New Drugs, Old Drugs

Forty years of combined oral contraception: the evolution of a revolution

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Abstract

- The combined oral contraceptive (COC) pill has become an integral part of fertility choice in almost every country since its introduction in 1960 in the United States. It was the first contraceptive method to provide sexual freedom of choice for women through reliable personal, private control of fertility.
- Modern, very low-dose pills have maintained a high degree of contraceptive efficacy, but the margin for error in pill-taking appears much smaller. These COCs have a much lower incidence of side effects and serious complications than early high-dose COCs. Serious health risks from venous thromboembolism are rare, and not measurably higher for pills containing third-generation compared with earlier progestogens.
- Most women feel very well taking modern COCs, but myths about these drugs still abound.
- Most non-contraceptive health benefits of COCs are still not widely appreciated in spite of much evidence. Controversy still persists over the association between COC use and breast cancer. Although slightly more breast cancers are detected in current COC users (relative risk 1.24; 95% CI, 1.15-1.33), they are less advanced and less aggressive.
- Some women have pre-existing medical risk factors for COC use, and a detailed history for cardiovascular risk factors is one of the most important precautions.

One of the most far-reaching events of the 20th century occurred in May 1960 with the marketing of the first combined oral contraceptive (COC) in the United States. The trade name of this daily combination of mestranol (150 μg) and ethynodiol diacetate (10 mg) was Enovid (marketed by G D Searle), but the popular name had already been coined by Aldous Huxley in *Brave new world revisited* -- "the Pill".[1] Huxley had foreseen the infinite complexity of the role of the oral contraceptive in birth control: "It is not merely a problem in medicine, in chemistry, in biochemistry, in physiology; it is also a problem in sociology, in psychology, in theology, and in education."[2] He went on to discuss the difficulties of gaining population acceptance of such complex ideas: "The English Fabians, Beatrice and Sidney Webb, made an historical study of the average time it took for an idea which, at its first enunciation,

seemed revolutionary and revolting, to be taken for granted and to be acted upon by the whole population. They concluded that the average time is 28 years -- roughly the length of a generation. It is very difficult to persuade adults to change their points of view; they have to die off before a new generation can accept new ideas."[2] Although uptake of the Pill was rapid by a minority, acceptance and understanding by the majority took at least two to three decades. The Pill still faces opposition from some religious groups, and some controversies about its safety, albeit minor, persist.

A historical perspective

The possibility of contraception by use of reproductive hormones was first suggested by Ludwig Haberlandt, a physiologist at the University of Innsbruck, who first showed in the 1920s that injections of extracts of the corpus luteum would render rabbits infertile. With remarkable foresight he suggested that similar extracts might provide an ideal method of birth control in women.[3] The first clinical evidence of this came with the demonstration in 1940 that dysmenorrhoea could be relieved and ovulation simultaneously inhibited by administration of oestrogens.[4]

The development of modern hormonal contraception awaited synthesis of orally effective progestogens and oestrogens in the early 1950s. Pincus, Rock and Garcia then showed that ovulation in women could be suppressed with these compounds, which were first marketed in the US in 1957 for "menstrual regulation".[5] After further refinement and political lobbying, Enovid was marketed as a contraceptive in mid-1960.[5]

These early versions of the Pill contained much higher doses of both oestrogen and progestogen than were pharmacologically necessary to suppress ovulation, and the subsequent history of the Pill has been dominated by a progressive and continuing reduction in dosage. This has been driven by the desire to reduce perceived side effects and the requirements of pharmaceutical companies to have clearly marketable characteristics for their new preparations. The newest COCs in Australia have a daily oestrogen (ethinyloestradiol) content of 20 μg and a daily progestogen (levonorgestrel) content of 100 μg.[6] This total steroid intake is only 1.2% of the original daily intake, and the modern combinations are just as effective as contraceptives, although the margin for error in tablet-taking may be less. A brief profile of COCs is shown in Box 1.

Revolutions, evolutions and controversies

This pharmacological revolution has been accompanied by equally impressive social and sexual revolutions. Oral contraception provided women, for the very first time, with the possibility of reliably controlling their fertility. This gave women the opportunity to separate career choices from relationships and family planning, and to begin to compete with men in the career marketplace. It also gave them the opportunity to express their full sexuality with minimal risk of an unwanted pregnancy. Women were at last able to consider their opportunities on an equal basis to men. However, controversy has never been far away, and the Pill has probably engendered more articles, opinions, research studies and research investment than

any other single class of drug.

The progressive evolution of the Pill has, in addition to the dramatic reduction in dosage, been accompanied by an increasing awareness of a range of positive and negative attributes.

Contraceptive effects

COCs have extraordinarily high contraceptive reliability, if taken meticulously (including protection against ectopic pregnancies)[7] (E1) (see Box 2 for an explanation of level-of-evidence codes). However, there is a considerable difference between the very low contraceptive failure rates in clinical trials and the high failure rates in general use, caused by missed pills and factors which interfere with absorption.[9] Compliance can be optimised by good counselling, health education and effective packaging.

Non-contraceptive health benefits

COCs have remarkable non-contraceptive health benefits.[10] These include dramatic reductions in lifetime risk of ovarian and endometrial cancer,[11] and more variable reductions in colorectal cancer, benign breast disease,[12] uterine myomata (fibroids),[13] endometriosis,[14,15] acute episodes of pelvic inflammatory disease,[16] benign ovarian cysts,[12] toxic shock syndrome, androgenic skin conditions such as acne, and perhaps even rheumatoid arthritis and some thyroid diseases ($E3_2$). COCs greatly reduce the risk of infertility[17] (presumably through protection against acute pelvic inflammatory disease, ectopic pregnancy and endometriosis). They also appear to have a beneficial effect on bone density. In many of these conditions, benefits become more marked with longer duration of COC use.

In most women, COCs are also able to provide amazingly effective control of menstrual cycle symptoms,[10,12] such as menorrhagia (E2), dysmenorrhoea (E1), premenstrual syndrome (E1) and perimenstrual symptoms ($E3_2$) (eg, migraine, epilepsy, depression, toxic shock syndrome, and diarrhoea) and mid-cycle pain ($E3_2$). COCs can be used to treat these menstrual symptoms and, sometimes, the symptoms of endometriosis, uterine myomata, recurrent ovarian cysts and adenomyosis. Decreased menstrual blood loss reduces iron-deficiency anaemia (E1).

COCs are not as effective in preventing transmission of sexually transmitted diseases (STDs) as in preventing pregnancy. Although they reduce the risk of acute upper genital tract pelvic inflammatory disease ($E3_2$),[16] they do not prevent cervical colonisation, and those at risk of encountering STDs are best advised to use condoms as well as COCs.

Adverse effects

Side effects are still poorly understood by the general public, who appear to believe long-standing myths about COCs. Several well executed, randomised, double-blind, placebo studies have shown that the incidence of so-called "minor" side effects differs little between the placebo group and the active COC-taking group (E1).[18,19] In modern double-blind clinical trials, the incidence of these so-called side effects is almost always quite high in women taking placebo (E2), and this seems to mirror preconceived expectations.

The only side effects which have slightly higher incidence in the COC group are mild nausea (in early cycles), breast tenderness, chloasma and occasional mild effects on mood and sexual function. Contrary to popular belief, weight change does not differ between COC users and control subjects ($E3_2$). For most women, feelings of well-being are usually greater when taking the Pill. For the few women who do experience minor adverse effects, it usually means that the particular preparation does not suit them. They may do well with a different preparation or may sometimes need to consider an alternative contraceptive.

Of more importance is the incidence of potentially serious complications. The main serious, albeit rare, complication is venous thromboembolism, which has a spontaneous incidence of 1-2 per 10 000 women per year. Incidence increases to 3-4 per 10 000 women per year in COC users,[20] much less than originally described, because of the reduction in hormone dosage and better identification of women with risk factors. The 1995 "scare" about increased risk of venous thromboembolism with COCs containing third-generation progestogens has been largely discounted by substantial subsequent epidemiological work identifying biases and risk factors in the original studies.[2] Many women who develop venous thromboembolism while using COCs have evidence of an inheritable thrombophilia, and there does appear to be a significant adverse interaction between the thrombophilias and COC use ($E3_2$). This complex and ongoing debate was recently well summarised.[21]

For many years, it has been recognised that cardiovascular diseases such as myocardial infarction and stroke are exacerbated by COC use, but considerable research has demonstrated that this risk is almost entirely confined to women who smoke cigarettes and those with hypertension ($E3_2$).[22,23] Women using Pills containing third-generation progestogens may actually have a reduced risk of acute myocardial infarction ($E3_2$).[24] Certain liver conditions may be exacerbated in predisposed individuals (eg, obstetric cholestasis and congenital hepatic enzyme disorders such as Dubin-Johnson syndrome).

Breast cancer is one of the most emotive conditions in our cancer-phobic society, and the media have publicised scientific articles that suggest a possible increase in risk of breast cancer in COC users. The largest epidemiological study ever undertaken in the field of reproduction was a thorough reanalysis of 54 epidemiological studies of the relationship between COC and breast cancer.[25] This did indeed show that more breast cancers were detected in current COC users than in control women, and that the relative risk was 1.24 (95% CI, 1.15-1.33). However, the tumours in COC users were clinically less advanced and less aggressive, and the relative risk had disappeared within a few years of stopping COC use. There is no evidence that COCs cause breast cancer, but they may have a subtle modulating effect on the rate of tumour growth. The important clinical messages are that all women are at some risk of breast cancer, and that appropriate screening techniques should be undertaken depending on age and other risk factors.

There are a number of other rare associations with COC use, including a significant

increase in benign hepatic adenomas ($E3_2$).[26] COCs may also be a weak cofactor for cervical cancer, but this is uncertain because of the difficulty of adequately controlling for sexual risk factors ($E3_2$).[27]

Conclusions Modern oral contraceptives are remarkably effective and safe drugs for long-term use by women without cardiovascular risk factors. The World Health Organization and others have developed a series of evidence-based guidelines to assess medical eligibility criteria for initiating and continuing use of COCs and other contraceptive methods.[28,29] This evidence suggests that there are only two prerequisites for the safe provision of COCs:

- a careful personal and family medical history, with particular attention to risk factors for venous and arterial cardiovascular disease; and
- an accurate blood pressure measurement.

To this we would generally add an annual review with blood pressure measurement, breast check and pelvic examination with a cervical smear every second year.

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1: Profile of combined oral contraceptives

Action: Combined oral contraceptives (COCs) act predominantly at a hypothalamic level to block the cyclical release of gonadotropin-releasing hormone and prevent follicular development and ovulation. Secondary actions on the corpus luteum, endometrium and cervical secretions may contribute.

Dosage: This is based on the daily ethinyloestradiol content, which varies from 20μg to 50μg in current Australian COCs. The oestrogen is balanced by an appropriate dosage of one of six progestogens in a variety of formulations known as monophasic, biphasic or triphasic.

Tablet-taking: Most COC packages are 28-day (every day) bubble-pack designs containing seven inactive or placebo tablets, designed to assist meticulous daily tablet-taking (at about the same time each day), with an exact seven-day break between successive cycles of active tablets.

Starting: Most packs are designed to begin tablet-taking in the placebo section on Day 1 of the last normal menstrual period. Most experts recommend condom use during the first 10-14 days of initial COC use in case of breakthrough ovulation. However, if "active" tablets are taken from Day 1, then full contraceptive action begins immediately.

Metabolism: Peak plasma levels are achieved in 1-2 hours and a gradual decline occurs over the next 36 hours or so. Metabolism occurs during gastrointestinal absorption and during the first pass through the liver.

Drug interactions: Numerous subtle interactions occur with several drug groups, but the most important clinical interactions are with several anticonvulsant drugs (not including sodium valproate and gabapentin) and with the antibiotics rifampicin and griseofulvin, which reduce serum levels of the contraceptive steroids and may lead to breakthrough bleeding, ovulation and contraceptive failure.

Contraceptive efficacy: This is extremely high if tablets are taken optimally (less than one failure per 500 women per year), but is much higher in general use, when missed pills, absorption problems (caused by diarrhoea and vomiting) and drug interactions may play a greater role.

Non-contraceptive health benefits: These are increasingly recognised as important in the benefit-risk equation, with significant reductions in incidence of ovarian, endometrial and colon cancer, acute episodes of pelvic inflammatory disease, infertility, iron-deficiency anaemia, benign breast lumps, benign ovarian cysts, uterine myomata and severe cyclical menstrual symptoms. There are probably also reductions in endometriosis.

Adverse effects: Mild side effects are commonly reported but are often not caused by the COC. The most important (but very rare) complication is venous thromboembolism. Other cardiovascular diseases, such as hypertension, myocardial infarction and stroke, are either not, or only minimally, increased by modern low-dose COCs. Slightly more breast cancers are detected in current COC users, but the tumours are less aggressive and less advanced than in controls.

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2: Level-of-evidence codes

Evidence for the statements made in this article is graded according to the NHMRC system[8] for assessing the level of evidence.

E1	Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
E2	Level II: Evidence obtained from at least one properly designed randomised controlled trial.
$E3_1$	Level III-1: Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
$E3_2$	Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
$E3_3$	Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
E4	Level IV: Evidence obtained from case-series, either post-test, or pre-test and post-test.

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3: Important messages for patients

- Modern low-dose combined oral contraceptives (COCs) are highly effective contraceptives if taken meticulously
- COCs are remarkably free of side effects and serious complications, but some very rare complications, such as venous thromboembolism, can occur.
- They may not be suitable for some women with pre-existing medical risk factors.
- They have some very important, non-contraceptive health benefits.

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Many web sites on contraception begin their narratives this way "Most women can safely use contraceptives today" or in similar words. When you consider the information is usually provided by a Family Planning organization it is understandable for that is many times another name used by Planned Parenthood.