**OPINION**

Combined oral contraception and the risk of venous thromboembolism

Angela Mills

Department of Gynaecology, University College Hospitals London, The United Elizabeth Garrett Anderson Hospital and Hospital for Women Soho, 144 Euston Rd, London NW1 7AJ, UK

How did the good news about venous thromboembolism (VTE) and the combined oral contraceptive pill (COC) become the biggest pill scare of the 1990s? What were the consequences and how do we re-educate the medical profession and the general public about the risks and benefits of COCs?

The first suggestion that third generation pills (contraceptive pills containing gestodene or desogestrel) may have a greater adverse effect on blood coagulation than some other COCs came in 1989 when Jung-Hoffmann and Kuhl presented data which suggested that the progestogen gestodene, might cause retardation of the inactivation and elimination of ethinyloestradiol. It was argued that this could adversely effect coagulation factors, which would increase the risk of VTE in women taking gestodene-containing contraceptive pills. Sales of gestodene-containing COCs fell sharply in Germany. Attempts have been made to replicate these results but without success (Orme et al., 1991; Hammerstein et al., 1993). In the Summer of 1995 an investigative television programme in the UK (World in Action), strongly implied that the government drug regulatory agencies in that country should investigate the risk of VTE with gestodene-containing COCs.

By October 1995, unpublished studies on VTE and COCs from four separate groups (Bloemenkamp et al., 1995; Jick et al., 1995; World Health Organization, 1995; Spitzer et al., 1996) were nearing completion. Three of these studies suggested that pills containing ethinyloestradiol and either the progestogen gestodene or desogestrel had an odds ratio (OR) for non-fatal venous thromboembolic disease of ~2 when compared with COCs containing <50 µg of ethinyloestradiol and levonorgestrel or norethisterone (second generation pills). The results of these studies, translated into absolute risk, implied that non-fatal venous thrombosis occurred in 15 out of 100 000 women per year using second generation COCs and 30 out of 100 000 women per year for those taking third generation pills (Bromham and O’Brien, 1995). This was good news. Absolute risks had been reported to be as high as 100 per 100 000 users (Vessey, 1989). Table I illustrates the risk of fatal VTE with the COC and compares it with other common risks to life.

The fourth study (Bloemenkamp et al., 1995) looked specifically at risks of VTE in women with Leiden factor V mutation who were using COCs. The report did not contain adequate data on COCs containing gestodene. This study reported that women who were heterozygote carriers of the Leiden factor V mutation and took desogestrel containing COCs were at 50-fold increased risk of non-fatal VTE when compared with non-carrier, non-users. The risk of death from VTE in women who are taking third generation COCs and are heterozygote for factor V Leiden mutation would thus be ~40 women per million per year. This is the equivalent to the number of deaths from a household accident. Of the population in Northern Europe, ~4% have this defect. The risk of VTE for women on the COC probably decreases after the first year of use (Reijnen and Atsma, 1995).

On October 18, 1995, the Committee on Safety of Medicines (CSM) issued a drugs alert to all newspapers and doctors in the UK. It recommended that women taking third generation COCs should change to second generation COCs. The alert did not emphasize the fact that the absolute risks were lower for both second and third generation COCs than that previously reported and accepted. Approximately 1.5 million women in the UK were taking third generation COCs. If the research data is accepted, this population of 1.5 million women would provide 400–500 cases of VTE and four or five deaths per year, including those due to the background risk in the population, in comparison with 200–250 cases of VTE and two or three deaths, if they were taking second generations COCs.

The effect of the CSM statement was dramatic: the message was interpreted by many women to mean that ‘the pill caused blood clots and killed’. One general practitioner recorded that 12% of her patients stopped taking the COC immediately (Hope, 1996). Many doctors and nurses were left with a deep distrust of the safety profile of the pill. Doctors can only advise patients if they are adequately informed. An audit by Murty et al. (1996) of 234 family planning professionals found that only 21 initially received their information from the CSM, approximately the same number initially received their information from their patients. None were well informed about the studies and doctors did not have adequate data to put the CSM statement into the context of other life risks.

Clinics ran out of second generation COCs. Newspaper cuttings claimed there was a shortage of hospital maternity beds, with some London hospitals claiming an increase in the number of maternity cases booked for July and August 1996 of 20–25%.

Doctors and women complied with the advice of the CSM. In England the proportion of usage of third generation COCs
Table I. Estimated risks of death from common life events compared with the risk of death from thromboembolic disease for users of combined oral contraceptives (COC)

<table>
<thead>
<tr>
<th>Event</th>
<th>Deaths/million women/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker, aged 35</td>
<td>1670</td>
</tr>
<tr>
<td>Road deaths</td>
<td>80</td>
</tr>
<tr>
<td>Household accidents</td>
<td>40</td>
</tr>
<tr>
<td>Per million heterozygote Leiden factor V + third generation COC users</td>
<td>19.5–40³</td>
</tr>
<tr>
<td>Per million third generation COC users</td>
<td>3</td>
</tr>
<tr>
<td>Per million second generation COC users</td>
<td>1.5</td>
</tr>
<tr>
<td>Background risk of fatal VTE in female population aged 15–44⁴</td>
<td>6</td>
</tr>
</tbody>
</table>

²This represents a range of risks for Northern European women (Mills and Wilkinson, 1998).
³This includes cases where the primary cause of death was pulmonary embolus and those where pulmonary embolus occurred during a terminal illness.
⁴VTE = venous thromboembolism.

fell by ~22% of the total pill market and that of second generation pills increased by ~25% between September and December 1995. This alteration of pill usage has remained steady since then. Second generation COCs are cheaper than third generation COCs, the change in doctors prescribing habits reduced the oral contraceptive bill in England from ~£12.4 million per quarter to £8.8 million within a 3 month period and this change has also remained almost constant up to March 1997 (Figures 1 and 2) (J.Ferguson, personal communication). There has been a gradual fall in the total use of oral contraception.

What has the effect been on women? The Office of National Statistics (1997) published data that recorded that, in the 9 months following the CSM announcement, 10 000 more abortions were performed than anticipated. The figures represent the highest proportion of women having abortions since records began ~30 years ago at 16 out of 1000 women aged 15–44. In 1995, the number of pregnancies in women aged 24 and under was 15% lower than it had been in the previous 5 years. This trend was reversed after October 1995. There were 30 000 more conceptions than expected in the 9 months following the pill scare, when compared with a similar period in previous years.

Many of these conceptions were neither unwanted nor unintended but pregnancy and abortion carry a morbidity in their own right. The estimated risk of non-fatal VTE from pregnancy is 60 per 100 000 women per year. This is twice the estimated risk for third generation COCs.

These official figures do not show the entire picture. Many women now attend gynaecological clinics requesting hysterectomy rather than consider the safer, less invasive, offer of the oral contraceptive pill to treat dysfunctional uterine bleeding. The doctor/patient relationship of trust is now frequently destroyed when a doctor recommends the contraceptive pill either as treatment for a gynaecological abnormality or as a safe and effective method of contraception. The woman instantly becomes suspicious of the doctor’s clinical skills. This is reflected by a Mori poll conducted in the UK and Germany soon after the statement of October 1995, which found that 69% of British and 47% of German women taking brands other than third generation COCs believed their pill was safe before the controversy; after the publicity only 29% in Britain and 11% in Germany thought their brands were safe. Explaining risk:benefit ratios to women is time-consuming and difficult against the negative message on contraception in the press and, on this occasion, a government body as well.

In retrospect it is debatable as to whether or not this data warranted the action of the CSM and the sequelae. The COC is prescribed to a well population, all risks must be minimised, and women must be given choices of contraception based on facts. This form of panic reaction based on inadequate scientific debate and information must not, however, be allowed to happen again.

Since the publication of the CSM drugs alert a heated debate has existed in the medical literature over whether the odds ratio for VTE between second and third generation COCs is a true finding or is due to bias and confounding factors. Farmer et al. (1997) found the odds ratio to be <2 between second and third generation COCs containing >20 µg. Helmerhorst et al. (1997) maintain that the findings are true. Most of the authors of these papers believe that the public health impact of their results should have been minimal.

A preliminary publication (Lewis et al., 1997) has suggested that third generation COCs may reduce the already low risk of myocardial infarction in women on the COC when compared with the second generation COCs with an odds ratio of 0.24 (confidence intervals 0.07–0.78). Further publications and debate are awaited. The safety profile for all COCs in normotensive women who do not smoke is good. The choice of pill for any individual is likely to be a balance of minimizing any side effects and cost. It is important to be able to offer women a range of COCs.

It is time to try to learn from the past. The research on COCs and VTE raises question as to whether or not we can improve our clinical practice by screening women for thrombophilia before prescribing the COC? Vandenbroucke et al. (1995) concluded that this is not appropriate. Calculations (Mills et al., 1998) have estimated that one death from VTE could be prevented per year by screening 1 million women for hereditary thrombophilia before prescribing a COC, and by not treating positive women with the COC. Approximately four deaths per million women per year could be prevented by screening 1 million women with a family history of VTE in a first-degree relative and by managing them in the same way. This is unlikely to be considered a cost-effective exercise. Yet it is probable that 30% of VTE in COC users, occur in women with hereditary thrombophilia. It would seem prudent to screen women with a known family history of thrombophilia or a personal history of VTE for thrombophilia and if positive advise them to consider the use of alternative methods of contraception to the COC.

I feel a debate is needed to consider how to keep doctors, health care professionals and women informed of the latest research findings and their clinical implications without creating a recurrence of this recent panic. Data should be presented, wherever possible, in terms of absolute risk as well as relative risk. Time needs to be created after the publication of papers
for open scientific debate amongst the experts and conclusions to be reached before unbalanced headlines appear in the newspapers. We must, on an international level, try to find a formal mechanism for this. A declaration is about to be made on communicating drug safety information, from a meeting held in Erice, Sicily, Italy (Lancet, 1997). This will need careful scrutiny and, if appropriate, to be adopted at an international level, as a code of good practice. If we do not take action, then the women of childbearing age will pay the cost. Finally, let us remember that in 1983, an official recommendation to abandon the use of levonorgestrel for contraception, had to be rescinded.

Acknowledgements
I should like to thank Dr John Ferguson, Medical Director of the Prescription Pricing Authority, for his kindness in providing the data on pill usage and pill sales.
References


Hope, S. (1996) 12% of women stopped taking their pill immediately they heard the CSM’s warning. Lancet, 312, 576.


Received on October 27, 1997; accepted on November 11, 1997