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International Consensus on Combination Oral Contraceptives and Cardiovascular Disease

Since the introduction of combined oral contraceptives (COCs) in the 1960s, the large amount of data collected about them worldwide has resulted in COCs becoming one of the most researched groups of pharmacological agents. COCs are now used by more than 90 million women in the world, and have brought underappreciated health benefits to many of these women. Women benefit not only from the efficacy of COCs in preventing unwanted pregnancy, but also from the prevention of anemia, dysmenorrhea, and heavy periods,[1] and from a significant reduction in certain gynecological cancers (e.g. endometrial and ovarian cancer[2]).

From a public health point of view, COCs remain a much needed and safe method of contraception. With the recognition of some COC-related side effects the reduction in dose and change in formulation over the years have combined to reduce the overall incidence of these side effects. Cardiovascular disease (CVD) remains a rare side effect that has attracted renewed attention with recent epidemiological studies. Since 1995, clinical and regulatory decision making in some countries have been driven by emerging data. Controversies about the nature and extent of CVD risk resulted in many new studies and analysesthat now clarify the relative and absolute risks. These findings are briefly reviewed and synthesized in this consensus paper.

At the meeting of June 20-21, 1998 in Goteburg, Sweden, several investigators came forward to present the results of their studies to the International Federation of Fertility Societies (IFFS) panel. All of the studies were observational in design, that is, the women and their doctors had made their own decisions as to whether to take COCs, as well as which COC to use. Experimental studies of COC use and CVDs have not been done, and may never be possible because of the extreme rarity of these conditions.

The Studies

The World Health Organization (WHO) carried out a case-control study from 1989-1993 in 21 centers globally; analyses were reported separately for developing and developed countries.[3] The study reports on a total of 1,143 cases of venous thromboembolism (VTE) (710 cases from developing countries and 433 cases from Europe). These cases were compared to 2,998 controls who were primarily selected from hospitalized women. Only the center in Oxford, United Kingdom included community-based controls. In addition, WHO reported results regarding 198 women in Europe and 168 women in developing countries with acute myocardial infarction (AMI) and 697 women with ischemic stroke (CVA). Information from all study subjects was obtained with in-person interviews.[4~6]

The Transnational case-control study was carried out between 1993-1995 in Europe, with analyses primarily of data from Germany and the United Kingdom. This study included 471 women with VTE and 182 women with AMI. There were 1,772 controls selected from both the hospital and the general population (community controls). Information in this case was also obtained using in-person interviews.[7,8]

The Danish national case-control study started in 1994-1995; case accrual is planned to

continue for a total of five years, and thus is ongoing. Thus far, analyses of 375 cases of VTE have been reported. Information from the 1,041 controls and the 375 cases was obtained through self-administered postal questionnaires. Cases of cerebrothrombotic attacks (including stroke and transient ischemic attacks) and AMI are also being evaluated.[9,10]

The first General Practitioner Research Database (GPRD) analysis was carried out using computerized information from 365 general practices in the United Kingdom. During the period 1991-1994, there were 80 women who experienced a nonfatal VTE among 238,130 women using oral contraceptives containing levonorgestrel (LNG), desogestrel (DSG), or gestodene (GSD). Information from the database was available for all of the women; for more detailed analyses, information was obtained from the original medical records for all cases and a random sample of the other women. This study addressed nonfatal VTE, and an additional analysis evaluated 15 cases of unexpected sudden death in the cohort.[11]

A subsequent, larger GPRD analysis was carried out using expanded information between 1989-1997 including all reproductive-age women (not just those using COCs); there were 328 cases of VTE in the analysis.[12] There have also been analyses from another United Kingdom database called Mediplus that included 83 cases of VTE among 235,000 reproductive-age women. These analyses have also been limited to VTE, not AMI or CVA.[13]

Study Variations

These studies varied slightly in their definition of OC exposure and the diseases. For instance, in the interview studies subjects could tell the interviewer whether they were taking an OC at the time of the attack and the type of OC. In the database studies, the investigators relied on information recorded about prescriptions that had been filled within three months before the attack. In general, to be accepted as a case of VTE a woman had to be hospitalized and had to receive anticoagulant medication for a period of time. The requirement for diagnostic tests varied. Level of certainty about the diagnosis of venous thrombosis may always be disputed; all of the studies used rigorous and acceptable definitions, but the spectrum of disease included in each study most likely differed.

The description of each study above includes the largest number of subjects reported; however, the number of subjects included and published in specific analyses was invariably smaller. In particular, those analyses that compared users of particular types of COCs had far fewer subjects than the number of subjects in the study as a whole. It is difficult to directly compare the results of the studies because the analyses use different reference points, different age boundaries and different disease definitions.

The analyses also differ with regard to definition of age bands used for comparing the cases to controls - some studies looking at five-year bands, and other looking at exact age. In addition, the studies do not take into account the duration of COC use in the same way, including the issue of whether women are new starters, ongoing users, switchers, or whether they are still nulliparous. In general, as the analyses of the studies have included more of these variables, the initial differences between OC formulations in their results have been markedly reduced. In recent studies, where these factors have been included in the analyses, there has been little difference found in risk between the new and the older pills.

Earlier studies of COCs and thrombosis focused on the impact of estrogen dose. We have already learned that by reducing estrogen doses the frequency of thrombosis declined.[14] The new studies that have generated so much controversy relate the frequency of thrombosis to the type of progestagen. Such comparisons between OCs are difficult because there are so

many different formulations. Investigators have sought to simplify the analysis of data regarding the many different types of progestin included in COC formulations by combining products into groups.

The current main focus is the so-called third-generation and second-generation pills which may also be described as "newer" and "older" pills. This practice has caused great confusion. There are no intrinsic biologic justifications for these groupings. Specific product comparisons may be better, but can be imprecise or even impossible because of the small number of subjects using a particular product in a particular study. The main definitions have included products containing levonorgestrel and sometimes noresthisterone (with less than 50 μg of estrogen) as "second generation" and the products containing gestodene or desogestrel have been defined as "third generation". Different studies have placed norgestimate-containing pills in either of these categories. Monophasic and multiphasic products have usually been combined. Although combining products has been efficient on statistical grounds, no strict biochemical, metabolic, or clinical criteria have ever been agreed upon to classify these products. Defining COCs as newer or older may have just as much validity and more explanatory power than other approaches.[15] The groupings have caused a lot of confusion, and may undermine some of the validity of the conclusions from individual studies that have caused the most recent pill scare.

We disapprove of the approach that combines and compares products in groups. In all of the previous epidemiological studies of the risks and benefits of COCs product comparisons have not been made. For the purpose of evaluating VTE and other risks, if comparisons must be made, grouped comparisons should only be defined by a compelling biological justification. The recent definitions of "second-generation and third-generation pills" do not have any biological justification.

A review of the laboratory studies evaluating the effects of COCs with regard to coagulation factors was presented at the meeting. There have been many such laboratory studies, often assessing single products. Because laboratory techniques have continued to evolve, drawing comparisons between studies performed over the years with different laboratory techniques is complicated. However, the main conclusion is that there is no obvious or even subtle difference between the various newer and older pills with regard to their effects on clotting.[16] This means that we have no plausible biological explanation for the differences that have been found in the observational epidemiological studies.

To assess the impact of oral contraceptives on cardiovascular disease in women's lives we need to use estimates of incidence, mortality, and disability for each of the conditions. There are differences between countries in the incidence rates and mortality. These differences may be due to environmental and genetic factors as well as differences in diagnosing the diseases. A concise review follows and more detailed treatments are available elsewhere.[17,18]

Venous Thromboembolism (VTE)

This condition includes deep vein thrombophlebitis and pulmonary embolus, both of which may be difficult to diagnose. The overall incidence of primary VTE is less than 10 cases per 100,000 women per year in women aged 15-44. About 1%~3% of recognized cases of VTE result in death. About 5% of cases have an associated long term disability.[9,10,17] The main risk factors for primary VTE are age, obesity, and family history. There is only a small increase of primary VTE with age, although VTE secondary to trauma, surgery, immobilization, and cancer increases with age resulting from the increase in those conditions. Obesity may increase the risk of VTE twofold to fourfold compared to nonobese women. A

close family history of primary VTE may indicate an inherited disorder of coagulation which causes an increased risk in family members with the same abnormality; in those cases, OC use is associated with a risk of about 30 cases per 100,000 women per year. Pregnancy is a major risk factor for VTE in women who are not using contraceptives; VTE may occur in 60-80 out of 100,000 pregnant or puerperal women. While varicose veins may be a risk factor for superficial phlebitis, there is no general agreement that they are a risk factor for deep vein thrombosis.

Studies have long indicated an increase of VTE among women using COCs. Older studies showed a relationship between estrogen dose and the degree of risk; however, the newest studies, including women using sub-50 μg of estrogen pills, do not show any beneficial effect of further reductions in estrogen dose. Contrary to any biological reasoning, some of the recent results seem to indicate that women using COCs with 20 μg of estrogen experienced a higher risk of VTE than women using COCs with more estrogen. For progestin type, some of the recent studies[3,11] found a difference between OCs containing older and newer progestins. Such difference is no longer present in the latest studies and analysis when the data are controlled for age and duration of OC use.[7,9,12,13]

There are various indications of genetic susceptibility to VTE such as APC resistance, and other as yet unidentified predispositions. At present, there is no known single marker that will be generally useful. For any marker, the positive predictive value is low. By relying on genetic markers of susceptibility, one would withhold the pill from many women who are at low absolute risk of VTE. The best way today to recognize susceptibility is to determine personal and family history. If a woman is susceptible, manifestation (VTE) may occur early in pill use, as a result that woman will stop the pill-conversely, women on the pill longer may be a low risk (nonsusceptible) population. Proof of predisposition by genetic testing is not able to completely predict clinical thrombosis.

Cerebro Vascular Accidents

CVA includes both thrombotic and hemorrhagic stroke, and some investigators have included transient ischemic attacks in their analyses. The incidence of these events in women of reproductive age ranges from about 1 case per 100,000 women per year among the youngest women to about 10 cases per 100,000 women aged 40-44 per year. Overall, stroke is about as uncommon as VTE in the young women, and is more common in women over 40 years. As is true for all of the CVDs there is considerable variability in incidence rates according to region and method of ascertainment of the condition. The mortality subsequent to CVA is as high as 25% and there is substantial morbidity among long-term survivors. The main identifiable causes for CVA are cigarette smoking and hypertension. Based on recent studies, the risk of stroke associated with COCs continues to decrease with further decreases in estrogen dose, and the risk is not related to the type of progestin.[5,6,10]

Acute Myocardial Infarction (AMI)

The incidence of AMI is extremely rare among young reproductive age women, and then increases more dramatically with age than do the other conditions. The incidence is less than 1 case per 100,000 young reproductive-age women, and increases to 30 cases per 100,000 among women aged 40-44. Eighty percent of cases in young women are attributable to cigarette smoking. It is not possible to calculate with any precision the risk of AMI in young female nonsmokers because there are so few cases in this group. The short-term mortality subsequent to AMI is about 30%, and there is substantial long-term morbidity. Aside from ci-

garette smoking the main risk factors are hypertension and diabetes mellitus.

As has been shown in both old and new epidemiological studies, the risks of AMI in COC users are interwoven with the risks associated with smoking. It appears that low-dose pills containing gestodene and desogestrel do not increase risk of AMI. Other low-estrogen dose COCs may increase risk of AMI.[4,8]

Cardiovascular Events - A Quantitative Summary

Table 1 quantifies the incidence of myocardial infarction, stroke, and venous thromboembolism by OC use in young women. This presentation is deliberately simplified and brief for use by clinicians who may lack sufficient time to read and evaluate more detailed and rigorous epidemiological studies.[17,18] Because the frequency of cardiovascular diseases varies with age, the estimates are given separately for women aged 20-24 who are in the peak OC-using age group and for women aged 40-44 who are in that part of the reproductive age group that has the highest risk of experiencing cardiovascular disorders. The estimated incidence rates among OC nonusers that were selected for presentation in the table each represent a midpoint of many reported incidence rates from around the world. These incidence rates may not apply perfectly to any particular population, but they do provide an excellent indication of the general magnitude of these problems among young women. The incidence rates that are presented for women using "old" or "new" oral contraceptives were calculated by identifying a representative relative risk for each outcome for OC users, and then multiplying that relative risk by the incidence rate among nonusers. A total for each group of women is also provided to indicate

Table 1. Incidence of cardiovascular disease by condition, by age and by current OC use. Rates per 100,000 women per year

Ages 20-24	OC use		
	None	"Old"*	"New"*
Myocardial infarction	0.2	0.5	0.2
Ischemic Stroke	1.0	2.5	2.5
Hemor. Stroke	2.0	2.0	2.0
Venous thromboembolism	3.0	9.6	7.7-21.1
Total CVD (range**)	6.2	14.6	11.4-25.8
Ages 40-44	**OC use**		
	None	"Old"*	"New"*
Myocardial infarction	30.0	78.0	30.0
Ischemic Stroke	2.0	5.0	5.0
Hemor. Stroke	7.0	14.0	14.0
Venous thromboembolism	6.0	19.2	15.4-42.2
Total CVD (range**)	45.0	127.0	64.4-91.2

All OCs containing 50 μg of estrogen or less. Most contained 35 μg or less. "Old" refers to OCs containing levonorgestrel or sometimes norethisterone. "New"* refers to OCs containing desogestrel or gestodene.
**The range is derived from the published low and high relative risks for the association of each condition with the use of OCs

the incidence of all CVD in that group. The relative risks that were selected represent a middle value from the many recent publications about these associations. This approach ignores the statistical imprecision of the individual relative risks, and also ignores the differences in size, quality, and analytic approaches between studies, as well as individual results. To partly address these limitations, a range was calculated for the VTE incidence for the users of newer OCs; these ranges were calculated by multiplying the incidence rates for nonusers by the lowest relative risks reported for each of the outcomes in the two subgroups, and similarly for the highest relative risks, and then summing these results to produce the ranges that are given.

There are several clear lessons to be learned from the table. First, all of the CVD outcomes are exceedingly rare in women aged 20-24 whether they use OCs or not. Differences seen between the older and newer OCs in total CVD derive from differences in the incidence of VTE. A clear explanation for these differences has not yet emerged, although some investigators have reported that the differences disappear when the total duration of OC use is considered in the analyses,[9,15] when analyses take account of age by year,[12,13] or when secular effects of marketing new pills are considered.[19] At ages 40-44 the incidence of CVD is much higher, particularly because of the steep increases in the incidence of AMI. In this age group the total incidence appears lower in the users of the newer OCs because of lower occurrence of AMI in this group. There is not yet a clear explanation for this apparent difference between the newer and older pills. The quantitative impact of other risk factors on CVD is beyond the scope of this presentation; however, smoking, hypertension, and obesity all have a greater impact on CVD risk than use of low-dose COCs.

Table 2 presents estimates of the CVD mortality seen in young women with or without COC use. The calculations here were made

Table 2. Mortality from cardiovascular disease by condition, by age, and by current OC use. Rates per 100,000 women per year

Ages 15-24	OC use		
	None	"Old"*	"New"*
Myocardial infarction	0.1	0.3	0.1
Stroke (all)	1.0	1.5	1.5
Venous thromboembolism	0.1	0.3	0.2-0.7
Total CVD mortality (range**)	1.2	2.1	1.8-2.3
Ages 35-44	OC use		
	None	"Old"*	"New"*
Myocardial infarction	3.0	7.8	3.0
Stroke (all)	6.0	12.0	12.0
Venous thromboembolism	0.2	0.6	0.5-2.8
Total CVD mortality (range**)	9.2	20.4	15.5-17.8

All OCs containing 50 μg of estrogen or less. Most contained 35 μg or less. "Old" refers to OCs containing levonorgestrel or sometimes norethisterone. "New"* refers to OCs containing desogestrel or gestodene.
**The range is derived from the published low and high relative risks for the association of each condition with the use of OCs

similarly to those in Table 1. However, there is an important additional limitation: Nearly all of the studies that have evaluated the effect of OC use on CVD have included only cases who survived their cardiovascular event. The effect of OCs on the risk of having a survivable case or a fatal case of CVD may be different; the numbers presented in Table 2 assume that the effects of OCs are unrelated to disease severity. In addition, the baseline mortality rates come from different information sources and are given for slightly different age groups than in Table 1. Mortality from CVD is substantially lower than incidence, particularly for VTE. Otherwise the relationships shown are similar to those for incidence because they were calculated using the same assumptions.

Public Health Issues

Because of the adverse publicity that followed release of the new studies of oral contraceptives and cardiovascular disease that began in October 1995, a significant number of young women have stopped using oral contraceptives. Abortion rates have risen in the United Kingdom as have conceptions and deliveries. Similar changes occurred in Norway and they, too, were temporally linked to adverse publicity about OCs. This publicity caused a crisis of confidence, especially among young women, in countries where regulatory authorities imposed restrictions on the use of new OCs (Norway, United Kingdom, Germany), but not in countries where no restrictions were applied (Finland, Denmark, France). A short-term consequence has been that many OC users stopped their pills because of fear of side effects and they did not substitute any other birth control method. Predictably there has been an increase in abortions and unwanted pregnancies. A long-term consequence could be that many young women will never start using OCs because of a perceived exaggerated danger associated with this contraception method. This is supported by data showing that three years after the most recent pill scare, OC prescriptions are still down 30% in the United Kingdom, particularly among the youngest women.

In the past, drug regulatory authorities have reacted with caution, promoted a scientific debate, and invariably did not act with haste as new studies were added to our knowledge base. Unfortunately, what characterized the last "pill scare" was that regulatory action occurred even before the evidence had been submitted to peer review.

To avoid unwanted panic in the future, a number of precautions need to be taken:

1. Editors must exercise care to ensure that the way data are presented does not lend itself to undue alarm.

2. Regulatory authorities should be aware that the public health consequences of restricting a drug or combination of drugs that are in widespread use is very different from the effect of delaying approval of a new drug. Consequently, they must first evaluate whether the observed risk is a true phenomenon. They must evaluate how the observed risk changes the risk/benefit profile of the drug combination (in light of possible specific beneficial effects of those drugs). They must also carefully establish the public health consequences of both restricting and not restricting the drug as well as the long-term consequences of the reported adverse effect. While doing this, regulatory authorities must inform the medical profession of the reported findings, the action they are taking to assess the situation, and how to properly inform users. Only after all such evaluation has been completed is regulatory action appropriated.

Conclusion - Clinical Evaluation and Recommendations

After intensive and careful review, the evaluating committee of the IFFS identifies no rea-

son to advise a selective prescribing of OCs containing different progestins on the basis of their effects on CVD. The usual precautions in selecting appropriate candidates for OCs need to be applied.[20] Women who smoke, who are obese, hypertensive, diabetic, or who have a personal or family history of thrombosis will need to have an individualized assessment of their risks of CVD, whether or not they use oral contraceptives. Only after this assessment can they make informed contraceptive decisions and modify their risk factors however possible. Because of testing limitations, specialized testing for coagulation disorders is not encouraged. If the parent or sibling of a prospective OC user has experienced a primary (idiopathic) venous thrombosis, one may consider testing; however, these screening tests have a poor positive predictive value, and may exclude many women from OC use who would use them safely.

Despite the continuing debate on the rare CV effects of COCs, the overall health benefits of COCs strongly outweigh the risks, provided an assessment is completed of all prospective users. Any currently available low-dose estrogen OCs, regardless of which progestin they contain, are more beneficial for a woman's short-and long-term health than the alternative, which may mean using either less effective or no contraception. Women who are considering taking COCs should have access to the updated research that confirms their safety.

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