ARTICLE

Choosing a combined oral contraceptive pill

Mary Stewart
Senior medical officer
Research and Education
Family Planning NSW

Kirsten Black
Associate professor
Discipline of Obstetrics, Gynaecology and Neonatology
University of Sydney

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SUMMARY

The combined oral contraceptive pill is an effective contraceptive method which can also offer other benefits. However, other contraceptive options should be discussed. If the pill is the chosen method, prescribe a pill with the lowest effective dose of oestrogen and progestogen.

Pills containing levonorgestrel or norethisterone in combination with ethinyloestradiol 35 microgram or less are considered first-line. They are effective if taken correctly, have a relatively low risk of venous thromboembolism, and are listed on the Pharmaceutical Benefits Scheme.

The pill is usually taken in a monthly cycle. Some women may prefer an extended pill regimen with fewer or no inactive pills.

Introduction

The combined oral contraceptive pill contains oestrogen and progestogen. It was introduced into Australia just over 50 years ago. Australia was the second country in the world to have access to 'the pill'. Women rapidly adopted the pill as it allowed the reliable separation of sex and reproduction and gave them the opportunity to plan when to have children. Since then the pill has been further developed to ensure good efficacy while minimising the adverse effects.

A key advance was a decrease in the dose of oestrogen to the currently used low-dose formulation (standard dose of ≤35 microgram ethinyloestradiol).[1] Subsequently it has been found that formulations with ethinyloestradiol 20 microgram are likely to be as effective as the 30–35 microgram pills while possibly reducing the oestrogenic effects such as nausea, bloating and breast tenderness.[2] However, there may be an increase in unscheduled bleeding.[3] More recent developments, which may improve the safety and efficacy of the combined oral contraceptive pill, include using oestradiol instead of ethinyloestradiol and extended pill regimens with fewer or no inactive pills.[4-6]

The pill today

The pill is the most commonly used contraceptive method and approximately 50–80% of Australian women use it at some stage during their reproductive lives.[7] There is now a large range of products available with over 30 different registered brands. While many of these pills contain similar hormones and doses, there are multiple formulations for the prescriber to consider (Table 1). These pills contain an oestrogen component (ethinyloestradiol, mestranol, oestradiol or its pro-drug oestradiol valerate) and a progestogen (levonorgestrel, norethisterone, gestodene, desogestrel, drospirenone, nomegestrol, dienogest or cyproterone).

Oestrogens

Ethinyloestradiol, a derivative of 17 beta-oestradiol, has been the predominant oestrogen in contraceptive pills because of its high oral bioavailability. Until recently oestradiol had not been used due to its rapid inactivation by the liver, short half-life and the occurrence of breakthrough bleeding when combined with older progestogens. However, formulations that combine oestradiol (1.5 mg) in a micronised form with a newer progestogen (nomegestrol) appear to offer good cycle control.[8] Oestradiol has also been combined with a synthetic ester in the form of oestradiol valerate to improve its oral bioavailability and extend its half-life.[9] At the doses prescribed in pills, oestradiol may have a more favourable impact on haemostasis and lipid and carbohydrate metabolism (and therefore on cardiovascular risk) when compared with ethinyloestradiol.[10,11] However, there is insufficient evidence to preferentially prescribe these pills to women with cardiovascular risk factors.[12]

Progestogens

Pills containing levonorgestrel or norethisterone have been used since the 1960s. The combination of these progestogens with 35 microgram or less of ethinyloestradiol is considered the 'gold standard' in relation to their safety profile. As most of these combinations are listed on the Pharmaceutical Benefits Scheme (PBS) they are an effective first-line option for women preferring an oral contraceptive.

Newer progestogens such as gestodene and desogestrel are structurally related to progesterone, but have greater specificity for progesterone receptors than the older progestogens. They reduce the potential for androgenic, oestrogenic and glucocorticoid effects. Drospirenone is a

Table 1 **Combined oral contraceptive pills**

Brand name	Oestrogen	Progestogen	PBS listing
Femme-Tab ED 20/100 Microgynon 20 ED Microlevlen ED Loette Micronelle 20 ED	20 microgram ethinyloestradiol	100 microgram levonorgestrel	Only Femme-Tab ED 20/100 PBS listed
Femme-Tab ED 30/150 Levlen ED Microgynon 30 ED Monofeme Nordette Evelyn 150/30 ED Eleanor 150/30 ED Micronelle 30 ED	30 microgram ethinyloestradiol	150 microgram levonorgestrel	PBS listed
Microgynon 50 ED	50 microgram ethinyloestradiol	125 microgram levonorgestrel	
Logynon ED Trifeme 28 Triphasil Triquilar ED	6 x 30 microgram ethinyloestradiol	6 x 50 microgram levonorgestrel	
	5 x 40 microgram ethinyloestradiol	5 x 75 microgram levonorgestrel	
	10 x 30 microgram ethinyloestradiol	10 x 125 microgram levonorgestrel	
Brevinor 21 and 28 Day Norimin 28 Day	35 microgram ethinyloestradiol	500 microgram norethisterone	PBS listed
Brevinor-1 21 and 28 Day Norimin-1 28 Day	35 microgram ethinyloestradiol	1000 microgram norethisterone	
Norinyl-1 21 and 28 Day	50 microgram mestranol	1000 microgram norethisterone	
Improvil 28 Day Synphasic 28	7 x 35 microgram ethinyloestradiol	500 microgram norethisterone	
	9 x 35 microgram ethinyloestradiol	1000 microgram norethisterone	
	5 x 35 microgram ethinyloestradiol	500 microgram norethisterone	
Marvelon 28 Madeline	30 microgram ethinyloestradiol	150 microgram desogestrel	Not PBS listed
Minulet	30 microgram ethinyloestradiol	75 microgram gestodene	
Brenda-35 ED Carolyn-35 ED Diane-35 ED Estelle-35 ED Jene-35 ED Juliet-35 ED Laila-35 ED	35 microgram ethinyloestradiol	2 mg cyproterone acetate	
Yaz Yaz Flex	20 microgram ethinyloestradiol	3 mg drospirenone	
Isabelle Petibelle Yasmin	30 microgram ethinyloestradiol	3 mg drospirenone	
Valette	30 microgram ethinyloestradiol	2 mg dienogest	
Qlaira	2 x 3 mg oestradiol valerate	–	
	5 x 2 mg oestradiol valerate	5 x 2 mg dienogest	
	17 x 2 mg oestradiol valerate	17 x 3 mg dienogest	
	2 x 1 mg oestradiol valerate	–	
Zoely	1.5 mg oestradiol	2.5 mg nomegestrol acetate	

PBS Pharmaceutical Benefits Scheme

spironolactone analogue and has a mild diuretic effect. Cyproterone has anti-androgenic effects which may be beneficial in women with severe acne.

Guiding pill prescription

The guiding principles when considering which pill to prescribe for an individual woman are to choose a formulation that:

- has the lowest dose of oestrogen and progestogen to provide good cycle control and effective contraception
- is well tolerated
- has the best safety profile
- is affordable
- offers additional non-contraceptive benefits if desired.

Effective regimens

The first available formulation of the combined oral contraceptive pill contained 50 microgram of ethinyloestradiol for cycle control. However, an association between the pill and venous thromboembolism soon emerged. This was due to the effect of oestrogen on the synthesis of clotting factors.[13] To mitigate this risk, and reduce oestrogenic adverse effects, the dose of ethinyloestradiol was reduced to 35 and 30 microgram and more recently 20 microgram without an apparent loss of contraceptive efficacy.[3]

Women with significant risk factors for venous thromboembolism are not suitable for any combined hormonal method

The pills available in Australia are mostly in 28-day packs with 21 active and 7 inactive pills, to mimic the menstrual cycle. Some formulations contain 24 active and 4 inactive pills (24/4 regimes) which may reduce the chance of contraceptive failure and breakthrough ovulation.[4] Extended pill-taking regimens are used by many women to delay or avoid a withdrawal bleed. This is most easily achieved with monophasic regimens in which each active pill contains the same amount of oestrogen and progestogen and the inactive pills are skipped. Typically this is done for three months at a time. Indeed evidence is available to support the safety of continuous use of the contraceptive pill for up to 12 months.[14]

Another approach is called a 'menstrually signalled' regimen. Women take the pill continuously until they experience four days of vaginal spotting or bleeding after which they have a four-day pill break.

Triphasic pills are commonly prescribed in Australia, but have no evidence-based advantage over monophasic pills in relation to their adverse effect profile or cycle control. A quadriphasic combined oral contraceptive pill that contains oestradiol valerate and desogestrel is formulated with an oestrogen step-down and progestogen step-up sequence.[15]

The pill is a user-dependent method. Its failure rate therefore differs between 'perfect use' (0.3% annually) by women who take it consistently and correctly and 'typical use' (9% annually) when the pill is used inconsistently or incorrectly.[16]

Safety and tolerability

Long-term cohort studies show that, compared to non-users of the combined oral contraceptive pill, users have lower rates of death from any cause. They also have significantly lower rates of death from cancer, cardiovascular disease and other diseases.[17]

Women may experience a range of adverse effects and managing these can be challenging. Table 2 outlines some common adverse effects and strategies that may improve the symptoms should the woman wish to continue with the pill.

Although trying another oral formulation can be helpful, sometimes a change to another form of contraception may be appropriate. This includes a progestogen-only method, such as the contraceptive implant or levonorgestrel intrauterine system, or the non-hormonal copper intrauterine device. These long-acting reversible contraceptive methods are much more effective at preventing unintended pregnancy compared to the pill. They should be discussed with all women requesting contraception, particularly those who cannot take the pill because of adverse effects or identified risk factors or who find it difficult to remember to take the pill daily.

The combined oral contraceptive pill is not recommended during lactation as it may affect breast milk volume.

Venous thromboembolism

There is a risk of venous thromboembolism associated with the combined hormonal contraception, but the risk is much less than that during pregnancy and the immediate postpartum period. Non-users of hormonal contraception have a baseline risk for venous thromboembolism of around 20 per 100 000 woman-years. Current research points to a three-fold increased risk of venous thromboembolism for women using a combined pill over baseline (Table 3).[19,20]

Women should be informed of the risk of venous thromboembolism with combined oral contraceptive pills and be aware of the signs. The factors that influence the risk include age, smoking, body mass index, immobilisation, and a personal or family history of thromboembolism or thrombogenic mutations. These factors need to be assessed when considering

Table 2 **Managing common adverse effects associated with the combined oral contraceptive pill**

Problem	Management strategies based on practice
Nausea	Reduce oestrogen dose Exclude pregnancy Take pills at night Change to progestogen-only method
Breast tenderness	Reduce oestrogen and/or progestogen dose Change progestogen Consider using a pill containing drospirenone
Bloating and fluid retention	Reduce oestrogen dose Change to progestogen with mild diuretic effect (i.e. drospirenone)
Headache	Reduce oestrogen dose and/or change progestogen If headache occurs in hormone-free week, consider: • extended use or • giving oestradiol 50 microgram transdermal patch in this week or • try oestradiol valerate/dienogest pill[18]
Dysmenorrhoea	Extended pill regimen to reduce the frequency of bleeding
Decreased libido	No evidence supports a benefit of one type of oral contraceptive pill over another
Breakthrough bleeding	If taking an ethinyloestradiol 20 microgram pill, increase oestrogen dose to a maximum of 35 microgram Change progestogen if already taking an ethinyloestradiol 30–35 microgram pill Try another form of contraception. Consider the vaginal ring.

Table 3 **Risk of venous thromboembolism** [19,20]

	Rate of venous thromboembolism per 10 000 women–years (10 000 women studied for one year)
Non contraceptive users and not pregnant	2
Oral contraceptive users of pills	7–10
Pregnancy	29
Immediately postpartum	300–400

the safety of the combined oral contraceptive pill. If a woman has a significant risk factor for venous thromboembolism, she is not suitable for any combined hormonal method. Progestogen-only methods are safer for women with risk factors for venous thromboembolism.

The risk of venous thromboembolism appears to vary with oestrogen dose and progestogen type. Pills containing 50 microgram ethinyloestradiol have the highest risk. Compared with pills containing levonorgestrel, those with desogestrel, gestodene, cyproterone acetate and drospirenone may have a higher risk, although the evidence is conflicting.[21-23]

Arterial disease

Combined oral contraceptive pills are associated with an increase in the risk of myocardial infarction and ischaemic stroke. While the odds ratio for these events is around 1.7 (compared to non-users), the absolute risk is very low and depending on age lies between 2 and 20 per million women.[24-26]

Women with significant risk factors for arterial disease such as a personal history of arterial disease, obesity, smoking (if over 35 years old), migraine with aura, diabetes with vascular complications or uncontrolled hypertension should not use any combined hormonal method.[27]

Affordability

Only the pills containing levonorgestrel and norethisterone are listed on the PBS (Table 1). The out-of-pocket expense for a four-month subsidised supply is approximately $20 compared to up to $120 or more for the newer non-PBS-listed pills.

Non-contraceptive benefits

There is not a great deal of evidence for the benefit of one pill type over another. Although the newer combined oral contraceptives have been marketed on their non-contraceptive benefits, it is important to understand which claims are well substantiated.

Acne and hirsutism

Most women with acne and hirsutism find that their skin improves when they take the combined oral contraceptive pill. This is in part because of a rise in sex hormone binding globulin. Pills containing cyproterone acetate, drospirenone, gestodene or desogestrel are often recommended, but the evidence for a benefit over levonorgestrel-containing pills is limited.

The pills containing cyproterone acetate and ethinyloestradiol appear to improve acne (judged by inflammatory lesions and global assessments) better than those containing levonorgestrel.[28] Studies comparing pills containing cyproterone acetate with pills containing drospirenone, gestodene or desogestrel have had conflicting results.[29] Women with hirsutism may benefit from pills containing one of the anti-androgenic progestogens, including cyproterone acetate or drospirenone, which have been found to result in improvements in clinical hirsutism scores.[30]

Heavy menstrual bleeding

All combined contraceptive pills can reduce the duration and heaviness of menstrual blood loss. Extending the days women take active pills while reducing or eliminating inactive pills can be useful for heavy menstrual bleeding.

The oestradiol valerate with dienogest pill has a quadriphasic regimen which reduces menstrual blood loss through its effect on the endometrium. It has an indication for the management of heavy menstrual bleeding. This pill appears to be more effective at reducing the number of days of bleeding and the amount of blood loss when compared to combinations of ethinyloestradiol and levonorgestrel.[10,31,32]

Premenstrual syndrome and premenstrual dysphoric disorder

Menstrual-related symptoms are commonly reported, but a proportion of women will experience more severe cyclic symptoms, known as premenstrual syndrome. A further subset of women will experience severe dysphoric symptoms, which have been labelled as premenstrual dysphoric disorder.

Combined oral contraceptives, by regulating hormonal fluctuations, improve the physical symptoms of menstruation such as breast discomfort and primary dysmenorrhoea, but there is little evidence on their effect on mood and behavioural symptoms.[33] The exception is the pill containing drospirenone 3 mg plus ethinyloestradiol 20 microgram, which may be more effective in treating severe premenstrual symptoms. Compared to placebo, it has been found to reduce impairment in productivity, social activities and relationships.[34,35]

Conclusion

Contraceptive counselling should involve the provision of evidence-based information on the safety, efficacy, advantages and disadvantages of all methods of contraception. This enables women to make choices based on their personal preferences and medical suitability.

All combined oral contraceptive pills in Australia have high efficacy provided they are taken regularly. There is little evidence for superior non-contraceptive benefits of the newer pills. The pills containing levonorgestrel or norethisterone in combination with ethinyloestradiol at doses equal to or below 35 microgram are considered first-line due to their possible lower risk of venous thromboembolism and their PBS listing. Other pills can be used if adverse effects develop, however 50 microgram pills are not recommended due to the risk of venous thromboembolism.

Mary Stewart is employed by Family Planning NSW which conducts clinical trials sponsored by pharmaceutical companies. Family Planning NSW receives fees from MSD for contraceptive implant training and sponsorship from Bayer Healthcare for intrauterine device training sessions.

Kirsten Black is a trainer on the implant insertion program supported by MSD. She is a consultant on an international advisory board for Bayer Healthcare and has received individual support to attend a conference as a presenter.

Q:

SELF-TEST QUESTIONS

True or false?

1. Users of the combined oral contraceptive pill have a higher cancer mortality rate than other women.
2. The risk of venous thromboembolism is higher with combined oral contraceptive pills containing 50 microgram ethinyloestradiol compared to those containing 35 microgram or less.

Answers on page 35

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