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RESEARCH

Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data

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ABSTRACT

Objective To compare the risk of non-fatal venous thromboembolism in women receiving oral contraceptives containing drospirenone with that in women receiving oral contraceptives containing levonorgestrel.

Design Nested case-control and cohort study.

Setting The study was based on information from PharMetrics, a United States based company that collects information on claims paid by managed care plans.

Participants The study encompassed all women aged 15 to 44 years who received an oral contraceptive containing either drospirenone or levonorgestrel after 1 January 2002. Cases were women with current use of a study oral contraceptive and a diagnosis of venous thromboembolism in the absence of identifiable clinical risk factors (idiopathic venous thromboembolism). Up to four controls were matched to each case by age and calendar time.

Main outcome measures Odds ratios comparing the risk of non-fatal venous thromboembolism in users of the two contraceptives; incidence rates and rate ratios of non-fatal venous thromboembolism for users of each of the study contraceptives.

Results 186 newly diagnosed, idiopathic cases of venous thromboembolism were identified in the study population and matched with 681 controls. In the case-control analysis, the conditional odds ratio for venous thromboembolism comparing use of oral contraceptives containing drospirenone with use of those containing levonorgestrel was 2.3 (95% confidence interval 1.6 to 3.2). The incidence rates for venous thromboembolism in the study population were 30.8 (95% confidence interval 25.6 to 36.8) per 100 000 woman years among users of oral contraceptives containing drospirenone and 12.5 (9.61 to 15.9) per 100 000 woman years among users of oral contraceptives containing levonorgestrel. The age adjusted incidence rate ratio for venous thromboembolism for current use of oral contraceptives containing drospirenone compared with those containing levonorgestrel was 2.8 (2.1 to 3.8).

Conclusions The risk of non-fatal venous thromboembolism among users of oral contraceptives containing drospirenone seems to be around twice that of users of oral contraceptives containing levonorgestrel, after the effects of potential confounders and prescribing biases have been taken into account.

INTRODUCTION

The first oral contraceptives were introduced in the early 1960s and contained high doses of both oestrogen and progestogen. The doses of oestrogen were found to be associated with an increased risk of venous thromboembolism.[1] Over the subsequent years, oral contraceptives containing smaller doses of oestrogen and progestogen were introduced to the market in an attempt to reduce cardiovascular risk. The type of progestogen became the focus of discussion in the mid-1990s, when concern was raised that women taking third generation oral contraceptives (which contained desogestrel or gestodene) were at an increased risk of venous thromboembolism compared with those taking second generation oral contraceptives (which contained levonorgestrel). Several studies found an increased risk, whereas others argued that confounding by indication or other biases could account for the findings.[2-6] In the end, the consensus was that an increased risk of venous thromboembolism existed in users of third generation oral contraceptives. The risk of venous thromboembolism was later also found to be increased for use of oral contraceptives containing cyproterone.[7] Thus, post-marketing surveillance to monitor newer contraceptives as they are introduced to the market is important, particularly for an established risk such as venous thromboembolism.

Four published studies have examined the risk of venous thromboembolism among women taking the newer oral contraceptives containing drospirenone compared with those taking other oral contraceptives (including third generation oral contraceptives), with inconclusive results.[8-11] Dinger et al and Seeger et al found no association between venous thromboembolism and drospirenone compared with "other" oral contraceptives. Two more recent studies published in the *BMJ* each found a small increased risk. A study by Lidegaard et al reported a relative risk of 1.6 (95%

confidence interval 1.3 to 2.1) comparing oral contraceptives containing drospirenone with those containing levonorgestrel, and a study by van Hylckama Vlieg et al yielded an odds ratio of 1.7 (0.7 to 3.9) for the same comparison.

All four studies included at least some non-idiopathic cases of venous thromboembolism—that is, cases for which another cause or strong risk factor for venous thromboembolism was present, which could result in attenuating an effect should it exist.[12] By not restricting the study to idiopathic cases, one cannot calculate the risk attributable to oral contraceptives among cases in the absence of other causes.

One study,[9] instead of using the reference exposure most commonly used in recent studies of oral contraceptives and venous thromboembolism (second generation oral contraceptives containing levonorgestrel), used a reference category that included women who had taken third generation oral contraceptives. These third generation oral contraceptives have been shown to increase the risk of venous thromboembolism compared with the second generation oral contraceptives. Their inclusion in the reference category would therefore dilute the estimate of risk.

Given the potential serious clinical consequences of venous thromboembolisms and the growing popularity of oral contraceptives containing drospirenone, examining the association between venous thromboembolism and oral contraceptives containing drospirenone compared with those containing levonorgestrel in studies that avoid the limitations of earlier publications is important. We therefore did a study that compared the risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone with that in women using oral contraceptives containing levonorgestrel. This study was restricted to current users of one of these two oral contraceptives and to idiopathic cases of non-fatal venous thromboembolism.

METHODS

Data resource

Data for this study came from the PharMetrics database. PharMetrics is a United States based, ongoing longitudinal database with information on around 55 million people going back as far as 1995. The database is made up of data contributed by managed care plans throughout the United States and contains information on paid claims for drugs, medical diagnoses, and procedures, as well as demographic information such as the patient's year of birth and sex and enrolment details for each patient in the database. Prescriptions for drugs are coded using the National Drug Code provided by the US Food and Drug Administration. Each drug claim is entered as a separate entry and includes information on the specific entity dispensed, the date of dispensing, the quantity dispensed, and the length of the supply. All diagnoses are coded using the ICD-9 (International Classification of Diseases, 9th revision) coding system. Procedure codes are also included in the database, coded using the Current Procedural Terminology-4 system. All events described above are noted with the date on which the initial service was delivered. This database has been used for many previous studies of hormonal contraceptives in relation to venous thromboembolism and other cardiovascular outcomes.[13-17]

We designed this study to take into account the evaluation of a relatively recently marketed drug and the use of a comparison drug that has been marketed for decades. We required that all cases and controls were current users of either study drug after 1 January 2002; drospirenone oral contraceptives were first marketed in the United States in May 2001. Important variables that we controlled for in the design were age, as users of the new drug may have a different age distribution than users of the older comparison drug, and calendar time (that is, the date of diagnosis), as the two contraceptives will have highly different usage characteristics in relation to calendar time. We also explored duration of use, which may be correlated with both drug use and the risk of venous thromboembolism.

Base population

We did a case-control study nested in the population of users of oral contraceptives containing drospirenone or levonorgestrel, aged 15 to 44, in the PharMetrics database updated to the end of December 2008. All patients had to have filled at least one prescription for a study drug after 1 January 2002. We excluded women with risk factors for venous thromboembolism, such as any history of cancer (other than non-melanoma skin cancer), renal failure, chronic cardiovascular disease, or inflammatory or autoimmune conditions, from the base population.

Cases

Cases were women aged 15 to 44 years who were current users of oral contraceptives containing drospirenone or levonorgestrel and who had a first time recorded claim for a clinically diagnosed deep vein thrombosis or pulmonary embolism with a hospital admission, a visit to the emergency room, or a positive indication of venous thromboembolism from diagnostic test results, and who subsequently received prolonged anticoagulation treatment. We included in the study all cases with a first time diagnosis of venous thromboembolism in 2002 or afterwards. Cases had to have at least six months of medical history before the diagnosis of venous thromboembolism (index date) and had to be currently taking one of the study drugs. We restricted the study to women currently taking a study oral contraceptive because the effect of oral contraceptives on the outcome, venous thromboembolism, is acute and diminishes rapidly after the drug is stopped. We determined oral contraceptive use from the prescription claims data before the date of diagnosis of venous thromboembolism and defined it as having a recorded claim for a prescription of a study contraceptive whose filled use extended to within 30 days before the index date or beyond the index date. Long term anticoagulation must have been

started promptly, and no contraceptive containing oestrogen could be prescribed after the date of diagnosis, indicating that the diagnosis of venous thromboembolism was considered to be confirmed.

To restrict the study to idiopathic cases, we excluded women from the case group if important clinical risk factors for venous thromboembolism were present in the 90 days before the index date. These included severe lower limb injury, major surgery, severe trauma, or pregnancy. An idiopathic case is one for which no other proximate cause (other explanation) exists for the venous thromboembolism. In cases for which another known cause for their venous thromboembolism is present, such as recent surgery, the distribution of drug use is expected to represent the distribution in the base population, and inclusion of these non-idiopathic cases would dilute any true increase in risk because the risk in the non-idiopathic cases is expected to be most influenced by the other proximate cause rather than by the oral contraceptive. By restricting the study to idiopathic cases, one can calculate the risk attributable to oral contraceptives among cases in the absence of other causes.

To assess the eligibility of each potential case, we reviewed each patient's computer record with the identity of the study oral contraceptive masked. We achieved agreement on inclusion of women as cases by consensus without knowledge of contraceptive use.

Controls

We matched four women who did not have a diagnosis of venous thromboembolism to each case by using risk set sampling, by year of birth and the index date of the case (calendar time). As with cases, all controls had to be current users of one of the study contraceptives, to have at least six months of enrolment in their health plan before the index date (the event date of their matched case), and to have used a study contraceptive after 2002. We applied the same exclusion criteria to controls as to cases. One of the authors reviewed the computer record of each control.

Statistical methods

We generated descriptive characteristics of the cases and controls, as well as distributions of risk factors by contraceptive use in the controls to assess potential confounding. We used conditional logistic regression to analyse the matched case-control data. When stratifying on variables other than the matched factors of age and index year, we had to break the matching and therefore calculated odds ratios adjusted for age and index year (instead of conditional odds ratios). We evaluated duration of contraceptive use before the index date, switching from a different hormonal contraceptive, obesity (if the record contained an ICD code for obesity), other comorbidities, and number of visits to a physician or emergency room in the six months before the index date as potential confounders. We used the 10% change in estimate rule to evaluate confounding by comparing the crude odds ratio with the odds ratio adjusted for each potential confounder individually.[18] Variables that resulted in a 10% or greater change in the odds ratio would have been considered to be material confounders; however, none of the risk factors evaluated were confounders according to this criterion.

We analysed the cohort data to estimate incidence rates and 95% confidence intervals. Current person time was accumulated from the first prescription of study drug to the last prescription plus 45 days. If a gap of greater than 100 days existed in the prescription fill dates, the person time accumulation stopped at the last prescription before the gap, plus 45 days; person time accumulation then resumed at the next record of a prescription for a study drug. We estimated the incidence rates and rate ratios by using Stata version 11.1 and Episheet.[19]

We stratified the case-control analysis on age category, index year, type of diagnosis (deep vein thrombosis versus pulmonary embolism), levonorgestrel dose, and new versus continuous use of the study oral contraceptive. We considered a woman to have a new episode of use if she had a previous episode for an oral contraceptive with a gap of at least 100 days before the current episode or no previous prescription for an oral contraceptive and at least four months of recorded history in her computer record. Among women who had a new episode of use of the study oral contraceptive, we further stratified the analysis on whether the woman had a previous episode of oral contraceptive use. We classified all other women as users of unknown duration—that is, those whose current episode of study drug began within four months of the start of their computer record. The four month period is based on the finding that contraceptive prescriptions in the PharMetrics database are written for no longer than three months at a time. A window of at least four months thus provided evidence that the first identified prescription was a new prescription and not a refill of an existing prescription. We classified women with a prescription recorded less than four months from the beginning of their record as users of unknown duration, because we could not determine with any confidence that the first prescription in the database was for a new episode of use. We defined duration of contraceptive use as the time interval (in months) from the first use of an oral contraceptive within the current episode (at the index date) to the index date or as unknown. We defined a woman as a switcher if the patient's record contained a prescription for a hormonal contraceptive product other than the one used at the index date in either the six months or the 12 months before the index date. We used SAS release 9.1 for analyses.

RESULTS

We identified 471 potentially eligible cases of venous thromboembolism, of which we determined 285 (61%) to be non-idiopathic after blinded review of each patient's computer record. Our final study population thus consisted of 186 cases of non-fatal venous thromboembolism and 681 controls (women without venous thromboembolism), matched by year of birth and

Table 1 | Descriptive characteristics by cases and controls and by exposure among controls. Values are numbers (percentages)

Characteristic	Cases (n=186)	Controls (n=681)	Controls only	
			Drospirenone users (n= 313)	Levonorgestrel users (n= 368)
Age (years):				
<30	77 (41)	281 (41)	153 (49)	128 (35)
30-39	77 (41)	279 (41)	111 (35)	168 (46)
40-44	32 (17)	121 (18)	49 (16)	72 (20)
Obesity	25 (13)	42 (6)	18 (6)	24 (7)
Hypertension	17 (9)	33 (5)	14 (4)	19 (5)
Coronary atherosclerosis	2 (1)	3 (<1)	2 (1)	1 (<1)
Other atherosclerosis	11 (6)	18 (3)	9 (3)	9 (2)
Hyperlipidaemia/ hypercholesterolaemia	22 (12)	44 (6)	24 (8)	20 (5)
Diabetes	6 (3)	23 (3)	11 (4)	12 (3)
Asthma	19 (10)	50 (7)	19 (6)	31 (8)
Endometriosis	2 (1)	8 (1)	5 (2)	3 (1)
Disorders of menstruation	44 (24)	152 (22)	84 (27)	68 (18)
Switch within 6 months	11 (6)	69 (10)	34 (11)	35 (10)
Switch within 12 months	24/148 (16)	96/502 (19)	46/222 (21)	50/280 (18)
Emergency room visits (≥1)	17 (9)	22 (3)	11 (4)	11 (3)
Physician visits (≥1)	29 (16)	60 (9)	31 (10)	29 (8)
Total duration (months):				
<3	59 (32)	254 (37)	143 (46)	111 (30)
3-6	34 (18)	97 (14)	52 (17)	45 (12)
6-9	22 (12)	54 (8)	27 (9)	27 (7)
9-12	6 (3)	41 (6)	21 (7)	20 (5)
>12	42 (23)	137 (20)	29 (9)	108 (29)
Unknown	23 (12)	98 (14)	41 (13)	57 (15)
Type of oral contraceptive use:				
New users	144 (77)	517 (76)	264 (84)	253 (69)
Continuous users	42 (23)	164 (24)	49 (16)	115 (31)

index date. Table 1 shows the characteristics of the cases and controls and also shows characteristics by exposure among controls only. Cases were more likely to have a diagnosis of obesity in their record and a visit to an emergency department or a physician in the six months before the index date. Users of oral contraceptives containing drospirenone were more likely than users of those containing levonorgestrel to be younger (aged under 30), to have a history of menstrual disorders, to have a shorter duration of use, and to have had a new episode of use (more than four months of history in their record before their first prescription for a study oral contraceptive within the current episode or had a previous episode of use).

Among the 186 cases of idiopathic venous thromboembolism, 121 (65%) women were currently using an oral contraceptive containing drospirenone and 65 (35%) were using one containing levonorgestrel. Among the controls, 313 (46%) were using an oral contraceptive containing drospirenone and 368 (54%) were using one containing levonorgestrel. The unadjusted matched odds ratio and 95% confidence interval for venous thromboembolism for oral contraceptives containing drospirenone compared with those containing levonorgestrel was 2.3 (95% confidence interval 1.6 to 3.2) (table 2). After adjustment for duration of exposure, the odds ratio was virtually unchanged (2.4, 1.7 to 3.4). Neither a history of obesity nor switching from another hormonal contraceptive had an effect on the odds ratio. When we stratified cases on type of venous thromboembolism (deep venous thrombosis compared with pulmonary embolism) the results did not materially differ (odds ratio 1.9 (1.1 to 3.2) for deep venous thrombosis and 2.6 (1.6 to 4.2) for pulmonary embolism). As users of oral contraceptives containing drospirenone were more likely to have a new episode of use than were users of those containing levonorgestrel, we stratified on new versus unknown duration of use to evaluate possible bias or modification of effect. We also stratified on calendar year to evaluate whether potential bias related to the recent marketing of oral contraceptives containing drospirenone could explain our results. Neither analysis materially changed the results. The odds ratios for venous thromboembolism, adjusted for age and index year, were 2.5 (1.7 to 3.8) for women with a new episode of use and 2.0 (0.91 to 4.3) for those with unknown duration of use (table 2). The conditional odds ratio was 2.1 (1.1 to 4.0) among women with an index date between 2002 and 2004 and 2.4 (1.6 to 3.6) among those with an index date between 2005 and 2008, comparing oral contraceptives containing drospirenone and levonorgestrel.

As users of oral contraceptives containing drospirenone were more likely to be younger (less than 30) compared with women using oral contraceptives containing levonorgestrel, we investigated for modification of effect by age. Women under age 30 who used oral contraceptives containing drospirenone had a higher risk of venous thromboembolism than did young women who used oral contraceptives containing levonorgestrel (odds ratio 3.7, 2.0 to 6.9). Among women aged 30 to 39, the odds ratio was not materially different from the effect in all women (1.9, 1.1 to 3.3). Among women aged 40 to 44, the odds ratio was 1.4 (0.65 to 3.0); this age stratum contained fewer women. Young women taking oral contraceptives containing drospirenone were more likely to have a shorter duration of oral contraceptive use than were young women taking oral contraceptives containing levonorgestrel; however, when we adjusted for duration in the analysis, the conditional odds ratio increased to 4.0 (2.1 to 7.7) in the younger age stratum.

Users of oral contraceptives containing drospirenone were slightly less likely to have a diagnosis of obesity in this database (5.8% compared with 6.5% in users of oral contraceptives containing levonorgestrel). When we added obesity to the model as a potential confounder, the conditional odds ratio increased to 4.1 (2.1 to 7.9) among younger women. The conditional odds ratios were virtually identical in the unadjusted analyses and those adjusted for obesity for all women in the study: adjusted odds ratio 2.3 (1.6 to 3.3). Finally, drospirenone treated women were more likely to have a record of a menstrual disorder;

Table 2 | Odds ratios for venous thromboembolism in users of oral contraceptives containing drospirenone compared with those containing levonorgestrel

Exposure	No (%) cases	No (%) controls	Crude* odds ratio (95% CI)	Adjusted† odds ratio (95% CI)
Overall				
Levonorgestrel	65 (15)	368 (85)	1.0	1.0
Drospirenone	121 (28)	313 (72)	2.3 (1.6 to 3.2)	2.4 (1.7 to 3.4)
Levonorgestrel 20 users only				
Levonorgestrel-20	20 (13)	131 (87)	1.0	1.0
Drospirenone	121 (28)	313 (72)	2.7 (1.6 to 4.7)	3.2 (1.8 to 5.5)
Levonorgestrel 30 users only				
Levonorgestrel-30	45 (16)	237 (84)	1.0	1.0
Drospirenone	121 (28)	313 (72)	2.1 (1.4 to 3.1)	2.2 (1.5 to 3.4)
New episodes of use only				
Levonorgestrel	42 (14)	253 (86)	1.0	1.0
Drospirenone	102 (28)	264 (72)	2.5 (1.7 to 3.8)	2.7 (1.7 to 4.1)
Users of unknown duration only				
Levonorgestrel	23 (17)	115 (83)	1.0	1.0
Drospirenone	19 (28)	49 (72)	2.0 (0.91 to 4.3)	2.1 (0.96 to 4.7)
New episodes of use with no previous episode				
Levonorgestrel	20 (17)	97 (83)	1.0	1.0
Drospirenone	52 (33)	106 (67)	2.7 (1.5 to 5.1)	2.8 (1.5 to 5.2)
New episodes of use with previous episode				
Levonorgestrel	22 (12)	156 (88)	1.0	1.0
Drospirenone	50 (24)	158 (76)	2.3 (1.3 to 4.0)	2.6 (1.4 to 4.6)

*For overall analysis, crude odds ratio is a conditional odds ratio; for stratified analyses, crude odds ratios are adjusted for age and index year.
†Also adjusted for duration.

adjustment for this condition in the model yielded an odds ratio of 3.7 (2.0 to 7.0) for women aged under 30 using oral contraceptives containing drospirenone compared with women under 30 using oral contraceptives containing levonorgestrel; the odds ratio adjusted for menstrual disorder in the entire study population was 2.3 (1.6 to 3.2). When we restricted the analysis to women with no history of menstrual disorders or obesity in the younger stratum, the odds ratio was 4.0 (1.8 to 8.8), adjusted for index year (40 cases in drospirenone users and nine in levonorgestrel users).

Because of concern that the risk of venous thromboembolism may be related to the dose of ethinylestradiol in the oral contraceptive, we restricted the analysis to cases and controls who received an oral contraceptive containing either drospirenone or levonorgestrel with 30 µg of ethinylestradiol (table 2). The duration adjusted odds ratio was not materially different from the main effect (2.2, 1.5 to 3.4). Among new users, we further restricted the analysis to women who had a previous episode of oral contraceptive use that preceded the episode at the index date to determine if the effect was modified in re-starters compared with women with no previous use recorded in their computer record. The duration adjusted odds ratio in this stratum of women was not materially different from the main effect (2.6, 1.4 to 4.6). When we restricted the analysis to women with no previous episode of use recorded, the odds ratio was slightly higher (2.8, 1.5 to 5.2) (table 2).

The study population contained 937 408 women who satisfied all the conditions for inclusion in this study. These women contributed an estimated 392 844 woman years for oral contraceptives containing drospirenone and 521 824 woman years for oral contraceptives containing levonorgestrel. The incidence rates for venous thromboembolism in the study population were 30.8 (95% confidence interval 25.6 to 36.8) per 100 000 woman years among users of oral contraceptives containing drospirenone and 12.5 (9.61 to 15.9) per 100 000 woman years among users of oral contraceptives containing levonorgestrel. The age adjusted incidence rate ratio for venous thromboembolism comparing current use of oral contraceptives containing drospirenone and levonorgestrel was 2.8 (2.1 to 3.8). The incidence rate of venous thromboembolism increased with increasing age for both oral contraceptives. The incidence rate per 100 000 woman years among users of oral contraceptives containing drospirenone was 24.8 (19.1 to 31.7) among women aged 15-29 years, 39.0 (28.1 to 52.7) among those aged 30-39, and 51.2 (29.3 to 83.2) among those aged 40-44. Among users of oral contraceptives containing levonorgestrel, the corresponding incidence rates were 5.39 (2.94 to 9.05), 18.7 (13.0 to 26.0), and 21.3 (12.1 to 34.5) (table 3).

DISCUSSION

These data provide evidence that current users of oral contraceptives containing drospirenone have an increased risk of non-fatal venous thromboembolism compared with current users of oral contraceptives containing levonorgestrel (adjusted odds ratio 2.4 (1.7 to 3.4); incidence rate ratio adjusted for age 2.8 (2.1 to 3.8)). We compared the risk of venous thromboembolism in users of oral contraceptives containing drospirenone with that in users of oral contraceptives containing levonorgestrel, because these second generation oral contraceptives have been shown to have among the lowest risk of venous thromboembolism of oral contraceptives on the market and have been used in past studies of oral contraceptives in relation to venous thromboembolism.[5-7 10 11 20] We also did an analysis restricted to women who were "new" users of the study oral contraceptive. We did this to ensure that the more recent availability of the oral contraceptives containing drospirenone did not bias the study findings, as all patients in the study had to have started the current episode of oral contraceptive use after 1 January 2002, soon after oral contraceptives containing drospirenone were first marketed. We also assessed the potential for confounding or modification of effect by age and obesity. Although we found some differences in effect in younger women compared with women aged 30 and older, the main finding that oral contraceptives containing drospirenone conferred an increased risk of venous thromboembolism compared with those containing levonorgestrel remained. The increased risk also remained when we adjusted for the effects of obesity and history of menstrual disorders.

Table 3 | Incidence rates and incidence rate ratios for venous thromboembolism in users of drospirenone and levonorgestrel oral contraceptives

Exposure	Cases (n=186)	Person years	Incidence rate (95% CI) per 100 000 person years	Incidence rate ratio (95% CI)
Drospirenone/ethinylestradiol				
Age <30	63	253 895	24.8 (19.1 to 31.7)	4.6 (2.6 to 8.2)
Age 30-39	42	107 701	39.0 (28.1 to 52.7)	2.1 (1.3 to 3.3)
Age 40-44	16	31 248	51.2 (29.3 to 83.2)	2.4 (1.2 to 4.8)
Levonorgestrel/ethinylestradiol 20 µg or 30 µg				
Age <30	14	259 522	5.39 (2.94 to 9.05)	1.0
Age 30-39	35	187 017	18.7 (13.0 to 26.0)	1.0
Age 40-44	16	75 284	21.3 (12.1 to 34.5)	1.0

Crude incidence rate ratio=2.5 (95% CI 1.8 to 3.3).
Incidence rate ratio adjusted for age=2.8 (95% CI 2.1 to 3.8).

The results of the cohort analysis of these data are consistent with those of earlier studies of oral contraceptives and venous thromboembolism. The rates increased with increasing age and were of the same magnitude as has been seen in previous studies.[5 6 13 14] The incidence rate ratio estimated from these data was similar to the odds ratio estimated from the case-control analysis, although it was slightly higher. We were not able to control as precisely for age and calendar time in the cohort study as in the case-control study, which could explain some of the small difference in the effect measures.

Although women who received oral contraceptives containing drospirenone tended to have shorter duration of use compared with those who received oral contraceptives containing levonorgestrel, both controlling for duration of use and stratifying by duration of use did not materially change the effect estimates, so duration of use does not explain the increased risk in users of drospirenone oral contraceptives. We also evaluated whether material bias existed related to the more recent availability of oral contraceptives containing drospirenone compared with the older ones containing levonorgestrel. We found only a small difference in the effect when we looked at the first several years after marketing compared with the later years; the effect was greater in the later years, suggesting that bias related to prescribing of a newly marketed oral contraceptive did not explain our finding.

Strengths and limitations

This epidemiological study used a case-control design that ensured comparability between cases and the comparison group at the time of the case event. Age and calendar time were closely controlled—that is, the controls were matched to cases on year of birth, and the date at which exposure was determined (the index date) was identical in cases and controls. This is important, as oral contraceptives containing drospirenone have been on the market for around 10 years whereas those containing levonorgestrel have been available for decades. We excluded patients with chronic medical conditions such as cancer, coronary artery disease, and autoimmune disease from the study population. Although these conditions were not commonly observed in this generally healthy young population of contraceptive users, the exclusion of such patients from the study population limits concerns about selective prescribing of the study drug on the basis of the presence of clinical risk factors (confounding by indication). More than 937 000 women who used one of the study drugs in our study population provided information on the risk of venous thromboembolism in relation to oral contraceptives containing drospirenone compared with levonorgestrel. Because of the prospective nature of data collection, the information on contraceptive use was recorded before the outcome had occurred, all eligible patients with the outcome were included, and the likelihood of correct diagnosis of venous thromboembolism was increased by the documentation of long term use of anticoagulants. Although some of the cases that we included in the study may not have been true idiopathic cases, the misclassification is highly unlikely to have been associated with contraceptive use, particularly as all cases were currently using some oral contraceptive at the index date. Most women in the study had been filling prescriptions for a study oral contraceptive for several months and as much as several years before the index date, so misclassification of exposure is unlikely to have been a material factor in this study.

This study does have some limitations. Because we could not validate the cases in this study through review of primary records, we may have included some cases that were not true cases of venous thromboembolism or that were not idiopathic cases, although any such misclassification would probably have been non-differential as we identified cases and controls without knowledge of the contraceptive that they had been using. Non-differential misclassification of a dichotomous variable tends to bias results toward the null and thus would not explain the increased risk found in users of the oral contraceptives containing drospirenone.[18] In addition, in the accompanying study using the General Practice Research Database, in which we were able to validate many cases, we found a similar magnitude of effect.[20] We could not evaluate the effect of smoking in this study, as it is not regularly recorded in the PharMetrics database. However, smoking has not been a material confounder in previous studies on the association between oral contraceptives and venous thromboembolism,[5 6] nor was it a confounder of the relation between oral contraceptives and venous thromboembolism in the accompanying General Practice Research Database study, which was able to control for smoking.[20] It is thus not likely to be a material confounder in this study. Neither height nor weight was available in this study. Although body mass index is independently associated with an increased risk of venous thromboembolism, it has not confounded the association between use of hormonal contraceptives and venous thromboembolism in previous studies.[3 5-7] Furthermore, when we evaluated the ICD-9 diagnosis for obesity, we found that obesity was associated with an increased risk of venous

thromboembolism (odds ratio 2.4, 1.4 to 4.0), but inclusion of obesity in the model with exposure did not materially change the effect of contraceptive use, providing additional reassurance that obesity is not likely to be an important confounder in this study. We found that users of the oral contraceptives containing levonorgestrel were more likely to be obese than were the users of those containing drospirenone, so confounding by obesity would not explain the increased risk for oral contraceptives containing drospirenone. So, although the diagnosis of obesity could be subject to reporting bias, whereby only the most obese women have the diagnosis recorded in the data, it would not explain the study result. Furthermore, we did have information on body mass index in the accompanying General Practice Research Database study, and it did not materially confound the relation between the oral contraceptives and venous thromboembolism.[20] As in the PharMetrics data, women who received oral contraceptives containing levonorgestrel were more likely to have a high body mass index than were users of those containing drospirenone, but inclusion of body mass index in the logistic regression model did not materially change the effect measure and did not account for the increased risk of venous thromboembolism in users of oral contraceptives containing drospirenone compared with levonorgestrel. Finally, we did not have information on family history of venous thromboembolism in the database. Some selection bias among women with a family history of venous thromboembolism is possible but is unlikely to account for a material portion of the effect, as idiopathic venous thromboembolism is not common.

These data are derived from the PharMetrics database, which contains health data for both insured and Medicaid patients, although most are insured. Although this study was carried out in women from the United States, other studies in other countries have provided no evidence that the association of oral contraceptive with venous thromboembolism differs in different populations.[10 11 21 22] Also, this study evaluated non-fatal venous thromboembolism and therefore did not directly assess the risk of fatal venous thromboembolism, although the effect in fatal and non-fatal cases would be unlikely to differ greatly. Finally, we studied the effect of two oral contraceptives on idiopathic cases of venous thromboembolism, so this study does not consider the risk in non-idiopathic cases.

Comparison with other publications

Among the four previously published studies that examined the risk of venous thromboembolism in women taking the newer oral contraceptives containing drospirenone compared with those taking other oral contraceptives,[8-11] the studies by Dinger et al and Seeger et al found no associations between drospirenone and venous thromboembolism compared with levonorgestrel and compared with "other" oral contraceptives. In two more recently published studies by Lidegaard et al and van Hylckama Vlieg et al, the authors reported relative risks of 1.6 (1.3 to 2.1) and 1.7 (0.7 to 3.9) comparing oral contraceptives containing drospirenone with those containing levonorgestrel. Women who were pregnant or postpartum were excluded from these two more recent studies, as were women with a previous venous thromboembolism. Women with previous cancer or cardiovascular disease were further excluded from the Lidegaard study. However, inclusion of other proximate causes such as recent surgery and injury could explain the lower effect estimates in these studies compared with our study. The Seeger and Dinger studies analysed all venous thromboembolisms, including patients with a previous venous thromboembolism, other risk factors, and other proximate causes. These factors could explain the null association found in these studies. The inclusion of non-idiopathic cases of venous thromboembolism has been shown to result in attenuation of an effect should it exist.[1] As in our study, the risk of venous thromboembolism in users of oral contraceptives containing drospirenone was compared directly with the risk in users of oral contraceptives containing levonorgestrel in the Lidegaard, van Hylckama Vlieg, and Dinger studies. By contrast, the reference group in the Seeger study included women using all other oral contraceptives, including those containing cyproterone and desogestrel, which have been found to have higher risks of venous thromboembolism compared with the second generation oral contraceptives. Inclusion of these women would have led to a higher risk in the reference group and a lower relative risk for the drospirenone oral contraceptive. Our study included only current users of oral contraceptives containing either levonorgestrel or drospirenone and avoided including oral contraceptives carrying a higher risk in the reference group.

Study implications

We found that, after adjustment for multiple potential confounders and biases, current users of oral contraceptives containing drospirenone were at around a twofold increased risk of non-fatal idiopathic venous thromboembolism compared with current users of oral contraceptives containing levonorgestrel. These findings support more recent studies that suggest that drospirenone oral contraceptives are not as safe as levonorgestrel oral contraceptives with respect to venous thromboembolism and, in the absence of other considerations, should not be the first choice in oral contraception. A close comparison of the methods of the four previously published studies and the two new studies show possible explanations for the differing results.

Unanswered questions and future research

Additional studies with the same definitions of cases and contraceptive use should be done to see if they reproduce the same results, particularly now that the drospirenone oral contraceptive has been on the market for more than a decade. A systematic review of the literature already published on this topic would be an important addition to the literature at this time.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous studies that evaluated the risk of venous thromboembolism in users of oral contraceptives containing drospirenone have found inconsistent results

Some studies have shown no increased risk compared with other oral contraceptives, and other studies have shown small increased risks with drospirenone

WHAT THIS PAPER ADDS

Users of oral contraceptives containing drospirenone had around a twofold increased risk of idiopathic venous thromboembolism compared with users of those containing levonorgestrel, although the overall risk was low

The effects remained when prescribing biases and confounding were taken into account

The incidence rates were 30.8 (95% confidence interval 25.6 to 36.8) and 12.5 (9.61 to 15.9) per 100 000 woman years among users of drospirenone and levonorgestrel oral contraceptives

Contributors: SSJ conceived and designed the study, obtained data and oversaw the conduct of the study, interpreted the results, and wrote the manuscript. RKH conducted the study and the analyses, interpreted the results, and contributed to the manuscript. Both authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. SSJ is the guarantor.
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Ethical approval: This study was exempt from review by the Boston University Medical Center Institutional Review Board. Data from PharMetrics are Health Insurance Portability and Accountability Act compliant.
Data sharing: Open access to the data used in this study would be in direct conflict with the data licensing agreement with the data vendor PharMetrics.

1 Porter JB, Hunter JR, Jick H, Stergachis A. Oral contraceptives and nonfatal vascular disease. *Obstet Gynecol* 1985;66:1-4.
2 Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ* 2001;323:131-4.
3 Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. *Arch Intern Med* 2004;164:1965-76.
4 Farmer RD, Lawrenson RA, Todd JC, Williams TJ, MacRae KD, Tyrer F, et al. A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. *Br J Clin Pharmacol* 2000;49:580-90.
5 Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995;346:1589-93.
6 Jick H, Kaye JA, Vasilakis-Scaramozza C, Jick SS. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000;321:1190-5.
7 Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives [letter]. *Lancet* 2001;358:1427-9.
8 Dinger JC, Heinemann LA, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344-54.
9 Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007;110:587-93.
10 Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009;339:b2890.
11 Van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921.
12 Rothman KJ, Poole C. A strengthening programme for weak associations. *Int J Epidemiol* 1988;17(suppl):955-9.
13 Jick S, Kaye J, Russmann S, Jick H. Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel. *Contraception* 2006;73:566-70.
14 Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 microg of ethinyl estradiol. *Contraception* 2006;73:223-8.
15 Jick SS, Kaye JA, Li L, Jick H. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of contraceptives containing norgestimate and 35 µg ethinyl estradiol. *Contraception* 2007;76:4-7.
16 Jick SS, Jick H. Cerebral venous sinus thrombosis in users of four hormonal contraceptives: levonorgestrel-containing oral contraceptives, norgestimate-containing oral contraceptives, desogestrel-containing oral contraceptives and the contraceptive patch. *Contraception* 2006;74:290-2.
17 Jick SS, Jick H. The contraceptive patch in relation to ischemic stroke and acute myocardial infarction. *Pharmacotherapy* 2007;27:218-20.
18 Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Lippincott Williams & Wilkins, 2008.
19 Episheet. Spreadsheets for the analysis of epidemiologic data [program]. Episheet, 2005.
20 Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 2011;340:d2139.
21 World Health Organization. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995;346:1575-82.
22 Spitzer WO, Lewis MA, Heinemann LA, Thorogood M, MacRae, KD. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996;312:83-8.

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