The ‘pill scare’: the responses of authorities, doctors and patients using oral contraception

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In October 1995, the regulatory authority in the UK issued a warning about an increased risk of venous thromboembolism in women taking third-generation combined oral contraceptives. This was done before publication of the scientific papers involved, and resulted in a huge media ‘pill scare’. The manner in which the information was released has been criticised, as many doctors did not receive their ‘Dear Doctor’ letter from the regulatory authority until after media reporting. The result of the scare has been a loss of confidence in the oral contraceptive pill in general, and a rise in abortion rates.

Key words: oral contraception/patient confidence/pill scare/regulatory authority/third-generation COC

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Immediate implications for pill takers and prescribers

In October 1995, the Committee on Safety of Medicines (CSM) released a ‘Dear Doctor’ letter, warning doctors about an increased risk of venous thromboembolism (VTE) in women taking third-generation combined oral contraceptive (COC) pills. These pills, containing the progestogens desogestrel and gestodene, had been on the market since the mid-1980s and were extremely popular. It has been estimated that in 1995 approximately 1.5 million women in the UK were taking this type of pill. Unfortunately, in many cases, the letter did not reach doctors before the media started to report the findings. A report was already on the lunchtime news on Thursday, October 19th, before most doctors had seen the letter; a colleague in north London found out about the scare when a patient returned to her with a prescription for a third-generation pill, which the pharmacist had refused to dispense. Another colleague in the North East was counselling a woman in a gynaecology clinic. He was in the process of writing a prescription for Merclon® (a third-generation COC), only to be told by the patient that “this pill has been banned, doctor! Haven’t you heard?” This type of experience was apparently common to many doctors throughout the country (Armstrong et al., 1995; Craft, 1995; Graham et al., 1995; Se earmark, 1995).

By the morning of Friday, October 20th, the stream of calls from anxious women was endless. A Department of Health helpline received thousands of calls, while the Family Planning Association had to call in extra staff to deal with inquiries (Craft, 1995). Many doctors and nurses were angry, having either not received the CSM’s letter, or failing to comprehend its contents. Many felt that they should have been forewarned. They enquired about a possible biological explanation for the increased risk of VTE in third-generation pills, and some even asked which were the second-generation COCs they could prescribe.

There was no patient information leaflet enclosed with the CSM’s letter to give guidance to primary care doctors and their patients. One of the authors of this paper (D.M.) devised a two-page ‘question-and-answer’ pamphlet giving absolute risks of developing a VTE with second- and third-generation pills, including the risk of VTE in pregnancy. The pamphlet was circulated to health professionals in the Newcastle upon Tyne area. This process was duplicated in only a small number of contraceptive centres around the country.

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The 'Dear Doctor' letter itself contained a medical error, leading to further confusion: 'Combined oral contraceptives containing gestodene and desogestrel should not be used by women with risk factors for venous thromboembolism including obesity, (severe) varicose veins or a previous history of thrombosis from any cause.' In fact, a previous history of thrombosis is an absolute contraindication to the use of any oestrogen-containing oral contraceptive pill (Guillebaud, 1989.). However, this wording suggested to many health professionals that women with these risk factors, including a past history of VTE, could take second-generation COCs.

An audit conducted by the Faculty of Family Planning and Reproductive Health Care National Audit Centre in Hull demonstrated this poor comprehension among those receiving the CSM letter (Killick and Murty, 1996). Less than 70% of responses were correct, and specific problems were identified with respect to 'at-risk' groups. Practitioners without a special interest in family planning had lower scores.

This immediately led to the next source of confusion. Venous thrombosis is perhaps the oldest established health risk attributed to the pill (Jordan, 1961). However, this risk has always been attributed to the oestrogen content of the pill (Inman et al., 1970), not the progestogen, and studies have suggested that the risk declines with lower-oestrogen dose pills (Vessey, 1980; Stadel, 1981; Gerstman et al., 1991). It was therefore difficult to understand why a difference in progestogen type could so greatly influence VTE risk.

The sources of confusion continued to mount. The actual figures being discussed were an absolute risk of 30 per 100 000 users per year. Studies have previously shown that women on low-dose, second-generation COCs also have a risk of VTE of approximately 30 per 100 000 per year (Vessey et al., 1986; Gerstman et al., 1991). Many doctors were therefore bewildered as to how the 'new' level of risk could be considered so dangerous, when it was the same as that which we had assumed to be present for the past 10 years. In addition, this figure is (as before) half that of the risk of VTE in pregnancy, quoted at 60 per 100 000 women per year.

With so many unanswered questions it was not only impossible to understand why the warning had been issued, but also difficult to talk intelligently to women about it. The papers to which the letter referred had not been published; to our knowledge this is an unprecedented step. It led, in the weeks that followed, to a bizarre 'bootlegging' of copies of the papers, contrary to all principles of scientific publication. We (the authors) were among those 'privileged' to see pre-publication copies of the papers, and with this, our bewilderment turned to amazement and disbelief: how could such a ruling have been considered necessary on the basis of this evidence?

Potential explanations: prescriber bias

Many doctors recognized that prescriber bias must have played a major part, and were willing to admit that they had been preferentially prescribing third-generation pills to first-time users. Women appeared to experience fewer of the 'minor' side effects with them (e.g. acne, hirsutism), and many doctors felt that this was important for a new, usually nervous user of the pill. In discussion with colleagues, it also became obvious that most tended to put women who had any kind of risk factors for cardiovascular disease (including family history, moderate obesity) preferentially onto third-generation pills. Before the pill scare, many in the field had not given very much thought to the difference between risk factors for arterial and venous disease; an increased awareness of these is perhaps a positive aspect of the scare. Although epidemiological evidence was lacking, the prevailing attitude was that third-generation pills were likely to be at least slightly safer, because of metabolic studies (for example, their potentially beneficial effects on lipids and cholesterol; for review see Crook, 1997), and since there seemed to be no negative effects (on the contrary, as has been mentioned, there were other benefits), many doctors felt they might as well offer women a potential benefit, even if it was not proven. In particular, there was a tendency to choose Mercylo (20 μg ethinylestradiol and 150 μg desogestrel) for women perceived to be at risk of any form of cardiovascular disease, be it venous or arterial. Indeed, such was the optimism about the safety of this COC that doctors were prescribing it to women whom, in the past, they might have advised against the combined pill at all. Even the British National Formulary recommended the 20 μg ethinylestradiol COC for obese or older woman (BNF, 1991). This would certainly provide an explanation for the paradox in all the studies of VTE risk, in which Mercylo appears to convey a considerably higher risk than Marvelon®, which contains the same amount of desogestrel (150 μg) and a higher dose (30 μg) of ethinylestradiol (Jick et al., 1995; WHO, 1995; Spitzer et al., 1996).

The role of information sources

An Institute of Population Studies (IPS) survey which was carried out immediately after the scare (Allison et al., 1997) showed that the media had been the major source of information for all age groups. Young women relied more heavily on television, while older women obtained their information through newspapers. The authors point out the danger of relying on television: 'while the newspaper may be locatable after several days in many households, television news stories will feature for a few minutes, at most, and then they are gone.'

This survey was carried out at the Margaret Pyke Centre and other family planning clinics, as well as in general practice (Allison and Roizon, 1996; Allison et al., 1997). It was found that, in general, women attending family planning clinics were less likely to change their pill brand than those who went to their GP; however, the Margaret Pyke Centre stood out as the place where fewest women by far changed their pill. The study
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also found that women were greatly influenced in their decisions by the counselling they received. The client population at the Margaret Pyke Centre is not typical, consisting mainly of well-educated women working in the West End of London. Although they were worried by the scare and wanted information, many of them, after discussion, decided that they would carry on using their third-generation pills. The survey found that the results for the Margaret Pyke Centre were somewhat different from the rest of the clinics included.

Young women were most affected by the pill scare (Allison and Roizon, 1996). Those over 30 years old had lived through several scares already, and tended to have a slightly more cynical view. They were much more likely to stay on their pill until their routine appointment was due, and then enquire about it during their consultation. Even those who were sufficiently worried to make a special appointment to discuss the scare had not stopped the pill in the interim; they stated they just wanted to be sure what to do, but they had been through scares before and the previous ones had turned out to be false alarms—was this going to be the same? By contrast, young women were much more frightened, and those who came for advice generally wanted to change their pill.

The IPS survey (Allison and Roizon, 1996) found that, overall, three-quarters of women under the age of 20 years who attended a family planning clinic or their GP, wanted to switch pill brand, compared with 57% of those aged 20–29 and 48% of those aged over 30. The workload of all concerned increased dramatically; for example, in Glasgow, family planning clinic attendances tripled in the week following the CSM’s letter (Armstrong et al., 1995).

**Longer-term sequelae**

By the Spring of 1996, an interesting effect became noticeable. ‘Feeling less well’ is not easily scientifically measurable, but doctors and nurses who prescribe the pill have heard this comment many times. It has been particularly common from women who changed from third- to second-generation pills following the scare, and then noticed a difference in their skin, hair and general well-being. Third-generation progestogens are less androgenic than second-generation products, and therefore tend to be better for women who have problems with acne, hirsutism and weight gain (Guillebaud, 1995). These are termed ‘minor’ side effects, but are not at all ‘minor’ to the women experiencing them (International Working Group on Enhancing Patient Compliance and Oral Contraceptive Efficacy, 1993). Acne and hirsutism are difficult to study scientifically, but clinical experience has for some time supported the beneficial effects of third-generation progestogens in these conditions (Levrier et al., 1988; Erkkola et al., 1990; Mango et al., 1996; Redmond et al., 1997; Walling, 1998). It has long been a problem with second-generation pills that if a women suffers from both breakthrough bleeding and acne, it is very difficult to improve both conditions at the same time. Breakthrough bleeding is improved by the use of more progestogen, or a stronger progestogen. However, this will almost certainly make the acne worse. The use of the selective, non-androgenic, third-generation progestogens, has been an enormous help in such cases.

Indeed, third-generation pills have been shown to give better cycle control, with fewer reports of breakthrough bleeding in the early months compared with second-generation pills (Loudon et al., 1990; Brill et al., 1991; Drug and Therapeutics Bulletin, 1992). A British multicentre, double-blind study (Loudon et al., 1990) compared 189 women taking Femodene® (30 µg ethinylestradiol with 75 µg gestodene) with 185 women taking Microgynon® (30 µg ethinylestradiol with 150 µg levonorgestrel) for 6 months. There was less breakthrough bleeding present in the first three cycles (17% compared with 28%)—at a time when many women discontinue their contraceptive method, particularly if they have so-called ‘nuisance’ side effects (Belsey, 1988; Hillard, 1989).

One of the problems which has occurred after the scare is that although many women who experienced problems did indeed change back to their third-generation pill, some still felt uneasy about doing so and, feeling disillusioned, decided to come off the pill altogether (Ferguson and Jenkins, 1996). There were a number of women—usually in the younger age groups—who did not feel convinced that the pill was safe in general, i.e. the specific scare regarding VTE had taken away their confidence in the pill overall. This effect has been documented in a recent survey of young women in Austria (Egarter et al., 1997). It was found that young women were more influenced by media reporting than were older women, who expressed greater doubt about the credibility of the reports. In addition, it was shown that despite all the publicity, young women remained ignorant of the facts relating to the scare, with only about half of them being able to define the term ‘thrombosis’. However, they did have the general perception that the pill poses a risk to health.

In the UK, the IPS survey mentioned earlier (Allison and Roizon, 1996; Allison et al., 1997) found that 62% of women said they were now less confident about the pill, while 8% indicated that they were ‘completely lacking in confidence’. This loss of confidence in the pill has no doubt contributed to the well-documented rise in the number of abortions following the scare (British Pregnancy Advisory Service; BPAS, 1996; Child et al., 1996; Iversion and Nilson, 1996; Bodard, 1997; Office for National Statistics, 1997; Skjeldstad, 1997; Szarewski, 1997; Wood et al., 1997). Overall, in England and Wales, abortions rose by 9% in 1996 compared with 1995 (see Table 1), the first increase in the annual number of abortions since 1990 (Office for National Statistics, 1997). The conception rates overall also rose in the three quarterly periods following the scare (ending December 1995, March 1996 and
June 1996 by 2%, 7% and 6% respectively, when compared with equivalent periods for 1994 and 1995. Conception rates leading to maternity in the first two quarters of 1996 rose by 3–6% above expected levels (Wood et al., 1997). The Office for National Statistics themselves comment that "there is evidence that reaction to publicity arising from the announcement contributed to an increase in the number of conceptions and consequently an increase in the number of abortions in 1996" (Office for National Statistics, 1997).

However, the hardest hit were young women under the age of 20: in this group there was an overall 15% rise in abortions (Office for National Statistics, 1997). As Mr Mervyn Kidd observed at the FIGO (International Congress of Obstetrics and Gynaecology) conference in 1997, "These statistics reflect an inordinate amount of human misery" (Szarewski, 1997).

Table 1. Abortions in England and Wales (Office for National Statistics, 1997)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1996</th>
<th>1995</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 16</td>
<td>3645</td>
<td>3270</td>
<td>+11.5</td>
</tr>
<tr>
<td>16–19</td>
<td>28790</td>
<td>24945</td>
<td>+15.4</td>
</tr>
<tr>
<td>20–24</td>
<td>46356</td>
<td>43394</td>
<td>+6.8</td>
</tr>
<tr>
<td>25–29</td>
<td>39311</td>
<td>37254</td>
<td>+5.5</td>
</tr>
<tr>
<td>30–34</td>
<td>28228</td>
<td>25759</td>
<td>+9.6</td>
</tr>
<tr>
<td>35–39</td>
<td>16118</td>
<td>14352</td>
<td>+12.3</td>
</tr>
<tr>
<td>40–44</td>
<td>5027</td>
<td>4868</td>
<td>+3.3</td>
</tr>
<tr>
<td>45+</td>
<td>428</td>
<td>457</td>
<td>-6.3</td>
</tr>
</tbody>
</table>

Since the pill's introduction in 1961, every pill scare has been followed by an increase in unplanned pregnancies for at least 18 months due to the failure of less effective contraceptive methods, or the use of no method (Bromham, 1996). It would appear that this latest pill scare will be no exception.

Practical prescribing issues

The Faculty of Family Planning stated in its guidelines (Statement, December 1995) that first-time users should preferentially be prescribed second-generation pills, unless there was a specific reason for using a third-generation pill, e.g. side effects of acne or hirsutism. They did, however, state that established users of third-generation pills did not need to change pills, provided they understood the position regarding the risks of VTE. In practice, there has been a massive shift in prescribing away from third-generation pills, towards second-generation pills—and Microgynon in particular (Ferguson and Jenkins, 1996).

Contraceptive consultations in general practice doubled in length (Hope, 1996); it takes time even with women who are informed and sceptical about the evidence, simply because one ends up discussing the media reporting and the whole issue with them. There is usually more time available for this in family planning clinics, where the staff have fewer of the time constraints which are experienced in general practice (Szarewski, 1998).

As regards overall usage of COC, prescribing data for 1996 (Organon Laboratories Ltd UK; data on file, 1996) suggest that there was an overall 10% fall in the prescribing of COC by doctors. Previous pill alerts in the 1980s have resulted in falls of 1–2%, with a quick recovery over 6–12 months. The introduction of new contraceptive methods may cause fluctuations of between 0.5–1%, such as the introduction of Persona®, the computerized, natural family planning method. Never has there been such a drop in prescribing of the pill and such a slow recovery.

A survey of GPs (Szarewski, 1998; Walling, 1998) has shown them to be far more preoccupied with medicolegal issues surrounding the pill scare, than with the medical evidence. Indeed, the problem has been summed up succinctly by Professor Stephen Killick: "We don't have a clinical or even a product problem, but we do have a legal problem" (Guillebaud, 1996). In the survey, this was the single greatest preoccupation of the doctors, despite the fact that 60% of them thought the CSM's action was not justified.

It is ironic to note that an article in The Mail on Sunday (February 15, 1998), headed "Victims and families sue over 'danger' pill", did not notice an anomaly in its own reporting. The article highlighted the legal action being taken over third-generation pills and VTE events, and revealed 'unpublished government figures' regarding reporting of deaths associated with VTE and pills in the past four years. It then gave a list of the pill brands and the number of deaths which had occurred on each brand. Top of the list came Microgynon, a second-generation pill and, since the scare, the most commonly prescribed pill in the country. Unfortunately, official figures are not yet available to corroborate this media story.

The situation has been further confused by the emergence of evidence that third-generation pills are not a higher risk of arterial disease compared with second-generation pills (Lewis et al., 1997a). The final analysis of the Transnational study (Lewis et al., 1997b) showed a statistically significant reduction in the relative risk of myocardial infarction for third- versus second-generation pills (0.3, 95% confidence intervals 0.1 to 0.9). It is a sad fact that, despite counselling, women who are on the pill are actually more likely to smoke than those who are not (Johnson et al., 1994), so there are significant numbers in this arterial risk category. Similarly, more women now use the pill in their 30s, when arterial risk starts to increase, regardless of smoking. Diabetic women (without complications) can use the pill, as can women with mild hypertension (diastolic blood pressure <95 mmHg); again, their risk of arterial disease is greater, and they might be better served by third-generation pills. This evidence of reduced arterial disease risk was not yet available when the CSM issued their statement, and therefore it was not taken into account. However, the European equivalent of the UK CSM, the European Agency for the Evaluation of
Medicinal Products/Committee for Proprietary Medicinal Products (EMEA/CPMP), did not issue—and has still not issued—a statement advising any change in prescribing practice. Rather, they called for further evidence and acknowledged the fact that studies on the risk of myocardial infarction were still to be reported (CPMP, 1996; Alexandre and Strandberg, 1997). Doctors have therefore been in the position where there is some evidence that third-generation pills are indeed safer for women with risk factors for arterial disease (as was assumed previously from the metabolic studies), but for legal reasons the risk of VTE—which is much smaller—has taken precedence. The CSM has not issued any statement regarding the data on arterial disease risk with third-versus second-generation COC.

Conclusions

Ever since the 1980s, doctors have been aware that low-dose (at the time, second-generation) pills carry a risk of VTE, of around 30 per 100,000 women per year. They, and their patients, have lived with this level of VTE risk for over 10 years, and it was not considered unacceptable until the same risk was found for third-generation COCs in 1995. If the CSM felt that a statement was necessary, then it should have been more positively worded, with a patient information leaflet enclosed. Emphasis could have been placed on the good news that these papers suggested that second-generation COCs appeared to have an even lower risk of VTE than previously thought.

Many doctors believe that regulatory action was unnecessary in 1995, and that the way in which it was carried out, before publication of the studies, was irresponsible (Mills, 1997; Edwards et al., 1997; Benagiano, 1998; Cohen, 1998; Spitzer, 1998; Mills and Edwards, 1999). This view is supported by the fact that the 1995 regulatory decision has been overturned on appeal (Department of Health, 1999; Szarewski, 1999) and third-generation pills have recently been restored to first-line prescribing (although a statement about the possible increased risk of VTE is still to be placed in the data sheets for third-generation COCs). It is to be hoped that the lessons learned from this saga will result in better practice in future.

References


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