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Fatal Venous Thromboembolism Associated with Different Combined Oral Contraceptives

A Study of Incidences and Potential Biases in Spontaneous Reporting

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Abstract

Background: Fatal venous thromboembolism (VTE) is a rare complication of combined oral contraceptive (COC) treatment. This study aims to determine incidences of fatal VTE in relation to the type of COC and the percentage of cases reported to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC). A further aim is to compare the characteristics of reported and not reported cases.

Methods: This retrospective study is a separate analysis using data from a larger study that included women aged 15–44 years between 1990 and 1999 with VTE coded as the underlying or contributory cause of death in the Swedish Cause of Death Register. COC use within 2 months of the date of symptom onset or death was identified in 28 cases. Sales data were obtained from the National Corporation of Swedish Pharmacies. Reported cases were identified in the SADRAC database.

Results: After excluding two cases where the type of COC was unknown, the crude incidences of fatal VTE were 5.1 (95% CI 2.3, 9.6), 8.6 (95% CI 4.3, 15.4) and 9.1 (95% CI 3.3, 19.8) cases per million women per year for levonorgestrel-, desogestrel- and norethisterone-containing COCs, respectively. Age-adjusted incidences were approximately twice as high for desogestrel- and norethisterone-containing COCs compared with levonorgestrel-containing COCs, although differences were not statistically significant. Thirty-six percent of cases were reported. Reporting was positively associated with information in medical records relevant to the VTE diagnosis that the patient was a COC user and was significantly higher in northern Sweden.

Conclusion: Results from this study support a higher incidence of fatal VTE with desogestrel-containing COCs than with levonorgestrel-containing COCs.

Background

Venous thromboembolism (VTE) is a rare but potentially fatal complication of combined oral contraceptive (COC) treatment. Death is usually attributed to pulmonary embolism resulting from the disengagement of a clot from the deep venous system. Apart from COC use, risk factors for VTE include advanced age, smoking, cancer, surgery, immobilisation, fractures, antiphospholipid syndrome, major medical illness such as myocardial infarction, stroke or congestive heart failure, treatment with certain drugs, hereditary coagulation disorders and pregnancy/puerperium.[1-5] Based on an annual incidence of idiopathic VTE in COC users of 1–2 cases per 10 000 women per year in the WHO study[6] and a generally accepted case fatality rate of 1–2%,[1,6,7] the incidence of fatal VTE has been calculated to be 1–4 cases per million women per year. Estimates from a few studies that provide direct information on the incidence of fatal pulmonary embolism among COC users are higher (9.0–14.1 cases per million women per year).[8-11] A part of this difference may be due to possible underdetection and, therefore, underestimation of the incidence of idiopathic VTE in the WHO study, which was of case control design. Indeed, incidences of idiopathic VTE among COC users from cohort studies have been higher, varying from 2.2–4.1 cases per 10 000 women per year.[9-14] Based on these studies, the assumed case fatality rate of 1–2% would result in an incidence of fatal VTE as high as up to 8.2 cases per million women per year. Differences between studies may, on the other hand, also be influenced by varying definitions of idiopathic VTE and possible differences in the distribution of risk factors and case fatality rates across studies.

In Sweden, the incidence of fatal pulmonary embolism associated with the use of COCs that had been reported as adverse drug reactions (ADRs) to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) between 1977 and 2001 was 2.5 cases per million women per year.[15] The total incidence could not be calculated because of an unknown degree of under-reporting.

This study is a separate analysis using data from a larger study of fatal VTE among women aged 15–44 years in Sweden between 1990 and 1999.[16] A total of 28 cases of fatal VTE associated with COC treatment were identified for an incidence of 7.5 (95% CI 5.0, 10.9) cases per million women per year.[16] The aim of this study was to determine the incidences of fatal VTE in relation to the type of COC and the percentage of cases reported to SADRAC. A further aim is to compare the characteristics of reported and not reported cases in order to identify potential biases in reporting.

Methods

This retrospective study is a separate analysis using data from a larger study where all cases of VTE (with the exception of cerebral vein thrombosis), coded as the underlying or contributory cause of death among women aged 15–44 years between 1990 and 1999, were identified in the Swedish Cause of Death Registry.[16] Cases with active cancer or where cancer was considered to be the underlying cause of death were excluded. Cases were also excluded if the VTE was judged to be due to terminal illness or if the VTE diagnosis could not be confirmed by an objective investigation including autopsy or diagnostic procedures such as scintigraphy, pulmonary angiography, magnetic resonance imaging, ultrasonography or phlebography (except in cases with a previous verified VTE where a well founded clinical suspicion was considered sufficient). A further requirement was that the VTE that caused or contributed to death had to occur within the study period. All cases fulfilling these criteria were included where use of a COC in the last 2 months prior to onset of symptoms of VTE or death was established based on a statement in medical records relevant to the VTE diagnosis that the patient was a COC user or, alternatively, where there were prescription records covering the period of up to 2 months prior to onset of symptoms of VTE or death, regardless of the presence of other risk factors for VTE. Death had to be caused by the VTE itself and not by a haemorrhagic complication to treatment with anticoagulants. The overall autop-

sy rate among women aged 15–44 years who died from causes other than cancer during the study period was 73.8%. All women aged 15–44 years who were diagnosed with sudden unexplained death during the study period underwent autopsy.

Medical records including hospital records, general practitioner records, records from family planning units or departments of obstetrics and gynaecology, and autopsy reports were requested as necessary in order to establish the cause of death, the possible use of COCs and the presence of potential risk factors for VTE such as cigarette smoking, obesity, concurrent diseases, immobilisation or surgery within 2 months prior to death, and heredity for VTE. Information was also sought on demographic variables such as geographic area and location of death, type of COC used and duration of use.

Average weight was defined as a body mass index (BMI) between 18.0 and 24.9 kg/m^2 or a subjective statement consistent with average weight. Moderate overweight was defined as a BMI between 25.0 and 29.9 kg/m^2 or a subjective statement consistent with moderate overweight. Obesity was defined as a BMI ≥ 30.0 kg/m^2 or a subjective statement consistent with severe overweight.

Annual sales volumes of COCs expressed as the number of defined daily doses per 1000 women aged 15–44 years were obtained from the National Corporation of Swedish Pharmacies (Apoteket AB). We also obtained the number of defined daily doses sold to women aged 15–44 years per 5-year age group; between 1990 and 1995 age information was based on a random sample, whereas since 1996 all prescriptions dispensed in pharmacies have been registered through barcodes including the year of birth and gender of the patient. The number of women aged 15–44 years in different regions was obtained from Statistics Sweden. The number of defined daily doses was converted into user years by dividing the number of daily doses by 365.25. COCs available on the Swedish market from 1990 to 1999 included up to 50 μg/day of ethinylestradiol in combination with norethisterone, lynestrenol, levonorgestrel or desogestrel. Norethisterone-containing COCs were first approved in Sweden in 1963, lynestrenol-containing COCs in 1964, levonorgestrel-containing COCs in 1971 and desogestrel-containing COCs in 1987. Because of the known *in vivo* conversion of lynestrenol to norethisterone,[17] lynestrenol was considered equivalent to norethisterone for purposes of comparison. All COCs that contained the same gestagen were included in the same category.

Since 1965, Sweden has had a system for spontaneous reporting of ADRs. Since 1975, reporting to SADRAC is compulsory for all suspected new or

Table I. Annual distribution of reported and not reported cases of fatal venous thromboembolism associated with combined oral contraceptives (COCs)

Year	Total no. of cases (no. reported/no. not reported)	No. of cases with levonorgestrel-containing COCs	No. of cases with desogestrel-containing COCs	No. of cases with norethisterone-containing COCs
1990	1[a] (0/1)	0	0	0
1991	2 (0/2)	0	1	1
1992	6 (3/3)	4	1	1
1993	4 (3/1)	0	3	1
1994	2[b] (0/2)	1	0	0
1995	3 (2/1)	0	3	0
1996	1 (0/1)	1	0	0
1997	4 (1/3)	1	2	1
1998	3 (0/3)	0	1	2
1999	2 (1/1)	2	0	0
Total	**28 (10/18)**	**9**	**11**	**6**

a The type of COC used was unknown.

b The type of COC used was unknown in one of the cases.

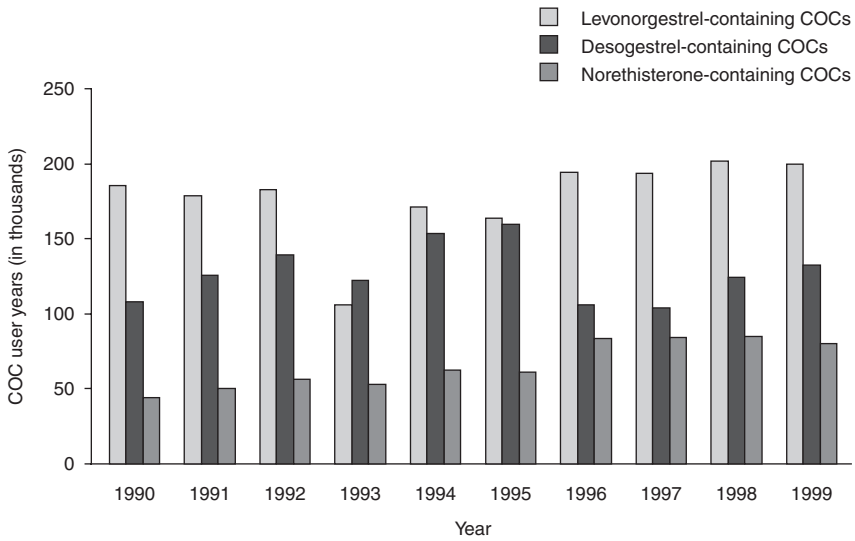

Fig. 1. Annual sales of combined oral contraceptives (COCs) in Swedish women aged 15–44 years.

serious ADRs. All cases of fatal VTE associated with COC use between 1990 and 1999 that had been reported to SADRAC were identified and compared with the total number of VTE-related deaths among COC users found in the Swedish Cause of Death Registry.

The Poisson distribution was used for the calculation of confidence intervals around incidences. Crude and age-standardised incidences (direct standardisation to the age distribution of all COC users) were calculated for different types of COCs. The Mantel-Haenszel method was used for direct age-adjusted incidence comparisons between different types of COCs. The Fisher's exact test and the Mann-Whitney U test were used for comparisons between reported and not reported cases as appropriate and the Chi-squared (χ^2) test was used in order to test differences in the distribution of cases. p-Values of ≤0.05 were considered statistically significant.

The study was approved by the local ethics committee of Umeå University in Sweden.

Results

The annual distribution of reported and not reported cases of VTE associated with COC use are shown in table I. Annual sales of the different COCs are shown in figure 1. There was a drop in COC sales in 1993. A decrease in sales of desogestrel-containing COCs and an increase in sales of levonorgestrel- and norethisterone-containing COCs were noted after media attention concerning a higher risk of VTE with COCs containing desogestrel than with COCs containing levonorgestrel in 1995. The age distribution of cases and its relation to sales of different COCs in different age groups are shown in table II. The type of COC used was unknown in two of the cases. Crude and age-adjusted incidences for different types of COCs, based on cases where the type of COC used was known, are shown in table III. Women using levonorgestrel-containing COCs were older than women using desogestrel- or norethisterone-containing COCs. There were no apparent regional differences in incidence. No consistent secular trends in age distribution were noted for any of the COCs.

Ten cases (36%) were reported as ADRs for a reporting incidence of 2.7 (95% CI 1.3, 5.0) cases per million women per year. Two cases were not reported as ADRs despite having been reported to the National Board of Health and Welfare (Socialstyrelsen) for investigation of possible malpractice. The distribution of different factors among reported and not reported cases are shown in table IV, table V and table VI. None of the cases had a previous

Table II. Distribution of cases of fatal venous thromboembolism and sales of different combined oral contraceptives (COCs) in relation to age in Swedish women aged 15–44 years

Age group (y)	Levonorgestrel-containing COCs			Desogestrel-containing COCs			Norethisterone-containing COCs			All COCs		
	No. of cases	COC user years	% of sales	No. of cases	COC user years	% of sales	No. of cases	COC user years	% of sales	No. of cases	COC user years	% of sales
15–19	2	316 358	17.8	1	300 349	23.6	0	158 431	24.0	3	775 138	20.9
20–24	1	523 248	29.5	3	463 562	36.4	3	236 259	35.7	9[a]	1 223 069	32.9
25–29	0	408 709	23.0	2	260 291	20.4	2	132 213	20.0	4	801 213	21.6
30–34	2	269 757	15.2	3	128 521	10.1	1	68 169	10.3	6	466 446	12.6
35–39	3	166 871	9.4	1	78 677	6.2	0	42 493	6.4	4	288 041	7.8
40–44	1	91 752	5.2	1	42 831	3.4	0	23 662	3.6	2	158 244	4.3
Total	**9**	**1 776 694**	**100.0**	**11**	**1 274 230**	**100.0**	**6**	**661 227**	**100.0**	**28**	**3 712 151**	**100.0**

a In two cases the type of COC used was unknown.

history of VTE. Median ages were 24.5 years (range 18–40 years) in reported cases and 29.0 years (range 17–42 years) in not reported cases (difference not significant). Median BMIs were 25.2 kg/m^2 (range 24.8–25.9 kg/m^2) [n = 4] in reported cases and 28.7 kg/m^2 (range 19.1–44.5 kg/m^2) [n = 13] in not reported cases (difference not significant). Among women who died in the ambulance, emergency ward or hospital, the proportions of reported and not reported cases that were admitted to a university/regional hospital (11.1%, 1/9 vs 41.7%, 5/12; p = 0.18), a central county hospital (33.3%, 3/9 vs 33.3%, 4/12; p = 1.00) or a district county hospital (55.6%, 5/9 vs 25.0%, 3/12; p = 0.20) did not differ significantly. Likewise, in the same group of women, there were no significant differences in the proportions of reported and not reported cases residing in a city with >300 000 inhabitants (22.2%, 2/9 vs 16.7%, 2/12; p = 1.00), between 50 000 and 300 000 inhabitants (33.3%, 3/9 vs 58.3%, 7/12; p = 0.39) or <50 000 inhabitants (44.4%; 4/9 vs 25.0%, 3/12; p = 0.40).

No apparent association between the type of COC used and the duration of use or the presence of risk factors for VTE was identified.

Discussion

The reporting incidence of 2.7 cases per million women per year during the 10-year period of the present study was close to the same as during the entire period of 1977–2001 in Sweden.[15] We identified a similar proportion of reported cases as did another study from New Zealand (36% vs 35%).[8] However, the total incidence of COC-associated fatal VTE was slightly lower in Sweden (7.5[16] vs 10.5 cases per million women per year), despite the fact that all deaths due to VTE with the exception of cerebral vein thrombosis had been included in the former study and only deaths due to pulmonary embolism were included in the latter study.[8] If the two cases of Budd Chiari are excluded, the total incidence in Sweden is reduced to 7.0 (95% CI 4.6, 10.3) cases per million women per year. If cases associated with immobilisation or surgery are also excluded (no such cases were included in the New

Table III. Incidences of fatal venous thromboembolism with different combined oral contraceptives (COCs) in Swedish women aged 15–44 years

Type of COC	No. of cases (n = 26)	Million COC user years	Crude incidence per million COC user years (95% CI)	Age-adjusted incidence per million COC user years[a] (95% CI)
Levonorgestrel-containing	9	1.78	5.1 (2.3, 9.6)	4.7 (1.6, 7.9)
Desogestrel-containing	11	1.27	8.6 (4.3, 15.4)	9.4 (3.8, 15.0)
Norethisterone-containing	6	0.66	9.1 (3.3, 19.8)	9.3 (1.8, 16.8)

a Adjusted to the age distribution of all COC users.

Zealand study) the incidence is further reduced to 6.2 (95% CI 3.9, 9.3) cases per million women per year. These incidence rates must be viewed as minimum estimates as prescriber records from family physicians/midwives could not be retrieved for all cases.[8,16]

The age-adjusted incidences of fatal VTE were numerically higher with desogestrel- and norethisterone-containing COCs: 9.4 (95% CI 3.8, 15.0) and 9.3 (95% CI 1.8, 16.8) cases per million women per year, respectively, compared with levonorgestrel-containing COCs: 4.7 (95% CI 1.6, 7.9) cases per million women per year, although differences were not statistically significant (relative risk 1.99; 95% CI 0.82, 4.83 for desogestrel-containing COCs vs levonorgestrel-containing COCs; p = 0.12 and relative risk 1.99; 95% CI 0.69, 5.74 for norethisterone-containing COCs vs levonorgestrel-containing COCs; p = 0.19). Whereas several studies have indicated an increased risk of VTE with desogestrel- or gestodene-containing COCs compared with levonorgestrel-containing COCs,[18] the risk associated with norethisterone-containing COCs appears to be less well investigated. In favour of our findings, a recent study has shown similar activated protein C (APC) effects on endogenous thrombin potential with norethisterone-containing COCs as with desogestrel- and gestodene-containing COCs.[19] Changes in APC sensitivity could be a plausible mechanism to explain thrombotic risk differences with different COCs. A recently shown correlation between changes in APC sensitivity and changes in serum sex hormone binding globulin (SHBG) during COC treatment[20] further supports our findings in light of the more profound increases in SHBG with norethisterone-containing COCs compared with levonorgestrel-containing COCs.[21] On the other hand, age was the only risk factor for VTE that we could adjust for and it cannot be excluded that the distribution of other risk factors for VTE differed among users of the different COCs. It may be speculated that the apparent difference in estimated absolute risk of fatal VTE in COC users between our study and others[8,9] may in part reflect the differing

Table IV. Demographic variables in reported and not reported cases of fatal venous thromboembolism (VTE) associated with combined oral contraceptives (COCs)

Demographic variable	All cases (n = 28) [n (%)]	Reported cases (n = 10) [n (%)]	Not reported cases (n = 18) [n (%)]	p-Value for the difference between reported and not reported cases
Northern Sweden (12.4% of COC user years)	4 (14.3)	4[a] (40.0)	0 (0.0)	0.01
Middle Sweden (39.2% of COC user years)	9 (32.1)	2 (20.0)	7 (38.9)	0.42
Southern Sweden (48.4% of COC user years)	15 (53.6)	4 (40.0)	11 (61.1)	0.43
Death in ambulance, emergency ward or hospital	21 (75.0)	9 (90.0)	12 (66.7)	0.36
Death at home or location other than the hospital	7 (25.0)	1 (10.0)	6 (33.3)	0.36
Patient sought healthcare for VTE symptoms prior to death	19 (67.9)	8 (80.0)	11 (61.1)	0.42
VTE diagnosis prior to death	5 (17.9)	3 (30.0)	2 (11.1)	0.32
Use of COCs noted in relevant medical records[b]	21 (75.0)	10[c] (100.0)	11[d] (61.1)	0.03

a One case was reported during a study.

b Relevant medical records were defined as all patient records including death certificates relevant to the detection of VTE, before or immediately after death.

c Hospital records from admission/institutional care associated with VTE at the time of death (n = 9) and autopsy report (n = 1).

d Hospital records from admission/institutional care associated with VTE at the time of death (n = 9), hospital records from non-institutional care for suspected pulmonary embolism 3 months before death (n = 1) and epicrisis from the psychiatric clinic where the patient was hospitalised at the time of death (n = 1).

patterns of the use of COCs, in particular the use of desogestrel- and gestodene-containing COCs.

Under-reporting is a well known phenomenon in spontaneous reporting systems. In two studies of mainly non-fatal VTE associated with COCs, much lower reporting rates were found (0% and 6%, respectively).[22,23] Such low reporting rates are not exceptional in spontaneous reporting systems.[24,25] Several possible explanations exist as to why reporting is incomplete, e.g. failure to suspect that an event is drug induced, ignorance about reporting rules, the belief that another healthcare professional is responsible for reporting, insufficient time to report or the opinion that other duties are more important than reporting of ADRs.[26-29] In general, reporting is higher for new drugs and for serious or unexpected ADRs. The most recently introduced COCs containing desogestrel were more commonly identified among reported cases than among not reported cases in this study, although the difference was far from statistically significant. The higher proportion of reported fatal cases in this study compared with the proportion of reported non-fatal cases in another study[23] supports the notion that seriousness is important for the decision to report an ADR.

We identified two factors that were associated with reporting: geographic area with higher reporting in the northern region of Sweden and existence

Table V. Type of combined oral contraceptive (COC) used and duration of use in reported and not reported cases of fatal venous thromboembolism associated with COCs

Characteristic	All cases (n = 28) [n (%)]	Reported cases (n = 10) [n (%)]	Not reported cases (n = 18) [n (%)]	p-Value for the difference between reported and not reported cases
Unknown type of COC	2 (7.1)	0 (0.0)	2 (11.1)	0.52
Desogestrel-containing COCs	11 (39.3)	6 (60.0)	5 (27.8)	0.23
Levonorgestrel-containing COCs	9 (32.1)	3 (30.0)	6 (33.3)	1.00
Norethisterone-containing COCs	6 (21.4)	1 (10.0)	5 (27.8)	0.37
Use ≤6mo	10 (35.7)	6 (60.0)	4 (22.2)	0.10
Use >6mo–1y	3 (10.7)	0 (0.0)	3 (16.7)	0.53
Use >1y	15 (53.6)	4 (40.0)	11 (61.1)	0.43

Table VI. Presence of potential risk factors for venous thromboembolism (VTE) in reported and not reported cases of fatal VTE associated with combined oral contraceptives

Risk factor	All cases [n (%)[a]]	Reported cases [n (%)][a]	Not reported cases [n (%)][a]	p-Value for the difference between reported and not reported cases
Age ≥35y	6/28 (21.4)	2/10 (20.0)	4/18 (22.2)	1.00
Immobilisation and/or surgery within 2mo prior to death	5/28 (17.9)	2/10 (20.0)	3/18 (16.7)	1.00
Obesity[b]	5/25 (20.0)	0/9 (0.0)	5/16 (31.2)	0.12
Moderate overweight[b]	9/25 (36.0)	4/9 (44.4)	5/16 (31.2)	0.67
Current smoker[b]	9/22 (40.9)	2/6 (33.3)	7/16 (43.8)	1.00
Alcohol or substance abuse	3/28 (10.7)	0/10 (0.0)	3/18 (16.7)	0.53
Malignant disease	1/28 (3.6)	0/10 (0.0)	1/18 (5.6)	1.00
Infectious/inflammatory disease	7/28 (25.0)	1/10 (10.0)	6/18 (33.3)	0.36
Cardiac disease	4/28 (14.3)	2/10 (20.0)	2/18 (11.1)	0.60
Vein or lymph system malformation	2/28 (7.1)	2/10 (20.0)	0/18 (0.0)	0.12
Thrombocythaemia/polycythaemia including splenectomy	3/28 (10.7)	0/10 (0.0)	3/18 (16.7)	0.53
Concomitant treatment with another drug known to increase the risk of VTE	3/28 (10.7)	1/10 (10.0)	2/18 (11.1)	1.00
Heredity for VTE known at the time of death[b]	6/14 (42.9)	2/6 (33.3)	4/8 (50.0)	0.63
Any of the above[b]	26/26 (100.0)	8/8 (100.0)	18/18 (100.0)	1.00

a No. of cases/total no. of cases of VTE with information available.

b Only cases with available information are included.

of a note in the medical records relevant to the diagnosis of VTE that the patient was a COC user. These results need to be treated with caution as all analyses on factors associated with reporting were exploratory and reported p-values were nominal. The higher reporting in the northern region is consistent with results from another study indicating a relatively higher reporting rate of ADRs from this region,[30] although one of the cases had been reported during a study.[22] The latter result indicates, as seems obvious, that awareness of drugs as potential causes of disease is important for the decision to report an ADR. However, it should be recognised that it may be difficult to obtain drug histories in situations where the patient may be unconscious or deceased and the closest relatives may not volunteer information. Five of the seven cases where COC use was not noted in medical records relevant to the diagnosis of VTE concerned women who died at home or at another similar location, of which three cases were subjected to forensic autopsy. One of the two remaining cases, where COC use was not noted in medical records relevant to the diagnosis of VTE, also concerned a woman who was subjected to forensic autopsy following her death during ambulance transport. The main purpose of the forensic autopsy is to exclude unnatural causes of death and it is understandable, therefore, if potential COC use is not thoroughly investigated. Nevertheless, since it is even more difficult to obtain accurate information on the use of COCs retrospectively (retrospective identification of prescriber records is tedious and not always successful), every effort should be made to confirm or refute the use of COCs at the time of death and to make this information available in the medical records related to the VTE episode or in the death certificate. This measure may also lead to increased ADR reporting. The ability to monitor the risk of fatal VTE with COCs may be further improved by the introduction of a nationwide drug-prescription database, which could be linked with death registry information.

Our study sample was too small to detect even comparatively large absolute differences between reported and not reported cases. Up to 6 months' duration of COC use tended to be more common,

albeit not significantly, among reported cases than not reported cases. The result is supportive of the notion that any ADR is more likely to be identified and reported in the early phase after start of treatment. Additional studies are needed in order to determine the importance of different factors for the reporting of fatal cases of VTE associated with COCs.

Conclusion

We found age-adjusted incidences of fatal VTE that were approximately twice as high for desogestrel- and norethisterone-containing COCs than with levonorgestrel-containing COCs, although differences were not statistically significant. These results suggest that the risk of fatal VTE is higher with desogestrel-containing COCs than with levonorgestrel-containing COCs and are in accordance with results from previous epidemiological studies. Only one-third of cases were reported to SADRAC as ADRs. A geographical difference in reporting was seen, with higher reporting in the northern region of Sweden. Reporting was also positively associated with information in medical records relevant to the diagnosis of VTE that the patient was a COC user.

Our study indicates that more attention needs to be paid among healthcare professionals and forensic pathologists to the fact that COCs can induce or contribute to the development of fatal VTE. If, in every case where a woman of childbearing age dies from VTE, the use of COCs is thoroughly investigated and assessed, this is likely to result in increased reporting and, consequently, in improved knowledge of the risks involved with the use of COCs. The surveillance of these drugs may be further improved by a nationwide drug-prescription database, which could be linked with death registry information.

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