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DEBATE – continued

Venous thromboembolism and the pill

The WHO technical report on cardiovascular disease and steroid hormone contraception: state-of-the-art

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Cardiovascular disease is the most frequently occurring major side-effect of steroid contraception. The World Health Organization (WHO) report on cardiovascular disease and steroid hormone contraception (WHO, 1998) gives us a well documented state-of-the-art review of the evidence. The aim of the independent Scientific Group convened by WHO was 'to review current scientific data on cardiovascular disease and use of steroid contraception, to identify risk factors which may predict, for individual women, an increased risk of cardiovascular effects with use of different hormonal contraceptives, and to assess whether the various compositions of combined oral contraceptives have different risk profiles for cardiovascular disease'.

Published and unpublished data were gathered, described and discussed. Clinical, epidemiological and basic investigators, various organizations in the field of cardiovascular disease and steroid hormone contraception, major manufacturers of hormonal contraceptives, as well as representatives of drug regulatory authorities had the opportunity to communicate with the Scientific Group. All participants had access to background papers, unpublished data and the draft report. The scientific background papers have been jointly published in the March 1998 issue of *Contraception*. Three clinical cardiovascular entities were highlighted: acute myocardial infarction (AMI), stroke, and venous thromboembolism (VTE).

Venous thromboembolism

Since venous thromboembolism has been the subject of major attention recently (Benagiano, 1998; Cohen, 1998; Helmerhorst *et al.*, 1998; Kapar, 1998; Leader, 1998; Spitzer, 1998), we will firstly consider the conclusions on this subject, and then balance them with the conclusions regarding AMI and stroke.

Risk of VTE in combined oral contraceptive (COC) users is 3–6 times that in non-users. After discontinuation, the risk diminishes quickly to that in non-users. This is no news so far (Helmerhorst *et al.*, 1997). Also the Scientific Group accepts the gradually emerging data that risk is highest in the first year of use. What is new, is their conclusion that the risk of VTE is not related to the dose of oestrogen in preparations containing <50 μg ethinyloestradiol. The Scientific Group reconfirms the finding that COCs containing desogestrel (DSG) or gestodene (GSD) 'probably carry a small risk of VTE beyond that attributable to COCs containing levonorgestrel (LNG)'. This conclusion rests upon the discussion of the recently published and unpublished studies in the report, and upon the scientific background paper by Walker (1998). DSG and GSD are representatives of third generation progestins, derivatives of the second generation progestin LNG. Second generation progestins have been coupled with lower doses of ethinyloestradiol (mostly 30 μg); all third generation progestins are combined with ≤30 μg ethinyloestradiol. The empirical observation that the risk of VTE is not diminished further when the dose of oestrogen in preparations is <50 μg ethinyloestradiol might also be due in part to the increased risk of third generation progestins which are always combined with lower doses of ethinyloestradiol. Norgestimate (NGM) is difficult to classify because it is partially metabolized to LNG and partially to other intermediates. Conclusions for NGM cannot be drawn because of the insufficient availability of data, which hopefully will be generated in the near future. The absolute risk of VTE for women using COC is low but rises with increasing age, with obesity, recent surgery and some forms of thrombophilia (Factor V Leiden, protein C and antithrombin deficiency).

Acute myocardial infarction

What we all know, but can hardly change, is the habit of smoking, which is a major risk factor in arterial disease. Meirik (1998a) concludes 'that for all women, regardless of age, the risk of arterial cardiovascular disease attributable to smoking is larger than that ascribable to COC use'. Women who use COCs, who refrain from smoking, who have a normal blood pressure, and who are not suffering from diabetes mellitus do not have an increased risk of AMI, regardless of their age. This conclusion by the Scientific Group is not new, but should be emphasized again: selective prescribing might explain low AMI frequency in countries with well developed health care systems where some form of screening for arterial risk factors takes place before prescription. Duration and past COC use are not related with an increased risk of AMI. The latter observation points to an acute effect of COCs, which is unlikely to be mediated by lipids. The claim that third generation pills have a lower risk of AMI relative to second generation preparations could not be substantiated on the basis

of available studies. However, we must await for several studies that are in the process of analysis. The studies may support the relationship between the intermediate endpoints, low density lipoproteins (LDL) and high density lipoproteins (HDL) levels and, separately, a lower risk of AMI. In this respect, the Scientific Group warns of misinterpretation when comparisons of cases and controls are made between studies rather than within the same study, as differences in screening and diagnostic procedures will be minimal within the same study (see also Vandenbroucke *et al.*, 1997).

Stroke

Risk of ischaemic (cerebral infarction caused by occlusion of an artery or rarely a vein) or haemorrhagic (caused by an arterial rupture) stroke associated with COC has decreased during the history of COC. Still, a 1.5-fold risk of ischaemic stroke is found in non-smoking, normotensive COC users relative to non-users; and older women may have some elevated risk of haemorrhagic stroke if they use COC. Duration of use has no extra effect. Ethinyloestradiol dose is positively correlated with ischaemic stroke. As soon as use of the pill has been discontinued, the risk disappears. Increased risk of cerebral venous sinus thrombosis (a very rare condition) also exists with COC, in particular in users of third-generation formulations (de Bruijn *et al.*, 1998).

Biological plausibility

Since the first case history of Jordan (1961) on the relationship between COC and VTE, clinicians and scientists are searching for biological understanding why COCs in some women cause VTE. 'Integrated models of disrupted vascular function' are now replacing conventional distinctions between 'atherogenesis' and 'thrombosis'. Hereditary defects in the clotting system, which may underlie at least one-third of idiopathic VTE in Caucasian women, may interact with steroid-induced changes in lipid metabolism, haemostasis, vascular wall and humoral regulators, e.g. insulin and the renin–angiotensin system. According to the Scientific Group, there is no reason to exclude a causal relationship or to minimize the importance of epidemiological data, in the absence of knowledge of the biological cause of cardiovascular disease. This is especially true in the study of side-effects, in which it is unlikely that a mechanism is presupposed as the side-effect is unexpected. Moreover, several interesting leads regarding an acquired activated protein C-resistance (resulting in a diminished anticlotting activity) mediated by COCs, might offer the beginning of an explanation. The effect of COCs on anticlotting activity in the blood has been found by different researchers through the now classic test for APC-resistance (Helmerhorst *et al.*, 1998).

Balancing risks

The small increase in risk of cardiovascular disease must be balanced against the very high contraceptive efficacy of COCs. This obvious statement does not stand alone. 'The very large number of women using COCs throughout the world means that even modest elevations in risk have the potential to affect a large number of women' (WHO, 1998). VTE is the commonest cardiovascular event among COC users. Although the incidence of mortality is low among the youngest group, death due to VTE is relatively higher than due to AMI. Considering the three cardiovascular diseases, the available data and balancing pros and cons (Farley *et al.*, 1998), the Scientific Group speculates that mortality among older women (>35 years) who smoke and use third generation preparations is lower than in women using second generation COCs. For healthy, first-time users, second generation COCs seem to remain the first choice of prescription; and this advice can be extended to all non-smoking women and to smoking women aged <35 years. Since risk of cardiovascular disease among COC users is increased by hypertension, the Scientific Group sees the benefit of blood pressure measurement. Increased attention to cardiovascular risk factors such as hypertension and smoking 'can achieve a greater reduction in cardiovascular mortality than switching from second to third generation oral contraceptives' (Farley *et al.*, 1998).

Progestogen-only pills (POPs)

Unfortunately, available data to demonstrate a relation between POPs and VTE, or between POP and stroke are insufficient. Data from an unpublished WHO study found no increase in risk of AMI among current POP users compared with non-users.

Criticism of the report

In a period of evidence based medicine, one may wonder why the Scientific Group composed a narrative instead of a systematic review. So far, systematic reviews are mainly based on randomized controlled trials (RCT) for which quality control by rather straightforward 'rule of thumb' exists. Although progress can be seen in making guidelines for quality control of non-randomized controlled trials, final judgement of observational research is a process in which several levels of argument and counterargument should be integrated. Cardiovascular disease as a side-effect of steroid contraception is mainly investigated in a non-randomized fashion. 'The low incidence of cardiovascular disease in women of reproductive age has precluded the conducting of RCTs with clinical endpoints' (Hannaford, 1998). We agree with Hannaford (1998) that 'observational cohort and case-control studies have provided the most useful clinical information about the main cardiovascular effects of steroid contraceptives'. Other critiques (Spitzer, 1997) that were published before the report was available (WHO, 1997) were rebutted by Meirik (1998b) and Jick *et al.* (1998).

Recommendations

More data on factors predisposing for cardiovascular diseases among women using COC must be generated. Differences in risk factors between developing and developed countries, e.g.

in screening for blood pressure may show us how steroids influence the incidence of cardiovascular disease

The major benefit of the recent third generation contraceptive debate is an intensification of research on the remarkable interaction between genetic and environmental factors which cause and perhaps prevent cardiovascular diseases We have gained knowledge that will help all parties to develop even safer contraceptives in the future

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