The 1995 pill scare revisited: anatomy of a non-epidemic

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Two years after the October 1995 pill scare that received worldwide attention, this synthesis of evidence goes back to the earliest research on risks of first generation oral contraceptives (OCs). It also covers epidemiological data published since, emphasising the 1995–1996 findings. Late breaking data are also examined. The key issue: are there differences in the risk profiles of second and third generation OCs. The ultimate question is: did any epidemics of venous thromboembolism (VTE) occur? This synthesis of evidence leads to the following conclusions and observations: (i) all OCs on the market are becoming progressively safer; (ii) relative risks of about 2 for VTE, even if real, are clinically unimportant and of no public health significance; (iii) the weak odds ratios contrasting third and second generation OCs, ranging from 1.5 to 2.3 in the 1995–1996 studies are more likely explained by bias than by a causal relationship; (iv) incidences of VTE among users of any OC have been declining over the past three decades; (v) absolute rates of VTE for third generation OC users reported in 1995–1996 are lower than those for users of second generation OCs in 1988 and 1991; (vi) there is no difference in risk of VTE between first starters on second generation OCs versus first starters on third generation OCs; (vii) users of third generation OCs are at much lower risk of acute myocardial infarction than users of second generation OCs; (viii) among users of any OC, the occurrence rates of stroke are low, they are declining, and no differences between second and third generation OCs are apparent; (ix) 2 years after the pill scare there are no epidemics of VTE; (x) there have been excessive rates of therapeutic abortions in some countries; and (xi) the benefit–risk ratio is favourable for users of any OC.

Key words: cardiovascular events/epidemiology/oral contraceptives/venous thromboembolism

Expanding mosaics of evidence: perspective, approach and rationale

This review presents a synthesis of the most relevant evidence bearing on the 1995 pill scare and my interpretation of the evidence. The synthesis and interpretation lead to opinions offered respectfully to decision-makers in public health and drug safety and even more respectfully to clinicians and women confronting important professional and personal decisions. My perspective is that of a clinical epidemiologist who designed, conducted and published one of the large studies which generated much of the evidence at play in the current controversy about the pill, the European Transnational Case Control Study of Oral Contraceptives and the Health of Women (Spitzer, 1996).

There are two intertwined issues in the pill controversy: firstly, whether there is any difference in the benefit–risk ratio between second and third generation of oral contraceptives (OCs); and secondly, the impact of undermining confidence in oral contraception in general. I will address both issues in this paper, which is both a synthesis and an opinion.

It seldom happens that a cluster of biomedical evidence emerges suddenly, completely, and clearly able to shed light about a particular question, hypothesis or issue. Typically, such information emerges a piece at a time. The parcels of evidence are like the tiles in a mosaic. The individual tiles and the mosaic can appear meaningless when they are first put together, one tile at a time. It usually happens by trial and error but occasionally with a great deal of luck. In experimental clinical research there are many examples of the same kind of process. I shall cite only one: the prospect of a realistic effective treatment for acute myocardial infarction (AMI) with thrombolytics was first evident in the early 1960s as summarized in the reviews of Fletcher et al. (1962) and Bolton et al. (1961).

Later in 1985, the phase I findings of the first thrombolysis in myocardial infarction (TIMI) trial demonstrated the proof of the concept that thrombolytics given to humans were effective in reducing morbidity and mortality, if they reach the patient within a few hours of inception of an AMI (TIMI Study Group, 1985). Other trials have shown that important reductions in mortality and morbidity could be attained for thrombotic stroke if the thrombolytic is administered within 3 h (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). In AMI, very large studies have established that different products based on different molecules can be even more effective than the original thrombolytics, e.g. the Global utilization of streptokinase and TPA for occluded coronary arteries (GUSTO) clinical trial (GUSTO Investigators, 1993). Additional experimental and observational work now focuses on safety issues, especially those having to do with haemorrhagic adverse events. I turn now to the growing body
of evidence on the safety aspects of OCs. OCs are used by some $70 \times 10^6$ women worldwide. As a category of intervention, they have become the best accepted and the most popular method of birth control (Shah, 1994). Their popularity is explained by several positive characteristics. OCs are very effective, well tolerated, they do not interfere with sexuality, and are under the control of the female. Arguably, OCs are the second most important public health intervention for women in the history of public health. Other than preventive measures to control communicable diseases, including sanitation, nothing has promoted the health of women more than effective contraception using the pill. With OCs, women have been able to control the size of their families, their own health and the health of their children. The pill has liberated women from unwanted childbirth and allowed them to attain their full potential as members of society. Women’s quality of life has been materially enhanced.

The efficacy and the safety of the use of OCs by healthy women have been issues that go back as early as 1923, with many milestones leading to the pivotal clinical trials of the 1960s (Goldzieher and and Rudel, 1974). Since approval of OCs, the mosaic on all issues of their safety and efficacy has been building for 35 years. A major tile was added with the studies of the Royal College of General Practitioners (RCGP, 1967) and Vessey and Doll (1968), which showed the risk of excess thrombotic and haemorrhagic disorders among women taking first generation OCs. These findings precipitated a pill scare, unfortunately the first of a number of smaller and larger ones, all related to real or perceived health risks of OCs.

One of the most important of such pill scares was triggered by a warning issued by the British Committee on Safety of Medicines (CSM) about third generation OCs in respect to venous thromboembolism (VTE) in October 1995. The warning was based on the then unpublished results of three epidemiological studies showing weak odds ratios (ORs) between third and second generation OCs for VTE as the outcome. The warning not only resulted in massive switching of OC brands, but also in overnight stopping of OC use by many women in the UK. One survey in a general practice showed that 12% of women on third generation OCs discontinued using the pill altogether (Hope, 1996). Less than 1 year later, data showed an increase of 8% in induced abortions in the UK compared with the annual incidence prior to the CSM warning (Office for National Statistics, 1997). Before the end of 1995, and before publication of the studies, the authorities in Norway and Germany also issued restrictions concerning the use of third generation OCs, with consequences of excessive unwanted pregnancies and abortions, very similar to those in the UK.

Other authorities, including the European Medicines Evaluation Agency and the US Food and Drug Administration, adopted a conservative approach. They waited for formal peer-reviewed publication of the studies and asked for more information from the investigators and from the companies producing third generation OCs. Until today, these authorities have seen no reason to recommend or impose restrictions on the use of the OCs concerned.

Since the events in late 1995, important additional data have become available. They allow a more comprehensive evaluation of the two most frequently used classes of OCs. These data place the results of the initial studies in perspective, with regard to both VTE alone and to the broader picture, including much more serious cardiovascular outcomes, that is, stroke and AMI. In this review paper I will revisit the data from the studies published in late 1995 and early 1996 and comment on the way in which the more recent reports afford a better interpretation of the entire body of epidemiological evidence about the safety of the pill. There is much more evidence now than was available then about the question of the relative safety of the newer, third generation OCs (containing desogestrel, gestodene or norgestimate as the progestogen) compared with low-dose OCs containing other older progestogens, now referred to as second generation OCs. I will also offer an interpretation of the clinical importance and of the public health significance of the findings in the light of a rapidly accruing body of evidence in an expanding mosaic.

### Results of the 1995–1996 VTE studies

Four major studies were published in December 1995 and January 1996 [Bloemenkamp et al., 1995; Jick et al., 1995; World Health Organization (WHO), 1995a; Spitzer et al., 1996]. They reported odds ratios (ORs) for VTE comparing third generation OCs (which contain desogestrel, gestodene or norgestimate as the progestogen) with second generation OCs (which mainly contain levonorgestrel) ranging from 1.5 to 2.30. One of the studies was a post-hoc secondary case-control analysis from the Leiden Epidemiological Thrombolysis Study group (LETs), re-defining progestogen type as the exposure factor. The results of the Leiden re-analysis were difficult to interpret since both cases and controls using gestodene-containing OCs had been omitted from the analysis. In addition, second generation OCs were pooled with even older first generation OCs as risk factors. Since none of the direct comparisons between OCs reported in the Leiden group resulted in statistically significant differences I shall focus this synthesis of evidence on the three major studies which were significant (Table I). Nevertheless, the trend of the Leiden findings was in the same direction as the other three studies and of the same order of magnitude.

<table>
<thead>
<tr>
<th>Study</th>
<th>WHO/Oxford region</th>
<th>BCDRPb</th>
<th>Transnationalb</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO, 1995a</td>
<td>88/124</td>
<td>75/300</td>
<td>162/386</td>
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<tr>
<td>BCDS</td>
<td>OR (CI)</td>
<td>OR (CI)</td>
<td>OR (CI)</td>
</tr>
<tr>
<td>1.5 (1.0-2.2)</td>
<td>1.5 (1.1-2.2)</td>
<td>1.5 (1.1-2.2)</td>
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<tr>
<td>2.3 (1.1-4.9)</td>
<td>2.2 (1.1-4.4)</td>
<td>1.5 (1.1-2.2)</td>
<td></td>
</tr>
<tr>
<td>3.7 (2.3-5.9)</td>
<td>4.0 (3.1-5.3)</td>
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</tbody>
</table>

*aThis analysis of the WHO study was chosen to maintain comparability with the other studies and because the Oxford centre provided 68% of the cases and 86% of the controls using third generation OCs.

bThe reference oral contraceptive (OC) for the WHO and BCDSP studies was levonorgestrel-containing OCs; in the Transnational Study all second generation OCs were the reference.

### Table I. Descriptions and main results (as odds ratios) of initial venous thromboembolism studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases/controls for OC generation contrasts</th>
<th>OC-use vs No use (CI)</th>
<th>DSG vs 2nd generation</th>
<th>GSD vs 2nd generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO/Oxford region</td>
<td>WHO, 1995a</td>
<td>88/124</td>
<td>3.7 (2.3-5.9)</td>
<td>2.0 (0.8-4.7)</td>
</tr>
<tr>
<td>BCDRP</td>
<td>Jick et al., 1995</td>
<td>75/300</td>
<td>2.3 (1.1-4.9)</td>
<td>2.1 (1.0-4.4)</td>
</tr>
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<td>Transnational</td>
<td>(Spitzer, 1996)</td>
<td>162/386</td>
<td>3.7 (2.3-5.9)</td>
<td>1.5 (1.0-2.2)</td>
</tr>
</tbody>
</table>

DSG = desogestrel; GSD = gestodene.
At first glance the studies summarized in Table I appear to have consistent results suggesting an increased risk of VTE with third generation OCs compared with second generation OCs. Looking more closely at the data, additional evidence and systematic error (bias) are revealed and alternative interpretations become plausible, even probable.

**Contradictions, systematic error and the historical context**

**The meaning of consistency**

The ORs for VTE are consistent but they are consistently weak. The consistency may have occurred simply because all of the studies were affected by the same biases in the same way. The lower limits of all the confidence intervals come close to or include 1.0. The signal of ORs this small, even when statistically significant, is difficult to distinguish from background noise that often occurs due to bias or confounding factors in observational case-control studies. Conventional epidemiological thinking regards weak ORs, hovering around 2.0, to be below the threshold of public health concern if the target disease investigated is rare and of low morbidity. If the ORs are derived from case-control studies, unavoidable bias in such research compels even greater caution.

**Low relative risks and absolute risk differences**

The results of the 1995–1996 studies were initially interpreted based only on the relative risks between third and second generation OCs. If one examines the absolute risk (the difference in incidence of VTE between users of third generation OCs and users of second generation pills per 10,000 users per year) the data do not in fact show a higher VTE incidence for third generation OCs. In reality, if one examines the data in historical chronological context, an appreciable reduction in the incidence of VTE for second generation OCs was observed compared to earlier estimates. Two earlier cohort studies found the incidence of VTE in users of second generation low dose OCs to be 3.9 and 4.2 per 10,000 women years (wy) respectively (Vessey, 1988; Gerstman et al., 1991). In the 1995–1996 studies, the BCDSP study found an incidence of 1.6 per 10,000 wy with second generation OCs and of 2.8 and 2.9 per 10,000 wy for the two third generation OCs studied (Jick et al., 1995).

Indirectly, the WHO study estimated an incidence of 1.0 per 10,000 wy for second and 2.1 per 10,000 wy for third generation OCs (WHO, 1995a). It is worth emphasizing that the 1995–1996 absolute rates for third generation OCs were also considerably lower than those for second generation OCs in cohort studies reported in 1988 and 1991. In absolute terms, therefore, for the population of women exposed there was no detectable increase in VTE risk with use of third generation OCs in the recent studies, compared to the prevailing occurrence rates of VTE among users of second generation OCs in studies reported 5–8 years earlier.

Another interesting phenomenon is the diminishing secular trend in the annual incidence of idiopathic venous thromboembolism among non-users. In 1981, reported incidences among non-users were three per 10,000. By 1985, the incidence rates reported were 0.4 per 10,000 and in 1995, 0.3 per 10,000.

**Table II. Paradoxical contrasts of odds ratios of venous thromboembolism**

<table>
<thead>
<tr>
<th>Study</th>
<th>Desogestrel combined with 30 μg ethinyloestradiol</th>
<th>20 μg ethinyloestradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO*</td>
<td>1.9 (0.9–2.5)</td>
<td>2.4 (1.3–3.5)</td>
</tr>
<tr>
<td>BCDSP*</td>
<td>7.6 (3.9–14.7)</td>
<td>38.2 (4.5–325)</td>
</tr>
<tr>
<td>Transnational*</td>
<td>1.5 (0.9–2.5)</td>
<td>2.7 (1.3–6.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Cyproterone acetate combined with 50 μg ethinyloestradiol</th>
<th>35 μg ethinyloestradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO*</td>
<td>3.8 (1.4–16.7)</td>
<td>14.9 (3.7–59.4)</td>
</tr>
</tbody>
</table>

*Compared with non-users.  
Compared with second generation OCs.  
Confidence intervals not given in the original publication.

(Stadel, 1981; Porter et al., 1985; WHO, 1996a). Despite this trend, which would militate toward higher ORs for second generation OCs, those odds ratios or rate ratios have decreased. The progressive secular decrease of VTE rate ratios associated with second generation OCs over time is consistent with time trends found for first generation high oestrogen dose OCs in the RCGP study. From the interim analysis in 1974 to the analysis in 1978, the incidence of VTE decreased significantly from 12–13 to 8–9 per 10,000 wy (RCGP, 1974, 1978). Such parallel decreasing trends for two distinct OC generations observed in independent studies are very unlikely to be the result of pharmacological changes of the same OCs with time, but very likely to be the consequence of cohort effects (also referred to as healthy user bias).

**Unexpected inverse gradient**

Several previous studies investigating the relationship between OCs and VTE, especially the cohort studies, have shown that the reduction in the dose of ethinyloestradiol in OCs had been associated with a reduction in VTE incidence. OCs containing 50 μg ethinyloestradiol per tablet were associated with incidences of 7–11 per 10,000 wy, and OCs containing 30–35 μg ethinyloestradiol with an incidence of ~4 per 10,000 wy (RCGP, 1974, 1978; Vessey, 1988; Gerstman et al., 1991; Farmer and Preston, 1995). Paradoxically, more recent studies showed inverse dose gradients with oestrogen as the exposure factor. In all the three 1995–1996 original studies the ORs for the OC containing 20 μg ethinyloestradiol combined with desogestrel were higher, to an extent of 1.5 to 5, than those of the same progestogen combined with 30 μg ethinyloestradiol (Table II). Similarly, in the WHO study the lower-dosed cyproterone acetate-containing product was associated with a three times higher OR than the product with the higher ethinyloestradiol dose. Again, these inverse ethinyloestradiol dose gradients cannot be reasonably explained pharmacologically. They are clinically and biologically implausible and militate against a causal interpretation of the weak ORs between third and second generation OCs. Rather, they favour systematic error (bias) as a more likely explanation of the ORs observed. One characteristic held in common by all these low-dose ethinyloestradiol contraceptives with apparent higher risks
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Product the highest. Each consecutive OC introduced had a systematic error in observational research as ‘play the winner’ are a more likely explanation. I have referred to this type of bias, attrition of susceptibles bias (healthy user effect, prudent doctor bias or play the winner bias) and referral bias. Following their publication, various groups have published and substantiated the presence of these biases.

Time trends and the ‘prudent doctor bias’

An additional analysis in the Transnational Study Database revealed very important time trends (Lewis et al., 1996a). Our analysis showed that the product longest on the market had the lowest OR for VTE and the most recently introduced product the highest. Each consecutive OC introduced had a higher OR for VTE than its predecessors. There was a clear correlation between the ORs for VTE and the recency of market introduction of the products concerned (P = 0.00012, analysis for linear trend) (Figure 1). Again, there is no known pharmacological rationale for this effect. Cohort effects over time, in which the newer products are used more often by pill-starters and women at risk for OC-associated adverse effects, are a more likely explanation. I have referred to this type of systematic error in observational research as ‘play the winner’ bias. Inman used the phrase ‘prudent doctor bias’ in respect to other pharmaceutical products (personal communication). What probably happens is that women doing well or free of a risk profile are kept on the older products that have served them well. The prudent doctor will not switch products for them, but rather play the ‘winning’ OC. Women believed to be at higher risk for earlier second generation OCs or new starters are thus more likely to be prescribed third generation OCs.

Missing biological plausibility

There is no known biologically plausible mechanism which can explain the reported rate ratios of second and third generation OCs for VTE. Many randomized controlled studies have investigated the haematological effects of second and third generation OCs (Rákóczi et al., 1985; Bonnar et al., 1987; Gramolini et al., 1987; Kloosterboer et al., 1987; Machin et al., 1987; Rabe et al., 1987; Vekemans et al., 1987; Zichella, 1987; Cohen et al., 1988; Kjaer et al., 1989; Omsjo et al., 1999, 1989; Prasad et al., 1989; Ball et al., 1990; Refin et al., 1990; Sirtori et al., 1990; Melis et al., 1991). None of these have shown any difference that could be considered to be indicative of a higher (pro)thrombotic potential of third generation OCs. Only in Factor VII were non-significant trends noted, but this factor has been shown not to be associated with VTE risk, but rather with the risk of AMI (Koster and Rosendaal, 1994). On the other hand, haematological studies comparing OCs with different ethinyloestradiol doses have consistently shown a decreasing effect on various coagulation parameters with decreasing oestrogen dose of the OCs (Bonner et al., 1987; Graeff et al., 1977; Meade, 1977; Norris and Bonner, 1996; Winkler et al., 1996). This and the reverse ethinyloestradiol dose gradient seen in the 1995–1996 epidemiological studies argues against biological plausibility.

More on systematic error—bias and confounding factors in epidemiological research

Observational studies are by their nature vulnerable both to systematic error and to factors over which the investigators usually do not have any discretion or control. Results are therefore less valid and less reliable than those from experimental randomized controlled studies. The 1995–1996 epidemiological studies on VTE and OCs seem to have been affected by at least two, and potentially three, types of bias: prescribing bias, attrition of susceptibles bias (healthy user effect, prudent doctor bias or play the winner bias) and referral bias. Following their publication, various groups have published and substantiated the presence of these biases.

Preferential prescribing

Prescribing bias results from differential prescribing of drugs depending on the characteristics of the patients and the drugs. Third generation OCs may have been preferentially prescribed to women with cardiovascular risk factors because of their perceived improved safety profile over second generation OCs. Preference of third generation OCs for higher risk women before October 1995 had been recommended by several sources, including the British National Formulary, data sheets and physicians’ reference books (British National Formulary, 1990). This and the reverse ethinyloestradiol dose gradient seen in the 1995–1996 epidemiological studies argues against biological plausibility.

![Figure 1. Effect of recency of market introduction of oral contraceptives (OCs) on odds ratios (ORs) for venous thromboembolism, in comparison with levonorgestrel (LNG) in a Transnational Study of women aged 25–44 years. LNG 30/35 = OC containing levonorgestrel + 30/35 μg ethinyloestradiol; DSG 30 = desogestrel + 30 μg ethinyloestradiol; GSD 30 = gestodene + 30 μg ethinyloestradiol; NGM 35 = norgestimate + 35 μg ethinyloestradiol; DSG 20 = desogestrel + 20 μg ethinyloestradiol.](https://academic.oup.com/humrep/article-abstract/12/11/2347/664577/Downloaded-from-https://academic.oup.com/humrep/article-abstract/12/11/2347/664577)
Attrition of susceptibles bias can affect any study that investigates drugs or other treatments with different duration of availability. Because of the importance of this type of systematic error described in an earlier section, I provide further detail in this section. This bias could explain all the elevated ORs observed in contrasts between third and second generation OCs for VTE in the 1995–1996 studies. Those users of drugs that are susceptible to (serious) side-effects will be partly or largely removed from the user cohort over time by prudent clinicians, either because the women are recognized as having a contraindication or because they experience a side effect to which they are susceptible. This leaves the original cohort with fewer susceptible users. Empirical evidence that the healthy user effect is also pertinent to the putative association of OCs and VTE has emerged in analyses that show a reduction in the OR for VTE with increasing duration of OC use (Sartwell et al., 1969; Poulter et al., 1996). Since second generation OCs had been available for much longer than third generation OCs (Farmer and Lawrenson, 1996; Heinemann et al., 1996; Jamin and De Mouzon, 1996; Van Lunsen, 1996; Lidegaard, 1997). A study in the UK, Germany, Sweden and The Netherlands found that in the presence of cardiovascular risk factors the likelihood of a prescription for a third generation OC was five times as high as that for a second generation OC (71 versus 14% respectively) (Van Lunsen, 1996). Similarly, a study in France showed that of the 60% of gynaecologists and 52% of general practitioners (GPs) who would actually prescribe an OC to women with a family history of thrombosis (90 and 68% respectively), would only prescribe a third generation OC (Jamin and De Mouzon, 1996).

Selective referral bias

Referral bias results from differential hospital diagnostic referral of patients for diagnosis with similar symptoms but different clinical backgrounds. The main 1995–1996 case-control studies were hospital-based. Thus, the studies on OCs and VTE are all likely to be affected by referral bias, because women with symptoms potentially indicative of a venous thrombosis and who use OCs are more likely to be referred for further diagnosis than women with similar symptoms not using OCs (Collet, 1994). There is indirect evidence that this bias may have also affected the comparison of third and second generation OCs. In an interview survey in Germany and the UK, physicians indicated higher referral rates in the presence of a family history of VTE or arterial thrombosis, varicose veins and obesity or of first-ever OC use (Heinemann et al., 1996). In the same surveys and others, the same risk factors were also strongly associated with preferential prescribing of third generation OCs (Farmer and Lawrenson, 1996; Heinemann et al., 1996; Jamin and De Mouzon, 1996; Van Lunsen, 1996; Lidegaard, 1997). Users of third generation OCs with symptoms of venous thrombosis were reported to be referred to hospitals more often. Accordingly, third generation OC users would be more likely to contribute to the cases in all three epidemiological studies, which all required hospitalization as an inclusion criterion. Adjustment for such bias in the analyses is not feasible since no information can be ascertained about VTE patients who were not referred and therefore not included.

Acute myocardial infarction—the other side of the coin

The three main 1995 and 1996 studies all investigated the association between OCs and AMI. At the time of the initial publication of the 1995 pill scare revisited (Lidegaard, 1996). The evidence that women with venous and arterial disease risk factors have indeed been selectively prescribed third generation OCs is convincing. The data emerge from physician surveys across Europe, as well as from prescription and epidemiological databases (Farmer and Lawrenson, 1996; Heinemann et al., 1996; Jamin and De Mouzon, 1996; Van Lunsen, 1996; Lidegaard, 1997). A study in the UK, Germany, Sweden and The Netherlands found that in the presence of cardiovascular risk factors the likelihood of a prescription for a third generation OC was five times as high as that for a second generation OC (71 versus 14% respectively) (Van Lunsen, 1996). Similarly, a study in France showed that of the 60% of gynaecologists and 52% of general practitioners (GPs) who would actually prescribe an OC to women with a family history of thrombosis (90 and 68% respectively), would only prescribe a third generation OC (Jamin and De Mouzon, 1996).

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None of the three studies had had the opportunity to control adequately for this bias in design or analysis because it was not suspected and because of the formidable ascertainment difficulties in the field that such control would have entailed.

Selective referral bias

Referral bias results from differential hospital diagnostic referral of patients for diagnosis with similar symptoms but different clinical backgrounds. The main 1995–1996 case-control studies were hospital-based. Thus, the studies on OCs and VTE are all likely to be affected by referral bias, because women with symptoms potentially indicative of a venous thrombosis and who use OCs are more likely to be referred for further diagnosis than women with similar symptoms not using OCs (Collet, 1994). There is indirect evidence that this bias may have also affected the comparison of third and second generation OCs. In an interview survey in Germany and the UK, physicians indicated higher referral rates in the presence of a family history of VTE or arterial thrombosis, varicose veins and obesity or of first-ever OC use (Heinemann et al., 1996). In the same surveys and others, the same risk factors were also strongly associated with preferential prescribing of third generation OCs (Farmer and Lawrenson, 1996; Heinemann et al., 1996; Jamin and De Mouzon, 1996; Van Lunsen, 1996; Lidegaard, 1997). Users of third generation OCs with symptoms of venous thrombosis were reported to be referred to hospitals more often. Accordingly, third generation OC users would be more likely to contribute to the cases in all three epidemiological studies, which all required hospitalization as an inclusion criterion. Adjustment for such bias in the analyses is not feasible since no information can be ascertained about VTE patients who were not referred and therefore not included.

The impact of bias and confounding has been important in the 1995–1996 studies. The biases, if they existed, would elevate odds ratios for VTE as in most observational case-control research, especially for the newer preparations. The presence of most of the biases discussed above has been demonstrated empirically. The possibility that most or all of the odds ratio of about 2.0 contrasting third and second generation OCs resulted from such systematic error cannot be set aside. The biases are also likely to account for the unexplained and otherwise inexplicable differences in OR differences between the OCs containing 30 and 20 μg ethinyl-oestradiol as shown in Table II.

Acute myocardial infarction—the other side of the coin

The three main 1995 and 1996 studies all investigated the association between OCs and AMI. At the time of the initial
publications, in December 1995 and January 1996, there were strong indications that third generation OCs exhibited lower ORs for AMI than second generation OCs. The initial priority analysis of the Transnational Study showed that use of second generation OCs compared with non-use of OCs resulted in an OR of 3.1 for AMI (Lewis et al., 1996b). For third generation OCs the OR was 1.1 when non-users were the reference. The OR contrasting third to second generation OCs was 0.36 (95% CI 0.1–1.2), P = 0.07, suggesting a protective effect of third generation OCs if the second generation is the reference. The BCDSP, with only very few cases, showed ORs of 0.7 (0.1–5.9) for AMI compared with levonorgestrel-containing OCs (Jick et al., 1996a) for both the gestodene and the desogestrel containing OCs.

None of these initial sets of results were statistically significant at the conventional level of α = 0.05, and they were just as likely to have been influenced by bias and confounding as those for VTE. However, the plausible direction of the effects of bias and confounding is opposite for the two outcome diseases. In the VTE studies, systematic error could have explained all or part of the observed difference. If the same logic was applied in the AMI studies, it probably would have hidden a larger true difference. It is reasonable to assume that selective prescribing of third generation OCs to women with cardiovascular risk factors and referral bias would drive the OR of third generation OCs up regardless of the type of cardiovascular disorder. On the other hand, the impact of attrition of susceptibles bias will most markedly affect those OCs longest on the market. In a study of AMI, the attrition of susceptibles bias is thus likely to influence the OR for second generation OCs in a desirable direction (i.e. lower and closer to 1.0). Accordingly, the true ratio between third and second generation OCs as risk factors for AMI is probably underestimated because of all plausible forms of systematic error that could have occurred.

The favourable results of the AMI studies have not received the widespread attention given to those on VTE. This is surprising because even if the published and publicized ORs for third and second generation OCs in respect to VTE were true, the public health impact of AMI ORs is much more important because of the very high case fatality rates of AMI. For the UK and Germany we pointed that out in the early publications of the Transnational Study results (Spitzer et al., 1996; Lewis et al., 1996b). Similar patterns emerged in a modelling study for the US population (Schwingl and Shelton, 1997). Rather than invoking the results and the potential impact of the two cardiovascular disorders taken together, most of the scientific and the regulatory debates have focused on the VTE findings in isolation. I consider such a compartmentalized consideration of the evidence to be inappropriate to the practice of drug safety and scientifically inadmissible in the interpretation of pharmacoepidemiology.

Evolution of the controversy
The warning letter by CSM in October 1995, the restrictions in Germany and Norway which followed soon after and the publication of the results of the studies 2 months later had important social and scientific repercussions. The social consequences were mainly negative. Predictably, massive media attention to the warning resulted in a pill scare of unprecedented magnitude. Tens of thousands of women stopped use of the pill altogether, often overnight and without backup contraception. Thousands of unplanned pregnancies and large increases in abortion rates were the consequences. The UK Birth Control Trust estimated that in the second quarter of 1996 abortions in England and Wales rose by 5541, compared with the second quarter of 1995, an increase of 14.5% (Jick et al., 1995). The same reaction was also seen in Norway and Germany; 25 000 women discontinued use of any OC in Norway in November and December 1995. Abortion rates that had been steadily declining from 1992 to 1995 in women aged ≤24 years were reversed to a 36% increase during the first quarter of 1996 (Skjeldestad, 1997). In Germany, abortion figures for 1996 were up 34% compared with 1995 (Statistisches bundesamt, 1995, 1996). The increase may have been partly the consequence of changes in reporting, but were probably also caused by the widespread negative publicity about OCs.

Reactions from the scientific and clinical communities were diverse. After an initial phase of shock (particularly among general practitioners, obstetricians and gynaecologists and family planning professionals), the background specialism determined the type of reaction and its extent. Many scientists and clinicians were of the view that the way the information from studies not yet peer-reviewed and published had been used and thereafter disseminated to the public was irresponsible at best and could have been predicted to cause a pill scare. When the data became available, a vigorous scientific discussion began among epidemiologists and clinicians, including the investigators of the 1995–1996 studies. The interpretation of the results of the studies was the main issue. The essence of the ongoing debates was, and still is, whether the associations observed denote causal relationships or whether they are best explained by bias or confounding. Even the investigators of the initial studies disagree. Whereas the WHO and the BCDSP groups favour an interpretation of possible causation (Poulter et al. 1996; Jick et al., 1996b), most Transnational investigators, including myself, are of the opinion that the data are so seriously affected by unavoidable systematic error that a causal association is not probable (Lewis et al., 1996a; Heinemann et al., 1996). This latter view has been shared in editorials by opinion leaders in the field. One such view is that of Westhoff who wrote: 'At this time, the only support for causality as an explanation for these new formulation-specific associations is the consistency of the findings across studies. As discussed above, it is possible for studies to show similar results due to consistent biases.' Further, 'Epidemiologists know that causal relationships are identified by a body of coherent evidence. Associations should be strong, and they should be supported by laboratory data or plausible biological hypotheses before one infers causality. The new relationships between certain oral contraceptives and venous thromboembolism do not meet these criteria, (Westhoff, 1996).

Unfortunately, the scientific exchanges of experts in the peer-reviewed medical literature frequently invited renewed media attention negative to OCs in general. The consequence
has been additional undermining of the credibility and the safety image of OCs as the best and safest medication for birth control available. Strongly polarizing positions of some experts further contributed to this climate even when the conclusion to be defended sometimes seemed more important than the scientific validity of the data on which it was based (Vandenbroucke et al., 1996; Vandenbroucke and Rosendaal, 1997). Specialists in primary care, in gynaecology and family planning have expressed feelings of surprise and unease about the way the whole issue was handled and have questioned the validity of the data on which the decisions and restrictions were based (Cohen, 1996; Johannisson, 1996; Leader, 1996).

Recent published and unpublished studies and analyses

New studies and analyses were initiated in October 1995 to investigate further the association of OCs and the main target adverse outcomes. The main topics of investigation were: (i) the difference (or lack thereof) between third and second generation OCs in respect to VTE occurrence rates; (ii) OC generation as a determinant of the rates of the other cardiovascular diseases AMI and stroke; (iii) biological differences between OC generations, with emphasis on haemostatic variables. Regarding the latter, to date, I have found no evidence about any known difference in biological mechanisms between third and second generation OCs that might explain the published VTE odds ratios. That is despite the claims of some investigators that this may be the case. Such claims, however, have so far been based on one non-randomized, cross-sectional study design involving a haemostatic variable (Factor VII) which has not been shown to be associated with VTE (Koster and Rosendaal, 1994; Plu-Bureau et al., 1996) and one study with a similar non-experimental design using a clinically unvalidated haematological assay (APC sensitivity ratio) (Rosing et al., 1997). In the same study there was no difference in the same parameter when assessed by the only validated methodology, namely, measurement of APC resistance. A properly designed study to investigate the presence or absence of differences in effects of haematological variables will soon be started by the manufacturers of third generation OCs, at the request of the Committee on Proprietary Medicinal Products (European Agency for the Evaluation of Medicinal Products, 1997).

More illuminating are the results that are now emerging from new studies on OCs and VTE or from new analyses of the data from the initial studies. With increased knowledge about the nature of systematic error that affected the results of the initial studies, such error could be better controlled or minimized in the study design or in the analysis of newer initiatives to investigate the relative risks of third and second generation OCs for VTE. One of these studies has now been published (Farmer et al., 1997) and results from three others have been submitted and are awaiting publication soon.

UK MediPlus study

This project, conducted on the MediPlus general practice medical record database in the UK (Farmer et al., 1997) in essence has the same architecture as one of the 1995–1996 initial studies, the BCDSP study based on the GPRD database. Both studies relied on ~80 OC-using women who were affected by VTE as the cases. They first conducted a conventional analysis of the cohort and subsequently a nested case-control analysis within the cohort to adjust for confounders. The main difference between the designs is in the age-matching of the controls to the cases. In the BCDSP study, controls could be up to 2 years different in age from the cases; in the study by Farmer et al. (1997), they had to have the same year of birth. The results seem to be dependent on this difference in age-matching criterion. In both studies the unadjusted cohort analysis shows different rate ratios between users of third and of second generation OCs. In the nested case-control analysis of the BCDSP study these differences remain. In the MediPlus study, when the nested case control study is done, they disappear (Table III).

German MediPlus study

A similar study was also done with the MediPlus Germany database (R.D.T.Farmer et al., unpublished data). The results were similar to those in the UK and showed that after matching cases and controls by exact year of birth the odds ratio for VTE of third generation OC users compared to second generation users was 0.77 (95% CI 0.38–1.57). An interesting finding in this study was that the cases had experienced twice the number of consultations for physical complaints prior to the (VTE) event date than the controls. Duration of use analysis in the transnational database

Suissa et al. (1997) reanalysed the data from the Transnational Study controlling for additional covariates. The ORs of third and second generation OCs were derived confining the subjects to OC starters (first time users). Logistic regression and quadratic spline models incorporated the function of duration of use. Equivalent adjusted ORs for third and second generation OCs were found over time, with the highest ORs in the first year of use and a decrease thereafter to ~2.0 after 2 years of use. In other words, the risk of VTE for starters on the pill was essentially identical whether they were prescribed third generation or second generation OCs.

Danish study

Lidegaard et al. (1997), in a Danish case-control study involving 375 cases and 1041 controls, also found that the ORs of
VTE among current OC users were influenced by duration of use (O.Lidegaard, unpublished data). After adjustment for duration of use no significant differences were found between users of third and second generation OCs.

**Publication of the definitive AMI findings**

The Transnational Study has now finished its acute myocardial infarction project (Lewis et al., 1997). The definitive results from the AMI component of the WHO study have also been published (WHO, 1997). In the final Transnational analysis, a total of 182 cases and 635 controls were assessed by structured interview. Of those subjects, 57 cases and 156 controls were exposed to an OC, including seven cases and 49 controls using third generation OCs. Use of any OC was associated with an OR for AMI of 2.3 (95% CI 1.4–4.1). For second generation OCs the OR for AMI was 2.8 (1.3–6.2) and for third generation OCs 0.8 (0.3–2.3). The rate ratio for third versus second generation OCs was statistically significant: OR 0.3 (0.1–0.9). The WHO study, with only three cases and five controls using third generation OCs, had insufficient subjects to establish whether progestogen type lowers AMI risk with statistical significance. Yet the data point in the same direction as those of the Transnational Study. In the European centres of the WHO study, OC users relative to non-users had an OR for AMI of 3.2 (1.9–5.3). The analysis of second and third generation OCs was further restricted and included only cases and controls from the UK and Germany. Second generation OCs had an OR of 1.6 (0.5–5.5) and third generation OCs of 1.0 (0.1–7.0).

**Has evidence on stroke been overlooked?**

Stroke and AMI were the main outcomes of clinical and public health concern to us when we designed the Transnational Study. The most prominent concern of women on the pill and their doctors may well be stroke. Its killing and disabling attributes occur even more frequently than those of AMI (if one includes haemorrhagic stroke) and the burden of disability is more visible to the family and the community than the sequelae of AMI.

It is noteworthy that the secular trend of absolute risks of occurrence of stroke among users of OCs compared to non-users has been declining steeply both in Europe and the US (Petitti et al., 1996; Lidegaard, 1993) concurrent with the switch from the use of high-to low-dose oestrogen preparations. The evaluation of rate ratios of second and third generation OCs for thrombotic stroke in the WHO and Transnational Studies has revealed no important differences in the safety profiles of the two classes of OCs (Heinemann et al., 1997; WHO, 1995b, 1996a). The Danish study shows similar results (Lidegaard and Kreiner, 1997). In summary, for all OCs on the market, the threat of stroke as an adverse event has been clearly diminishing over the last three decades. I have found no evidence of meaningful differences between the two generations in relation to stroke, whether thrombotic or haemorrhagic.

**Conclusions suggested by the most recent findings**

The way cases and controls are matched by age may have an important impact on the results of the studies. When exact age-matching takes place no differences are found in VTE ORs between third and second generation OCs. In the 1995–1996 studies by WHO, Transnational and BCDSP groups, controls were matched to cases with 5, 5 and 2 year age bands respectively.

Adjustment for duration of use also affects the results in a material way. From the first priority analysis of the Transnational Study, we found that, adjusting for duration of use of the most recent OC used and for lifetime use of any OC, both drove the ORs downward when VTE is the outcome. In the Suissa reanalysis of the Transnational data and in Lidegaard’s study, any elevation of the ORs for third versus second generation OCs in respect to VTE either totally disappears or becomes statistically non-significant when duration of use is accounted for. The first set of analyses in the 1995–1996 studies did not adjust for this covariate with the same care.

Most studies investigating AMI have insufficient power for the evaluation of ORs of third compared to second generation OCs. The Transnational Study is the exception and finds a statistically significant lower risk for AMI for third generation OC users than for users of second generation products: OR 0.3 (0.1–0.9) *P <* 0.05. In line with this, all other studies, although too small for statistical powers find lower ORs for third than for second generation OC users. These studies are as likely to have been affected by systematic error as the studies on VTE. However, in the AMI studies the effect of bias would have been an underestimation of the true difference between the OC generations, so that the protective effect of third generation OCs compared with second generation OCs may in fact be even larger than would now appear to be the case. The adverse influence of smoking when taking the pill has been reconfirmed. The urgent need for a meta-analysis is obvious.

Stroke occurs with decreasing frequency, and no differences have been observed between classes of OC. The stroke studies highlight the need to control hypertension in users of OCs.

The most recent data reinforce my opinion that the hasty reactions of some health authorities in Europe were unnecessary and unwarranted. Had they taken the time to evaluate data as it unfolded and listened to prevailing expert opinion about the possibilities of bias and confounding, a major pill scare in several countries could have been avoided. There was no such scare in other countries where the authorities took a ‘watch and wait’ attitude.

The data now available strengthen the notion that the impact of bias and confounding on the results of the WHO, BCDSP and Transnational Study was substantial and always unfavourable for the newest OCs on the market. The studies had no possibility of controlling adequately for this type of systematic error a priori and, consequently, yielded inflated ORs when comparing third and second generation OCs for VTE. The most recent studies were able both to minimize bias and adjust for confounders more adequately. Subsequently, they no longer showed elevated rate ratios between these OC generations, which further persuades me that bias is a more likely explanation than causality of the observed ORs in the 1996–1997 studies.
The bottom line—was there an epidemic? Was an epidemic averted? Was an epidemic provoked?
I have found no reported evidence in countries where prescribing and use of third generation OCs fell dramatically after the October 1995 pill scare that a commensurate drop in the rates of deep vein thrombosis or pulmonary embolism or of death mediated by those disorders ensued. Nor have I found any reports of differences in morbidity or mortality between countries where the controversy raged for months and countries where the whole matter was not an issue at all (e.g. in France where the problem is referred to as the ‘English affair’). I believe that we have lived through a non-epidemic in the last 2 years. The absence of unusual and unexpected increases in the outcome events of concern is coherent with the view I have attempted to justify in this review, that the observed ORs in the 1995–1996 studies are unlikely to be true effects and are likely to be explained entirely or almost entirely by bias. Moreover, for the two outcomes of most concern to women using the pill and for clinicians, AMI and stroke, the data suggest that at worst, there is no difference deleterious for third generation OCs and at best the third generation OCs convey clinically important protection for heart attacks. With respect to strokes, WHO, Transnational, and Danish data suggest that there is no difference. The best news is that the secular trend of risks, estimated in studies going back over two decades, clearly indicate continuing increasing safety of all OCs. The worst news, sadly, is that epidemics of unnecessary abortions and of anxiety did occur, especially in the UK and Germany.

Summary
The main points of this synthesis of the evidence are: (i) all OCs continue to become progressively safer; absolute rates of VTE that were in the range of 7–10 per 10 000 w/y in the 1960s and 1970s have now been found to be 1–4 per 10 000 w/y; (ii) relative risks of ~2.0, even if one were to concede that they are real, are clinically unimportant and of no public health significance when the adverse outcome is rare, such as in VTE; (iii) the absolute rates for VTE of third generation OCs derived from the 1995–1996 studies are similar to or lower than those estimated for second generation OCs 5–8 years earlier; (iv) the absolute rates of occurrence of cardiovascular and cerebrovascular events per 10 000 w/y on the pill are less than half of those associated with pregnancy; (v) the weak ORs for VTE ranging from 1.5 to 2.3 observed in the 1995–1996 studies that compared third and second generation OCs are more likely to be explained by bias inherent in observational research than by a causal relationship. Later studies show even lower rate ratios. Biological implausibility also militates against causality; (vi) attrition of susceptibles bias alone (‘prudent doctor’ or ‘play the winner’ bias) can explain weak ORs under 2.3 as well as many incoherent and paradoxical patterns in the data of the 1995–1996 studies; (vii) there is no difference in the risk of VTE between first starters on second generation OCs versus first starters on third generation products; (viii) for AMI, third generation OCs convey a risk one third that of second generation OCs. This protective effect is statistically significant and clinically important and in one study. Trends in other studies point in the same direction; (ix) with respect to stroke, the absolute rates are low, they have been steadily declining for all OCs and no differences have been detected between second and third generation OCs; (x) 2 years after the 1995 warnings by health authorities there have been no epidemics of deep vein thrombosis or pulmonary embolism. But epidemics of anxiety and therapeutic abortions have occurred in several countries; (xi) research priorities should incorporate better ascertainment of the benefits of various classes of OCs on the market.

Conclusions
I reiterate my view that OCs are one of the most effective interventions in health promotion and illness prevention for women. As I look at the mosaic of evidence about OCs and cardiovascular disease today in late 1997, the pattern I see is reassuring. The benefits for all OCs approved far outweigh the risks and extend from women to children, to families and to society. Anything that unjustifiably undermines credibility of any OC is a serious threat to the public health, particularly in developing countries. As a public health doctor, I have resisted and will continue to resist any such threat. All scares should be assiduously avoided and vigorously contained if they do occur. In public health, including drug safety, the Hippocratic imperative applies: ‘Above all, do no harm’.Judicious use of OCs, with more care in history taking, more focused evaluation of women’s risk factors and more diligent ongoing monitoring of those who have chosen to take the pill is the best defence against the unavoidable but very small risks associated with oral contraception. It would be as naive and foolish to deny the risks of OCs as it would be foolish to deny the inherent risks of any effective medication. However, the risk–benefit ratio of OCs is overwhelmingly positive. The worst-risk scenarios for any OC are very much less risky than those of pregnancy, wanted or unwanted.

It is incumbent on academic investigators, clinical scientists, clinical practitioners, manufacturers, and governmental agencies to rally together in the quest for ever safer pills for contraception. Research priorities include more systematic documentation of the benefits of all classes of OCs and pursuit of a better fit of the pill prescribed with the needs of women seeking advice about oral contraception. More tiles are needed for the mosaic about oral contraception and the occurrence of important yet uncommon cardiovascular events. I am confident that a constructive alliance of all the stakeholders will provide the kind of valid data that is needed for a balanced interpretation of the profiles of safety and efficacy which are emerging in the rapidly expanding mosaic of oral contraception and the health of women.

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The 1995 pill scare revisited

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