CURRENT OPINION

Drug Safety 2002; 25 (13): 893-902
0114-5916/02/0013-0893/$25.00/0

Oral Contraception and the Risk of Thromboembolism

What Does it Mean to Clinicians and Their Patients?

James Drife

Department of Obstetrics and Gynaecology, University of Leeds, Leeds, United Kingdom

Abstract

For four decades the oral contraceptive pill has remained popular with young women because of its convenience and effectiveness. There have, however, been continuing concerns about adverse effects. In the 1960s the risk of venous thromboembolism was linked to the dose of estrogen, which was consequently reduced. Later the risks of arterial disease were linked to progestogen dose, which was also reduced.

In 1995, three case-control studies linked the risk of venous thromboembolism, not to dose, but to the type of progestogen. Newer 'third-generation' progestogens appeared to carry a higher risk than older formulations. Although the contraceptive pill was already known to increase the risk of venous thromboembolism 3- to 6-fold, and the risks in the three studies were within this range, the public perception was that a new risk had been discovered. In the UK there were two consequences – a rapid change in prescribing patterns and a sharp increase in the abortion rate.

Critics suggested that the studies may have been affected by confounding – e.g. by a 'new user' effect and differential prescribing. Views became very polarised. Between 1995 and 2001 second- and third-generation formulations were compared in 16 studies. Thirteen found that third-generation pills carried a higher risk of venous thromboembolism.

Editorials and reviews recommended second-generation pills as the first choice for new users but official advice was that third-generation pills could still be prescribed, provided the risks were explained. Rates of thrombosis, per 100 000 women, are five for nonusers, 15 with second-generation pills and 25 for third-generation pills. The increase in mortality rates is around 1 to 2 per million.

Drug-industry sponsored studies tended to find lower risks than independent studies and it was assumed that sponsorship produces bias, conscious or unconscious. It is also possible that some 'independent' researchers, motivated by antipathy to multinational pharmaceutical companies, are biased in the opposite way.

Compared with the energy put into this debate, other aspects of pill prescribing remain under-researched. For example, doctors on opposite sides of the Atlantic are given different advice about whether gross obesity (a major risk factor for thromboembolism) is a contraindication to oral contraception.

Women in developing countries continue to die of pregnancy-related causes and many deaths could be prevented by effective contraception. Rather than bickering, drug manufacturers and academics should be discussing ways of providing the pill to the women who need it most.

It has been known for 40 years that there is a link between oral contraception and thromboembolism. The first case reports raising this suspicion appeared soon after the contraceptive pill was introduced in 1961[1] and these were followed by detailed epidemiological studies published during the late 1960s.[2] What is fascinating is that in the 1990s this adverse effect was still capable of generating panic among the public and indeed doctors in the UK[3] and even now it is still causing bitter controversy among researchers.[4-7] The reasons for this run deeper than mere pharmacoepidemiology.

1. Balancing Benefits and Risks

Despite the early concerns about its safety and repeated scares over the years, the oral contraceptive pill has remained very popular. This is because young women – who are not in fact 'patients' but healthy people choosing whether or not to take hormones – are continually weighing the benefits against the risks. The pill has considerable health benefits, ranging from reduction of menstrual problems to prolonged protection against ovarian and endometrial cancer[8,9] but young women are less interested in protection against cancer later in life than in its effectiveness and convenience as a contraceptive. Although it has been found that in general women tend to overestimate the risks and underestimate the effectiveness of hormonal contraceptives,[10] nevertheless the popularity of the pill continues, and about 80% of British women use it at some time before the age of 24.[11]

Nowadays, in the UK at least, young women start sexual activity at an earlier age and tend to have more partners than they did in the past. In a survey of young women in Somerset, England, in 1996, among those who had had sex the mean age at first intercourse was 15.75 years. The predominant pattern was of serial monogamy rather than casual relationships.[12] Awareness of 'safe sex' has increased[11,12] but condoms are still seen as being less effective than the pill and less under the woman's control. Other contraceptive methods such as the intrauterine device are seen as more invasive, more 'medical' and more liable to produce serious adverse effects. For a young woman, contraception means taking the contraceptive pill and her decision to do so, as well as being a matter of taking sensible precautions, is a statement about commitment to a relationship and about reaching a certain stage of personal and sexual development.

A woman's decision to stop taking the contraceptive pill also depends as much on social and psychological factors as on medical ones. The proportion of British women using oral contraceptives is over 40% in the 20 to 30 age group but begins to fall before the age of 35, which is when it becomes medically advisable for smokers to stop oral contraceptives (or, of course, to stop smoking). Doctors often hear a woman say that after 10 years of taking the pill she decided she had been taking it for long enough – though none of the adverse effects of the contraceptive pill (except its effect on cervical cancer risk) is related to long duration of use. Patterns of contraceptive use vary in different countries but in the UK the pill is perceived as a young woman's method, and by the age of 40, about 50% of British couples have opted for sterilisation of one or other partner.[9]

2. 'Pill Scares'

The fact that most users of the contraceptive pill are relatively young may affect their reaction to medical warnings. Teenagers may perceive older doctors, particularly males, as being out of touch[13] and may suspect that some doctors 'talk up' the adverse effects of the contraceptive pill because they disapprove of sexual activity among young people. On the other hand, the young may be more influenced by the media, leading them to overreact to 'scare' stories. In October 1995 in the UK, there was considerable publicity linking venous thromboembolism with oral contraceptive formulations containing desogestrel or gestodene, which were then the market leaders. This was followed in the first quarter of 1996 by 45 651 abortions in England and Wales, a 16% rise on the previous

quarter, and the increase in abortions continued more slowly until 1998.[14] The rise was deeply disappointing for doctors working in family planning clinics, as the UK abortion rate had been falling slowly but steadily over the previous 5 years. That improvement was wiped out by a single weekend of bad publicity.

It is easy to blame journalists and indeed it has been shown that the media, in countries like the US and UK, ignore research studies with reassuring findings about the contraceptive pill but publicise those showing adverse effects.[15] The public, however, are used to the media's fondness for bad news, and doctors and organisations have been looking harder at their own role in 'pill panics'. Conflicting advice from experts increases public concern. Incompetent release of research results can generate intense press interest but careful news management can reduce the risk of panic.[16] Scares may be localised to one country or even to a region within a country. In the Grampian area of Scotland (about 600 miles away from London) women took little notice of the 1995 contraception pill scare and abortion rates remained unchanged.[17] Doctors throughout the UK, however, reacted rapidly in 1995 by changing their prescribing patterns,[18] as indeed did doctors in Ireland, even though the Irish regulatory authority issued no advice to about switching contraceptive pill formulations.[19]

The 1995 scare was not the first to suggest that some formulations of the contraceptive pill might carry higher risks than others. In 1983 a report on breast cancer risk[20] had done the same thing and users had received confusing messages about the relative safety of different types of oral contraceptives.[21] Doctors and patients find overall warnings affecting all types of pill easier to cope with than a warning about some formulations and not others – particularly when clinicians know that the steroid dosage in all brands is now very similar. Such 'differential warnings' tend to be hotly disputed by the manufacturers of the affected formulations. In 1983 their indignation proved to be justified because the scientific basis of the differential warning – a grading system of progestogen potency – was quickly shown to be inappropriate.[22] In 1995, however, the differential warning over thromboembolism risk could not be easily dismissed.

3. Adverse Events and Steroid Dosage

Until 1995, the risk of thromboembolism had been thought to be related only to the dose of steroids. A link between the dose of estrogen and thromboembolism had been established in the 1960s. The first brand introduced on the market, Enovid,®[1] contained 100μg of mestranol and 250μg of norethynodrel (several times the dosage of current preparations). Mestranol was found to carry a higher risk of thromboembolism than ethinylestradiol[2] and therefore almost all mestranol-containing brands were discontinued, as were high-estrogen preparations, to be replaced with pills containing 50μg of ethinylestradiol. The efficacy of formulations containing still less estrogen was then established and by 1980 well over 50% of contraceptive pill prescriptions in the UK were for formulations containing 30 or 35μg of ethinylestradiol.[23] In the US, the change to low-estrogen formulations took place some years later.[24] Thirty micrograms of ethinylestradiol is regarded as the standard strength but formulations with 20μg have also been available for some years and recently a formulation with 25μg in combination with newer progestogens has been shown to have low contraceptive failure rates.[25]

The change to low-dose estrogen formulations was accompanied by little professional debate or public alarm. One reason was that it made good sense. Another, perhaps, was that almost all formulations contained ethinylestradiol and therefore there was no basis for competing claims from different manufacturers. Competition depended on the marketing of progestogens and therefore any debate about the relative safety of different progestogens would affect commercial interests.

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

The first concerns relating to progestogen, however, were about the dose only. Early in the 1980s, progestogen dose was linked to the risk of arterial disease – an effect that applied to all types of progestogen examined. Three large cohort studies,[26-28] started in the 1960s, revealed an age-related risk of myocardial infarction which was highest among smokers, leading to a warning in the UK that women over 35 should not take the pill. (The attendant publicity is probably a major reason why the oral contraceptive is still unpopular among British women over 30, even though modern formulations can be taken by older women who do not smoke.) The cohort studies then showed that for a constant estrogen dose, the risk of myocardial infarction was related to the progestogen dose.[27]

Meticulous case-control studies were carried out[29] and eventually concluded that when women at high risk are excluded, low-dose estrogen and low-dose progestogen formulations carry no increased risk of myocardial infarction.[30] This welcome news, which applies to all types of progestogen, caused no controversy and was greeted with no media publicity.

Another adverse reaction that has been uncontroversial is the risk of ischaemic stroke, which is estimated to be increased by 1 in 24 000 among nonsmoking normotensive pill users[31] irrespective of the type of pill.[32]

Until 1995 then, the epidemiological picture seemed reasonably clear. Venous thromboembolism was related to estrogen dose and could be kept to a minimum by using the lowest effective dose of ethinylestradiol. Arterial thrombosis was linked with progestogen dose but could be reduced by using low-dose progestogen pills and by excluding women at high risk, particularly older women who smoked. Interest in the relative merits of different progestogens was intense but was focussed on their acceptability to women and on their safety in relation to arterial disease. The effects of progestogens on blood lipids were believed to predict their effects on cardiovascular risk, and much was made of their associated lipid profiles in the marketing of competing brands.

4. Progestogens and Thromboembolism

Norethisterone (norethindrone) had been introduced in the 1964[33] and is still used (in lower doses) in several formulations. Levonorgestrel, more potent and more specific for the progesterone receptor, was in clinical use in the 1970s[34] but was subsequently called a 'second-generation' progestogen. Then, in the late 1980s, came the so-called 'third-generation' progestogens, desogestrel and gestodene, and norgestimate (classified by some, but not all, as third-generation).[33] Though similar to levonorgestrel these seemed to be a further advance,[35] with improved cycle control[36] and a more favourable lipid profile, giving rise to optimism that they might carry a lower risk of cardiovascular disease.[37]

Before 1995 it had been established that the pill caused a 3- to 6-fold increase in venous thromboembolism and that this risk was unrelated to duration of use.[38,39] Some studies, in particular a cohort study from Michigan[40] had suggested that reducing the estrogen dose to between 20 and 35μg of oestradiol had brought about a reduction in risk of venous thromboembolism.

In 1995, three studies confirmed this trend towards lower risk. A WHO international study gave a relative risk of venous thromboembolism of 4.15 (95% CI 3.09 to 5.57) in Europe and 3.25 (95% CI 2.59 to 4.08) in developing countries with any type of oral contraceptive.[41] The increased risk appeared within 4 months of starting the pill and disappeared within 3 months of stopping it. The study also confirmed that increased body mass index is an independent risk factor for venous thromboembolism. An unexpected finding, however, was that the progestogen component of the oral contraceptive appeared to affect the risk of venous thromboembolism. When low-dose estrogen preparations containing second-generation and third-generation progestogens were examined separately, the risk appeared to be two to three times greater for prep-

arations containing desogestrel and gestodene than for those containing levonorgestrel.[41,42]

This finding was examined in two other studies which were already in progress. One, based on the UK General Practice Research Database, also concluded that pills containing third-generation progestogens had approximately double the risk of venous thromboembolism than those containing levonorgestrel.[43] The other, a transnational case-control study of 471 women in ten centres in Germany and the UK, concluded that the odds ratio was 1.5 (95% CI 1.1 to 2.1) for third-generation versus second-generation products.[44] A case-control study based on the Leiden Thrombophilia Study, concluded that contraceptive pills containing desogestrel carried a higher risk than all other contraceptive types combined.[45] It pointed out also that some women (e.g. those carrying the factor V Leiden mutation) are already at increased risk of thromboembolism but the higher risk of third-generation pills was not confined to this sub-group.

When UK cases in the WHO study were analysed, the risk estimates compared with nonusers were 2.6 (95% CI 1.5 to 4.6), 5.3 (95% CI 2.5 to 10.9) and 5.7 (95% CI 2.5 to 13.2) for levonorgestrel, desogestrel and gestodene, respectively. These risks are within the range that had been widely known for several years before 1995. The UK Committee on Safety of Medicines (CSM), however, followed by the British media, gave the public the impression that the new studies had revealed an unexpectedly high risk of venous thromboembolism.[3] In reality, the 1995 studies showed, if anything, an unexpectedly low risk associated with preparations containing levonorgestrel. With even moderately skilful news management, the results could have been presented as a 'good news' story or at least a 'no news' story.

The mortality from venous thromboembolism is widely estimated at 1% of cases and the risk of death from thromboembolism among oral contraceptive users is around two to three per million.[46] Thus, the difference in fatality rates between second and third-generation progestogens in the 1995 studies is about 1 in a million.[47] This is a low risk in absolute terms but most of the 1995 papers expressed their results as relative risks and press publicity concentrated on these without troubling to calculate the absolute risk. The public got the impression of a newly discovered high risk, and when the CSM advised doctors to prescribe second-generation rather than third-generation formulations, prescribing patterns in Britain changed within months. By February 1996 the proportion of pill users taking third-generation formulations had fallen from over 50 to about 20%.[18]

5. A Developing Controversy

Immediately after the 1995 studies were published it was pointed out that all three might have been affected by bias or confounding. For example, the risk of thromboembolism is higher among women who have just started the pill and such 'new users' may have tended to use the newer, third-generation formulations. By contrast, women who had been on the pill for a long time (and for whom it was safer) were more likely to be still using second-generation formulations. Another suggested bias was that because third-generation pills had more favourable lipid profiles, they may have been preferentially prescribed for women with known risk factors for cardiovascular disease.[37]

The CSM stood its ground, however,[48] and since 1995 the debate has continued, with much energy and resource being devoted to further case-control studies comparing different formulations. The increasingly polarised views of epidemiologists and clinical pharmacologists alarmed journal editors, though fortunately the debate has remained within the professional journals[49,50] and does not seem to have done further damage to the confidence of users of oral contraceptive pills. Sixteen studies have now been carried out comparing second and third-generation pills.[51] Three of these found no difference in the risk of thromboembolism but the others found higher risks with third-generation pills – the increase relative to second-

generation pills varying between 1.4 and 4. In 2001, a meta-analysis of 13 of the studies[52] concluded that the risk of thromboembolism with third-generation pills is 1.7 times that with second-generation pills (95% CI 1.4 to 2.0). Kemmeren and colleagues[52] systematically checked for bias and confounding in the original studies and concluded that these were insufficient to explain the observed difference.

6. The Current Consensus

Six years after this debate began, prescribers are entitled to expect some consensus among the experts, and one does seem to be emerging. Several editorials and reviews have advised that second-generation pills are the preparation of first choice[51,53,54] but official advice is more cautious. For example, guidelines from the Faculty of Family Planning of the Royal College of Obstetricians and Gynaecologists do not specify a first choice but point out that there is a higher risk of venous thromboembolism with third-generation pills which 'has not been satisfactorily explained by bias or confounding'.[55] In England, the Department of Health advises that third-generation pills may be offered as first choice provided that the slightly increased risk is explained to the woman.[56]

Women have by and large forgotten the scare of 1995, and nowadays it is possible for a clinician to explain the pros and cons of different formulations to a potential pill user without the feeling that her mind has been made up by the media. Nonetheless, the facts and figures are not easy to summarise. The British National Formulary sets them out in a way that is helpful to the clinician if not the patient. The baseline risk of deep venous thrombosis among young women without risk factors is about five per 100 000 person-years for non-users, 15 for second-generation pill users, and 25 for third-generation users.[57] If a woman asks about her chance of dying of contraceptive pill-induced thromboembolism, she can be told that it is around two in a million (the mortality of deep venous thrombosis being generally quoted as 1 to 2%).

This assessment of the mortality rate was challenged by a New Zealand study which calculated a fatality rate of 10.5 per million users of all ages.[58] Other authors, however, estimate that the combined number of excess deaths from both venous and arterial disease among young pill users is two to six per million users per year.[51] It is widely accepted that the risk of fatal embolism with oral contraception is much less than that associated with pregnancy.[54] The most accurate assessment of the risk in pregnancy is provided by the Confidential Enquiries into Maternal Deaths in the United Kingdom, which in its most recent report gives a figure of 14 per million maternities.[59] Most of these pregnancy-associated deaths were in women with obvious risk factors for thromboembolism, such as obesity.

7. Attitudes and Bias

As mentioned above, young women may suspect that a doctor 'talks up' or 'talks down' the risks of the pill, depending on the doctor's attitude to sexual behaviour. A worrying aspect of what we might call the '1995 controversy', however, is that researchers' conclusions may reflect their attitudes to the pharmaceutical industry. There have been accusations that the industry has kept unpalatable results secret[5] and some authors have compared the results of oral contraceptive studies with and without pharmaceutical funding.[53] When Kemmeren and colleagues[52] made this comparison they concluded that studies funded by manufacturers of oral contraceptive pills produce more favourable results than independent studies. The implication was that industry-funded studies were biased, while 'independent' studies were accurate.

It is worth asking, however, how often a study is truly independent. All researchers are motivated by some driving force and a few see themselves as academic Davids fighting pharmaceutical Goliaths. Scientists mistrustful of multinationals form loose alliances across the world and in the present cli-

mate of cynicism about big business they may have more influence than they think. Bias based on such mistrust may be difficult to detect. Editors rightly require a declaration of interest when a study is financially supported by a drug company but other agendas are not always formally declared in print. At scientific congresses, personal contact with authors, especially in informal settings, may reveal motivations that are not obvious on paper.

The most insidious type of bias is not deliberate manipulation but unconscious prejudice. This may explain the difference in results noted by Kemmeren et al.[52] and may apply both to the pharmaceutically funded and the 'independent' studies. Realists are beginning to recognise that 'science is not a dispassionate activity'[60] and that true objectivity in medical research is rarer than we like to admit in this era of evidence-based medicine. Most clinicians who read papers have always known this and are shrewd enough to allow for bias when interpreting results. They have become tired of the 1995 controversy consuming so much time, energy and expertise when there are other important questions to be answered.

8. Under-Researched Risk Factors

For example, more effort should be made to reach consensus on the importance of risk factors for thromboembolism. Paying attention to risk factors has dramatically reduced the incidence of fatal thromboembolism after caesarean section in the UK[59] and the same approach could be applied to thromboembolism and oral contraceptives. According to one American review 'obesity is not considered a contraindication to the use of oral contraceptives'[51] but the British National Formulary[57] states that the pill should be avoided if the BMI is above 39 kg/m^2. The Faculty of Family Planning guideline gives no clear advice on this.[55]

Another risk factor is a family or personal history of thromboembolism. In 2001 a consensus statement from the American College of Medical Genetics recommended against screening for factor V Leiden in asymptomatic women contemplating the use of oral contraceptives unless they have a personal or family history of thromboembolism or other risk factors.[61,62] It has been calculated that 8000 women would need to be screened for factor V Leiden mutation in order to prevent one episode of thromboembolism.[63] The estimated risk of fatal thromboembolism in contraceptive pill users who are heterozygous for factor V Leiden is 1 in 90 000 and with a 5% prevalence of the mutation in the population, it would be necessary to test 1 800 000 woman and withhold oral contraception from 90 000 women to prevent one death.[61] The conclusion that universal screening is not worthwhile[64] has been criticised on the basis that every woman has a right to know whether she has a predisposition to thrombosis before deciding whether to start the pill.[65] The recommendation on selective screening has also been disputed. A study in Bologna concluded that family history has unsatisfactory sensitivity and positive predictive value for identifying women with thrombophilic defects, and that selective screening may miss a substantial number of women at increased risk.[63]

9. The Global View

Risks of the order of one to ten in a million may not seem important to young people, many of whom do not allow medical warnings to deter them from using tobacco or recreational drugs. Women making decisions about contraception should have all the information they ask for but prescribers have to make sensible decisions about what information must be given whether the woman wants it or not.

The risks of contraception should also be viewed in the context of risks of pregnancy. In the UK the chance of a woman dying of a pregnancy-related cause is currently 1 in 8772.[59] In developing countries it is 1 in 48.[66] The global number of maternal deaths, mainly from sepsis, haemorrhage or unsafe abortion, is around 600 000 per year. In the early 1990s, it was estimated that 48% of couples in the developing world were using some form of contraception[67] and the proportion is slowly ris-

ing. In many developing countries family size is falling much more quickly than it did in the west at the same stage of the demographic transition from large to small families. Nevertheless, at present half the population in the developing world is below the mean age at marriage and the rate of population growth will continue to increase during the next decade. The lives of many thousands of women could be saved each year if contraception were more widely available.

The supply of oral contraceptives in many developing countries is still over-regulated, and in some countries unnecessary and expensive tests are insisted upon before the contraceptive pill is prescribed. In developing countries women's perceptions of the safety of the contraceptive pill are influenced by scares in Western countries.[68] Women in developing countries have the same right to contraceptive options as those in the developed world, and the oral contraceptive should be one of those options. Marketing low dose pills in developing countries is something that manufacturers could do if commercial realities and social circumstances allowed. Rather than trying to demonise drug manufacturers, academics with a social conscience should be engaging in dialogue with them, to see if ways can be found of using the contraceptive pill to save women's lives.

10. Conclusion

Research efforts should always be matched as closely as possible to patients' needs. Looking back at the progestogen/thromboembolism debate with the benefit of hindsight, we can see that in 1995 the CSM failed to put the risks into perspective and that a polarised debate continued for 6 years to very little effect as far as users of the oral contraceptive are concerned. What is needed now is a research agenda that puts clinical need first, without ignoring commercial or academic interests. Co-operation between academics and drug companies has a long and honourable history, to the benefit of patients. Specifically, in developed countries research is needed to clarify which risk factors for thromboembolism contraindicate the pill, and on a global scale research is urgently needed into ways of getting contraception to the women who need it most.

Acknowledgements

The author has in the past received research funding from Schering UK, an oral contraceptive manufacturer, though the research was not on contraception.

No sources of funding were used to assist in the preparation of this manuscript. The author has no conflicts of interest that are directly relevant to the contents of this manuscript.

References

1. Jordan AM. Pulmonary embolism. Lancet 1961; II: 1146-7
2. Inman WHW, Vessey MP, Westerholm MB, et al. Thromboembolic disease and the steroidal content of oral contraceptives: a report to the Committee on Safety of Drugs. BMJ 1970; 2: 203-9
3. Sensible alerts [editorial]. Lancet 1995; 346: 1569
4. Drife J. The third-generation pill controversy (continued). BMJ 2001; 323: 119-20
5. Weber W. Study on risks of third-generation pill 'kept secret by industry' [news item]. Lancet 2001; 357: 779
6. Brock P. Wyeth responds to news story on oral contraceptives and DVT [letter]. BMJ 2001; 322: 1605
7. Skegg DCG. Pitfalls of pharmacoepidemiology. BMJ 2000; 321: 1171-2
8. Drife JO. The benefits of combined oral contraceptives. Br J Obstet Gynaecol 1989; 96: 1225-8
9. Drife JO. The benefits and risks of oral contraceptives today. Carnforth: Parthenon, 1996
10. Edwards JE, Oldman A, Smith L, et al. Women's knowledge of, and attitudes to, contraceptive effectiveness and adverse health effects. Br J Fam Plann 2000; 26: 73-80
11. McEwan J, Wadsworth J, Johnson AM, et al. Changes in the use of contraceptive methods in England and Wales over two decades: Margaret Bone's surveys and the National Survey of Sexual Attitudes and Lifestyles. Br J Fam Plann 1997; 23: 5-8
12. Ford NJ, Halliday J, Little J. Changes in the sexual lifestyle of young people in Somerset, 1990-1996. Br J Fam Plann 1999; 25: 55-8
13. Donovan B. Never underestimate the force of reproduction. BMJ 2000; 321: 461-2
14. Office for National Statistics. Abortion statistics: legal abortions carried out under the 1967 Abortion Act in England and Wales, 1999. London: The Stationery Office, 2000
15. Lebow MA. The pill and the press: reporting risk. Obstet Gynecol 1999; 93: 453-6
16. Hammond PB. Reporting pill panic: a comparative analysis of media coverage of health scares about oral contraceptives. Br J Fam Plann 1997; 23: 62-6
17. Flett G, Gurney E, McKessock L, et al. Impact of the October 1995 pill scare in Grampian. Br J Fam Plann 1998; 24: 18-20
18. Van Heteren G. Wyeth suppresses research on pill, programme claims [news item]. BMJ 2001; 322: 571

19. Williams D, Kelly A, Carvalho M, et al. Effect of the British warning on contraceptive use in the General Medical Service in Ireland. Ir Med J 1998; 91: 202-3
20. Pike MC, Henderson BE, Krailo MD, et al. Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet 1983; II: 926-30
21. Drife JO. Which pill? BMJ 1983; 287: 1397-9
22. Swyer GIM. Oral contraceptives and cancer [letter]. Lancet 1983; II: 1019
23. Thorogood M, Vessey MP. Trends in use of oral contraceptives in Britain. Br J Fam Plann 1990; 16: 41-53
24. Gerstman BB, Gross TP, Kennedy DL, et al. Trends in the content and use of oral contraceptives in the United States, 1964-88. Am J Public Health 1991; 81: 90-6
25. Kaunitz AM. Efficacy, cycle control, and safety of two triphasic oral contraceptives: Cyclessa (desogestrel/ethinyl estradiol) and Ortho-Novum 7/7/7 (norethindrone/ethinyl estradiol): a randomized clinical trial. Contraception 2000; 61: 295-302
26. Vessey MP, Lawless M. The Oxford-Family Planning Association contraceptive study. Clin Obstet Gynaecol 1984; 11: 743-57
27. Kay CR. The Royal College of General Practitioners' oral contraception study: some recent observations. Clin Obstet Gynecol 1984; 11: 759-86
28. Ramcharan S, Pellegrin FA, Ray R, et al. The Walnut Creek contraceptive drug study: a prospective study of the side effects of oral contraceptives. Vol. III: an interim report. A comparison of disease occurrence leading to hospitalisation or death in users and nonusers of oral contraceptives. J Reprod Med 1980; 25: 345-72
29. Thorogood M. Oral contraceptives and cardiovascular disease: an epidemiologic overview. Pharmacoepidemiol Drug Saf 1993; 2: 3-16
30. Dunn N, Thorogood M, Faragher B, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. BMJ 1999; 318: 1579-83
31. Gillum LA, Mamipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. JAMA 2000; 284: 72-8
32. Poulter NR, Chang CL, Farley TMM, et al. Effect on stroke of different progestagens in low oestrogen dose oral contraceptives. Lancet 1999; 354: 301-3
33. Gillmer MDG. Metabolic effects of combined oral contraceptives. In: Filshie M, Guillebaud J, editors. Contraception: science and practice. London: Butterworth, 1989: 11-38
34. Hawkins DF, Elder MG. Human fertility control: theory and practice. London: Butterworth, 1979
35. London RS. The new era in oral contraception: pills containing gestodene, norgestimate and desogestrel. Obstet Gynecol Surv 1992; 47: 777-82
36. Fotherby K, Caldwell ADS. New progestogens in oral contraception. Contraception 1994; 49: 1-32
37. MacRae K, Kay C. Third generation oral contraceptive pills [editorial]. BMJ 1995; 311: 1112
38. WHO Collaborative Study. Cardiovascular disease and use of oral contraceptives. Bull World Health Organ 1989; 67: 417-23
39. Drife J. Complications of oral contraception. In: Filshie M, Guillebaud J, editors. Contraception: science and practice. London: Butterworth, 1989: 39-51
40. Gerstman BB, Piper JM, Tomita DK, et al. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. Am J Epidemiol 1991; 133: 32-7
41. World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. Lancet 1995; 346: 1575-82
42. World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. Lancet 1995; 346: 1582-8
43. Jick H, Jick SS, Gurewich V, et al. Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet 1995 Dec 16; 346: 1589-93
44. Spitzer WO, Lewis MA, Heinemann LA, et al. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. BMJ 1996; 312: 83-8
45. Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, et al. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995; 346: 1593-6
46. Guillebaud J. Advising women on which pill to take. BMJ 1995; 311: 1111-2
47. Weiss N. Third-generation oral contraceptives: how risky? [commentary]. Lancet 1995; 346: 1570
48. Rawlins M. Combined oral contraceptives and thromboembolism [letter]. BMJ 1995; 311: 1232
49. Farmer RDT, Williams TJ, Simpson EL, et al. Effect of 1995 pill scare on rates of venous thromboembolism among women taking combined oral contraceptives: analysis of General Practice Research Database. BMJ 2000; 321: 477-9
50. Smith R. Editorial footnote. BMJ 2000; 321: 1172
51. Vandenbroucke JP, Rosing J, Bloemenkamp KWM, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001; 344: 1527-35
52. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ 2001; 323: 131-4
53. Skegg DCG. Third generation oral contraceptives. BMJ 2000; 321: 190-1
54. Poulter NR. Risk of fatal pulmonary embolism with oral contraceptives [commentary]. Lancet 2000; 355: 2088
55. Faculty of Family Planning and Reproductive Health Care, Royal College of Obstetricians and Gynaecologists. First prescription of combined oral contraception: recommendations for clinical practice. Br J Fam Plann 2000; 26: 27-38
56. Mayor S. Department of Health changes advice on third generation pills [news item]. BMJ 1999; 318: 1026
57. British National Formulary. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2001
58. Parkin L, Skegg DCG, Wilson M, et al. Oral contraceptives and fatal pulmonary embolism. Lancet 2000; 355: 2133-4

59. Lewis G, editor. Why mothers die 1997-99. Fifth report of the confidential enquiries into maternal deaths in the UK. London: RCOG Press, 2001
60. Hannaford P. Science is not a dispassionate activity [letter]. BMJ 2000; 320: 382
61. Seligsohn U, Lubetsky A. Thrombophilia. N Engl J Med 2001; 345: 697-9
62. Grody WW, Griffin JH, Taylor AK, et al. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med 2001; 3: 139-48
63. Cosmi B, Legnani C, Bernardi F, et al. Value of family history, in identifying women at risk of venous thromboembolism during oral contraception: observational study. BMJ 2001; 322: 1024-5
64. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001; 344: 1222-31
65. Caplin N, Edelman L. Thrombophilia. N Engl J Med 2001; 345: 697-9
66. World Bank. Safe motherhood and the World Bank. Lessons from 10 years of experience. Washington DC: World Bank, 1999
67. Potts DM, Crane SF. Contraceptive delivery in the developing world. Br Med Bull 1993; 49: 27-39
68. Grubb GS. Women's perceptions of the safety of the pill: a survey in eight developing countries. J Biosoc Sci 1987; 19: 313-21

Correspondence and offprints: Professor *James Drife*, School of Medicine, Department of Obstetrics and Gynaecology Level D, Clarendon Wing, University of Leeds, Belmont Grove, Leeds, LS2 9NS, UK.
E-mail: j.o.drife@leeds.ac.uk