

General Information

Cardiovascular disease and hormonal contraceptives: latest results

Steroid hormone contraceptives have been available since the 1960s and are estimated to be used by more than 100 million women throughout the world, of which 93 million are users of the combined oral contraceptive pills. Over the years, there have been successive changes in the composition and use of these preparations, most notably with regard to the combined products. These have had their hormone content reduced, multiphasic formulations have been developed, and different progestogens introduced. Additionally, women using this contraceptive method are now likely to be selected and monitored more carefully than in the past and they also tend to be younger. Oral and injectable progestogen-only preparations are used less frequently, and mostly by women for whom combined oral contraceptives are contraindicated.

Reports linking combined oral contraceptives with venous and arterial thrombotic events began to appear soon after their introduction. Since then, a large number of epidemiological studies have investigated whether users of combined oral contraceptives are at increased risk of cardiovascular disease. Information is now available from several large, recent studies, including the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, on the effects of the more recently introduced combined oral contraceptives.

Current scientific data on use of steroid hormone contraception as it relates to risk of myocardial infarction, ischaemic and haemorrhagic stroke, and venous thromboembolic disease was recently reviewed at a meeting of a WHO Scientific Group in Geneva arranged by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Development. The Scientific Group also studied the incidence of cardiovascular disease among women of reproductive age in general. The combined effect of risk factors for cardiovascular disease and use of hormonal contraceptives, and whether different compositions of combined oral contraceptives have different cardiovascular risk profiles, were also discussed.

The Scientific Group was composed of experts from different regions of the world, including researchers involved in recent large-scale studies on cardiovascular disease and hormonal contraception. During its discussions, the Group relied, to a large extent, on published literature — although it was also provided with unpublished information from several new studies. In view of the major changes that have taken place over time in the hormonal content of combined oral contraceptives and in prescribing patterns, the Group paid particular attention to studies using data collected after 1980. General comments concerning cardiovascular disease and hormonal contraception were also presented.

The Scientific Group was also able to draw on the expertise provided by the principal investigators of several recent studies, on researchers working on new data, and representatives of the United Nations Population Fund (UNFPA) and the International Planned Parenthood Federation (IPPF). Members of the drug regulatory authorities of Germany, the United Kingdom, the United States of America, and the European Union, as well as representatives of the major pharmaceutical companies marketing steroid contraceptives, were also invited.

The Group concluded that the incidence and mortality rates of all cardiovascular diseases in women of reproductive age, including stroke, myocardial infarction, and venous thromboembolism, are very low. Any additional cardiovascular disease incidence or mortality attributable to oral contraceptives is very small if the users do not smoke and do not have other cardiovascular risk factors. In women who do not smoke, who have their blood pressure checked regularly, and who do not have hypertension or diabetes, the relative risk of myocardial infarction in users of combined oral contraceptives is not increased regardless of age. Neither is there an increase in the risk of myocardial infarction in past users of combined oral contraceptives. These conclusions seem to apply equally in developed and developing countries. On the other hand, the available data do not allow a conclusion to be made that the risk of myocardial infarction in users of low-dose combined oral contraceptives is related to progestogen type. The suggestion that gestodene

or desogestrel-containing low-dose combined oral contraceptives may carry a lower risk of myocardial infarction compared with low-dose formulations containing levonorgestrel remains to be substantiated.

In women who do not smoke, have their blood pressure checked, and do not have hypertension, the relative risk of ischaemic stroke is increased by about 1.5 fold in current users of combined oral contraceptives in comparison with past users. There is no increase in the relative risk of ischaemic stroke with increasing duration of use of combined oral contraceptives. Neither is there an increase in the relative risk of ischaemic stroke in women who have ceased use of oral contraceptives. These conclusions seem to apply equally in developed and developing countries. There are, however, insufficient data to allow a conclusion to be made about whether the risk of ischaemic stroke is related to progestogen type in combined oral contraceptives.

In women under 35 years of age who do not smoke and who do not have hypertension, the relative risk of haemorrhagic stroke associated with oral contraceptive use is not increased. There is no increase in the risk of haemorrhagic stroke with increasing duration of use and there is no increase in the relative risk of haemorrhagic stroke in women who have previously used oral contraceptives. The incidence of haemorrhagic stroke increases with age, and current use of combined oral contraceptives appears to magnify this effect of ageing. These conclusions seem to apply equally in developed and developing countries.

The Scientific Group noted that the already elevated risks of myocardial infarction and stroke among women who smoke or who have high blood pressure, are further increased if such women use combined oral contraceptives.

Recently, there has been much publicity about the risk of venous thromboembolic disease associated with use of oral contraceptives, and in particular about a possible excess risk associated with use of the more recently introduced pills containing new progestogens (desogestrel, gestodene, or norgestimate). In this respect, the Scientific Group concluded that current users of combined oral contraceptives have a low absolute risk of venous thromboembolism which is none the less three- to sixfold higher than that in non-users. The risk is probably highest in the first year of use and declines thereafter, but persists until discontinuation.

Combined oral contraceptive preparations containing desogestrel and gestodene probably carry a small risk of venous thromboembolism beyond that attributable to combined oral contraceptives containing levonorgestrel. There are insufficient data to draw conclusions with regard to combined oral contraceptives containing norgestimate.

Although the Scientific Group conclusions focused on the cardiovascular effects of steroid hormone contraceptives, other considerations also influence women and couples when they make their choice of contraceptive method. These factors include real and perceived risks and benefits associated with each method of contraception. Social, economic, psychological and cultural factors are also important. The conclusions and recommendations of the Scientific Group should not, therefore, be taken in isolation. Instead, they should form part of the detailed information needed when making informed choices in this important area of family planning and preventive health care.

Reference: World Health Organization. WHO Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraceptives: Summary of Conclusions. *Weekly Epidemiological Record*, 72: 361–363 (1997). The complete report of the Scientific Group will be published as WHO Technical Report Series, No. 877, 1998.

Current availability of vaccines for diarrhoeal diseases and typhoid

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The control of diarrhoeal diseases and typhoid fever is still an important public health challenge for many developing countries. It is estimated that these diseases are responsible for the death of 2.5 million children each year and one virus — rotavirus — and four bacteria — *Salmonella typhi*, shigella, *Escherichia coli* ETEC, and *Vibrio cholerae* — are held responsible. Preventive measures based on sound hygiene, such as purifying water supplies, improving water delivery, and providing sanitary installations and sewage systems (1), are efficient long-term means of control of bacteria. However, the high incidence of rotavirus infection in children from developed countries with high standards of hygiene suggests that the incidence of rotavirus infection needs to be addressed by other means.

Although it is crucial to introduce and sustain preventive measures, it is also recognized that implementation is difficult in some developing countries or in particularly difficult situations such as following natural disasters or in refugee camps. Efforts to develop effective treatment and vaccines against the pathogens responsible for diarrhoeal diseases and typhoid have consequently been identified as urgent. Improved vaccines are currently available for cholera and typhoid, and a vaccine against rotavirus has recently been developed and submitted for licensing. Development of vaccines is also continually hampered by the problem of emergence of antibiotic-resistant bacterial strains (2).

Cholera vaccines

New oral cholera vaccines have rendered the previous parenteral killed vaccine outdated. The new vaccines are more effective, and able to confer higher and longer-lasting protection. Until 1992, *V. cholerae* serogroup O1 was the only organism implicated in epidemics. However, a further serogroup, labelled O139, was later identified during outbreaks in India and Bangladesh (3–5). The currently available vaccine is based on O1 serogroup, and a vaccine for the O139 serogroup is awaiting licensing review.

Of the two oral vaccines now on the market, the first is composed of B subunit cholera toxin added to *V. cholerae* strains (classical and El Tor) killed by formalin or heat. This vaccine elicits antibodies against B subunit, avoiding fixation of the toxin on GM1 ganglioside receptors and against LPS (lipopolysaccharide). It is given in low oral doses one week apart and provides protection seven days after the second dose. Evaluated in endemic areas, it provided 86% protection during six months after vaccination in all age groups (6, 7). After three years of follow up, vaccinees over 5 years of age were still protected at a level of 72%. However, in children less than five years of age, the level of protection had decreased six months after the second dose. This vaccine is produced in Sweden and is licensed in Argentina, El Salvador, Guatemala, Honduras, Nicaragua, Norway, Peru and Sweden. Because of a similarity between B subunit structure and the heat labile toxin (LT) of *E. coli*, this vaccine confers protection for three months against diarrhoea due to *E. coli* ETEC at a level of 67%.

The second cholera vaccine is a live oral attenuated vaccine administered in one dose. Protective efficacy is obtained seven days later. This vaccine

is produced from a pathogenic strain in which a deletion mutation has been introduced leading to a loss of capacity to produce pathogenic A subunit of the cholera toxin (8). Given in one oral dose, it provided excellent protection (96%) in volunteers after challenge with a pathogenic cholera strain (9). This vaccine is produced in Switzerland and is licensed in Argentina, Canada, Finland, Peru, Philippines and Switzerland. It is also expected to be licensed in the USA and other European countries in the near future.

Typhoid vaccine

The parenteral, killed whole-cell vaccine is used less and less and is being phased out because of its side effects. Two new, safe and effective vaccines are currently licensed which are based either on defined subunit antigens or on whole-cell live attenuated bacteria. One is composed of Vi capsular polysaccharide of *Salmonella typhi* given in one single dose parenterally, and elicits protection seven days after injection (10, 11). The protective efficacy provided is still more than 50% five years after a single dose and ten years after immunization, 58% of vaccinees are still carrying more than 1 mg/ml of IgG antibodies in their blood (12). This vaccine is licensed in more than 63 countries throughout the world. The other vaccine is composed of a live attenuated mutant *Salmonella typhi* Ty21a given by oral route in three doses two days apart (13). The protective efficacy, evaluated seven years after the last dose, was 67% in endemic areas (14).

Rotavirus vaccine

It is important to underscore that rotavirus is not transmitted by food or water and that the incidence of rotavirus infections in developing countries is similar to developed countries (15). This means that the recommendations for the control of bacterial diarrhoeal disease do not apply to rotavirus.

A live oral vaccine has recently been produced and submitted for licensing (16). This is a tetravalent reassortant (animal strain with human strain) vaccine (17) given in three doses one month apart in a small volume (2.5 ml). It provided 85% protection against severe diarrhoea due to rotavirus — it is this kind which causes death in infants — and 56% protection against less severe diarrhoea due to rotavirus (18, 19). The WHO Vaccine Research and Development Unit placed rotavirus vaccine high in its priorities. During a recent meeting in Geneva, recommendations on rotavirus vaccine use in developing countries were adopted (15).

Conclusion

Given the considerable progress made in the development of vaccines against diarrhoeal diseases and typhoid fever, the future prevention of these diseases may be possible. Vaccines could be used as a complementary action for such time as it takes countries to implement adequate food-handling and water sanitation measures. Because multiple enteric infections often occur simultaneously, it would seem logical that future strategies will be directed to the development of comprehensive combined vaccination against the major infections – rotavirus, shigella, salmonella, ETEC and cholera.

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