Mortality from venous thromboembolism among young women in Europe: no evidence for any effect of third generation oral contraceptives

R D T Farmer, R B Newson, K MacRae, R A Lawrenson, F Tyrer

Abstract

Study objective—To investigate whether there has been an increase of venous thromboembolism (VTE) mortality in European countries, concurrent with the replacement of second generation by third generation combined oral contraceptives (COCs). Such an increase has been predicted, and reportedly detected, because published studies have detected an increased incidence of VTE associated with third generation rather than second generation COC use.

Design—Data were collected on population and annual VTE mortality in women 15–34 and 35–49 years old, and on second and third generation COC sales, from 1981 to 1994 in 13 European countries. Data from the seven most populous countries were analysed by linear regression of annual VTE mortality, in the 15–34 and 15–49 age groups, with respect to calculated total and third generation COC use rates, and the regression coefficients used to estimate mortality differences between second generation users and non-users and between third and second generation users, respectively.

Main results—The estimated mortality differences in all seven countries had confidence intervals wide enough to contain both zero and the excess mortalities expected from the results of published studies. This was true both for the mortality difference between third and second generation COC users and for that between second generation users and COC non-users.

Conclusions—Mortality differences of the size expected from the published studies cannot be measured using annual national VTE mortality and COC sales data alone, because of residual interannual variation in VTE mortality, and possibly confounding between rising third generation market share and total COC use.

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Four epidemiological studies published during the latter part of 1995 and early 1996 found an increased risk for venous thromboembolism (VTE) among women using third generation combined oral contraceptives (COCs) compared with those using second generation COCs. One of the studies was based on a UK general practice clinical data base, two were hospital based case-control studies, and the fourth was based on the cases registered with three anticoagulant clinics. The publication of the first four papers prompted considerable debate and, in some countries action by the national licensing authorities. Some of the investigators themselves, notably the Transnational team, proposed that some, if not all, of the differences between preparations could be explained by bias, confounding or both. However, others dismissed this possibility.

A major concern is that, if third generation COCs increase the incidence of morbidity, then they are likely to increase mortality. An increased mortality associated with a drug that is used for the prevention of pregnancy, rather than for the treatment of a disease, is arguably unacceptable, unless there are compensating reductions in mortality from other causes. No significant reduction in mortality has yet been demonstrated for third generation products, although there is a suggestion that they reduce the incidence of acute myocardial infarction.

McPherson3 applauded the prompt action by the UK Committee on the Safety of Medicines (CSM) in warning doctors and patients about the “dangers” of third generation COCs, calculating that it was likely to prevent one death per 500 000 woman years. Subsequently, Vandenburgroucke et al4 and Thomas5 claimed that trends in mortality in the Netherlands, and in England and Wales, were consistent with third generation oral COCs causing a higher mortality than their predecessors. Their interpretation of the data has been challenged.6–10

In view of the numbers of women in Europe using third generation COCs at the end of 1995, it was thought that it might be possible to measure their impact, if any, on mortality from venous thromboembolic disease. It is hypothesised that VTE mortality is higher in women taking second generation COCs than in women taking no COCs, and higher in women taking third generation COCs than in women not taking second generation COCs. This paper reports an attempt to measure these hypotheses mortality differences, using the trends in mortality and oral contraceptive use from 1981 to 1994 in Europe.

Methods

The causes of death included as VTE were pulmonary embolism (ICD9: 415.1) and venous thrombosis (ICD9: 451–453). All VTE deaths associated with pregnancy were thereby
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excluded, as they are classified separately within ICD9. The annual numbers of deaths from the selected causes, registered in Austria, Belgium, Denmark, Finland, France, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the UK, were abstracted from the official statistics published by the respective government bodies, for each year between 1981 and 1994, for men and women separately. The estimated populations were abstracted from the same sources.

The estimated annual numbers of packs of oral contraceptive by progestogen type and oestrogen content, for each country and year, were supplied from the MIDAS data base, proprietary to Intercontinental Medical Systems (IMS) Global Services, 7 Harewood Avenue, London NW1 6JB, England. IMS conducts audits of pharmaceutical sales in each country, based on censuses or sample surveys of pharmacies and hospitals. The sampling schemes vary between countries, reflecting variation in distributional practice, and are detailed in documentation available on request from IMS. Usage data from Norway were available only for 1987–1994.

Throughout Europe, virtually all COCs are used by women under 50 years old, and between 80% and 90% are used by women under 35. The deaths from pregnancy unrelated VTE were therefore converted into rates per million woman years, covering the age groups 15–34 years and 15–49 years. The oral contraceptive usage data were analysed as general usage rates of all COCs and of third generation COCs. The latter were defined as COCs containing one of the newer progestogens (desogestrel, gestodene or norgestimate). As age specific usage data are not available, the usage rate for each combination of country, year and age group was estimated by using sales figures for that country and year in “woman years” (cycles per year divided by 13) as the numerator, and the female population of that country, year, and age group as the denominator.

The data were analysed using a linear regression model for each country, with female mortality rate as the predicted variable and the rates of usage of all COCs and of third generation COCs as predictor variables. The regression coefficient for total COC usage is interpreted as the difference in mortality rate between second generation COC users and COC non-users, whereas the regression coefficient for third generation COC usage is interpreted as the difference in mortality rate between third and second generation COC users. The base mortality rate for women not

### Table 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Women aged 15–49 years (thousands)</th>
<th>COC years per 100 woman years</th>
<th>Year of introduction</th>
<th>% 3rd* generation in 1995</th>
<th>% Change 1985–1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>469.3</td>
<td>2001.8</td>
<td>23.4</td>
<td>1958</td>
<td>1988</td>
</tr>
<tr>
<td>Belgium</td>
<td>901.3</td>
<td>2417.1</td>
<td>37.3</td>
<td>1980</td>
<td>1988</td>
</tr>
<tr>
<td>Denmark</td>
<td>237.9</td>
<td>1311.2</td>
<td>18.1</td>
<td>1984</td>
<td>1985</td>
</tr>
<tr>
<td>Finland</td>
<td>222.5</td>
<td>1278.8</td>
<td>15.7</td>
<td>1981</td>
<td>1989</td>
</tr>
<tr>
<td>France</td>
<td>4470.5</td>
<td>14451.2</td>
<td>30.9</td>
<td>1984</td>
<td>1988</td>
</tr>
<tr>
<td>Italy</td>
<td>2064.5</td>
<td>14280.9</td>
<td>14.4</td>
<td>1984</td>
<td>1987</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1570.2</td>
<td>4022.5</td>
<td>16.9</td>
<td>1984</td>
<td>1989</td>
</tr>
<tr>
<td>Norway</td>
<td>170.4</td>
<td>1066.2</td>
<td>16.0</td>
<td>1984</td>
<td>1989</td>
</tr>
<tr>
<td>Portugal</td>
<td>702.7</td>
<td>2551.2</td>
<td>27.5</td>
<td>1984</td>
<td>1989</td>
</tr>
<tr>
<td>Spain</td>
<td>1209.3</td>
<td>9961.2</td>
<td>12.1</td>
<td>1984</td>
<td>1989</td>
</tr>
<tr>
<td>Sweden</td>
<td>410.4</td>
<td>2059.6</td>
<td>19.9</td>
<td>1984</td>
<td>1989</td>
</tr>
<tr>
<td>Switzerland</td>
<td>402.4</td>
<td>1776.6</td>
<td>22.6</td>
<td>1981</td>
<td>1987</td>
</tr>
<tr>
<td>UK</td>
<td>3101.6</td>
<td>12529.8</td>
<td>24.8</td>
<td>1989</td>
<td>1991</td>
</tr>
</tbody>
</table>


### Table 2

VTE mortality differences (per million woman years) between COC use groups, estimated from rates in 15–34 year olds

<table>
<thead>
<tr>
<th>Country</th>
<th>Start</th>
<th>2nd generation users versus non-users</th>
<th>3rd generation users versus 2nd generation users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>1981–1987</td>
<td>−67.43 (−428.83, 293.97)</td>
<td>51.99 (−235.87, 330.86)</td>
</tr>
<tr>
<td>France</td>
<td>1981–1992</td>
<td>−29.6 (−18.76, 12.84)</td>
<td>−3.62 (−18.94, 11.71)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1981–1993</td>
<td>7.92 (−30.95, 46.79)</td>
<td>−7.43 (−52.57, 37.95)</td>
</tr>
<tr>
<td>Portugal</td>
<td>1984–1994</td>
<td>−55.51 (−172.90, 65.87)</td>
<td>24.52 (−52.47, 101.50)</td>
</tr>
<tr>
<td>Spain</td>
<td>1981–1992</td>
<td>73.80 (−70.09, 217.68)</td>
<td>−54.55 (−129.10, 217.68)</td>
</tr>
<tr>
<td>UK</td>
<td>1984–1992</td>
<td>41.24 (−88.37, 170.86)</td>
<td>−13.50 (−87.32, 60.31)</td>
</tr>
</tbody>
</table>
taking COCs is estimated by the constant (intercept) term in the model. The software used for the modelling exercise was PROC GENMOD of SAS.14

In Austria, Denmark, Finland, Norway, Sweden, and Switzerland, the annual numbers of deaths were zero in some years and generally very low, because of the sizes of their populations. In the case of Germany, the data were complicated by reunification during the period being investigated, as the certification and coding practices of the Federal Republic differed from those of the Democratic Republic, and the data on oral contraceptive usage in the former Democratic Republic were not available. It was therefore decided to exclude these countries from the regression analysis and to concentrate attention on the other seven (Belgium, France, Italy, the Netherlands, Portugal, Spain, and the UK). There were no major changes in the coding practices in any of these countries, except the UK, where the Office of Population Censuses and Surveys (OPCS) changed their interpretation of WHO rule 3 relating to coding the cause of death in 1984. The effect of this was to reduce the numbers of deaths coded as pulmonary embolus and venous thrombosis. In 1993, the interpretation of rule 3 was changed back to the internationally accepted version with the introduction of automated cause coding software.15 The regression analysis for the UK was therefore restricted to the years 1984–1992.

Figure 1 COC usage and VTE death rates for women aged 15–34, plotted against time for seven countries (A–G). Lines are total COC usage (solid) and third generation COC usage (dashed). Bullets are annual VTE death rates. Reference line in (G) represents a change in coding practice in the United Kingdom.
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There is no useful analysis of male death rates and other causes of death for the above analysis. Plausible explanations for differences in multiple regression coefficients are given in tables 2 and 3. The regression coefficients of table 2 are presented graphically as figure 2. Regression coefficients for total and third generation COC use are given with 95% confidence intervals (CIs). All of these are wide enough to include the value of zero, indicating that there is a lot of residual variation between years, unrelated to COC use, and that this variation masks any increase or decrease associated with changing COC use patterns.

It is plausible that some of this residual variation might be caused by factors varying with time and affecting men as much as women. A possible example of such a factor is a change in coding practice for causes of death. Accordingly, the above analysis was augmented, with male VTE death rates in the corresponding age group as an additional predictor variable. This analysis yielded similarly large confidence intervals for the COC effects, and the regression coefficients for male mortality were not significantly different from zero (not shown). It was therefore concluded that the inclusion of male death rates in the analysis would serve no useful purpose in measuring the parameters of interest, namely the incremental rates associated with second and third generation COCs.

Discussion

Under normal circumstances, secular trends and international variations of the order demonstrated in this paper would not warrant any comment. However, the concern raised by recent epidemiological investigations, coupled with the claims there has been a significant increase in mortality from venous thromboembolic disease in the UK and the Netherlands, requires that the issue be considered with care. Patterns of COC use have varied between countries. From table 1, the highest rates of COC use (expressed per 100 women aged 15–49 years) were in the Netherlands, Belgium, France, and Portugal, whereas the lowest usage rates were in Spain, Italy, and the Scandinavian countries. The market share of third generation COCs was very high in Italy (84.4%), Denmark (75.9%), and Finland (73.4%). By 1995, five of the countries had not introduced norgestimate, and two had not introduced gestodene. In all countries except Denmark, the overall usage increased during the period investigated. The greatest increase was in Italy (144.6%), but in most of the countries the increase in usage was between 25% and 40%.

For women aged 15–34, trends in COC use and VTE mortality are juxtaposed in figure 1. In Belgium and Portugal, mortality fluctuates, as would be expected in small countries, but no clear trend is visible. In Italy, mortality is less variable, as would be expected in a larger country, but no clear time trend stands out, despite increases both in total COCs and in third generation COCs. In France there was a steady decrease in mortality from VTE between 1981 and 1992, together with a steady

Results

Table 1 summarises the overall national usage of COCs in 1995, for each of the countries under consideration. The COC usage rates and death rates for the 15–34 age group, in the seven countries selected for the regression analysis, were plotted against time to form figure 1.

Tables 2 and 3 show the mortality differences calculated from the multiple regression models for the same seven countries, for the 15–34 and 15–49 age groups, respectively. The regression coefficients of table 2 are presented graphically as figure 2. Regression coefficients for total and third generation COC use are given with 95% confidence intervals (CIs). All of these are wide enough to include the value of zero, indicating that there is a lot of residual variation between years, unrelated to COC use, and that this variation masks any increase or decrease associated with changing COC use patterns.

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increase in the use of combined oral contraceptives. The established trend in VTE mortality was uninterrupted by the growth in use of third generation COCs in 1985. In Spain, the growth in usage in COCs was modest between 1981 and 1992, and VTE mortality was relatively constant except for 1981 and 1986, during which there were aberrantly high rates, both predating the introduction of third generation products. In the UK, the trend in mortality seems to follow the trend in COC usage very closely, and there is no indication that the introduction of third generation products had any additional effect. In the Netherlands, the first European country to license and use third generation products, there is no obvious trend in mortality between 1981 and 1992. The 1993 mortality rate seems high, but it represents an increase of only two deaths over the number in 1992.

Most VTEs are attributable to pre-existing medical conditions, such as surgical operations, fractures and other trauma, certain infections, corticosteroid therapy, and systemic lupus erythematosus. Pregnancy and the post-partum period are also associated with a high incidence of VTEs, but these are always classified separately in mortality statistics and, in principle, should not be included in the data presented here. Otherwise, it would be usual for a VTE death certificate to state that the VTE was the immediate cause of death, entered in part 1 of the death certificate, whereas the other conditions that might have led to the VTE would be entered in either part 1 or part 2 (whether or not the death was certified after medicolegal investigation). Under WHO rules for coding the primary cause of death, the immediate cause is coded as the primary cause, unless the immediate cause is considered to be a direct consequence of another underlying disease. For instance, a death from a pulmonary embolus secondary to a fracture would usually be coded as pulmonary embolus rather than a fracture, as the embolus was not a direct consequence of the fracture but a complication of the fracture. For this reason, the distinction between "idiopathic" and "non-idiopathic" VTEs is not easy to define using national statistics, and we do not attempt to do so here, except for the exclusion of pregnancy associated VTEs, which are patently non-idiopathic. Official VTE mortality figures will therefore be dominated by people with a range of risk factors other than exposure to oral contraceptives. These risk factors may cause problems if they vary between years, either concurrently with the market shares of different COCs (in which case they will be confounders), or "randomly" (in which case they will create additional background variation and obscure COC effects). Changes in coding practice, such as occurred in the UK in 1984 and 1983 (see Methods), are additional potential confounders, for which we have attempted to compensate.

VTE incidence rates increase exponentially with age. Few studies have attempted to estimate the total incidence of VTE (idiopathic and non-idiopathic) among women in the reproductive age group. The most recent, which included events among women with concurrent disease, indicates that it is in the order of 100 per million woman years for women neither pregnant nor exposed to oral contraceptives. For idiopathic VTE among women in the reproductive age group, it is estimated that the incidence amongst non-users of oral contraceptives is between 30 and 40 per million woman years, whereas the incidences among women using second and third generation products have been estimated at about 160 and 290, respectively, per million woman years. There are few data on the case fatality rates of idiopathic VTE among young women, as most studies have been based on older populations with a variety of concurrent conditions, but the indications are that it is in the order of 1 in 100. It follows that, if COC related and non-COC related VTEs are equally likely to be fatal, then the mortality rates per million woman years from idiopathic VTE would be in the order of 0.4 for non-users of COCs, 1.6 for second generation COC users, and 2.9 for third generation COC users. The mortality difference between third generation and second generation COC users would therefore be 1.3 per million woman years, whereas the mortality difference between second generation users and COC non-users would be 1.2 per million woman years.

In figure 1, death rates from pregnancy unrelated VTE (idiopathic or otherwise) are typically in the order of 10 per million woman years. Idiopathic VTE deaths are expected to be a small proportion of the total. Maguire et al., studying the incidence of thromboembolism in the USA, found that there was a "predisposing" cause for the event in about 79% of cases, so that about 21% were idiopathic. If the proportion is similar in Europe, and if idiopathic and non-idiopathic VTEs are equally likely to be fatal, then the death rate from idiopathic VTE should be in the order of 2 per million woman years. The alleged mortality difference of 1.3 per million woman years between COC generations would be an even smaller proportion of the total, even if a country progressed from 100% second generation to 100% third generation COC use in the observed time. This is arguably a reason for concentrating attention on the 15–34 age group, as we have done here, rather than including data from the 35–49 age group, among whom COC usage is lower and the background VTE mortality rate higher.

In figure 2, the wide confidence intervals for third generation COC effects in the younger age group are consistent with the "null hypothesis" that third generation COCs are no more hazardous than second generation COCs. However, they are also consistent with a wide range of other hypotheses, including the possibilities that third generation COCs are associated with an excess mortality of 1.3 per million woman years, compared with second generation COCs, or, alternatively, with a degree of protection. The confidence intervals for second generation COC effects are even wider, containing both zero and the calculated excess
mortality of 1.2 per million woman years. This indicates that an analysis of between year, within country variation in the 1980s and 1990s cannot even measure the mortality difference between second generation COC use and no COC use, although this difference is generally agreed to be positive.

Thomas's original communication\(^5\) associated the increase in use of third generation COCs with an apparently increasing trend in VTE deaths among young women in the UK from 1984 to 1992 (see fig 1(G)). He did not give data on the size of the increase in third generation COC use, or ask how large an increase in VTE deaths would be expected from it under his hypothesis, or even whether the observed increase might result from rising COC usage in general rather than third generation usage in particular. In a second communication,\(^6\) replying to criticism from Farmer and Lewis\(^7\) and Van Lunsen,\(^8\) he suggested that a linear regression model should be used, with mortality as the predicted variable and usage data for second and third generation COCs as predictor variables. Such a model is a reparameterised form of the one used here. The drawback of Thomas's approach is that the regression coefficient for second generation COC use will then measure the mortality difference between second generation COC use and no COC use, and the regression coefficient for third generation COC use will measure the mortality difference between third generation COC use and no COC use, whereas we really wanted to measure the mortality difference between third generation and second generation COC use. The model used here measures this latter difference, while allowing for the mortality difference between second generation COC use and no COC use.

For either of the two regression models, the two x variables are likely to be correlated, either positively, as is probably the case of the model used here, because third generation products are capturing an expanding share of an expanding market, or negatively, as is probably the case with Thomas's model, because the two x variables are the sales rates of two competing products. This problem does not invalidate the linear regression method, although it causes the estimated regression coefficients to be correlated, increasing the width of the confidence intervals for each coefficient.

The design and analysis of this study has the disadvantage of failing to control for possible time dependent confounders, with the important exception of total COC usage. However, it has the advantage of not being affected by selective prescription bias, whereby, in any one country and year, women considered to be especially vulnerable are especially likely to be prescribed the more recent product (because it is assumed to be safer, or because women already dissatisfied with the old product are likely to switch). In our analysis, none of the seven countries showed a significantly positive association between VTE mortality and third generation COC use. The confidence intervals are very wide, and do not rule out small excess mortalities of the size inferred from the case-control studies. However, there is no justification for claiming that the observed mortality trends, on their own, show an increase in VTE mortality among young women associated specifically with the rising market share of third generation COCs.

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Conflicts of interest: none.