Health consequences of combined oral contraceptives

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During the past 40 years, combined oral contraceptives (COCs) have become a key component of modern fertility regulation programmes. Today, an estimated 100 million women throughout the world use this method of contraception. With such wide-spread usage, it is perhaps not surprising that COCs have been the subject of extensive medical research.

When considering evidence about postulated risks and benefits associated with COC use, it is important to remember that:

1 Over the years there have been major changes in the composition of available preparations, as well as in the characteristics of women using COCs. This means that it can be difficult (if not impossible) to determine whether important temporal changes in risk have occurred because of product development or changes in the selection and monitoring of the typical user.

2 Epidemiological associations do not necessarily represent causal relationships. Alternative explanations (such as bias or confounding) might account for an apparent association between COC use and the development of disease. Observational studies, from which most safety data about COC use are derived, are prone to bias and confounding.

3 Many studies have had limited statistical power to detect differences between products that might exist. This problem is likely to occur whenever use of a particular preparation, or the background incidence of a particular disease, is low.

4 Epidemiological studies tend to concentrate on relative risks, calculated directly in cohort studies or estimated by the odds ratio in case-control studies. Interpretations about the clinical significance of these epidemiological measures require complimentary information about the background incidence of disease in the population being studied so that absolute risks can be estimated. A large relative risk applied to a rare disease still results in few women affected. Conversely, a small relative risk applied to a common disease results in many women being affected.

5 Care should be taken when extrapolating data from laboratory studies, or from populations that are very different to young healthy COC users (such
as middle-aged men). Particular caution is needed when considering possible biological mechanisms for COC effects.

6 Risks may be balanced by benefits.

In terms of public health importance, the most serious adverse effects of COC use would be those leading to an increased risk of vascular disease or cancer.

Vascular associations

Raised blood pressure

COCs have been found to raise the blood pressure of some women, even among those using preparations containing low doses of oestrogen (<50 μg) and newer progestogens (such as desogestrel and gestodene). The effect is usually modest and rarely crosses the threshold at which clinicians might diagnose hypertension. Whilst most of the change occurs within the first 6 months of use, blood pressure levels can increase further with prolonged duration of use. The effect is generally reversible once COCs are stopped, usually within a few months.

Venous thrombosis

Numerous studies have shown, with remarkable consistency, an increased risk of venous thrombosis among current users of COCs. None of the recent studies which compared COC users with non-users found a relative risk of less than two; most observed relative risks within a 3–6-fold range. The effect may be stronger during the first year of use before falling to a smaller, but still elevated, risk which continues until COCs are stopped. The risk of venous thrombosis declines rapidly once COCs are stopped, perhaps within 3 months.

Age, smoking or a history of varicose veins does not affect the risk of venous thrombosis among COC users. Obese users may have an enhanced risk, although the evidence is inconsistent. COC users with hereditary clotting disorders, such as factor V Leiden mutation, protein C, protein S or anti-thrombin deficiency have a substantially increased relative risk of venous thrombosis. The absolute risk, however, remains low even among women with coagulation defects; perhaps three extra cases of venous thrombosis per annum per 1000 users with factor V Leiden mutation compared with users without this defect. The low background risk of venous thrombosis in young women means that screening tests for clotting abnormalities have a very poor predictive
value. As a consequence, the high economic, social and other costs, argue against the routine screening of women for clotting deficiencies prior to their use of COCs.3,5

A number of studies since 1995 have reported a higher (about 2-fold) risk of venous thrombosis among users of low oestrogen-dose COCs containing desogestrel or gestodene than among users of similar preparations containing other progestogens, mainly levonorgestrel3,4. These unexpected results have been the subject of great debate, with some observers attributing all of the differences to study artefacts, such as bias or confounding. There have been, however, few empirical data to substantiate these arguments, leading a recent World Health Organization (WHO) Scientific Group to conclude that COCs containing desogestrel or gestodene probably carry a small risk of venous thrombosis beyond that attributable to COCs containing levonorgestrel3. The absolute risk, however, is small; annually, perhaps 25 additional cases of venous thrombosis per 100,000 users of COCs containing desogestrel or gestodene, compared with 10 extra cases per 100,000 users of products containing levonorgestrel (each group being compared with non-users).

Myocardial infarction

There has been less consistency in the results of studies examining the risk of myocardial infarction in COC users.3-4 Several recent studies have found significantly elevated overall risks among current COC users (about 5 times that of non-users)6-8, unlike several others9-11. The studies observing an increased risk did not find a relationship with duration of use, or any continuation of risk once COCs are stopped. The differences in risk estimates may be due to study design issues, or due to differences in the prevalence of risk factors such as smoking and hypertension among the populations studied. It has become increasing apparent that most (if not all) of the myocardial infarction risk is concentrated in COC users who also smoke, who have a history of hypertension, or who report not having had their blood pressure checked prior to the episode of current use.3,4. However, the absolute risk of myocardial infarction among current users remains very small, even in young women who smoke.3,4

One study has reported a significantly lower risk of myocardial infarction among users of low oestrogen-dose COCs containing desogestrel or gestodene than among users of other low-dose preparations7. This result, however, was based on small numbers, and other factors, such as differences in the checking of blood pressure among users of the different products, may explain the finding.12 Other studies have been unable to demonstrate differences between preparations6,11,13.
Ischaemic stroke

Studies of ischaemic stroke have found a fairly consistent pattern of increased risk among current users; most studies finding an overall 3–4-fold greater risk than that of non-users\(^3,4\). This risk is not affected by duration of use. There is no evidence of an increased risk in past users of COCs. Like myocardial infarction, the risk of ischaemic stroke among current users seems to be mainly (although perhaps not entirely) in women with other risk factors, such as smoking, hypertension or migraine\(^3,4\). Women in two studies who reported having their blood pressure checked prior to COC use had smaller risks than those who denied receiving this assessment\(^14,15\). The absolute risk of ischaemic stroke among COC users remains very low\(^3,4\). Data relating to the effects of specific COC formulations are too sparse to permit conclusions about possible differences in ischaemic stroke risk.

Haemorrhagic stroke

Current users of COCs appear to have only a modestly elevated risk of haemorrhagic stroke\(^3,4\). Thus, although all studies have reported relative risks of above one, none have been above two, and only one has reached statistical significance. Data from a large WHO study suggest that users aged less than 35 years, who do not smoke and who do not have hypertension probably do not have an increased risk of haemorrhagic stroke\(^16\). There is insufficient information to know whether there are important differences between COC preparations. However, given the low incidence of haemorrhagic stroke in young women, any differences will be of only marginal clinical importance.

Overall cardiovascular risk

It is important not to exaggerate the absolute risk of cardiovascular disease in COC users (Table 1). Most of the excess risk is due to venous thrombo-embolic events, very few of which are fatal (possibly 1–2%).

| Table 1 Estimated total number of venous thrombo-embolic, myocardial infarction and stroke events and deaths attributed to COC use in industrialised countries, per million woman years (from WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception) |
|---|---|---|---|
| | Ages (years) | 20–24 | 30–34 | 40–44 |
| Events in non-smoking users | | 67 58 | 97.34 | 183 50 |
| Events in smoking users | | 83 77 | 132 40 | 312 20 |
| Deaths in non-smoking users | | 2 06 | 3 31 | 21.46 |
| Deaths in smoking users | | 6 78 | 13 60 | 59.70 |
At all ages, the effects of smoking on cardiovascular risk are greater than those of COC use.

**Cancer associations**

**Ovarian cancer**

Nearly all of the studies examining the relationship between COC use and invasive epithelial ovarian cancer have found a lower risk among current or ever users. A beneficial effect on other types of ovarian tumour may also exist. Overall, the reduction is about 40–50%, an effect that gets stronger with longer periods of use. The substantial protection persists after COCs are stopped, although it is unclear for how long. Current data suggest that it is for at least 10 years. Most studies investigated the effects of older COCs which had higher hormonal contents than currently available formulations. Research is needed, therefore, to determine whether newer low oestrogen-dose preparations still protect against ovarian cancer.

**Endometrial cancer**

Virtually all of the studies investigating COC use and endometrial cancer have found a lower risk among current or ever users. Like ovarian cancer, the overall reduction in endometrial cancer risk is about 40–50%, with stronger effects among longer-term users. The protection persists after COCs are stopped, perhaps for 20 years or more. Most of the evidence relates to older, high oestrogen-dose COCs; comparatively little is know about the effects of currently available low-dose preparations on endometrial cancer risk.

**Cervical cancer**

There is uncertainty as to whether COCs affect the risk of cervical cancer. Most studies have investigated squamous intra-epithelial neoplasia, or its pre-invasive lesions, cervical dysplasia or carcinoma in situ. Although a number of studies have found an increased risk of all of these conditions among current users, there might be alternative explanations for these epidemiological associations.

In industrialised countries, most cases of cervical cancer are detected by Papanicalou smears. COC users are more likely than non-users to have a regular smear, partly because this service is often offered in comprehensive
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reproductive health programmes. The greater frequency of screening increases the chances of detecting pre-invasive disease in COC users. Without adequate statistical adjustment for screening history, studies of pre-invasive cervical disease tend to find an increased risk among current COC users. On the other hand, the greater opportunity to detect and, therefore, treat pre-invasive disease should result in COC users having a reduced risk of invasive cervical cancer. In this case, inadequate statistical adjustment for screening history tends to produce erroneously low risks of invasive disease among COC users.

Some studies have compared COC users with women using barrier methods of contraception (who have a reduced risk of cervical cancer), or with women using no contraception (who may be at increased risk). No study has been able to adjust fully for differences in the sexual history of women using different contraceptives. COC users may start having sexual intercourse at an earlier age, have more sexual partners and have partners who themselves have had more sexual partners, than women using other contraceptives. These life-style characteristics are themselves important risk factors for cervical cancer; failure to control for such confounding might explain an apparently increased risk of cervical cancer among COC users.

Recent studies have certainly tried to address many of these methodological difficulties, although the nature of the information required is such that it is probably impossible to conduct the perfect study. Well-conducted recent studies have found a modestly elevated overall risk among COC users; ranging between 1.3 and 2.2. Investigations of the less common adenocarcinoma of the cervix have also tended to find an increased risk among COC users. The risk of cervical cancer may be restricted to, or concentrated in, women who have used COCs for prolonged durations, perhaps for 5 years or more. It is unclear whether use at a crucial age, such as in the teens when the cervix is still developing, exaggerates any deleterious effects of COC use. The human papilloma virus (HPV) has an important role in cervical carcinogenesis. A growing body of evidence points towards an important interaction between COC use and HPV infection. For example, two studies found that COC users with a history of HPV infection had up to 6 times the risk of invasive cervical cancer as non-users with a similar history. There is no substantial evidence that COCs accelerate the progression of cervical abnormalities. Screening protocols for COC users, therefore, should be the same as those for all sexually active women.

breast cancer

Our understanding of the possible relationship between COC use and breast cancer has been advanced by the re-analysis of original data by the Collaborative Group on Hormonal Factors in Breast Cancer. This
re-analysis assembled 90% of the original data from studies conducted throughout the world with at least 100 cases of breast cancer; information relating to 53,297 women with breast cancer and 100,239 women without breast cancer. Published reports about the missing data suggest that their omission did not materially affect the results of the re-analysis.

COC users were found to have a small increased risk of breast cancer while using this method of contraception and during the first 10 years after stopping (Table 2). The excess risk disappeared by 10 years after stopping. Similar patterns of risk were found among women recruited to studies of different design, living in different countries, of different ethnic origin, reproductive history or family history of breast cancer, and using different COC formulations for varying lengths of time. There was a suggestion of a slightly enhanced risk of breast cancer among women who use COCs at an early age, although the effect was modest: the relative risk (RR) in women who used COCs before the age of 20 years was 1.22 (95% confidence interval, 1.17–1.26), 20–24 years at first use 1.04 (CI, 1.02–1.06), 25–29 years at first use 1.06 (CI, 1.03–1.08), 30–34 years at first use 1.06 (CI, 1.03–1.09), 35+ years at first use 1.11 (CI, 1.08–1.14).

The pattern of increased risk in current or recent users means that the absolute risk associated with COC use is highly dependent on the age at which COCs are stopped (Table 3). Thus, if women use and stop the pill at a young age, the excess risk will be minimal. For example, for every 10,000 women who use COCs for 5 years and who stop by the age of

| Table 2 | Relative risk of breast cancer in women during and after COC use, compared with non users (from Collaborative Group on Hormonal Factors in Breast Cancer and Hormonal Contraceptives) |
|-----------------------------------------------|
| Relative risk (95% confidence interval)        |
| Current users                                  | 1.24 (1.15–1.33) |
| 1–4 years after stopping                       | 1.16 (1.08–1.23) |
| 5–9 years after stopping                       | 1.07 (1.02–1.13) |
| 10+ years after stopping                       | 1.01 (0.96–1.05) |

| Table 3 | Cumulative risk of breast cancer in women who used COCs for 5 years and who were followed up for 10 years after stopping, compared with non-users of COCs (number of cases per 10,000 women; from Faculty of Family Planning and Reproductive Health) |
|-----------------------------------------------|
| Age while using COCs (years) | 15–20 | 20–25 | 25–30 | 30–35 | 35–40 | 40–45 |
| Age at end of follow-up (years) | 30 | 35 | 40 | 45 | 50 | 55 |

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<tr>
<th>Breast cancer risk (no. of cases)</th>
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<tr>
<td>Never-users</td>
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<td>Users (10 years after stopping)</td>
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<td>No. of extra cases of breast cancer</td>
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*British Medical Bulletin 2000, 56 (No 3)*
35 years, 10 extra cases of breast cancer will have accumulated by the age of 45 years. Intriguingly, COC users in the re-analysis tended to have less clinically advanced cancers than never-users, with less spread beyond the breast.

Possible explanations for the re-analysis' findings include detection bias among COC users, and biological effects of COCs on cancer growth and its tendency to metastasise.

**Other cancers**

Several studies conducted in countries with a low incidence of hepatitis have found an increased risk of hepatocellular carcinoma among COC users, principally among those who have used these preparations for 8 years or more. However, in these countries, the background incidence of this cancer is extremely low, so the absolute risk of a COC user developing hepatocellular carcinoma is also very small. Two studies in countries with a high prevalence of hepatitis have not found an association with COC use.

There is no robust evidence of an association between COC use and malignant melanoma, kidney cancer, gallbladder cancer or pituitary tumours. Studies of colorectal cancer have been inconclusive; none indicate an increased risk among COC users, some even suggest a beneficial effect.

**Other associations**

Initial concerns that COCs may be diabetogenic have not been substantiated. Early reports suggesting a higher incidence of gallbladder disease among COC users have been followed by evidence that COCs may accelerate the presentation of disease in women predisposed to it, rather than initiate its onset. Important associations between COC use and multiple sclerosis or liver disease have not been found. On the other hand, there is tentative evidence of an increased risk of ulcerative colitis and Crohn's disease among current, but not former, COC users.

Associations between genital tract infections and COC use are complex. Current users appear to have an increased risk of chlamydial infection in the lower genital tract but, paradoxically, a reduced risk in the upper genital tract. Evidence of protection against pelvic inflammatory disease caused by other sexually transmitted infections is contradictory. Uncertainty remains as to whether COCs affect transmission of the human immunodeficiency virus.

Studies examining the mental health effects of COCs need to disentangle problems which might be truly related to COC use from episodes in which the COC is a convenient scapegoat for other causes of psychological stress.
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(such as relationship difficulties). The Royal College of General Practitioners’ (RCGP) Oral Contraception Study observed a small increased risk of general practitioner-reported neurotic depression in current users (RR 1.35; CI, 1.30–1.40) and a modest decrease in former users (RR 0.88; CI, 0.84–0.92)\textsuperscript{28}. The incidence rates fell with increasing duration of use. Users of low oestrogen-dose (30 or 35 μg) preparations had the same rate of neurotic depression as non-users, approximately half that reported among users of high oestrogen dose (100+ μg) preparations. Both current and former users had a small increase in reported episodes of general practitioner-reported attempted suicide (RR 1.42; CI, 1.11–1.81 and RR 2.12; CI, 1.66–2.71, respectively). The rates of attempted suicide were not affected by duration of use or the oestrogen content of the COC. Selection biases and confounding could have accounted for these small elevations in risk. For example, compared with other women in the study, a larger proportion of women who later attempted suicide stopped their COC because they had ‘ceased to cohabit’. The Oxford/Family Planning Contraception Study, which reported on psychiatric illness resulting in referral to hospital, found little evidence of psychiatric problems among its COC users\textsuperscript{38}. At present, the data are not sufficiently robust to conclude that COCs cause psychiatric illness.

There is still contention about whether COCs offer protection against rheumatoid arthritis\textsuperscript{39}. Studies of the effects of COC use on bone mass have produced conflicting results; some suggesting a beneficial effect, others failing to demonstrate any effects. The two large British cohort studies have been unable to find a protective effect against fracture among ever users of COCs, although in both studies most of the data related to fractures occurring in premenopausal women\textsuperscript{40,41}. On the other hand, a Swedish case-control study observed a 25% reduction in hip fracture risk, mostly among those women who reported using oral contraceptives after the age of 40 years\textsuperscript{42}.

It is still unclear whether other non-contraceptive benefits found among users of older higher oestrogen dose COCs (such as a reduced risk of benign breast disease and functional ovarian cysts)\textsuperscript{34}, are also enjoyed by users of newer formulations.

**Overall balance of risks and benefits**

When deciding whether to use oral contraceptives, women need to know the balance between associated risks and benefits. Mortality data from large cohort studies show that, broadly, current users have a very small increased risk of dying from circulatory disease or cervical cancer, and a reduced risk of death from ovarian cancer\textsuperscript{43,44}. The effects, however, are confined to current (or in the RCGP study, current and recent – within 10
years) use. Hence, in the long-term, ever-users of COCs have the same similar risk of death as never-users\textsuperscript{43-45}.

Mortality data, however, could still mask important increases in the risk of serious, but non-fatal, diseases occurring among COC users. A recent analysis of data from the RCGP Oral Contraception Study, considered the risk of COC-related serious disease (defined as that caused by diseases which are often life-threatening and/or associated with long-term disability, and which has been found, or postulated, to be associated with COC use)\textsuperscript{46}. Compared with never-users, ever-users had a small increased risk of any serious disease (RR 1.17; CI, 1.09–1.25). The increase was seen only in younger women, compatible with an increased risk of cardiovascular disease among current users. Furthermore, the risk of serious disease appeared to be confined to women using older COCs containing 50 μg or more of oestrogen. Thus, both mortality and morbidity data indicate small increases in risk of serious disease during current use which do not persist after stopping, and no evidence of latent effects appearing later in life.

Conclusions

Forty years of extensive research has shown that COCs are very safe. Although users of currently available COCs have an increased risk of cardiovascular disease, the effects appear to be concentrated in women with recognised risk factors, principally smoking and hypertension. Even in these women, however, the absolute risk of experiencing an adverse effect is very small. Currently available COCs have been associated with an increased risk of cervical or localised breast cancer, although uncertainty remains as to whether a causal relationship exists. These effects may be offset by a reduced risk of ovarian and endometrial cancer. COC users wishing to maximise their safety, should avoid smoking or using this method of contraception when other cardiovascular risk factors exist, should participate in a cervical cancer screening programme and have their blood pressure checked to ensure that it is not raised.

Acknowledgements

Declaration of interest: the RCGP Centre for Primary Care Research and Epidemiology has received in the past unconditional grants from each of the COC manufacturers for its work. The author has been paid honoraria by all of the manufacturers for presentations at various meetings. The author was a paid consultant of the World Health Organization when he was rapporteur for a Scientific Group on cardiovascular disease and steroid hormone contraception.
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