Oral contraceptives and mortality from venous thrombosis

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Letters to the Editor

Oral contraceptives and mortality from venous thromboembolism

SIR—Vandenbroucke and colleagues (Aug 10, p 401)[1] and Thomas (Aug 10, p 402)[2] believe that the modest increase in mortality from venous thromboembolism (VTE) among young women that occurred between the mid-1980s and the early 1990s might have been due to the increased use of oral contraceptives (OCs) containing one of the newer progestagens (desogestrel or gestodene). We question their interpretation of the findings.

Death from VTE accounts for less than 1% of total mortality in women aged 15–44 years. Moreover, only a few deaths are not associated with trauma, surgery, or major illness. It follows that most of the 2–8 deaths per million women could not be associated with OCs. Because of its association with other illnesses the apparent frequency of death from VTE will be affected both by the preference of doctors (and coroners) when completing death certificates and by coding practices adopted by national statistical authorities. Investigators should be cautious in their interpretation of both absolute rates and secular trends in mortality.

Vandenbroucke and co-workers draw conclusions about the association between OC exposure and VTE from consideration of the secular trends in the death rates in 15–44 year olds estimated from a maximum of 20 deaths annually. In this age group about 60% of the VTE deaths will be in those over age 30, whereas about 70% of OC use is by women under this age. If any changes in mortality from VTE had been due to OC use then they would be limited to women. The Dutch mortality rates indicate that the female to male ratio fell between 1985 and 1990 and remained stable thereafter. Thus, if the recent modest rise in female mortality was caused by changes in the patterns of OC use, then to explain the proportionately greater rise in males during the same period we would need to identify an agent that uniquely affects the male. In England and Wales, according to Thomas, the ratio between males and females aged 30–44 remained more or less stable and for neither sex is there a discernible secular trend. Mortality from VTE in males aged 15–29 is so low that year by year changes in female to male mortality cannot be ascertained. There seems to have been an increase in death rates among 15–29-year-old women between 1989 and 1990; between 1990 and 1992 rates were stable.

Since all combined OCs carry an increased risk of thromboembolic disease it is important to establish whether any trends are associated with overall usage before focusing on particular products. Between 1984 and 1990 the number of cycles used in the UK increased by 23·7% (from 31·6 to 39·1 million), and there was a modest increase in mortality from VTE among 15–29-year-old women (1·6 to 4·4 per million). Between 1990 and 1992 the number of cycles used increased by 11·2% (to 43·5 million), and there was no change in mortality. However, between 1990 and 1993 the proportion of OCs used that contained one of the suspect progestagens increased from 20·1% to 44·0%.* Multiple linear regression for the death rates amongst 15–29 year olds against total cycles and the proportion containing the newer progestagens gives a regression coefficient of 0·87, with an x coefficient for total use of +0·59 and that for the proportion of use of OCs containing newer progestagens of −0·09: the equivalent figures for 30–44 year olds are 0·15, +0·40, and −0·13. For the Netherlands, in women aged 15–44, the regression coefficient is 0·41 with an x coefficient for total OC use of 0·39 and that for the proportion containing newer progestagens being −0·02. Assuming that the principal determinant of VTE death were OC use these calculations indicate that the modest changes in VTE mortality could be accounted for in part by changes in the overall use of OCs, but that any such effect was limited by the introduction of OCs containing newer progestagens. This conclusion is consistent with the hypothesis that the newer products are safer than those they replaced.

*Tables showing full data for England and Wales and the Netherlands are available from *The Lancet* or the authors, on request

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1 Vandenbroucke JP, Bloemenkamp KWM, Helmerhorst FM, Rosendaal FR. Mortality from venous thromboembolism and myocardial infarction in young women in the Netherlands. *Lancet* 1996; **348:** 401–02.
2 Thomas SHL. Mortality from venous thromboembolism and myocardial infarction in young adults in England and Wales. *Lancet* 1996; **348:** 402.

SIR—The debate on the safety of OCs is further confused by Vandenbroucke' and colleagues[1] and Thomas'[2] reports on mortality rates from VTE in the Netherlands and the UK. These investigators believe that their data support a hypothesis that third-generation OCs are associated with an increased frequency of VTE. Such a consideration would be relevant if bias could be excluded. Recent work indicates, however, the existence of biases,[3,4] and suggests that earlier epidemiological studies were not able to adequately adjust for these biases. One of the initial studies[5] also assessed mortality from cardiovascular disease and found no difference between users of preparations with second-generation and third-generation progestagens; this is not surprising because the frequency of VTE morbidity in OC users in that study was not higher than that of 15 years ago.

The data on which Vandenbroucke and colleagues base their conclusion fail to indicate any rise in mortality in the female group that was not present in the male group. Vandenbroucke is worried about the mortality rate in Dutch women during 1993 and 1994 compared with the end of the 1980s but does not comment on the unchanged female to male ratio in that period (1988, 2·1; 1989, 2·6; 1994, 1·9*). If anything, this ratio indicates a slight decrease in VTE mortality in women relative to men, which contradicts any concern over VTE in women using third-generation OCs. Moreover, the sudden increase in VTE mortality in 1993 and 1994 is unlikely to be related to the increasing use of third-generation OCs because changes in OC use in the Netherlands occurred much earlier. Third-generation pills were introduced in the early 1980s; by 1987 25% of OC users were taking a third-generation formulation. Since then there only has been a gradual increase, to 31·2% in 1991 and 36·8% in 1995 (data from a yearly population-based survey, unpublished). The data from Thomas provide merely erratic shifts in the female to male

ratio and thus do not allow any interpretation.

The absence of a biological explanation of the differential VTE frequencies, the absence of confirmation by mortality data, and the increasing evidence of bias in the initial studies should end the efforts of scientists trying to revive a pill scare that should not have occurred in the first place, and that already has led to increasing unwanted pregnancy and abortion rates in several European countries.

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1 Vandenbroucke JP, Bloemenkamp KWM, Helmerhorst FM, Rosendaal FR. Mortality from venous thromboembolism and myocardial infarction in young women in the Netherlands. *Lancet* 1996; **348:** 401–02.
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*Full data available from *The Lancet* or the author, on request

SIR—The latest eruption of epidemiology into modern medicine is again unjustifiable and may have negative consequences. Vandenbroucke and colleagues[1] and Thomas[2] suggest that third-generation OCs increase mortality from VTE in women—yet another example of disputable effects of epidemiology. Both groups base their interpretation on a slight increase in mortality from VTE in women in the past few years. However, they fail to explain the proportionally similar trends in men over the same period. In addition, it is not logical that suggested effects of third-generation OCs are observed years after (Dutch data) or before (UK data) they were widely used, whereas OC-associated VTE occurs mainly in women just starting on OCs.

Vandenbroucke and Thomas' interpretations are even more surprising since the suggested increase in mortality from VTE cannot be related to the use of OCs. The frequency of OC-associated VTE did not increase in the time of their investigation, as evident from cohort studies. In the early 1980s four cases of VTE were recorded in 10 000 OC users[3] per year, whereas, at most, three cases of VTE in 10 000 OC users[4,5] per year were found in the recent cohort studies from the early 1990s, when third-generation OCs were available.

An increasing number of new publications on the OC and VTE issue point out that the observed difference in frequency of VTE between OCs of the second and third generation may result from biases and confounders rather than a biological effect. As pointed out by Thomas, "death certificate diagnoses may not be accurate, changes in mortality with time may reflect changes in other risk factors, and there may be diagnostic bias".

These considerations re-emphasise the need for critical evaluation of epidemiological data and their clinical relevance. Will we ever learn from this and previous pill scares?

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1 Vandenbroucke JP, Bloemenkamp KWM, Helmerhorst FM, Rosendaal FR. Mortality from venous thromboembolism and myocardial infarction in young women in the Netherlands. *Lancet* 1996; **348:** 401–02.
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Authors' reply

SIR—Discussion about the time trend in venous thromboembolism was started to point to a discrepancy:[1] it has been said that no increase had been demonstrated among young women, whereas an increase would have been expected if third-generation contraceptives carried twice the risk. On checking data for two countries, we found increases in mortality. Whether this is accepted as further evidence for the association between venous thrombosis and third-generation contraceptives depends on one's previous beliefs. Nevertheless, it becomes difficult to use the mortality data as an argument against the epidemiological studies.

Your correspondents propose that the data should be analysed proportionally, without explaining why rise and fall of diseases ought to be proportional in men and women. If proportional, the absolute increase among women remains larger than among men. The British data reported by Thomas do not fit the proportionality argument: mortality from venous thrombosis among young men shows no sign of change, whereas there is a continuous increase among young women.

Farmer and Lewis try to solve an equation with too many unknowns: it is impossible to calculate the relative mortality between two subgroups only from total mortality and the proportions of the subgroups without making an assumption on mortality in one of the groups. In their regression analysis, they use two explanatory variables (total use of contraceptives and percentage of third generation) that are strongly interdependent (correlations of 0·95 and 0·99), which leads to unstable estimations. The instability of their estimates is demonstrated by very large p values (which we recalculated). Moreover, plotting the data shows that the increase in the use of third-generation contraceptives strongly violates the linearity assumption of the regression analysis. The use of a linearising transformation in the Dutch data (squaring), clearly improves the fit of the model and the picture completely reverses: the coefficient of third-generation use now becomes positive (with a smaller p value) and that of total use becomes negative. We do not need this reanalysis to maintain that the mortality data are in line with the epidemiological studies.

We are amazed by the continuing insistence that bias and confounding explain the epidemiological studies. The starter bias argument is answered by looking separately at first-time users in the WHO, the Transnational, and the UK-General Practice Research Database (GPRD) study, and during the first year of use in a reanalysis of the WHO study.[2] The referral bias argument is answered by the observation that certainty of diagnosis did not influence the results in the WHO and the UK-GPRD study. The prescribing bias argument is answered by the observation that patients with major underlying disease were excluded (so that most cases are either idiopathic or linked to unpredictable intercurrent events like trauma or immobilisation), and by the adjustment

for the important long-term risk factors for venous thrombosis.

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1 Lidegaard Ø, Milsom I. Oral contraceptives and thrombotic diseases: impact of new epidemiologic studies. *Contraception* 1996; 53: 135–39.
2 Poulter NR, Farley TMM, Chang CL, Marmot MG, Meirik O. Safety of combined oral contraceptive pills. *Lancet* 1996, 347: 547.

Author's reply

SIR—Mortality statistics have limitations, as I stated in my letter, but Farmer and Lewis are wrong to suggest that most of these thromboembolism deaths are likely to relate to trauma or serious medical illnesses. In such cases the underlying illness (not the terminal thromboembolism) was coded as the cause of death throughout the study. Some misdiagnosis or miscoding might have occurred, but one would expect most young women dying from idiopathic thromboembolism to have the diagnosis established by a coroner's necropsy unless it was already apparent from antemortem investigations.

Farmer and Lewis suggest that increases in mortality may relate to increases in overall consumption of oral contraceptives during the period. The source of their pill-use data is not defined, it does not refer to the same geographic area, and it is not age specific. At least some of the increase in use will relate to women aged over 30.[1] Their multiple regression analysis is flawed because the two x variables they use (total utilisation and proportion of new pills) are not independent, one being a component of the other: this produces so-called multicollinearity, with unstable and unreliable estimates. They fail to mention that the relations they describe between their utilisation data and the mortality changes I reported are not statistically significant. To some extent the shortcomings of their analysis can be overcome by using utilisation of old (total minus new pills) and new pills as separate variables. Interestingly, this analysis reveals a significant relation between mortality in young women and use of new ($p<0·02$) but not old ($p>0·1$) preparations. Inclusion of Farmer and Lewis's utilisation data therefore supports the temporal association between uptake of third-generation products and the increase in mortality.

A more appropriate method is to estimate the expected increase in mortality from thromboembolism in women aged 15–29 resulting from these changes in use. If the new products carry the same risk as older products and an overall exposure of 37% in 1984 is assumed, the expected rise in mortality due to increased use between 1984 and 1992 would be 12%, which is much smaller than the observed increase. If new preparations carry double the risk (as estimated in the epidemiological studies) the expected increase in mortality would be 44%, which is lower than the observed mortality increase, but within its 95% CI. Of course, larger increases in mortality would occur if there was selective use of newer preparations in younger women.

Cohen and van Lunsen are unwise to draw conclusions from the direct comparison of incidence rates from old and more recent cohort studies. Differences in study methods (eg, ages studied) and changes in the use of oral contraception (eg, patient selection and monitoring, reduced oestrogen doses) will affect the findings. The one study cited that compared preparations containing different progestagens showed that those containing levonorgestrel are now associated with a lower risk than previously, but the risk is significantly higher with preparations containing desogestrel or gestodene.[2]

Your correspondents play down the problem by referring to the doubling in mortality in young women as a "slight" or "modest" increase; van Lunsen refers to an "absence of confirmation by mortality data". Three separate case-control studies (including one of which Lewis is a co-author[3]) and a cohort study indicate an increased risk of thromboembolism with preparations containing desogestrel or gestodene. Since their introduction mortality from this cause has increased in younger women. I believe this is ample justification for the concern I expressed previously.

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1 Office of Population Censuses and Surveys (OPCS). General Household Survey, 1993. Series GHS no 24. London: HM Stationery Office, 1995.
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3 Spitzer WO, Lewis MA, Heinemann LAJ, Thorogood M, Macrae KD. Third generation oral contraceptives and risk of thromboembolic disorders: an international case-control study. *BMJ* 1996; 312: 83–87

Coordination of poliomyelitis immunisation programme in China's border areas

SIR—Since the World Health Organization adopted a goal to eradicate poliomyelitis by the year 2000, the number of reported cases has gradually decreased. Well-organised AFP (acute flaccid paralysis) surveillance systems with laboratory networks and supplementary immunisation programmes, including national immunisation days, designed to promote oral poliovirus vaccine (OPV) immunisation, have greatly contributed to this decrease.[1–3]

Of the four wild poliovirus strains isolated in China between 1995 and April, 1996, all occurred in Yunnan Province, in four children with paralytic polio. They lived in Myanmar and were seen at the De Hong Prefectural Hospital (table). Isolates were confirmed as wild strains by the PCR-RFLP.[4] Yunnan Province, which is in southwestern China, shares 4060 km of its border with Myanmar, Laos, and Vietnam.

Three national immunisation days were held in China between 1993 and 1996, with more than 90% coverage reported. Myanmar conducted its first such programme in February and March of 1996. Despite these efforts, the border areas remained susceptible to outbreaks of polio. These areas have transient populations that often move across the border. The four patients who were paralysed came to China to see the doctor, although they were residents of Myanmar. Investigations at nine hospitals in De Hong Prefecture revealed that they provided medical services to 22 062 patients from Myanmar in 1995.

Even though races, culture, and languages are fairly uniform in these areas, it is difficult for health authorities to

Case	Age	Residence	OPV history	Paralysis onset	Poliovirus isolated
1	1 yr 4 mo	Myanmar	None	Nov 8, 1995	Type I, wild
2	1 yr 11 mo	Myanmar	None	Feb 24, 1996	Type I, wild
3	3 yr 11 mo	Myanmar	None	Mar 11, 1996	Type III, wild
4	2 yr 0 mo	Myanmar	None	Apr 1, 1996	Type III, wild

OPV=oral polio vaccine.

Table: **Four patients from whom wild polioviruses were isolated in China (Jan, 1995–Aug, 1996)**