Combined OCPs

How to choose the right one

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With so many combined oral contraceptive pills available, each patient must be assessed individually to choose the right one. Noncontraceptive effects and side effect profiles must be considered when making this choice.

KEY POINTS

- The progestogen component is responsible for the primary contraceptive effect in a contraceptive preparation.
- The oestrogen component of the combined oral contraceptive pill (COCP) is associated with the more serious side effects of venous thromboembolism and cardiovascular and cerebrovascular events; however, it is responsible for the noncontraceptive benefits of the COCP, such as improvements in acne, hirsutism and cycle control.
- The qualities of a COCP are governed by the dose of the compounds it contains and the interactions between them.
- When starting a COCP, a woman should generally be commenced on a preparation containing either levonorgestrel or norethisterone; however, if the initial choice does not suit the patient or noncontraceptive benefits drive the decision, a preparation containing one of the newer progestogens could be considered.

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The past decade has seen an increasing emphasis on the promotion of long-acting reversible contraceptives in view of their advantages in terms of convenience and efficacy. It is likely, however, that combined oral contraceptive pills (COCPs) will continue to occupy an important place in the contraceptive constellation as they have unique attributes in terms of cycle control and noncontraceptive benefits. Progestogen-only pills remain an important contraceptive option for women with medical contraindications to the use of oestrogen; however, these pills will not be covered in this article.

In a 2012 survey examining more than 4000 contraceptive consultations in a general practice setting, about 69% were related to oral contraceptive pill prescription.[1] Therefore, it is important that all clinicians have a working knowledge of the pharmacology of the steroid hormones used in COCPs so the various preparations can be better tailored to each individual patient. The COCPs available in Australia at the time of publication are listed in Table 1.[2]

The oestrogen component

In COCP preparations, it is progestogen that confers the primary contraceptive effect, by suppressing luteinising hormone to effectively prevent ovulation. Oestrogens enhance this contraceptive effect by suppressing follicle-stimulating hormone and therefore the development of a mature ovarian follicle. However, the main reason for adding oestrogen to the mix is

TABLE 1. COMBINED HORMONAL CONTRACEPTIVE PILLS AVAILABLE IN AUSTRALIA

Trade name	Oestrogen	Progestogen	PBS listing
Femme-Tab ED 20/100 Lenest 20 ED Loette Microgynon 20 ED Microlevlen ED Micronelle 20 ED	20 µg ethinyloestradiol (EE)	100 µg levonorgestrel	Only Femme-Tab 20/100 is PBS listed
Logynon ED Trifeme 28 Triphasil 28 Triquilar ED	6 x 30 µg EE 5 x 40 µg EE 10 x 30 µg EE	6 x 50 µg levonorgestrel 5 X 75 µg levonorgestrel 10 x 125 µg levonorgestrel	PBS listed
Eleanor 150/30 ED Evelyn 150/30 ED Femme-Tab ED 30/150 Levlen ED Microgynon 30 ED Micronelle 30 ED Monofeme 28 Nordette 28	30 µg EE	150 µg levonorgestrel	
Microgynon 50 ED	50 µg EE	125 µg levonorgestrel	
Brevinor Norimin 28 day	35 µg EE	500 µg norethisterone	
Brevinor-1 Norimin-1 28 day	35 µg EE	1 mg norethisterone	
Norinyl-1/28	50 µg mestranol (equal to about 35 µg EE)	1 mg norethisterone	

Information correct at the time of publication. Adapted from McNamee K, Harvey C, Bateson D. Med Today 2013; 14(7): 18-32.[2]

to stabilise the endometrium in order to minimise the irregular bleeding that characterises progestogen-only contraceptive methods. Oestrogens also have beneficial effects on acne and hirsutism.

The final side effect profile of a COCP represents a balance between the dose of oestrogen used in the preparation and the qualities of the progestogen it is paired with. It is the oestrogen component of the COCP that is responsible for the potentially serious side effects associated with its use, such as venous thromboembolism (VTE) and adverse effects on the patient's cardiovascular and cerebrovascular systems. Less serious oestrogen-related side effects include breast tenderness, nausea and fluid retention. Ethinyloestradiol has been the most widely used oestrogen in COCPs for the past 50 years and has several qualities that make it ideal for this use. A closely-related oestrogen, mestranol, is still used in some older COCPs. Mestranol is a prohormone that must be metabolised to ethinyloestradiol to become active. A dose of 50 µg mestranol is equivalent to about 30 to 35 µg ethinyloestradiol.

Ethinyloestradiol binds poorly to circulating transport proteins endowing it with high bioavailability; however, once attached to oestrogen receptors it then binds strongly. The fact that it is chemically quite different to any of the oestrogens produced in a natural menstrual cycle also allows it to resist metabolism by the liver, giving it a long half-life of about 24 hours.[3]

Combined pills are usually classified on the basis of their ethinyloestradiol dosage. 'High-dose' COCPs have an ethinyloestradiol dose of 50 µg or more, 'low-dose' COCPs have an ethinyloestradiol dose between 30 and 40 µg and 'very low-dose' COCPs have an ethinyloestradiol dose of 20 µg or less. There has been a trend to lower the oestrogen dose in COCPs over time, with preparations in the 1960s containing about four times the dose of ethinyloestradiol seen in modern pills. As the oestrogen dose decreased so did the risk of developing VTE, without sacrificing contraceptive efficacy.[4-6] However, some very low-dose ethinyloestradiol preparations have the disadvantage of more irregular bleeding, particularly in the first few months of use.

TABLE 1. COMBINED HORMONAL CONTRACEPTIVE PILLS AVAILABLE IN AUSTRALIA continued

Trade name	Oestrogen	Progestogen	PBS listing
Improvil	35 µg EE	7 x 500 µg norethisterone 9 x 1 mg norethisterone 5 x 500 µg norethisterone	Non-PBS listed
Madeline Marvelon 28	30 µg EE	150 µg desogestrel	
Minulet	30 µg EE	75 µg gestodene	
Brenda-35 ED Carolyn-35 ED Chelsea-35 ED Diane-35 ED Estelle-35 ED Jene-35 ED Juliet-35 ED Laila-35 ED	35 µg EE	2 mg cyproterone acetate	
Yasmin	30 µg EE	3 mg drospirenone	
Yaz Yaz Flex	20 µg EE	3 mg drospirenone	
Valette	30 µg EE	2 mg dienogest	
Qlaira	Oestradiol valerate 2 x 3 mg 5 x 2 mg 17 x 2 mg 2 x 1 mg	Dienogest 5 x 2 mg 17 x 3 mg	
Zoely	1.5 mg oestradiol	2.5 mg nomegestrol acetate	

Information correct at the time of publication. Adapted from McNamee K, Harvey C, Bateson D. Med Today 2013; 14(7): 18-32.[2]

More recently, oestradiol and oestradiol valerate have been used as the oestrogen component in some COCPs. Once metabolised, both these compounds are chemically identical to the 17β-oestradiol produced by a woman's own ovaries. Such relatively weak oestrogens must be paired with a progestogen that has a profoundly suppressive effect on the endometrium to enable acceptable cycle control.

The dose of oestradiol used in both the oestradiol-containing COCP preparations available in Australia is approximately equivalent to 20 µg ethinyloestradiol, although as ethinyloestradiol and oestradiol are metabolised so differently a direct comparison is difficult. For example, oestradiol compounds do not increase levels of sex hormone binding globulin in the liver to the same extent that ethinyloestradiol does, resulting in a lesser effect on circulating natural androgen levels. Although evidence is limited, less suppression of androgen levels could potentially have less impact on libido. However, it could also result in less suppression of acne and hirsutism than is seen with pills containing ethinyloestradiol.

The progestogen component

Progestogens tend to counterbalance the effect of the oestrogen component of the COCP. At an equivalent oestrogen dose, therefore, it is the progestogen with which it is paired that differentiates one contraceptive preparation from another. The Box shows the derivation of most of the progestogens used in modern COCPs.[7]

Progestogens derived from 17-acetoxyprogesterone are chemically the most similar, although by no means equivalent, to the progesterone made by a woman's ovaries in the luteal phase of her menstrual cycle. Progestogens derived from 19-nortestosterone are a varied group. Some of these compounds retain mildly androgenic qualities that reflect their testosterone origin, whereas others have been chemically modified so that they are antiandrogenic. Drospirenone is a unique progestogen derived from the diuretic compound spironolactone. It retains both the antiandrogenic and antimineralocorticoid qualities of its parent compound.

All progestogens have an antiproliferative effect on the endometrium. This

DERIVATIONS OF PROGESTOGENS USED IN COMBINED OCPS[7]

From 17-acetoxyprogesterone
- Chlormadinone acetate
- Cyproterone acetate*
- Medroxyprogesterone acetate*
- Nomegestrol acetate*

From 19-nortestosterone
- Desogestrel*
- Dienogest*
- Gestodene*
- Levonorgestrel*
- Norelgestromin
- Norethisterone*
- Norethynodrel
- Trimegestone

From spironolactone
- Drospirenone*

* Compounds available in Australian preparations.

protects the endometrium from hyperplasia but the degree of suppression achieved also greatly affects the pattern of bleeding experienced by the user. The more androgenic progestogens may mitigate the oestrogen's positive effects on acne and hirsutism and can also affect the patient's mood. Older progestogens such as levonorgestrel and norethisterone tend to have a more adverse effect on lipid balance, increasing low-density lipoprotein and decreasing high-density lipoprotein.[8] This appears to be less of an issue with the newer progestogens.[8] Contrary to popular perception it is actually the progestogen and not the oestrogen in the COCP that affects glucose metabolism and insulin resistance.[9] This impact on insulin resistance varies with both dose and type of progestogen used, with levonorgestrel, desogestrel, gestodene and dienogest having the greatest effect and cyproterone acetate and nomegestrol acetate the least.[10]

The potential effects on either lipid balance or glucose metabolism are unlikely to be of clinical significance for most women choosing to use the COCP. However, a GP's understanding of the differences between these compounds could influence the choice of preparation offered to women with potential risks for diabetes or cardiovascular disease. A closer examination of the specific qualities of progestogens used in modern COCPs may also assist the clinician to maximise potential positive effects and deal with negative side effects should they occur.

SOME WOMEN FIND A LACK OF BLEEDING ALARMING, BUT THEY CAN BE REASSURED THAT IT DOES NOT ... HAVE ANY ASSOCIATIONS WITH FUTURE FERTILITY.

Norethisterone

Norethisterone is a low-potency progesterone that was first synthesised in the 1950s. It has a relatively short half-life, which may reduce its efficacy in the event of a series of missed pills.[11] At a dose of 1 mg it provides very potent suppression of the endometrium and when taken in the usual regimen of 21 active pills and seven inactive pills it is not uncommon for withdrawal bleeding to be extremely light or even absent over time. Some women find a lack of bleeding alarming, but they can be reassured that it does not indicate any underlying problem or have any association with future fertility. Alternatively, this property can be harnessed for women who wish to consider extended cycling of the COCP (running two or more packs of a monophasic pill sequentially without a break from active pill taking). It is usually possible to suppress bleeding for several months on a COCP containing 1 mg of norethisterone when taken continuously.

Norethisterone is also a relatively nonandrogenic progestogen and preparations containing it tend to be oestrogen dominant. In fact, a small fraction of norethisterone is converted metabolically to ethinyloestradiol, underlining the reality that steroid metabolism in vivo is a complex and decidedly 'unpure' process.[12] Although reviews suggest that most COCPs are likely to result in an overall improvement in skin problems, the oestrogen dominance of preparations containing norethisterone may make them a useful first choice in patients with acne, especially as they are listed on the PBS.[13]

Levonorgestrel

Synthesised in the early 1960s, levonorgestrel tends to be the progestogen against which all others are judged. It is a relatively potent progestogen, requiring only one 10th the dose of norethisterone for effective suppression of ovulation. When combined with 30 µg of ethinyloestradiol it provides excellent cycle control and predictable withdrawal bleeds. However, women taking lower dose levonorgestrel COCPs (20 µg ethinyloestradiol/100 µg levonorgestrel) may experience more irregular bleeding, particularly in the first few months of use.[14,15] Such unpredictable bleeding may result in higher discontinuation rates unless intending users are pre-warned.

Interestingly, unlike any other progestogen used in COCPs, levonorgestrel appears to counteract the effect of oestrogen on sex hormone binding globulin, potentially allowing for higher circulating free natural androgens.[16] For this reason, it has been recommended as the progestogen to consider in women who experience decreased libido on other preparations.[16] Unfortunately in some women higher androgen levels may lead to other side effects, such as mood changes, weight gain and acne, particularly when levonorgestrel is paired with a very low dose of oestrogen.

The newer progestogens

Developed from the 1970s onwards, these progestogens are often classified as the so-called 'third-generation' progestogens. The term is actually of little value clinically as their properties vary

TABLE 2. TROUBLESHOOTING SIDE EFFECTS OF COCPS

Problem	Suggested management
Nausea (exclude pregnancy)	Take COCP at night after main meal
	Reduce oestrogen dose
	Change to vaginal ring with its steady-state delivery system
	Consider switching to a progestogen-only contraceptive method
Breast tenderness	Reduce oestrogen and/or progestogen dose
	Change to a more potent progestogen such as levonorgestrel or to drospirenone, which has a mild diuretic effect
	Change to vaginal ring with its steady-state delivery system
	Consider switching to progestogen-only contraceptive method
Bloating and fluid retention	Reduce oestrogen dose
	Change to preparation containing drospirenone
	Change to vaginal ring with its steady-state delivery system
	Consider progestogen-only contraception
Persistent breakthrough bleeding	Exclude pathology, e.g. chlamydia infection
	Check pill-taking regimen and that the patient is not taking medications that can interfere with absorption, e.g. hypericum
	Change to a different progestogen, preferably one that is more endometrially suppressive, such as norethisterone, nomegestrol acetate or dienogest
	Consider vaginal ring with its steady-state delivery system
	As a last resort, increase oestrogen dose
	No evidence that triphasic pills are better than monophasic
Missed (or very light) periods which are of concern to patient (do not neglect possible pregnancy)	Change to alternative progestogen, e.g. levonorgestrel
	Change from oestradiol COCP to ethinyloestradiol COCP
	As a last resort, increase oestrogen dose
Headache/ migraine during pill-free week (if migraine with aura cease combined contraception)	Prescribe oestradiol 100 µg patch during pill-free week
	Advise a shorter (2- to 4-day) pill-free interval
	Consider extended COCP regimen
	Consider progestogen-only contraceptive method
Persisting acne/ hirsutism beyond 6 months	Change to a progestogen with an antiandrogenic effect
	Change to a less potent progestogen, e.g. norethisterone
	As a last resort, increase oestrogen dose
Decreased libido (minimal evidence)	Change progestogen to levonorgestrel or try oestradiol-containing pill
	Change to progestogen-only or nonhormonal method

Abbreviation: COCP = combined oral contraceptive pill.

widely. Progestogens in this group include desogestrel, gestodene, dienogest, drospirenone, cyproterone acetate and nomegestrol acetate. It has been suggested that some of these compounds may not counterbalance the effect of the oestrogen component as effectively as norethisterone or levonorgestrel and that this could therefore result in a higher risk of VTE.[3,17-19] This, however, remains controversial with several large prospective studies indicating no significant difference in VTE risk between various preparations.[20,21]

In general, progestogens such as desogestrel and gestodene tend to have less androgenic side effects when compared with levonorgestrel. Other progestogens such as cyproterone acetate, drospirenone, dienogest and nomegestrol acetate have been specifically developed for their antiandrogenic qualities. Designed to bind to both progesterone and androgen receptors, the aim is to reduce the effect of circulating androgens and to enhance the positive effect of COCPs on acne, although evidence of their superiority over other progestogens is limited.[13]

Similarly, although several studies indicate that women using COCPs containing antiandrogenic progestogens such as cyproterone acetate and drospirenone experience a significant improvement in clinical hirsutism scores over time,[22,23] there are very few good-quality comparison studies with older preparations. However, if a patient has moderate acne or hirsutism, or has failed to achieve sufficient improvement in their symptoms on an alternative COCP, a trial of a preparation containing one of these antiandrogenic progestogens is worthwhile. For women who experience significant fluid retention while taking other COCPs a preparation which contains drospirenone (preferably with the lowest dose of oestrogen) may be useful.

Like norethisterone, both dienogest and nomegestrol acetate have a profoundly suppressive effect on the endometrium and a significant number of women using

COCPs containing these compounds experience extremely light or absent withdrawal bleeding. They may be a possible option for women experiencing poor cycle control on other COCPs or for those who wish to consider extended cycling. In addition, nomegestrol acetate has a minimal effect on carbohydrate metabolism, which may also make it a good choice in women with insulin resistance.[24] None of the preparations containing these newer progestogens is presently PBS listed, making them a more expensive option for the patient.

Putting it all together

Family Planning in each state of Australia recommend that in the absence of general contraindications to the use of COCPs, women should be commenced on a low-dose oestrogen preparation containing either levonorgestrel or norethisterone. This not only makes financial sense, as these COCPs are PBS listed, but if it were to be accepted that these older preparations may hold a lower risk of VTE, it makes good clinical and medicolegal sense as well. Of course, any contraceptive discussion should cover the alternative longer-acting methods that are increasingly being seen as first-choice options because of their greater efficacy and ease of use.

Strategies should be discussed with the patient to minimise the chance of missed pills and information given about what to do should this occur. All patients who are about to start taking a COCP should be warned of the symptoms that might suggest VTE or stroke and be encouraged to return for clinical review should they have any concerns.

It is good clinical practice to document a patient's baseline weight and blood pressure before commencing any contraceptive method. Women should be reminded that oral contraception is classified as a medication and that it is important that they list it on any medical history. Irregular bleeding, breast tenderness and mild nausea are common in the first pill cycle and patients should be advised to persist unless such symptoms are severe. Women with acne and hirsutism should also be advised that improvements in these symptoms may take several months to occur.

ALL PATIENTS WHO ARE ABOUT TO START TAKING A COCP SHOULD BE WARNED OF THE SYMPTOMS THAT MIGHT SUGGEST VTE OR STROKE.

A routine appointment should be scheduled about three to four months after the start of treatment with a COCP to ensure that the initial preparation chosen is suitable. Weight and blood pressure should be rechecked at this point and any problems or side effects identified. This facilitates an informed adjustment of the compounds in the preparation to best suit the woman's individual response.

Table 2 provides some suggestions for troubleshooting some of the more common problems seen in women taking the COCP, although it must be noted that many of these recommendations are based on relatively low-level evidence.

Conclusion

We have come a long way since 1961 when only one pill was available in Australia. The wide range of hormonal preparations available today makes it more likely that most women will eventually find a preparation that suits them. Such individualised prescribing does, however, require that clinicians form an understanding of the unique qualities of the compounds used in contemporary hormonal contraception and of the interplay between them. MT

References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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