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The pill and venous thromboembolism: a disarray of several layers of debate

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In the transient period that we are waiting for the full report of the independent Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives [World Health Organization (WHO), 1997], many are anxious to present their view on the third generation oral contraceptives debate. In the overwhelming publication waves so far, different layers of debate can be distinguished, which may hamper a balanced view on the subject.

The issues in the scientific debate are clear. Since 1961, the history of oral contraceptives and venous thromboembolism (VTE) has known of several acmes: involvement of a oestrogens in the development of VTE, the interaction between an inheritable coagulation disorder (Factor V Leiden) and oral contraceptive use, and the recent finding that gestagens are also engaged in the ontogenesis of VTE. Although the last observation has been criticized – some epidemiologists are carrying the criticism so far as to jeopardize the core of their own profession's knowledge – the independent WHO Scientific Committee, having the disposal of all available information, confirmed its existence as demonstrated in the four original studies (WHO, 1995, Jick *et al.*, 1995; Bloemenkamp *et al.*, Spitzer *et al.*, 1996). While a biological explanation of the phenomenon that steroids may evoke a process leading to VTE has been lacking since the early 1960s, the epidemiological findings of the 1990s have opened the way towards a beginning of a mechanistic explanation. Resistance to activated protein C (APC) as an effect of oral contraceptives, also reported in the original test for APC resistance (Østerud *et al.*, 1994; Meinardi *et al.*, 1997; Lowe *et al.*, 1997) is an encouraging first step in our understanding.

Despite the thrilling scientific progress on this matter, the finding that some gestagens carry more of an extra risk of VTE than others, leads to debates on the prescription of oral contraceptives – a situation we experienced earlier with the increased risk of VTE in women using high-dose oestrogens and more recently with carriers of Factor V Leiden (Vandenbroucke *et al.*, 1996). Some commentators are minimizing the risk of VTE in oral contraceptive users by admonishing the public that the absolute risk is negligible. Claiming that 'two times a low absolute risk of VTE remains a low absolute risk' is a reaction that does not consider the existence of highly effective alternatives for third generation pills. In younger women, VTE rather than myocardial infarction, has made the major contribution to mortality. On that point, we can say that second generation (levonorgestrel containing) products bear no disadvantage over third generation (desogestrel and gestodene containing) formulations; rather the contrary. Moreover, and not only for developing countries, economical reasons may play a role in making a wise choice between a new and more expensive drug and the one we have trusted for a long time. Since we know that the risk of VTE is highest in the first year of use, second generation pills are the first choice for first time users (Helmerhorst *et al.*, 1997). If results on small subgroups do confirm that third generation pills do raise the risk of myocardial infarction to a lesser degree then previously reported, then these preparations may have a place on a our prescription list as an interesting option for the slightly older woman who wants to continue using low dose combined preparations, say, after age 35 or 40 years.

The way in which the media have reacted to the advice from the drug regulatory authorities on the third generation pill findings since October 1995 is another level of debate, apparently attracting much attention from commentators (e.g. Mills, 1997; Benagiano, 1998). Perhaps it is recommendable to ask independent scholars from other disciplines, for example sociologists, to clarify the several reasons for this reaction from our collective societal unconsciousness. A disapproval of the conduct of the authorities, or at least the media reaction to it, is nearly always accompanied in these commentaries by some disregard for the scientific debate. It has been even suggested that the four original publications were not in the public's interest, insinuating that scientific debates cannot be held in scientific media. However, scientists have the duty to publish their data, scientific journals have the responsibility to inform the scientific community, and readers of scientific journals may react on publications. Of course, we will not shy away from the debate about how one should inform the public as optimally as possible about health issues. However, this pivotal and urgent problem is no reason to distract scientists from their work which can generate data to inform professionals and indirectly the public about the balance between doing more good than harm. The publication of the full WHO report will be an important step towards a balanced scientific debate.

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Learning from the past: an essential need

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Two and a half years after the events in the autumn of 1995 which created the most recent pill scare, (Mills, 1997) and (Benagiano, 1998) point out accurately that it is time to learn from the past. It is also argued that scientific consensus should be reached before far-reaching and rash decisions are taken on the basis of controversial epidemiological data. This, indeed, is the bottom line of the recent events that have led to confusion, anxiety and loss of confidence in a contraceptive method that has changed society.

There has been a lack of scientific consensus from the very moment that the epidemiological data were first discussed in 1995, illustrated by opposing views which were expressed in the correspondence sections of medical journals. Since the publication of the first three epidemiological studies on this issue there has been, however, a continuing emergence of new data which have provided a better insight in the unexpected initial findings.

Benagiano refers to a Scientific Group meeting of the World Health Organization (WHO) which arrived at more balanced conclusions than expressed before by the same group, including a crucial statement that for current users of combined oral contraceptives 'the risk is probably higher in the first year of use and declines thereafter'. Because of their more recent introduction, newer oral contraceptives have generally been used for a shorter duration. This, together with a reduction of the risk of venous thromboembolism (VTE) with increasing duration of use, formed the basis for one of the most important distorting factors in the initial three studies (Kaper, 1996; Rosenberg *et al.*, 1996). New epidemiological studies and a re-analysis of one of the 1995 studies have taken the increased knowledge on this and other distorting factors on board in order to make more appropriate adjustments for these confounders (Spitzer, 1997).

In a recent review, Spitzer cites the results of these studies and analysis, all of which have observed identical risks of VTE in users of second and third generation oral contraceptives after closer adjustment and/or matching for essential confounders, such as duration of use and age. All new data support the currently prevailing opinion that the initial three studies of 1995 were not able to sufficiently correct for essential distorting factors.

Now that the confusion is being replaced by a growing scientific consensus, which indicates that second and third generation oral contraceptives are associated with identical risks of VTE, it is essential that the lessons from the past are learned. Premature actions by health authorities and subsequent alarmist media attention based on unexpected, unpublished, partly unfinished, potentially biased and implausible epidemiological data, should be prevented at all cost in the future.

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