

An extended-regimen combined hormonal contraceptive pill

KATHLEEN McNAMEE MB BS, FRACGP, DipVen, GradDipEpiBio, MEpi
DEBORAH BATESON MA(Oxon), MSc(LSHTM), MB BS

A combined hormonal contraceptive pill with an extended regimen (84 active pills plus seven inactive pills) became available in Australia in 2016. It has the advantage of straightforward dedicated packaging designed to limit withdrawal bleeds to four per year.

A combined hormonal contraceptive pill with a 91-day extended regimen became available in Australia in 2016. It contains 30mcg ethinylestradiol (EE) and 150mcg levonorgestrel for 84 consecutive days, followed by 10mcg EE for seven days (84/7 EE regimen). Users can expect four withdrawal bleeds per year, compared with 13 for users of a traditionally packaged cycle of 21 active hormonal pills followed by seven inactive sugar pills (21/7 regimen). Although women who use a 21/7 regimen pill may choose to run three or four packs together, followed by a seven-day hormone-free break, substituting the hormone-free week with a low daily dose of EE may be an advantage for those who experience oestrogen-withdrawal symptoms during the break.

How is the 84/7 EE pill used?

The 84/7 EE formulation can be recommended as a first-line choice for women wishing to start a combined hormonal contraceptive pill. As this pill combines a low dose of EE with levonorgestrel, it is considered to be a 30mcg EE-containing pill, which is associated with the lowest excess risk of venous thromboembolism.¹ The 84/7 EE pill is more than 99% effective in perfect use and appears to be at least as effective as other combined

MedicineToday 2017; 18(10): 67-69

Dr McNamee is Medical Director Family Planning Victoria, Melbourne; and Adjunct Senior Lecturer in the Department of Obstetrics and Gynaecology, Monash University, Melbourne, Vic. Dr Bateson is Medical Director of Family Planning NSW; and Clinical Associate Professor in the Discipline of Obstetrics, Gynaecology and Neonatology, University of Sydney, Sydney, NSW.



hormonal methods of contraception (summarised in Box 1).²

In line with current recommendations, the package is designed to start with an active pill and comes with seven sets of 'day of the week' stickers.³ The user places the sticker strip at the top of the pack corresponding to the day of the week on which she starts taking the daily pill. This helps ensure earlier contraceptive cover than with some other currently available pills that are packaged to begin with either an active or inactive pill, depending on the day of the week on which use begins. This straightforward packaging, which supports extended use of the pill for three months at a time, can help minimise confusion. 'Day of the week' packaging is available in only two other combined hormone pill formulations in Australia: estradiol valerate–dienogest and estradiol–norgestrel.

Although the 84/7 EE pill is not PBS listed and is considerably more expensive than a traditionally packaged pill containing the same dose of contraceptive hormones, it may offer advantages to some women through both its packaging and the replacement of the hormone-free week with a low-EE break.

Features of extended regimens Fewer scheduled bleeds

Extending the length of the menstrual cycle is a widespread, albeit mostly off-licence, practice that was first reported in a 1992 Australian study.⁴ International studies show that most women prefer less than one bleed per month, with a substantial minority preferring no bleeding.⁵

Some women express concern about a build up of the endometrial lining and a delay in the return of fertility as a result of fewer bleeds, although evidence does not support these concerns.⁶ A study of women taking a low-dose EE–levonorgestrel pill designed for a year's use without a hormone-free break showed return of ovulation for most women within 32 days of stopping the method.⁷ Biopsies showed no adverse changes in the endometrial lining in users of the 84/7 EE formulation either during the combined hormone or 10mcg EE phases of the cycle.⁶

1. SUMMARY OF AVAILABLE COMBINED HORMONAL CONTRACEPTIVE PILL REGIMENS

- 21/7 regimen: 21 combined hormonal pills and 7 inactive sugar pills in a 28-day pack
- 24/4 regimen: 24 combined hormonal pills and 4 inactive sugar pills in a 28-day pack
- 84/7 EE regimen: 84 combined hormonal pills and 7 low dose 10mcg EE only pills in a 91-day pack
- 84/7 regimen: 84 combined hormonal pills and 7 inactive sugar pills (commercial product not available; created by running four 21-day pill packs together)

Abbreviation: EE = ethinylestradiol.

Women taking combined hormonal contraception who wish to reduce episodes of bleeding can do so by skipping the hormone-free break. Those using combined pills can skip the inactive sugar pills, and those using a vaginal ring can replace the ring every three to four weeks without a hormone-free break. For combined pills, this is most straightforward with traditional 21/7 regimens.

Extended use can also be applied to the pills containing 24 hormone pills and four inactive sugar pills (24/4 regimen): estradiol–norgestrel and 20mcg EE–drospirenone. The estradiol–norgestrel 24/4 formulation is the easier of these for extended use as the starting ‘day of the week’ sticker can be changed with each pack.

As an alternative to extended use of a pill with a scheduled break, women can employ a menstrually signalled regimen, whereby hormonal pills are taken continuously until unscheduled bleeding occurs for more than four days in row. The woman then takes a four-day hormone break. This is most easily achieved using a 20mcg EE–drospirenone pill dispensed by an ‘intelligent’ device that can be programmed to allow for the four-day breaks.⁸ It can also be achieved with regular pill packaging, but there is greater potential for confusion.⁹

The 84/7 EE formulation is designed for women to have four withdrawal bleeds per year. The dedicated packaging will be of benefit to some women.

Unscheduled bleeding

Unscheduled bleeding is more likely to be a problem with extended regimens than with traditional 21/7 regimens.¹⁰ Over the course of four 91-day cycles of the 84/7 EE pill, the mean number of days of unscheduled bleeding or spotting markedly decreased. In the first 91-day cycle, there was a mean of 14.3 days of unscheduled bleeding or spotting.² By the fourth 91-day cycle this had dropped to 7.6 days, similar to the unscheduled bleeding profile of a traditional 21/7 regimen.^{2,11} Part of this drop might be accounted for by a higher rate of discontinuation due to unscheduled bleeding. One study showed that 7.4% of women using the 84/7 EE formulation discontinued for this reason compared with 1.1% using the traditional 21/7 regimen.¹⁰

However, limited data suggest discontinuation for all reasons of the 84/7 EE regimen pill is similar to that of traditional 21/7 regimens.^{10,12}

Efficacy

During the hormone-free interval in 21/7 regimens, the ovarian suppression induced by synthetic hormones ceases, levels of follicle-stimulating hormone (FSH) and estradiol rise, and follicle sizes increase. If active pills are missed either side of this break then breakthrough ovulation may occur.¹³ The lower exposure to these vulnerable times as a result of an extended regimen potentially increases efficacy. This is supported by physiological data showing that women who extend their use of active combined pills do not experience a four-weekly cyclical rise in FSH and estradiol levels. Limited clinical data in a typical use setting also support a lower risk of pregnancy with 84/7 regimens compared with 21/7 regimens.¹⁴

In addition, supplementing the traditional seven-day hormone break with low dose EE, as in the 84/7 EE pill, is associated

with less follicle development than occurs with an 84/7 regimen with a seven-day hormone-free break. Hence it is likely to lower the risk of breakthrough ovulation even further.^{15,16}

Oestrogen withdrawal

The drop in synthetic oestrogen levels during the hormone-free interval of hormonal contraceptive regimens is thought to be associated with symptoms such as headache, pelvic pain and breast tenderness.¹⁷ Many studies show that extended regimens are associated with fewer of these withdrawal symptoms.¹² Fewer symptoms also occur in women using the quadruphasic estradiol valerate–dienogest pill which was designed to limit the oestrogen drop.¹⁸ The 84/7 EE regimen pill has been designed to incorporate both these mechanisms, but evidence to support a reduction in oestrogen withdrawal symptoms in its users is lacking.

Prescribing combined hormonal methods

Contraindications, serious risks and side effects

Although few studies have progressed beyond one year, there are thought to be no additional safety concerns for the 84/7 EE pill compared with traditional 21/7 regimen pills. Contraindications, serious risks and side effects are considered to be no different to those of other combined hormonal pills. As for all combined hormonal pills, the most important contraindications relate to the risk of arterial vascular disease and venous thromboembolism as well as a history of breast cancer (Box 2). Eligibility for all methods of contraception can be most easily determined by use of the UK Medical Eligibility Criteria, freely available for download (www.fsrh.org).¹⁹

Serious risks of combined hormonal methods of contraception include venous thromboembolism and a probable increased risk of myocardial infarction and stroke. There is a small increase in the risk of cervical cancer and possibly of breast cancer. In addition, there is a small

2. MAJOR CONTRAINDICATIONS TO COMBINED HORMONAL CONTRACEPTIVES

- Migraine with aura
- Body mass index over 35 kg/m²
- Past or current
 - venous thromboembolism
 - ischaemic heart disease
 - cerebrovascular disease
 - breast cancer
- Family history of venous thromboembolism in a first-degree relative aged under 45 years
- Hypertension
- Severe liver disease or liver tumours
- Breast feeding in the first six weeks postpartum

increase in the risk of gall bladder disease and inflammatory bowel disease.

Reported side effects of the 84/7 EE pill, with the exception of higher rates of unscheduled bleeding, are similar to those of other combined hormonal methods. They include weight gain, headaches and nausea.²⁰

Medication interactions and potential benefits

As with all combined hormonal methods of contraception, concurrent use of liver enzyme-inducing medications is associated with lower efficacy of the 84/7 EE regimen pill.

Although there are no long-term studies, the benefits in relation to acne and a reduction in ovarian and endometrial cancers are expected to be similar to those of other combined hormonal methods.

Monitoring

All women taking combined hormonal methods generally need yearly blood pressure monitoring and calculation of body mass index.

Summary

The 84/7 EE pill can be prescribed as a first-line combined hormonal method of

contraception. The benefits of an extended cycle can be achieved with less expensive pills; however, the straightforward dedicated packaging of the 84/7 EE pill may be preferred by some women. The substitution of seven days of 10 mcg EE tablets for the traditional hormone-free interval may additionally help women who experience oestrogen-withdrawal symptoms, although studies of this formulation are currently lacking.

MT

References

1. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ* 2015; 350: h2135.
2. Anderson FD, Gibbons W, Portman D. Safety and efficacy of an extended-regimen oral contraceptive utilizing continuous low-dose ethinyl estradiol. *Contraception* 2006; 73: 229-234.
3. Family Planning New South Wales, Family Planning Victoria, True Relationships and Reproductive Health. *Contraception: an Australian clinical practice handbook*. 4th edition. Sydney: FPA; 2016.
4. Kovacs G, Rusden J, Evans A. A trimonthly regimen for oral contraceptives. *Br J Fam Plann* 1994; 19: 274-275.
5. Nappi RE, Kaunitz AM, Bitzer J. Extended regimen combined oral contraception: a review of evolving concepts and acceptance by women and clinicians. *Eur J Contracept Reprod Health Care* 2016; 21: 106-115.
6. Anderson FD, Feldman R, Reape KZ. Endometrial effects of a 91-day extended-regimen oral contraceptive with low-dose estrogen in place of placebo. *Contraception* 2008; 77: 91-96.
7. Davis AR, Kroll R, Soltes B, Zhang N, Grubb GS, Constantine GD. Occurrence of menses or pregnancy after cessation of a continuous oral contraceptive. *Fertil Steril* 2008; 89: 1059-1063.
8. Jensen JT, Garie SG, Trummer D, Elliesen J. Bleeding profile of a flexible extended regimen of ethinylestradiol/drospirenone in US women: an open-label, three-arm, active-controlled, multicenter study. *Contraception* 2012; 86: 110-118.
9. Weisberg E, Merki-Feld GS, McGeechan K, Fraser IS. Randomized comparison of bleeding patterns in women using a combined contraceptive vaginal ring or a low-dose combined oral contraceptive on a menstrually signaled regimen. *Contraception* 2015; 91: 121-126.
10. Europeans Medicines Agency. Assessment report. Seasonique and associated names. London: European Medicines Agency; 2015. Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Seasonique_29/WC500181068.pdf (accessed September 2017).
11. Oddsson K, Leifels-Fischer B, Wiel-Masson D, et al. Superior cycle control with a contraceptive vaginal ring compared with an oral contraceptive containing 30 microg ethinylestradiol and 150 microg levonorgestrel: a randomized trial. *Hum Reprod* 2005; 20: 557-562.
12. Edelman A, Micks E, Gallo MF, Jensen JT, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *Cochrane Database Syst Rev* 2014; (7): CD004695.
13. Zapata LB, Steenland MW, Brahm D, Marchbanks PA, Curtis KM. Effect of missed combined hormonal contraceptives on contraceptive effectiveness: a systematic review. *Contraception* 2013; 87: 685-700.
14. Howard B, Trussell J, Grubb E, Lage MJ. Comparison of pregnancy rates in users of extended and cyclic combined oral contraceptive (COC) regimens in the United States: a brief report. *Contraception* 2014; 89: 25-27.
15. Schlaff WD, Lynch AM, Hughes HD, Cedars MI, Smith DL. Manipulation of the pill-free interval in oral contraceptive pill users: the effect on follicular suppression. *Am J Obstet Gynecol* 2004; 190: 943-951.
16. Vandever MA, Kuehl TJ, Sulak PJ, et al. Evaluation of pituitary-ovarian axis suppression with three oral contraceptive regimens. *Contraception* 2008; 77: 162-170.
17. Sulak PJ, Cressman BE, Waldrop E, Holleman S, Kuehl TJ. Extending the duration of active oral contraceptive pills to manage hormone withdrawal symptoms. *Obstet Gynecol* 1997; 89: 179-183.
18. Jensen JT, Parke S, Mellinger U, Serrani M, Mabey RG Jr. Hormone withdrawal-associated symptoms: comparison of oestradiol valerate/dienogest versus ethinylestradiol/norgestimate. *Eur J Contracept Reprod Health Care* 2013; 18: 274-283.
19. Faculty of Sexual and Reproductive Healthcare. UK medical eligibility criteria for contraceptive use (UKMEC). London: FSRH; 2016. Available online at: <http://www.fsrh.org> (accessed September 2017).
20. Teva Pharma Australia. Product information: Seasonique (levonorgestrel and ethinylestradiol). Sydney: Teva Pharma Australia; 2016.

COMPETING INTERESTS: Dr McNamee has received support to deliver a conference talk by MSD. Dr Bateson has received support to present at educational conferences and attend advisory committees on behalf of Family Planning NSW from Bayer Healthcare and MSD. She has also attended an advisory committee for Teva Pharmaceuticals.

This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

