Balancing risks and benefits of oral contraception

We publish in this issue an authoritative and timely opinion on the effects of third-generation oral contraceptives on the incidence of venous thromboembolism (VTE) and acute myocardial infarction (AMI) among users (Spitzer, 1997). The author is a highly experienced and leading epidemiologist in the field, and his conclusions are disturbing. He details what seems to be serious misinterpretations of epidemiological data by certain regulatory authorities, especially in the UK. Serious social consequences were set in train in many countries as a result of their public pronouncements questioning the safety of third-generation, as compared with second-generation progestagens in oral contraceptives (OCs). Coping with the situation that emerged from the ‘non-epidemic’, to use his term, has raised totally new matters which urgently need clarification. These are concerned with decision-taking and public relations. Unless these matters are resolved, society may face further rounds of unnecessary abortions, discontinued use of a highly safe group of OCs, perhaps many unwanted pregnancies and apparently unnecessary crises in public confidence.

Epidemiology is a far-from-easy subject, especially when statistical parameters such as odds ratios reach low levels, as in datasets comparing the safety of OCs. Interpretations demand a high awareness of the effects of bias and confounders that can mislead deductions drawn from a too-simple analysis of available statistical evidence. Expert advice is essential to enable realistic conclusions to be reached when doubts arise about the correct interpretation of new data.

Balanced interpretations are only possible after the passage of time, and we have today some advantages of hindsight concerning the events of two years ago. The role of regulatory authorities is made more difficult when experts disagree, which may still be the case today as we await publication of further studies which may add new aspects to this particular field. Perhaps some clarification is emerging about certain aspects of epidemiological analyses. The effects of confounders and biases such as preferential prescribing, duration of use effects and prudent doctor bias in conducting and interpreting trials on OCs, are well described by Spitzer (1997) and we have no need to reiterate them here. Yet disagreements between analysts on the relative risks of second- and third-generation progestagens might be as great today as they were two years ago (Farmer and Lawrenson, 1997; Poulter et al., 1997; Vandebroucke et al., 1997). Firmer conclusions about safety can be drawn from preliminary abstracts published this year. These report similar rates of absolute incidence, morbidity and mortality for AMI and VTE in users of second- and third-generation progestagens after adjustment for duration of use, and an enhanced safety of third-generation OCs with respect to AMI (Lidegaard et al., 1997). These studies were performed on the entire Danish population, which reduces referral bias. On the other hand, Helmerhorst and his colleagues (1997) still draw attention to the greater proven safety of second-generation OCs and do not recommend third-generation OCs for first-time users. They write ‘biases cannot devalue the conclusion that the increased risk of VTE in especially first-time and younger users of third-generation OCs is highly likely’. Committees dealing with public safety also face non-epidemiological problems, such as insufficient biological evidence on the actions of new progestagens, and recent reminders that diagnoses of VTE are incorrect more than half the time (Farmer and Lawrenson, 1997).

It is essential to recognize the enormous responsibility placed on regulatory authorities when a potential threat to public health emerges. Nevertheless, it is difficult to comprehend the reasons for those hasty decisions made in some nations. Regulatory authorities in other countries did not follow suit. Decisions to issue public warnings were criticized intensely at the time by leading epidemiologists, including Dr Spitzer, who had contributed their data and analyses to the overall results. Now, two years later, the net effect of the public statements appears to have been very damaging overall. Would the same decision have been taken in retrospect? Maintaining contraceptive use would have benefited some women by reducing their risk of AMI (a more threatening condition not discussed in any depth two years ago), and through the many other advantages of OCs. The fear of a slightly higher risk of VTE in other women, which might have been confirmed by future studies, clearly outweighed the dangers of third-generation OCs can be widely corrected in public confidence. The social implications are even wider than this, since misleading information can impair the wider distribution of OCs as a means of family planning. The last thing needed at present is any back-tracking on the rewards of the brilliant scientific, clinical and epidemiological research that has produced one of the world’s most efficient, safe and self-controlled forms of contraception. If a mistake was made in 1995, we hope that those early assumptions about the dangers of third-generation OCs can be widely corrected in the media and elsewhere. We are not sanguine about the prospects of proving or disproving an earlier error.

The means of taking and distributing decisions that can affect the lives of so many people must be closely examined. In Britain, we witnessed over many years some astonishingly complacent statements from government ministers about the dangers of contracting CJD from eating beef. What are we to do now about future decisions on OCs or any other matters affecting reproductive health? We believe that one thing is clear: we need more epidemiology, not less, even though our
clinical colleagues often have to cope with a bewildering set of statistics and mathematics before advising their patients (Cohen, 1996; Walters, 1996). Highly-trained epidemiologists, statisticians and meta-analysts are more and more relevant to medical research and public affairs when data has to be interpreted correctly and placed quickly in a social perspective. This new form of interpretive science must be mastered, as urgent biological data on the effects of steroids on physiological processes are obtained. OCs are not alone as a source of unresolved public conflicts. A consensus panel of the US National Institute of Health ran into similar difficulties in a statement questioning whether the benefits of routine mammography outweighed its risks (Culliton, 1997). Some of her phrases sound highly familiar: ‘...as public health policy this makes sense, but as public policy it was a disaster’, and ‘...in the face of uncertainty it is quite reasonable to recommend that individuals make their own choices’.

A full appreciation of the risks of third-generation OCs has yet to emerge. In the meantime, two sections of society appear to have been harmed. Many women have felt compelled to take what may be unnecessary decisions about their personal life. In the current state of epidemiological turmoil, even a public apology seems unwarranted. Then there are the huge financial risks for pharmaceutical companies and the disastrous falls in their sales of new-generation OCs. Will the pharmaceutical industry accept the situation as part of their immense commercial risk? Or will their huge losses of sales and customer confidence jeopardize their continued involvement in research on new OCs? If so, we shall all be losers. Perhaps the rule should be to maintain public silence about safety when concern is not unanimous and let patients consult their GPs, especially in view of the highly unpredictable responses of society over the safety of OCs. This will not be an easy decision for committees acting in good faith on matters of public safety.

References