Efficacy and side-effects of oral contraceptives

ANNE MACGREGOR

For the majority of women, oral contraception is safe, convenient and effective, but users should be counselled about potential adverse effects and the importance of good adherence. This review discusses the efficacy, advantages and disadvantages of both combined and progestogen-only oral contraceptives.

Since their introduction in the 1960s, oral contraceptives have been rapidly accepted as an effective method of contraception, with over 100 million users worldwide. Lower-dose pills have been formulated over the years so that, for the majority, the pill is extremely safe, often with added health benefits. Major risks related to pill use are now also recognised so that women at particular risk can be identified and offered alternative contraception.

Combined oral contraceptives

In the UK, combined oral contraceptives (COCs), containing both estrogen and progestogen, are the most popular method of contraception for women under the age of 30 years. The most common estrogen used is ethinylestradiol, in doses between 20 and 35µg, although COCs containing natural estrogens are also available.

Progestogens are classified according to their steroid structure and the timing of their introduction to the market. The progestogen-dominant COCs contain the first- and second-generation progestogens, norethisterone and levonorgestrel. These are derived from testosterone and tend to exhibit androgenic actions, counterbalancing the estrogenic activity.

The third-generation progestogens, desogestrel and gestodene, have neutral androgenic or estrogenic actions; nor- gestimate acts mostly, but not exclusively, through conversion to levonorgestrel.

Drospirenone differs from other progestogens in COCs: it has very mild diuretic properties due to antimineralocorticoid activity. This may help to oppose the salt- and fluid-retaining effects of ethinylestradiol and so reduce symptoms of fluid retention. Drospirenone is also an antiandrogen, so the combination with ethinylestradiol may be an alternative to cyproterone acetate for conditions such as polycystic ovarian syndrome (PCOS).
Dienogest is a progestogen with antiandrogenic activity of approximately one-third of that of cyproterone acetate. It is combined with estradiol valerate, a natural estrogen that is metabolised to 17-beta-estradiol, the same hormone produced by the ovaries. This multiphasic COC (Qlaira) has four different phases over 26 days delivering hormones in an estrogen step-down and a progestogen step-up sequence, followed by two placebo pills. The next pack is started immediately, without a break. A potential advantage of the short two-day hormone-free interval is that it may lessen the likelihood of ‘withdrawal’ symptoms such as headaches. The missed pill advice is notably different from standard pills (see Figure 1): if one pill is missed in the first 24 days, additional precautions are necessary for the next nine days. To avoid confusion, missed pill instructions are printed on every pill pack.

 Nomegestrol acetate is a potent progestogen with strong antigonadotropic and mild antiandrogenic activity. It is combined with estradiol (as hemihydrate) as the COC Zoely in packs of 24 white active tablets and four yellow placebo tablets, hence sharing with Qlaira the advantage of a shortened pill-free interval. However, Zoely is a monophasic pill with the same advice for missed tablets as for COCs with ethinylestradiol. It is an effective contraceptive option, usually providing good cycle control.

 Most pills containing ethinylestradiol are monophasic, ie fixed doses are maintained throughout a 21-day pill-taking

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**Figure 1.** Advice for women using a 21/7 combined oral contraceptive (COC) regimen if a pill is missed. From Guillebaud J. Contraception Today, 8th edn. London: CRC Press, 2016. With permission
cycle. This is usually followed by a seven-day pill-free interval, during which there is a withdrawal bleed.

Triphasic preparations are less popular, but may be useful – once pathology has been excluded – for the control of persistent breakthrough bleeding that has not settled after at least three COC cycles. Triphasic preparations include Logynon (ethinylestradiol/levonorgestrel), Synphase (ethinylestradiol/norethisterone) and Triadene (ethinylestradiol/gestodene). A Cochrane review has suggested less spotting, breakthrough bleeding or amenorrhea in triphasic versus monophasic COC users but no randomised trials exist to confirm this approach. Clinical trial data for both Qlaira and Zoely suggest that absent withdrawal bleeds are not uncommon, which may not be acceptable to some women.

**Mode of action**

Contraceptive efficacy is maintained by several mechanisms. The principal mode of action is to suppress folliculogenesis, inhibiting ovulation. Secondary mechanisms include:

- Development of a suppressed endometrium that is unresponsive to implantation
- Development of viscous cervical mucus that impedes sperm transport
- Possible interference with gamete transport through the fallopian tubes and therefore interference with fertilisation.

**Efficacy**

The efficacy of a contraceptive method is expressed as the failure rate per 100 woman-years of exposure (Pearl Index). The theoretical failure rate of COCs is extremely low, being 0.3 per 100 woman-years. However, poor adherence is a major factor in limiting effectiveness, particularly in younger users. Although up to four pills can be missed in the middle week of a pack without the need for emergency contraception, late starts are the main problem when the pill-free interval is extended beyond the usual seven days. Consequently, the failure rate with typical use can be up to 9 per 100 woman-years (see Figure 2).

**Advantages**

COCs provide a reversible and convenient method of contraception that is independent of intercourse. An extensive body of evidence has established several noncontraceptive benefits of COCs including better cycle control; improved premenstrual symptoms, acne, dysmenorrhoea, heavy menstrual bleeding and iron-deficiency anaemia; and a reduction in ovarian cysts, benign breast disease and possibly pelvic inflammatory disease. Their use is associated with a 40–50% reduction in ovarian and endometrial cancers and, possibly but to a lesser degree, a reduction in colorectal cancer.

**Principal side-effects**

Breakthrough bleeding is common in early use. In most cases this settles with time, although missed pills can be a common cause. Further evaluation, particularly exclusion of sexually transmitted infections, pregnancy and gynaecological pathology, is indicated if breakthrough bleeding persists or develops for the first time in established users.

Other side-effects are often specific to the relative excess of estrogen or progestogen in different formulations. Symptoms of nausea, fluid retention and increased noninfective vaginal discharge can indicate a relative excess of estrogen. This is usually resolved by changing to a progestogen-dominant combined pill. Similarly, progestogenic symptoms of vaginal dryness, depression, acne and loss of libido may respond to a more estrogen-dominant combined pill.

Side-effects are mostly limited to the first few cycles of use, so women should be advised to persevere for at least three cycles before considering a different formulation. Reassurance and adequate counselling can usually prevent unnecessary discontinuation and enhance compliance.

Extended-cycle and continuous COCs are licensed in several countries and, although not currently available in the UK, tailoring regimens in this way is supported by the Faculty of Sexual and Reproductive Healthcare (FSRH). Women using tailored regimens should be made aware that such use is ‘off-licence’. Reducing the number of hormone-free days improves contraceptive efficacy and results in greater improvement in menstrual-hormonal symptoms compared to cyclical regimens. Clinical trials show that ovulation can occur as early as eight days after the last pill taken. Hence it is increasingly recommended that all COC users have a shortened four-day hormone-free interval in place of the usual seven days.

**Principal risks**

COCs have been the subject of intense research since their introduction. The results of these studies have confirmed the overall safety of this method but have also highlighted some important risks relevant to a minority of users. Based on the
Advantages of using the method generally outweigh the theoretical proven risks

Theoretical or proven risks usually outweigh the advantages of using the method

Unacceptable health risk if the method is used

Table 1. UK medical eligibility criteria (UKMEC) category definitions for contraceptive use

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No restriction for use of the method</td>
</tr>
<tr>
<td>2</td>
<td>Advantages of using the method generally outweigh the theoretical proven risks</td>
</tr>
<tr>
<td>3</td>
<td>Theoretical or proven risks usually outweigh the advantages of using the method</td>
</tr>
<tr>
<td>4</td>
<td>Unacceptable health risk if the method is used</td>
</tr>
</tbody>
</table>

Table 2. Risk of venous thromboembolism (VTE) with different types of hormonal contraception

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of women per 10,000 women likely to experience a VTE in one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women not using a combined hormonal pill/patch/ring and are not pregnant</td>
<td>2</td>
</tr>
<tr>
<td>Women using a COC containing levonorgestrel, norethisterone or norgestimate</td>
<td>5–7</td>
</tr>
<tr>
<td>Women using the etonogestrel/ethinylestradiol vaginal ring or norelgestromin/ethinylestradiol transdermal patch</td>
<td>6–12</td>
</tr>
<tr>
<td>Women using a COC containing drospirenone, gestodene or desogestrel</td>
<td>9–12</td>
</tr>
<tr>
<td>Women using a COC containing dienogest (Qlaira) or nomegestrol (Zoely)</td>
<td>Not yet known</td>
</tr>
</tbody>
</table>

Breast cancer

A collaborative meta-analysis of 54 epidemiological studies suggested a 24% increased risk of breast cancer in women using COCs versus nonusers. However, reanalysis of the data showed that there was little difference between women who had and those who had not used COCs in terms of breast cancer risk. The natural estrogen in Qlaira and Zoely confers a neutral clotting profile compared to ethinylestradiol. Surveillance data suggest that Qlaira is associated with similar or lower risk compared to ethinylestradiol COCs but there are no data on risks associated with Zoely. Until further data are available, the indications and contraindications are the same as for other COCs.

First-time users are of more concern than continuing users since any excess risk of VTE is greatest in the first few months of starting or when restarting after a break of over one month, as those with a genetic predisposition are ‘unmasked’. Many factors further increase the risk of VTE, including immobility, smoking, hypertension and diabetes, as well as obesity. These should be taken into consideration when deciding which is the most suitable method of contraception, and COCs should be prescribed with caution to obese women (BMI >35).

The FSRH advises that COC use is relatively contraindicated for women with a positive first-degree family history (UKMEC 2 if first-degree relative age ≥45 years/UKMEC 3 if first-degree relative <45 years) of VTE. There is no indication for thrombophilia screening since currently unidentified thrombophilias exist so a negative result does not exclude a thrombophilic tendency. Alternative contraception includes all progestogen-only methods since there is evidence that contraceptive doses of most progestogens do not increase the risk of VTE.

Given that it confers the lowest associated risk of VTE and is the cheapest, a levonorgestrel-containing pill is preferred as the normal ‘starter’ COC. However, any COC can be used at the request of the woman or to control side-effects or achieve therapeutic advantage.

Arterial thromboembolism

Myocardial infarction (MI) risk is not increased in healthy COC users compared to nonusers. Age, smoking, hypertension, diabetes, obesity and family history are additional factors that increase risk.

Haemorrhagic stroke risk is not increased in healthy COC users. In contrast, COC use is associated with a two-fold increased risk of ischaemic stroke in healthy users, which translates to an additional 4.1 ischaemic strokes per 100,000 non-smoking, normotensive women using low-dose COCs, or one additional ischaemic stroke per year per 24,000 such women. However, this should be compared with the risk of stroke in pregnancy, estimated to be approximately 34 per 100,000 deliveries.

Hypertension and smoking are the most important independent risk factors for both MI and ischaemic stroke. There is also evidence that migraine with aura, but not migraine without aura, increases the risk of ischaemic stroke and is a contraindication (UKMENC 4) to use of COCs.

Blood pressure must be measured before and at every visit during COC use. Mild hypertension (140–159/90–99mmHg) does not in itself absolutely contraindicate COCs unless other arterial risk factors are present. A lipid screen is not routinely recommended but should be tested if there is a known lipid disorder or arterial disease in a close relative under the age of 45 years. Smoking should be discouraged.

Breast cancer

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of the estimated cumulative number of breast cancers diagnosed during the period from starting use up to 20 years after stopping.21 Furthermore, cancers diagnosed in women who had used COCs were less advanced clinically than the cancers diagnosed in never users. That there is little or no association between COC use and breast cancer is supported by data from the RCGP’s oral contraception study, which included 339,000 woman-years of observation for never users and 744,000 woman-years for ever users, and which showed no increased risk of breast cancer in ever vs never users.6

Neither does use of COCs by women with a family history of breast cancer appear to be associated with an increased risk of breast cancer over and above the background risk.22 The average woman has a 1 in 625 risk of developing breast cancer up to the age 35 years, rising to 1 in 56 by age 50 years. A woman with two first- or second-degree relatives with breast cancer diagnosed under the age 60 years has a risk two to three times higher than the background risk.

Although these data are reassuring, an increased risk in younger women cannot be ruled out, particularly those with BRCA1 or BRCA2 gene mutations. A population-based case-control study assessed COC use as a risk factor in Caucasian carriers and noncarriers of BRCA1 and BRCA2 mutations.23 Use of low-dose COCs was not associated with increased risk of breast cancer in either BRCA2 mutation carriers or noncarriers. Furthermore, the results suggested a reduced risk of breast cancer in BRCA1 mutation carriers.

In contrast to these data, results from the retrospective international BRCA1/2 Carrier Cohort Study suggested that ever users of COCs had an increased risk of breast cancer – adjusted hazard ratio 1.47; 95% CI 1.16–1.87. Duration of use before first full-term pregnancy further increased risk.24

Women with a family history of breast cancer can use COCs (UKMEC 1) but should be counselled about the increased background risk. Furthermore, there are the benefits of COCs to consider, in particular reduced risk of ovarian, colon and endometrial cancer, and pelvic inflammatory disease, as well as relief from many period-related problems.

The lowest dose of estrogen that provides good cycle control is recommended, which should be reassessed at least every five years. Women can be reassured that, should they develop breast cancer while taking COCs, the prognosis is likely to be better than for women not using hormonal contraception.

Use of low-dose COCs may also be associated with reduced risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers.25 For women who are carriers of BRCA mutations, current guidance for use of COCs is UKMEC 3; although COC use protects against ovarian cancer in BRCA mutation carriers, it is not known where the balance of risk lies.

Cervical cancer. The risk of cervical cancer is strongly related to the lifetime number of sexual partners, age at first intercourse, smoking and duration of use of oral contraceptives.26 COCs appear to be only a weak co-factor with smoking, and the presence of certain types of the human papilloma virus (HPV) is more important.27

Women using COCs should be counselled against smoking, to use condoms to protect against sexually transmitted infections and to avail themselves of the cervical screening programme. COCs can be started and continued during treatment for cervical intraepithelial neoplasia.

Other cancers. Benign and malignant liver tumours are more common in women using COCs but both conditions remain rare.

### Principal contraindications

Use of COCs is considered to represent an unacceptable health risk in several conditions (UKMEC 4; see Table 3). In addition, the presence of multiple relative-risk factors usually contraindicates COCs. These contraindications affect only a minority of prospective users. Most of the risks are related to the estrogen component of COCs, so progestogen-only and nonhormonal methods are suitable alternatives.

### Principal interactions

Drugs that induce hepatic enzymes (see Table 4) reduce the efficacy of COCs. Consider alternative contraception such as injectable contraceptives, the intrauterine system (IUS) or nonhormonal methods. Depot medroxyprogesterone acetate (DMPA) is the preferred hormonal method of contraception in women taking enzyme-inducing drugs, which should be given at the usual 12-week interval since the rate of clearance of the drug is unchanged by enzyme inducers. If COCs are preferred, at least 50µg ethinylestradiol (maximum 70µg ethinylestradiol) is necessary to ensure contraceptive action; efficacy may be further increased by extended use and shortening the pill-free interval to four days or taking the pill continuously.28
The antibiotics rifampicin and rifabutin are such powerful enzyme inducers that alternative contraceptive methods should be used. Even short courses of two days reduce contraceptive efficacy for a month, and longer courses for up to two months, after stopping.

Contraceptive effectiveness of COCs is not affected by co-administration of most broad-spectrum antibacterials; additional precautions are only required for antibacterials that are enzyme inducers.

The efficacy of the antiepileptic drug lamotrigine is reduced during COC use, with increased risk of seizures during pill-taking and increased lamotrigine levels during the pill-free interval; with lamotrigine monotherapy, use of COCs is UKMEC 3. COCs can be used if lamotrigine and sodium valproate are taken together, as no reduced effect occurs with this combination.

**Progestogen-only pills**

Progestogen-only pills (POPs) contain the progestogens desogestrel, levonorgestrel or norethisterone. They are taken every day, without a break.

*Mode of action*

The main mode of action of traditional POPs (i.e. those containing norethisterone or levonorgestrel) is to thicken cervical mucus and thus prevent sperm penetration. They also have an effect on the endometrium, reducing uterine receptivity. Unlike COCs, ovulation is inhibited in only 15–40% of cycles, which accounts for the reduced efficacy of traditional POPs in younger women. In contrast, the primary mode of action of the desogestrel POP is ovulation inhibition, enhancing efficacy.

*Efficacy*

POPs can be very effective with failure rates for perfect use as low as 0.3 per 100 woman-years during the first year of use. More typical use is associated with a failure rate similar to COCs. Contraceptive efficacy improves with age as natural fertility declines.

The main cause of failure is missed pills. If a traditional POP is taken more than 27 hours after the last dose, or if desogestrel is taken more than 36 hours after the last dose, contraceptive protection is reduced (see Figure 3).

*Advantages*

POPs provide a reversible and convenient method of contraception, independent of intercourse and without estrogen-associated risks. Most women for whom ethinylestradiol is contraindicated can use them.

*Principal side-effects*

Menstrual irregularities, from breakthrough bleeding to amenorrhoea, are common. A few women develop functional ovarian cysts. If ovulation is not inhibited, ectopic pregnancy is more likely; anovulant methods are the contraceptives of choice if there is a past history of ectopic pregnancy.

Breakthrough bleeding, once pathology or user failure has been excluded, may resolve with time but otherwise a change to a different POP is worth considering. Amenorrhoea can cause concern about possible pregnancy but, once this has been excluded, actually suggests better efficacy from an anovulant effect.

*Principal risks*

The only relevant risk relates to breast cancer. Although likely to be minimal, the risk of POPs and breast cancer is uncertain since studies have failed to reach statistical significance due to the small number of users.

*Principal contraindications*

Only current breast cancer contraindicates POP use (UKMEC 4).

*Principal interactions*

Hepatic enzyme-inducing drugs reduce the efficacy of POPs (see Table 4). POP users starting enzyme-inducing drugs should use alternative contraception such as DMPA, the IUS or a non-hormonal method.

**Place of COCs and POPs in contraception**

COCs are the most popular method of contraception for young women in the UK. They have the advantage of being effective, reversible and independent of intercourse. For the majority of

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**Table 4.** Hepatic enzyme-inducing drugs that reduce the efficacy of combined oral contraceptives (COCs) and progestogen-only pills (POPs)

<table>
<thead>
<tr>
<th>Antiepileptics</th>
<th>Antibacterial</th>
<th>Antidepressant</th>
<th>Antiretroviral</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine</td>
<td>rifabutin</td>
<td>St John’s wort</td>
<td>efavirenz</td>
<td>Modafinil</td>
</tr>
<tr>
<td>eslicarbazepine</td>
<td>rifampicin</td>
<td></td>
<td>nevirapine</td>
<td></td>
</tr>
<tr>
<td>fosphenytoin</td>
<td></td>
<td></td>
<td>ritonavir</td>
<td></td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td></td>
<td></td>
<td>ritonavir-boosted protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>phenobarbital</td>
<td></td>
<td></td>
<td>(eg darunavir or lopinavir)*</td>
<td></td>
</tr>
<tr>
<td>phenytoin</td>
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<td></td>
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</tr>
<tr>
<td>primidone</td>
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<tr>
<td>rufinamide</td>
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<td></td>
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<tr>
<td>topiramate</td>
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</tbody>
</table>

*except ritonavir-boosted atazanavir – COC containing ≥30µg ethinylestradiol can be used*
users, they are very safe with added health benefits, and can be used by healthy women right up to the menopause.

Although it is unlikely that COCs are overprescribed, women are often not counselled about the full range of contraceptive methods available, particularly the long-acting reversible contraceptives (LARCs), which are associated with lower failure rates. Women starting COCs must be counselled about potential side-effects and the importance of adherence. A review three months after initiating the contraceptive should be scheduled in order to assess the method and consider whether a change is necessary.

Women should also be alerted to the list of symptoms in the Family Planning Association (FPA) leaflets for which urgent medical attention is recommended and which may require immediate cessation of COCs (see Table 5). Emergency contraception may be indicated if there is a risk of pregnancy.

If adherence is an issue, consider the combined contraceptive patch (Eura, containing norelgestromin/ethinyl estradiol), which is changed weekly for three out of every four weeks. Another option is the combined vaginal ring (NuvaRing, containing etonogestrel/ethinyl estradiol), which is used continuously for three out of every four weeks. Risks and benefits are otherwise the same as for COCs.

For a minority of women, the risks of COCs outweigh the benefits and alternative methods of contraception are recommended. These include the POP which also benefits from being effective, reversible and independent of intercourse. In younger women, traditional POP efficacy is lower than for the COC, but both are of similar efficacy in women over 35 years. However, the anovulant desogestrel POP has similar, if not greater, efficacy than the COC for contraception study. BMJ 2007;335:653.


10. Stegeman BH, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analy-

Declaration of interests
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