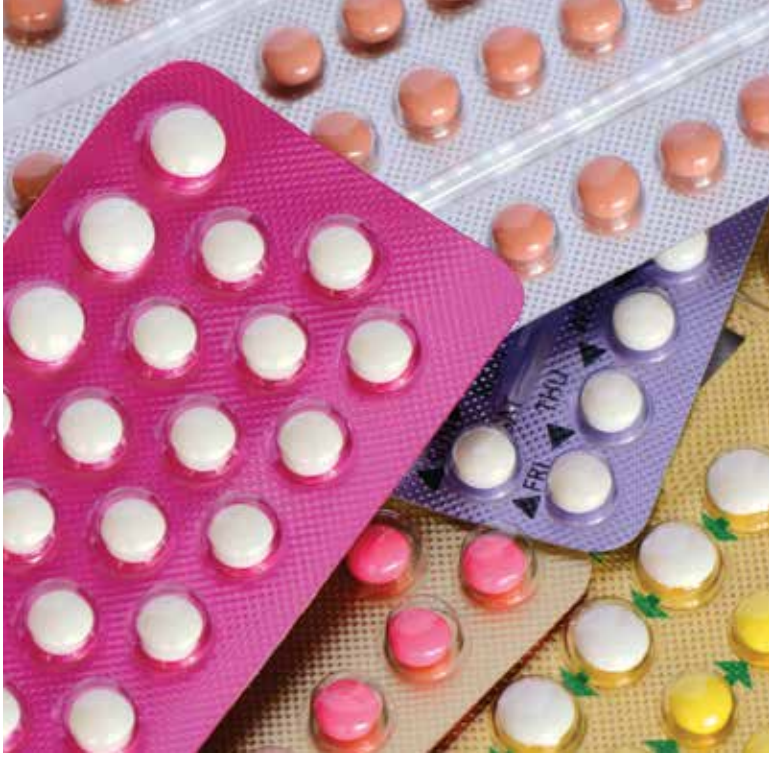
An update on combined hormonal contraceptive pills



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Latest developments in combined oral contraceptives (COCs) offer women more choice. Extended-cycle regimens are available and some COCs have non-contraceptive uses.

Although women in Australia are following the international trend of increasingly choosing more effective long-acting reversible contraception, combined oral contraceptives (COCs) continue to be used by about 33% of women.[1] Clinicians should therefore be aware of the latest developments in COCs.

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The earliest COCs contained the synthetic oestrogen ethinyl oestradiol (EE) or its prodrug mestranol combined with either of the progestogens levonorgestrel (LNG) or norethisterone (NET). They had high hormonal doses, high risks and troublesome side effects. Reduced dosages and new hormonal constituents and regimens have enhanced the safety and side effect profile of COCs and provided additional non-contraceptive benefits for conditions such as acne and heavy menstrual bleeding.[2,3]

This article provides guidance to currently available COCs for medically-eligible women who do not have contraindications to oestrogen.[4] The table provides a summary of COC formulations and brands. All COCs containing NET and most containing LNG are listed on the PBS, whereas others are non-PBS listed.

First-line COC choice

A monophasic PBS-listed LNG pill containing 30 µg EE or less is a good first choice of COC. As well as being relatively cost-effective, COCs containing LNG appear to have the lowest risk of venous disease, with those containing 20 µg of EE being associated with a lower risk of venous and arterial disease than those with 30 µg EE.[5]

Pills with lower EE doses

Early pills contained the equivalent of 100 to 150 µg EE. However, this dose has been reduced to as low as 20 µg EE in newer pills in Australia, usually in combination with 100 µg LNG or 3 mg drospirenone.

Multiple brands of pills with the lowest EE dose are available but only one is listed on the PBS: the COC containing 20 µg EE and 100 µg LNG (Femme-Tab 20). Pills with 20 µg EE are likely to have fewer hormonally-related side effects such as headaches or mood swings than those with 35 or 30 µg EE, although trials comparing pill types are lacking.

A recent French national database study reported a statistically significant lower risk of pulmonary embolism, ischaemic stroke

TABLE. COMBINED HORMONAL CONTRACEPTIVES AVAILABLE IN AUSTRALIA

Trade name	Oestrogen	Progestogen	Packaged to start with an active hormone	PBS listing
Femme-Tab ED 20/100	20 µg ethinyl oestradiol (EE)	100 µg levonorgestrel (LNG)	Yes	Yes
Lenest 20 ED Loette Microgynon 20 ED Microlevlen ED Micronelle 20 ED	20 µg EE	100 µg LNG	Yes	No
Logynon ED Trifeme 28	6 x 30 µg EE 5 x 40 µg EE 10 x 30 µg EE	6 x 50 µg LNG 5 x 75 µg LNG 10 x 125 µg LNG	No	Yes
Triphasil 28 Triquilar ED	6 x 30 µg EE 5 x 40 µg EE 10 x 30 µg EE	6 x 50 µg LNG 5 x 75 µg LNG 10 x 125 µg LNG	No	Yes*
Eleanor 150/30 ED Evelyn 150/30 ED Femme-Tab ED 30/150 Lenest 30 ED Levlen ED Micronelle 30 ED Monofeme 28	30 µg EE	150 µg LNG	No	Yes
Microgynon 30 ED	30 µg EE	150 µg LNG	No	Yes*
Nordette 28	30 µg EE	150 µg LNG	Yes	Yes*
Seasonique†	30 µg EE	150 µg LNG	Yes	No
Microgynon 50 ED	50 µg EE	125 µg LNG	No	Yes
Brevinor Norimin 28 day	35 µg EE	500 µg norethisterone	Yes	Yes
Brevinor-1 Norimin-1 28 day	35 µg EE	1 mg norethisterone	Yes	Yes
Norinyl-1/28	50 µg mestranol	1 mg norethisterone	Yes	Yes
Madeline Marvelon 28	30 µg EE	150 µg desogestrel	No	No
Minulet	30 µg EE	75 µg gestodene	Yes	No

and myocardial infarction (MI) in women taking LNG-containing COCs with 20 µg EE rather than those containing 30 to 40 µg EE.[5] It is uncertain whether the pill containing 20 µg EE and 3 mg drospirenone is associated with a lower risk of venous thromboembolism (VTE) compared with pills containing 30 µg EE and 3 mg drospirenone.[6] The absolute risk of these serious conditions is, however, very low for women without additional vascular risk factors. The lower risk of vascular diseases with the lower EE-dose COCs has to be balanced against a higher chance of breakthrough bleeding, which can lead to early discontinuation of the COC.[7] Note that there is no place for pills with 50 µg EE in the management of women with breakthrough bleeding. These pills are also unsuitable for women taking concurrent liver enzyme-inducing medication because they contain insufficient progestogen. Combinations of lower-dose pills making up at least a total of 50 µg EE can be used for women taking concurrent liver enzyme-inducing medication who prefer not to switch to another method.

TABLE. COMBINED HORMONAL CONTRACEPTIVES AVAILABLE IN AUSTRALIA *continued*

Trade name		Oestrogen	Progestogen	Packaged to start with an active hormone	PBS listing
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	No	No
Yasmin		30 µg EE	3 mg drospirenone	Yes	No
Yaz[†]/Yaz Flex Petibelle		20 µg EE	3 mg drospirenone	Yes	No
Valette		30 µg EE	2 mg dienogest	Yes	No
NuvaRing		15 µg EE	120 µg etonogestrel		No
Qlaira	Days 1 to 2	3 mg oestradiol valerate (E2V)	–	No (First pill contains EV only)	No
	Days 3 to 7	2 mg EV	2 mg dienogest		
	Days 8 to 24	2 mg EV	3 mg dienogest		
	Days 25 to 26	1 mg EV	–		
	Days 27 to 28	–	–		
Zoely[‡]		1.5 mg 17ß-oestradiol	2.5 mg nomegestrol acetate	Yes	No

* Additional charges apply above PBS price for this brand.
† Seasonique pack contains 91 tablets, 84 hormonal tablets each containing 30 µg EE and 150 µg LNG, and seven reduced hormone tablets containing 10 µg EE.
‡ Packaged with 24 active hormone pills and four inactive tablets.

Pills with oestradiol or oestradiol valerate in place of EE

Since 2010 COCs containing 17β-oestradiol (E2; Zoely) or its prodrug oestradiol valerate (EV; Qlaira) instead of EE have been available. E2 and EV are sometimes referred to as 'body identical' hormones because they are structurally identical to oestradiol produced by the ovaries. Given that the major risks of COCs relate to the effect of EE on liver metabolism, in particular on coagulation factors and glucose metabolism, this development offers potential safety benefits and may be a useful choice for perimenopausal and other medically eligible women with raised background risks of arterial and venous disease. Studies have shown that pills containing E2, and to a lesser extent those containing EV, have a reduced effect on lipid and carbohydrate metabolism, haemostatic parameters and markers of endocrine function,[8] but evidence for an effect on VTE, MI and ischaemic stroke is not yet available.

These COCs are a useful alternative choice for some women, but are not available on the PBS. Both are associated with a moderately high rate of amenorrhoea[9,10] and the pill containing EV has been shown to be associated with fewer oestrogen withdrawal symptoms than a traditional pill with a seven-day hormone break.[11,12]

Pills with a shortened or absent hormone-free break (extended-cycle regimens)

The benefits of reducing or eliminating the seven-day hormone-free break are now well established.[11,12] Two COCs have been formulated with 24 hormone pills and four inactive pills (the COC containing 20 µg EE and 3 mg drospirenone [Yaz] and the COC containing E2 and nomegestrol acetate [Zoely]), whereas the quadriphasic pill containing EV and dienogest (Qlaira) substitutes the hormone-free break with four days of EV only and two days of inactive tablets. Reducing the number of inactive pills provides a greater margin for error if the first hormone pills

in the cycle are missed and may provide higher contraceptive effectiveness than the traditional 21 day/seven day regimens.[13,14]

Extended COC use without a hormone-free break can be used to avoid bleeding at inconvenient times, minimise withdrawal bleeding and avoid symptoms of PMS, withdrawal headaches or pelvic pain in the hormone-free break.[15,16] Evidence supports the safety of up to 12 months of continuous active pill use, and breakthrough bleeding with extended use generally improves over time as the endometrium stabilises. Although no studies of continuous use beyond 12 months are available, no safety concerns have been identified.[15]

Many women have historically self-initiated extended-cycle COC use with support from their GPs. Traditionally, this has involved 'tricycling' by running three cycles of hormone pills together and omitting the hormone-free break for two packs out of three. Some women also continue to take active hormone pills without a break for up to 12 months at a time. An electronic dispensing device is available to support the use of a flexible extended-cycle regimen for a COC containing 20 µg EE and drospirenone (Yaz Flex).[17] However, women can be instructed how to manage this regimen with any standard COC pack.

Recently, a new pill (Seasonique) has become available in Australia that provides a prepackaged extended cycle of three consecutive months (84 days) of tablets containing 30 µg EE and 150 mg LNG followed by seven days of tablets containing 10 µg EE. Compared with traditional 'do-it-yourself' tricycling by taking extended consecutive active pills followed by a seven-day hormone-free interval, there is greater suppression of the pituitary ovarian axis and follicle development due to the reduced, rather than absent, hormone break.[18] This is likely to be beneficial for women who experience withdrawal symptoms in the hormone-free break because the EE levels are not reduced to zero. In addition, this new pill provides a lower risk of breakthrough bleeding particularly after the first cycle, and overall blood loss is reduced compared with traditional regimes.[18,19] Although Seasonique is not PBS-listed and cost may be a deterrent, it offers a convenient and easy to use alternative for women who can afford it, with additional potential benefits over running together packs of PBS-listed LNG/EE pills followed by a hormone-free interval.

Rather than following a tricycling regimen, some women may prefer a 'menstrually-signalled' regimen that involves continuing hormone pills until four days of bleeding or spotting occur and then instituting a four-day hormone-free break.[17]

Explaining that extended-cycle use is not damaging to health and that 'blood is not building up inside' can be reassuring to a patient. However, despite the advantages of either prepackaged or 'do-it-yourself' extended-cycle regimens, some women still prefer the predictability and reassurance of a regular withdrawal bleed.

Pills with progestogens other than LNG

Progestogens including cyproterone acetate, gestodene, desogestrel, drospirenone, dienogest and nomegestrol acetate have been developed to avoid androgenic side effects and to have a minimal influence on EE-induced lipid changes. Some studies suggest that pills containing 30 to 35 µg EE and either desogestrel, gestodene, cyproterone acetate or drospirenone increase the risk of VTE compared with pills containing LNG or NET by a factor of about 1.5 to 1.8. However, the absolute risk of VTE associated with any COC remains low.[20]

Some of these newer formulations offer additional potential benefits for hormonally-dependent conditions such as acne or premenstrual dysphoric disorder (PMDD), and some have TGA-approved indications for these conditions (Table). These indications are largely based on studies that prove superiority against placebo rather than against other COCs. There is insufficient clinical evidence to routinely and preferentially prescribe these progestogens over LNG formulations.

However, selecting a COC with a progestogen other than LNG for a pre-existing condition can be considered in the clinical situations described below.

Acne and hirsutism

The oestrogen in any COC may improve acne due to its effect on increasing sex hormone-binding globulin levels, which results in a reduction in free testosterone, even at a low dose or when combined with a relatively androgenic progestogen.

COCs containing an antiandrogenic progestogen (i.e. cyproterone acetate, drospirenone or dienogest) or a less androgenic progestogen (i.e. gestodene, desogestrel or nomegestrol acetate) have a theoretical advantage for the management of patients with androgenic symptoms. However, the older PBS-listed COCs containing NET may confer a potential benefit as NET is partially converted to EE (albeit at a rate of less than 0.5%).[21] A beneficial effect can take up to six months and, importantly, a Cochrane review concluded that there is little difference between COC types in treating acne.[2]

Premenstrual syndrome and premenstrual dysphoric disorder

The 20 µg EE/3 mg drospirenone pill (Yaz) has been shown to be more effective than placebo in treating patients with PMDD over a three-month course.[22] The effect is likely to be due to a combination of the shortened hormone-free break and the spironolactone-like properties of drospirenone. It is unknown whether the effect is similar in women with milder symptoms of premenstrual syndrome (PMS), if it persists beyond three months or is superior to other COCs.

Extended-cycle regimens of other COCs have been shown to be beneficial in managing women with PMDD or PMS.[9,10]

Heavy menstrual bleeding

All COCs are potentially effective in reducing menstrual blood loss through their overall antiproliferative effect on the endometrium. The quadriphasic EV/dienogest pill (Qlaira) and the E2/nomegestrol acetate pill (Zoely) are associated with rates of amenorrhoea up to 20% and 30% in their two-day and four-day hormone-free breaks, respectively.[9,10] Qlaira is very effective compared with placebo in the treatment of women with heavy menstrual bleeding,[3] but it is unclear whether it is superior to other COCs in this regard. Using an extended-cycle COC, such as Seasonique, or running individual pill packs together in an extended regimen without a hormone-free break may also be helpful. If COCs with E2 or EV are found to confer safety benefits at least equivalent to EE pills, they could potentially become a first-line choice for medically eligible women over 40 years of age with idiopathic heavy menstrual bleeding who prefer not to use a hormonal IUD.

Conclusion

New constituents and extended-cycle regimens for COCs offer potential safety advantages and reduced nuisance side effects and provide non-contraceptive benefits for women with hormonally-dependent conditions. Women preferring a COC over a long-acting reversible contraceptive method need to be made aware of the pros and cons of the different COCs to find the 'best fit' for their circumstances and stage of reproductive life. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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