

The risks and benefits of the combined oral contraceptive pill

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ABSTRACT The combined oral contraceptive pill has been used by an estimated 300 million women worldwide since it was first developed. In recent years it has been linked with both an increased risk of some forms of cancer and a protective effect against other cancers – leading to considerable confusion for women. In order to provide much-needed clarity, Dr Richard Russell and Mr Charles Kingsland provide an overview of the risks and benefits of the combined oral contraceptive pill.

KEYWORDS Breast cancer, combined oral contraceptive pill, COCP, oral contraception, ovarian cancer, risks and benefits of oral contraceptive pill

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The combined oral contraceptive (COC) pill is often credited with kick-starting the sexual revolution of the 1960s. Initially developed in the US and trialled in South America, the oral contraceptive pill remains an extremely effective reversible method of contraception, with a failure rate of 0.1–3/100 woman years (pearl index of 0.16). The pearl index is a standardised measure of contraceptive effectiveness, calculated using the number of unintentional pregnancies in 100 woman years of use (for example, 100 women using contraception for one year, or ten women for ten years). A lower pearl index represents a lower chance of unintentional pregnancy.

Having been used by an estimated 300 million women worldwide and currently being used by 100 million women, the COC pill's impact on public health, healthcare provision and healthcare cost is substantial. Although formulations and dosages have been modified over time, concerns for safety persist. Divergent perspectives have ranged from conferring a clean bill of health to proclaiming the pill the greatest iatrogenic risk to female health.

The contraceptive properties of the pill are irrefutable, and its use in the successful management of menstrual disorders and benign gynaecological conditions are far beyond the scope of this review article. Instead, we focus on the risks and benefits that have a significant impact on patient morbidity and mortality, as well as healthcare costs.

BENEFITS OF COMBINED ORAL CONTRACEPTION

Ovarian cancer

The association between the protective effect of the COC pill and ovarian cancer has long been established. A recent large study suggested that in high-income countries, ten years' use of the COC pill is estimated to reduce the incidence of ovarian cancer ($p < 0.0001$) before the age of 75 from 1.2 to 0.8 per 100 users, with a

reduction in mortality from 0.7 to 0.5 per 100 users.¹ That is to say for every 5,000 woman years of use, about two ovarian cancers and one death from the disease are prevented.

The protective effect of the pill becomes apparent after a short latency period and increases with duration of use, with each year of use conferring an estimated 5% reduction in risk. Women who take the COC pill for less than a year also have a reduced ovarian cancer risk (odds ratio, OR=0.45)² compared with non-users. In women who use it for longer, a persistent associated risk reduction of more than three decades following cessation of use is observed, although this effect seems to reduce over time since the last use.

The proportional risk reduction for ovarian epithelial cancers with COC pill use is 29% for individuals who stopped using the pill less than ten years ago; 19% for those who stopped between 10 and 19 years previously, and 15% for those who stopped 20 to 29 years previously.¹ Time since the first and last use modifies the association between COC pill use and ovarian cancers independently of the duration of use, with histological type being unaffected with the exception of mucinous tumours.

A recent report suggested that oral contraceptive use has already prevented 200,000 ovarian cancers and 100,000 deaths from the disease. Over the next few decades, the number of cancers prevented is expected to rise to at least 30,000 per year.¹

Endometrial cancer

Several epidemiological studies have observed a protective effect from endometrial cancer conferred by the use of the oral contraceptive pill, with this benefit persisting for more than 25 years.³ The majority of current COC preparations are potent enough to have a beneficial

influence, but it has been found that women with a lower body mass index (BMI) ($<22.1 \text{ kg/m}^2$) receive a greater protective effect than those with a higher BMI on formulations containing a low dose of progesterone.

Colorectal cancer

Following the publication of several studies regarding hormone replacement therapy, considerable interest has evolved regarding the role of exogenous hormones and bowel carcinogenesis. The use of the COC pill has been associated with a modest risk reduction of developing colorectal cancer (relative risk, $RR=0.72$),⁴ with a consistent effect on all tumour subsites within the rectum. However, no apparent correlation between the duration of use and benefit has been observed. The current evidence suggests some support for a potential role of COC pills in reducing the risk of colorectal cancer.

MORBIDITY AND MORTALITY

We are often complacent when observing trends in mortality and morbidity figures related to pregnancy in the developed world. Pregnancy, particularly when repeated and complicated, presents a significant risk to female health. Although good healthcare provision contains this risk to some degree, many developing countries are unable to provide the required standard of care. Every year, eight million women will come to harm as a result of pregnancy-related complications, and more than half a million of these women will die as a result. By contrast, the 2000–2002 Confidential Enquiry into Maternal and Child Health found a total of 261 deaths in the UK related either directly or indirectly to pregnancy. In sub-Saharan Africa, a woman's lifetime risk of dying related to pregnancy is one in 16, in comparison to one in 2,800 in the developed world.

Unsafe and often illegal abortions continue to be a leading cause of morbidity and mortality in developing countries, while many obstetric complications occur in pregnancies that are neither planned nor wanted. The introduction of the oral contraceptive pill has had a considerable positive effect on female health in the developed world: it is hard to imagine that it would not have a significant and dramatic effect were it more available in the developing world.

DISADVANTAGES OF THE ORAL CONTRACEPTIVE PILL

Breast cancer

A large cohort of studies have shown that women who have used the COC pill are associated with a marginally increased risk of breast cancer ($OR=1.15$).⁵ No strong associations in relation to age started, duration of use, time since first or last use or use related to pregnancy have been observed. This associated risk of developing breast cancer returns to the same level as women who have never used the pill within ten years of last use.

Recently published data sets from the Royal College of General Practitioners' Oral Contraceptive Study⁴ were at odds to this consensus finding, showing no apparent increased incidence of breast cancer with COC pill use. However, a collaborative reanalysis of this data demonstrated a 25% increased risk of breast cancer among its population in a remarkably short exposure of three years, leading to the adjustment of the original results so that they were more consistent with other data sets.

The Women's Environment, Cancer and Radiation Epidemiology (WECARE) study found that oral contraceptive use prior or subsequent to a diagnosis of unilateral breast tumour was not associated with the risk of developing asynchronous bilateral breast cancer. Furthermore, studies found neither a harmful or beneficial effect on breast cancer mortality. However, there has been a recent study suggesting that the use of high-dose oestradiol-containing preparations within five years prior to diagnosis may negatively affect survival, but study numbers were small.

There is no evidence that oral contraceptive use among women who carry the *BRCA1* or *BRCA2* genes confers any greater risk of breast cancer beyond its effect in the general population. However, the duration of COC pill use in relation to the timing of a first full-term pregnancy may increase the incidence of breast cancer in this patient population. (*BRCA1* and *BRCA2* are breast cancer susceptibility genes. The normal gene plays a role in repairing breaks in DNA, but mutations are thought to disable this repair mechanism, resulting in more DNA replication errors and resultant cancerous growth. People carrying a mutation in this gene are therefore at an increased risk of breast or ovarian cancer.)

Interestingly, a recent paper released from the Norwegian Women and Cancer Study has shown a significant increase in the incidence of breast cancer in women using hormone replacement therapy with a history of COC pill use, compared with women who have never used COC pills ($OR=1.67$). This may have a significant impact on post-menopausal breast cancer risks as the population of post-menopausal women who have used the pill increases.⁶

Cervical cancer

The International Agency for Research on Cancer classifies the COC pill as a cause of cervical cancer. Yet there has long been debate as to whether there is a direct causal association between the pill and the disease or an indirect effect relating to changes in sexual behaviour leading to an increase in exposure to carcinogens, primarily the human papillomavirus.

The International Collaboration of Epidemiological Studies of Cervical Cancer recently published results suggesting that, compared with women who have never used COC pills, there was an associated relative risk of

cervical cancer of 1.90⁷ in women who use or have previously used oral contraception. The risk has been shown to return to normal within ten years of stopping use. The recent Royal College of General Practitioners' collaborative study reported an adjusted risk of 2.73 and is consistent in trend with the World Health Organization's collaborative study.⁸

It is estimated that with ten years of COC pill use there is an increase of 7.3–8.3 cases per 1,000 population in less developed countries and an increase of 3.8–4.5 per 1,000 in developed countries.⁷ However, it is important to note that many studies have not contextualised the success of national screening programmes.

Venous thromboembolism

High-dose oestrogen preparations are associated with an increased risk of venous thromboembolism. It was previously thought that using low-dose preparations would substantially reduce this risk, but it has become apparent that the effect is also dependent on a complex interaction with the progestogen component. Second-generation COC pill use, compared with no use, shows a relative risk of 3.2; third-generation preparations demonstrate a relative risk of 4.8.

The incidence of venous thromboembolism in the general population is five per 100,000 per year. The incidence in second-generation COC pill users is 15 cases per year, and in third-generation COC pill users 25 cases per year. To put this risk into perspective, 60 cases per 100,000 occur in pregnancy each year. Despite this apparent association, however, a population screening approach for pro-coagulant conditions before prescribing the pill has been found to be neither feasible nor cost beneficial.

Cerebrovascular events

Ischaemic stroke occurs in five per 100,000 women per year in the population who are usually prescribed the pill. The use of COC pills is an independent risk factor for ischaemic stroke by a factor of 1.5. In patients who are also hypertensive the risk of stroke is doubled, and for patients who also smoke the risk is comparatively trebled.

The additional risk is apparent in the first six to 18 months but returns to normal after cessation, with no apparent benefit between second- and third-generation preparations. Patients who carry the Factor V Leiden mutation have a 13 times greater risk of ischaemic stroke on the contraceptive pill, while homocysteinuria patients have a nine-fold increase. There appears to be no increased risk of haemorrhagic stroke in patients under the age of 35 years without additional risk factors.

Cardiovascular disease

Oral contraceptive use is associated with an increased risk of myocardial infarction (RR=1.84). Many studies have attempted to attribute this as a direct causal effect. Several

recent studies have shown that in patients younger than 35 years with an uncomplicated medical history and no additional risk factors (i.e. hypertension, smoking or obesity) there is no significant additional risk. But in women older than 35 there appears to be a two- to three-fold increase in the incidence of cardiovascular events among those who take combined oral contraception.

Several studies have looked at the role of differing formulations of progesterone and their cardiovascular effect. Although there is no conclusive evidence, it has been suggested that there may be a reduced cardiovascular risk associated with third-generation preparations over second-generation pills. Interestingly, there seems to be no accumulative incidence of myocardial infarction in patients with a prothrombotic condition who use the oral contraceptive pill and those who do not use it.

Hepatic disease

A recent meta-analysis of oral contraceptive use failed to prove a statistical link between such use and hepatic cancer, despite discrepancies in the literature suggesting increases ranging from two to 20 times. It has been suggested that further studies are required that focus on the duration, intermittency and recency of oral contraceptive use.

Gallstones

There remains a strong correlation between oral contraceptive use and incidence of gallstones, although this is dependent on age. In patients aged 21–30 years using the COC pill, 39% have ultrasound evidence of gallstones, compared with 14% in non-users. In COC pill users aged 31–40 years, 40% have evidence of gallstone disease, compared with 18% in non-users. An inverse pattern has been seen in older patient groups, although this may be explained by the small number of patients using COC at this age.

CONCLUSION

Although widely criticised, the Royal College of General Practitioners' study observed a 12% overall reduction in cancer diagnosis in women taking the COC pill. However, as discussed, it took no account of the increase in breast cancer risk consistently observed in other studies. In spite of this, the important question remains: of the 30 to 40 deaths per year attributed to the use of the pill, how many would not have died if they were not prescribed combined oral contraception? Conversely, how many women would have died through conditions related to pregnancy and childbirth if they had not had access to this undeniably effective form of birth control? The design of a public health model becomes even more complex when adjusting for morbidity alongside mortality, particularly when considering the differing healthcare systems across the developing world. For now the crucial question looks likely to remain: is the oral contraceptive pill friend or foe?

KEY POINTS

- The use of the combined oral contraceptive (COC) pill is associated with a significant reduction in the incidence of ovarian and endometrial cancer.
- The risk of breast cancer increases with the length of use of the COC pill.
- Oral contraceptive use is a highly effective form of contraception.
- Venous thromboembolism increases in COC pill users and is influenced by the generation of pill and the constituent progesterone component.
- While evidence exists for an increased risk of thrombotic cerebrovascular disease, the cardiovascular risk is less clear.
- Gallstones occur more frequently in oral contraceptive pill users.

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