité – les caractéristiques d'une contraception efficace et les conditions particulières du conseil aux adolescentes [10].

Les méthodes utilisables

La pose d'un stérilet au cuivre peut être utilisée en contraception d'urgence sous réserve qu'elle n'intervienne pas plus de 5 jours après l'ovulation (probablement par effet sur la fécondation et non sur l'implantation) [10].
La mifépristone (RU 486) largement utilisée à l'étranger à la dose usuelle de 10 mg n'a pas cette indication en France.
Le lévonorgestrel peut être dispensé hors prescription médicale. Sans contre-indications, il est efficace à la dose de 1,5 mg (1 cp en une seule prise dans les 72 heures suivant le rapport). L'ulipristal, commercialisé depuis, théoriquement efficace dans les 120 heures suivant le rapport, est beaucoup plus cher et n'a pas démontré d'efficacité supérieure. Sa plus longue efficacité supposée repose sur des arguments bien fragiles. Les deux sont pris en charge par l'Assurance-Maladie.

Quelle efficacité ?

Une revue portant sur 8 300 poses de stérilets en contraception d'urgence rapporte un taux d'échec de 0,1 à 0,2 % [10]. La contraception hormonale d'urgence est d'autant plus efficace qu'elle est utilisée plus précocement après le rapport non protégé, bien que les cohortes analysées ne soient généralement pas suffisantes pour que l'on puisse réellement chiffrer la décroissance d'activité [10]. Une récente revue américaine des publications sur ce point, notamment 4 essais randomisés de l'OMS, ne montre pas de variations d'efficacité durant les premiers jours, avec un taux de grossesses d'environ 0,5 % [11]. La vraie question est donc bien celle d'une disponibilité immédiate. Au-delà du « raisonnable » (72 heures après le rapport), seul le stérilet devrait être en discussion. L'éventualité d'une prescription en avance se discute au cas par cas. Le groupe de travail de l'ANAES recommandait en 2004 qu'une information soit donnée sur la contraception d'urgence à l'occasion de toute nouvelle consultation pour première contraception [10].

L'information sur la contraception reste la priorité

La loi a précisé que la délivrance du lévonorgestrel sans ordonnance est précédée d'un entretien avec le pharmacien qui doit *« s'assurer que la situation correspond aux critères d'urgence... et fournir à la mineure une information sur l'accès à une contraception régulière, sur la prévention des IST et sur l'intérêt d'un suivi médical. Il communique les coordonnées du centre de planification d'éducation familiale le plus proche »* [10]. Le rapport de l'ANAES rappelait les principes de **l'entretien individuel** chez les adolescents selon l'OMS : confidentialité, écoute attentive et positive, questions sur les habitudes de vie, représentations, préférences et réticences en matière de contraception... **L'approche éducative collective** en milieu scolaire semble entraîner à court terme une diminution du taux de grossesses chez des adolescentes de 14 à 18 ans, mais son efficacité à long terme n'est pas mesurée.

Que conclure pour notre pratique ?

La priorité n'est pas de banaliser l'imprévu, mais d'informer sur toutes les mesures préventives possibles, faire connaître la contraception d'urgence, dans un ensemble de connaissances sur la sexualité et la reproduction. L'usage du préservatif reste la seule méthode de prévention du risque infectieux, même s'il est manifestement chez les jeunes une méthode contraceptive insuffisamment efficace. Tout recul de ce simple message reste jusqu'à nouvel avis porteur de mort...
Comme le souligne Nisand, si l'IVG de la femme adulte traduit souvent une ambiguïté face à la reproduction et un désir inconscient de grossesse, l'IVG de la femme jeune recouvre habituellement un manque de connaissances. *« Pour des raisons psychologiques évidentes, ni les parents, ni les enseignants (qui sont des "pro-parents") ne sont bien placés pour aborder aisément et au bon moment (c'est-à-dire avant les premières expériences sexuelles) les conseils élémentaires et les précautions qui permettent d'éviter les grossesses non désirées. C'est donc le corps médical au sens large qui doit remplir ce rôle »* [3]. Pharmaciens, infirmières scolaires, intervenants sociaux et médecins sont tous concernés.

Contraception d'urgence : craintes injustifiées, attentes déçues

La possibilité de délivrance, dans les pharmacies ou les infirmeries scolaires, du levonorgestrel en contraception d'urgence à des mineures sans prescription, anonyme et gratuite, vise à prévenir les IVG chez ces très jeunes femmes en cas de rapports non protégés. La simplification de l'accès à cette solution de « rattrapage » explique sans doute en partie la forte augmentation de son utilisation chez les adolescentes. Des données d'origine diverse (IGAS [12], INPES [13], COCON [14], DREES [5], une enquête sociologique [15]) permettent d'analyser l'évolution de la situation en France.

Le « rattrapage » n'est pas devenu habituel

Le recours à la contraception régulière s'est accru chez les 18-19 ans entre 1999 et 2004 malgré l'accès direct et sans prescription à la contraception d'urgence [12]. Le recours à celle-ci se fait en rattrapage des échecs (problème de préservatif 1 fois/3) ou erreurs (oubli de pilule 1 fois/3), surtout chez les 15-24 ans dont 1/3 y a eu recours. Selon les données de l'Assurance-Maladie, 50 000 boîtes avaient été délivrées gratuitement aux mineures en 2002, près de 300 000 en 2007 [in 12]. Mais ce recours fréquent à la contraception d'urgence n'a pas diminué l'utilisation de la contraception régulière : plus de 2 femmes sur 3 qui ont utilisé la contraception d'urgence ne l'ont fait qu'une seule fois et plus de 8 fois/10, elles utilisaient une contraception régulière dès le mois suivant ; et chez les 2 863 femmes de la cohorte COCON [14], les 272 recours à la contraception d'urgence n'ont pas modifié notablement les pratiques contraceptives antérieures.

Mais le taux d'IVG n'a pas vraiment diminué...

Le nombre s'est stabilisé en France en 2009 (données DREES/AFP [5]) à un peu plus de 222 000 IVG (pour environ 800 000 naissances), soit 15/1 000 femmes, ce qui est la moyenne européenne. Le taux d'IVG s'est stabilisé en 2008 et 2009 chez les plus jeunes, a même un peu reculé chez les mineures alors qu'il augmentait régulièrement : 10/1000 chez les 15-17 ans, 22/1000 chez les 18-19 ans et 27/1000 chez les 20-24 ans, avec de grandes disparités régionales : de 11/1000 dans les Pays de la Loire à 21 en PACA et 27 dans les DOM.

Recours insuffisant à la contraception d'urgence ?

En utilisant les différentes données disponibles, l'IGAS estime à environ 24 millions le nombre annuel théorique de rapports à risque de grossesse non désirée liée à des défauts d'utilisation de la pilule et du préservatif, sans préjuger des autres causes [12]. Le niveau d'utilisation de la contraception d'urgence est de l'ordre de 1 à 20 (1,2 million de boîtes vendues en 2006)... Quelques explications peuvent être avancées à partir d'études sociologiques [15] : fausses représentations des risques, notamment en cas d'utilisation fréquente (est-ce l'insistance du discours officiel sur le fait que ce « dépannage » ne saurait être utilisée régulièrement ?), ambiguïté de la dénomination « pilule du lendemain » (ou maintenant du « surlendemain ») l'assimilant à la « pilule abortive » qu'est le RU486, recours conditionné à une appréciation approximative de la période supposée « dangereuse ». L'information théorique des manuels scolaires (ovulation au 14e jour du cycle) est souvent prise à la lettre, alors que le message à faire passer est au contraire que l'ovulation, surtout chez les jeunes femmes, est possible à n'importe quel moment du cycle. Il reste aussi de nombreux obstacles pratiques : jours fériés, lieu isolé, passage obligé, dans un délai très court, par une pharmacie ou un médecin, réticence à *« venir en urgence raconter son immédiate vie sexuelle »*...

Quelques propositions de l'IGAS

En ce qui concerne les adolescentes, le rapport recommande une contraception encore plus accessible : gratuité (de la prescription et de l'acte) reposant sur un réseau de professionnels (médecins, sages-femmes, pharmaciens) assurant le développement des actions d'information et d'éducation à la sexualité, promotion de la prescription par anticipation de contraception d'urgence en complément de la contraception orale...

Que conclure pour notre pratique ?

La contraception d'urgence n'a pas (encore ?) les effets attendus. L'efficacité du levonorgestrel est corrélée à sa rapidité d'utilisation (95 % à 24 h, 85 % à 24-48 h, 58 % à 49-72 h). Il n'est pas démontré que l'ulipristal, beaucoup plus cher, fait mieux.

L'urgence se prévoit, en parlant systématiquement de la contraception de rattrapage (et en la prescrivant) lors de la consultation pour contraception...

La question centrale chez les adolescentes reste celle de la contraception régulière. Or, comme le soulignait le rapport Nisand (2006), le paradoxe français est que l'IVG et la contraception d'urgence sont devenues anonymes et gratuites, contrairement à la contraception orale ; alors qu'il *« vaut mieux prévenir les IVG chez les jeunes plutôt que d'avoir à les réaliser, que ce soit du point de vue éthique, psychologique ou économique »*.

Interruption volontaire de grossesse à l'adolescence

La plupart des grossesses survenant chez les adolescentes sont imprévues. La décision d'IVG est fortement corrélée à l'âge ou aux conditions de vie de l'adolescente [16]. Sur l'ensemble des IVG, environ 6 % concernent des mineures aux USA, 9,5 % en Grande-Bretagne, 15 % en France [16-18], soit en 2009 (dernières statistiques françaises publiées) 11 670 chez les 15-17 ans (il n'y a pas de données en 2009 chez les moins de 15 ans, qui étaient 850 2 ans avant). Le taux global (11,1/1000 mineures), un peu plus faible que pour l'ensemble des femmes (14,5), variait alors de 8,5 en Pays de Loire à 28,1 dans les départements d'outre-mer. Après une progression régulière jusqu'en 2006, il semblait se stabiliser en 2007 [17] et a diminué globalement en 2009 [5, 18] ; les questions d'accessibilité et de responsabilité semblent au moins partiellement résolues [12]. Une étude de cohorte finlandaise [16] apporte des données rassurantes sur l'IVG médicamenteuse chez les adolescentes.

L'accès des mineures à l'IVG a été facilité

L'autorisation parentale est toujours la règle, avec possibilité de déroger (loi 2001) pour les situations de détresse, d'isolement ou de dialogue impossible. Le médecin doit cependant s'efforcer de convaincre l'adolescente de consulter ses parents. À défaut, elle doit être accompagnée dans sa démarche par une personne majeure de son choix. Le nombre de mineures ayant recours à l'IVG hors autorisation parentale est inconnu (chiffres estimés variant du 1/3 à la quasi-totalité, sans corrélation avec des critères territoriaux ou populationnels [12]). Les consultations psycho-sociales restent obligatoires, de nature variable selon les professionnels qui les assurent, au gré des possibilités locales. Le coût de l'IVG est intégralement pris en charge par l'Assurance-Maladie. La plupart des professionnels rencontrés par l'IGAS soulignent que la législation actuelle a permis de mieux gérer les situations délicates, notamment de conflits familiaux, malgré quelques dysfonctionnements ou maladresses.

La question de la responsabilité des professionnels

La responsabilité du médecin n'est pas engagée si l'ensemble des conditions légales est remplie [12]. Une anesthésie peut être pratiquée si nécessaire sans le consentement des parents. Le Ministère insiste cependant sur la nécessité de pouvoir prouver qu'il y a eu discussion avec l'adolescente pour tenter de la convaincre de consulter ses parents. S'il y a suspicion sur la personne accompagnante, le recours à une procédure de signalement (conseil général ou procureur) est nécessaire.

IVG chirurgicale ou médicamenteuse ?

On sait depuis des décennies que l'IVG chirurgicale est plutôt plus sûre chez les très jeunes femmes que chez les adultes. Sa mortalité est évaluée à 1/100 000 [19]. La mortalité de l'IVG médicamenteuse est identique, mais peu d'études ont évalué les risques de morbidité de l'IVG médicamenteuse chez l'adolescente. L'étude rétrospective finlandaise analyse les données du registre des IVG de Finlande, soit une cohorte de 27 000 femmes dont 3 000 adolescentes entre 2000 et 2006 [16]. La législation finlandaise permet une IVG jusqu'à 20 semaines de grossesse. Celle-ci est réalisée par une prise unique de 200 mg de mifépristone, suivie ou non 1 ou 2 jours après de misoprostol. Le taux d'effets indésirables (aucun effet majeur) a été équivalent ou moindre chez les adolescentes : moins d'hémorragies (*odds ratio* OR 0,87 ; 0,77-0,99), d'avortements incomplets (0,69 ; 0,59-0,82), de curetages évacuateurs (0,78 ; 0,67-0,90) ; résultats analogues dans le sous-groupe des primipares. En régression logistique, la durée de la gestation était le principal facteur de risque pour les infections, les avortements incomplets et les curetages. L'IGAS [12] souligne que la technique de l'IVG médicamenteuse, dont on ne connaît pas le taux en France pour les mineures, est parfois plus délicate à administrer en l'absence d'autorisation parentale. Le risque d'effets indésirables et les éventuelles procédures de rappel pour la visite de contrôle rendent difficiles le respect de l'anonymat et de la confidentialité.

Que conclure pour notre pratique ?

L'accès des mineures à l'IVG a été facilité dans les textes et dans les faits. Malgré quelques maladresses ou dysfonctionnements, la législation actuelle a permis de mieux gérer les situations difficiles de conflits familiaux.

La question de la responsabilité des professionnels de santé concernés a pu susciter quelques craintes lorsqu'il n'y a pas de consentement parental. Comme pour de nombreux actes médicaux, il est essentiel de garder dans le dossier de l'adolescente la trace écrite du contenu de l'entretien.

Rappelons les 2 points clés de la prévention des IVG chez ces très jeunes femmes : l'information sur les possibilités de rattrapage, leur efficacité et les conditions d'accès en cas de rapport non ou mal protégé et la mise en route d'une contraception régulière efficace dès qu'elle est nécessaire, dans les meilleures conditions possibles pour cette première contraception (dossier précédent).

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Contraception d'urgence et IVG chez l'adolescente

- **Le nombre d'IVG reste stable en France**, autour de 200 000 par an pour 750 000 grossesses, malgré une diffusion massive des méthodes contraceptives. Après avoir constamment augmenté jusqu'en 2006, le nombre d'IVG semble maintenant diminuer chez les adolescentes, mais reste élevé.

- **L'une des clés de ce problème est l'accessibilité à la contraception d'urgence.** Son efficacité dépend de nombreux paramètres. Sa délivrance doit être accompagnée de l'information nécessaire : il ne s'agit pas de banaliser l'imprévu, mais d'informer sur toutes les mesures préventives possibles. La question de fond est celle des connaissances sur la sexualité et la reproduction. Pharmaciens, infirmières scolaires, intervenants sociaux et médecins sont tous concernés, les médecins notamment en parlant systématiquement de la contraception d'urgence (et en la prescrivant) lors de la consultation pour contraception...

- **L'accès des mineures à l'IVG** a été facilité dans les textes et dans les faits **et la question de la responsabilité des professionnels** prévue en cas d'absence de consentement parental, ce qui a permis de mieux gérer les situations difficiles de conflits familiaux.

Agence nationale de sécurité du médicament et des produits de santé

CONTRACEPTIFS ORAUX COMMERCIALISES EN FRANCE AU 1ER SEPTEMBRE 2012

Contraceptifs oraux commercialisés en France au 1er septembre 2012
Estro-progestatifs

Génération progestatif	Dénomination commune (DC)	Phases	Dosage	Spécialités	Posologie
1ère	Noréthistérone	Triphasique	Noréthistérone 500 puis 750 µg puis 1000 µg, EE 35 µg	Triella	21 cp (+ 7 j d'arrêt)
2ème	Lévonorgestrel	Monophasique	Lévonorgestrel 150 µg, EE 30 µg	Minidril – Ludéal - Zikiale	21 cp (+ 7 j d'arrêt)
			Lévonorgestrel 100 µg, EE 20 µg	Leeloo - Lovavulo	21 cp (+ 7 j d'arrêt)
				Optilova	21 cp actifs + 7 placebo
		Biphasique	Lévonorgestrel 150 puis 200 µg, EE 30 puis 40 µg	Adépal - Pacilia	21 cp (7+14) + 7 j d'arrêt
		Triphasique	Lévonorgestrel 50 puis 75 puis 125 µg, EE 30 puis 40 puis 30 µg	Trinordiol – Amarance – Daily - Evanecia - Perléane	21 cp (6+5+10) + 7 j d'arrêt
	Norgestrel	Monophasique	Norgestrel 500 µg, EE 50 µg	Stédiril	21 cp (+ 7 j d'arrêt)
3ème	Désogestrel	Monophasique	Désogestrel 150 µg, EE 20 µg	Mercilon - Désobel 150/20 - Désogestrel Ethinylestradiol Biogaran 150/20	21 cp (+ 7 j d'arrêt)
			Désogestrel 150 µg, EE 30 µg	Varnoline - Désobel 150/30 - Désogestrel Ethinylestradiol Biogaran 150/30	21 cp (+ 7 j d'arrêt)
				Varnoline continu	21 cp actifs + 7 placebo
	Gestodène	Monophasique	Gestodène 60 µg, EE 15 µg	Mélodia – Minesse – Sylviane - Edenelle - Gestodène Ethinylestradiol 60/15 Biogaran / Teva	24 cp actifs + 4 placebo
			Gestodène 75 µg, EE 20 µg	Harmonet, Méliane - Carlin 75/20 - Efezial 75/20 - Félixita 75/20 - Gestodène Ethinylestradiol 75/20 Actavis / Arrow / Biogaran / EG / Ranbaxy / Ratiopharm / Sandoz / Teva / Zentiva / Zydus	21 cp (+ 7 j d'arrêt)

	Gestodène		Gestodène 75 µg, EE 30 µg	Minulet – Monéva - Carlin 75/30 - Efezial 75/30 - Félixita 75/30 - Gestodène Ethinylestradiol 75/30 Actavis / Arrow / Biogaran / EG / Ranbaxy / Ratiopharm / Sandoz / Teva / Zentiva / Zydus	21 cp (+ 7 j d'arrêt)
		Triphasique	Gestodène 50 puis 70 puis 100 µg, EE 30 puis 40 puis 30 µg	Phaéva - Tri-Minulet	21 cp (6+5+10) + 7 j d'arrêt
	Norgestimate	Monophasique	Norgestimate 250 µg, EE 35 µg	Cilest - Effiprev	21 cp (+ 7 j d'arrêt)
			Norgestimate 180 µg puis 215 µg puis 250 µg, EE 35 µg	Tricilest - Triafemi	21 cp (7+7+7) + 7 j d'arrêt
Autres	Chlormadinone	Monophasique	Chlormadinone 2 mg, EE 30 µg	Bélara	21 cp (+ 7 j d'arrêt)
	Drospirénone	Monophasique	Drospirénone 3 mg, EE 30 µg	Jasmine – Convuline - Drospibel 3 mg / 30 µg - Drospirenone Ethinylestradiol 3 mg / 30 µg Biogaran	21 cp (+ 7 j d'arrêt)
			Drospirénone 3 mg, EE 20 µg	Jasminelle – Bélanette - Drospibel 3 mg / 20 µg - Drospirenone Ethinylestradiol 3 mg / 20 µg Biogaran	21 cp (+ 7 j d'arrêt)
				Jasminelle continu - Drospirenone Ethinylestradiol 3 mg / 20 µg Biogaran continu	21 cp actifs + 7 placebo
				Yaz – Rimendia	24 cp actifs + 4 placebo
	Diénogest	Multiphasique	Diénogest 5 paliers en mg : 0, 2, 3, 0 puis 0 Valérate d'estradiol 5 paliers en mg : 3, 2, 2, 1 puis 0.	Qlaira	26 cp actifs (2+5+17+2) et 2 placebo
	Nomégestrol	Monophasique	Nomégestrol acétate 2,5 mg, estradiol 1,5 mg	Zoely	24 cp actifs + 4 placebo

cp : comprimé - EE : éthinylestradiol - j : jour

Contraceptifs oraux commercialisés en France au 1er septembre 2012
Progestatifs

Génération progestatif	Dénomination commune (DC)	Phases	Dosage	Spécialités	Posologie
2ème	Lévonorgestrel	**---**	Lévonorgestrel 30 µg	Microval	28 cp
3ème	Désogestrel	**---**	Désogestrel 75 µg	Cérazette - Désogestrel Ratiopharm 75 µg	28 cp

cp : comprimé ; EE : éthinylestradiol ; j : jour