Evolution of extended use of the combined oral contraceptive pill

Sabeena Panicker,¹ Sue Mann,² Jill Shawe,³ Judith Stephenson⁴

¹Specialist Registrar in Obstetrics & Gynaecology, Sexual and Reproductive Health Research Group, Institute for Women's Health, University College London, London, UK

²Consultant, Kings College Hospital, London; Clinical Research Associate, Sexual and Reproductive Health Research Group, Institute for Women's Health, University College London, London, UK

³Senior Research Associate, Sexual and Reproductive Health Research Group, Institute for Women's Health, University College London, London, UK

⁴Margaret Pyke Professor of Sexual & Reproductive Health, Sexual and Reproductive Health Research Group, Institute for Women's Health, University College London, London, UK

Correspondence to

Professor Judith Stephenson, Institute for Women's Health, University College London, Medical School Building, 74 Huntley Street, London WC1E 6AU, UK; judith.stephenson@ucl.ac.uk

Received 28 January 2013

Revised 4 September 2013

Accepted 3 February 2014

ABSTRACT

Background Extended use of the combined oral contraceptive pill (COC), defined as taking active pills for at least 28 days, has been used in order to avoid bleeding at important times and to treat gynaecological conditions such as endometriosis. We examined the main issues involved in extended use of the COC and how it has evolved from being one of medicine's best-kept secrets to becoming more widely accepted by women and the medical community.

Study design Literature review, using Medline, Embase, Pubmed, CINHAL Plus, the Cochrane Database of Systematic Reviews and the Ovid database for all relevant clinical trials, systematic reviews, meta-analyses, literature reviews, scientific papers and individual opinions between 1950 and October 2013.

Results Accumulating evidence supports various forms of extended pill use as suitable alternatives to the standard (21/7) regimen. In terms of user preference, much hinges on whether women wish to reduce the frequency or duration of scheduled bleeding on the combined pill. Available data on the safety of extended pill regimens do not give cause for concern, but longer term data should be collected.

Conclusions Information for women considering extended COC regimens should keep pace with research findings to ensure that women and clinicians are better informed about the choices available.

INTRODUCTION

The combined oral contraceptive pill (COC), introduced in the late 1950s, provided a means of controlling fertility that revolutionised women's lives. When the COC was developed by Gregory Pincus and John Rock its dosage regimen was designed to mimic the natural menstrual cycle, with the first hormonal pills to be licensed for use in 1957¹ being a high dose combination of 150 µg mestranol and 10 mg norethynodrel for the treatment of menstrual disorders. It was only in 1960 that an oral contraceptive pill

Key message points

- ▶ Extended combined oral contraceptive (COC) use, with suppression or reduction in frequency of menstruation, is now an acceptable option and information about this approach should be made more widely available.
- ▶ Continuation rates for extended COC use are similar to the standard regimen.
- ▶ There are no current safety concerns about extended COC use but longer-term data are needed.

(Enovid®), containing 75 µg mestranol and 5 mg norethynodrel, was licensed for use in the USA, giving women hormonal control over their fertility for the first time.²

Half a century later, it is widely accepted that there is no scientific rationale to support the induction of a scheduled bleed every 28 days.³ The standard 21/7 regimen (in which a pill is taken daily for 21 days, followed by a 7-day pill-free interval) was decided upon more to pre-empt potential objections on religious and psychological grounds as the induced monthly bleed carries no documented health benefit to the woman.³ In fact, this artificially induced bleed that is not comparable with the monthly menstrual bleeding of non-pill users can be associated with hormone withdrawal symptoms⁴ and a small risk of escape ovulation and unintended pregnancy. Nonetheless, it was believed that women would feel uneasy about not having monthly 'periods' and would welcome a predictable scheduled bleed. The 21/7 regimen was therefore rapidly adopted.³

The extended use of the COC, defined as greater than 28 days of active pills,⁵ has thus gradually gained acceptance

To cite: Panicker S, Mann S, Shawe J, et al. *J Fam Plann Reprod Health Care* 2014;**40**:133–141.

among users and clinicians alike, with the US Food and Drug Administration (FDA) granting approval to the first extended-cycle COC in 2003; it is now viewed by many clinicians as a positive development that liberates and empowers women.⁶

Extended COC regimens fall into three categories: (1) scheduled extended cycles – where the COC is taken for a predetermined number of days followed by a hormone-free interval (HFI) of seven or fewer days, including tri-cycling (where three packs of 21 pills are taken without a HFI); (2) unscheduled extended cycles – when the COC is taken continuously for a minimum of 28 days after which the occurrence of persistent unscheduled bleeding would be the signal for a HFI; or (3) continuous use – continuous use of the COC without a HFI, whether or not bleeding occurs, for as long as the woman wishes.⁷ This review looks at the main issues involved in these novel pill regimens and the ways in which they have gradually changed from being deviations from the norm to becoming accepted both by pill users and the medical establishment.

METHODS

A literature review was conducted using the Cochrane Database of Systematic Reviews, Medline, Embase, Pubmed, CINAHL Plus and the Ovid database for all relevant clinical trials, systematic reviews, meta-analyses, literature reviews, scientific papers and individual opinions between 1950 and October 2013. Search terms used included: history extended contraception; history extended pill; history contraception; extended cycle; contraception; pill-free break; pill-free interval; short pill-free interval; hormone-free interval; combined pill; combined oral contraceptive pill; combined oral contraceptive; oral contraception; continuous combined contraception; extended pill use; tri-cycling and pill; back-to-back; break-through bleeding; intermenstrual bleed; irregular bleed; unscheduled bleed; menstrual; frequency of menses; amenorrhoea; withdrawal bleed; monthly bleed; periodic withdrawal; hormone withdrawal; cycle length; compliance; discontinuation; well-being; side-effects; skin changes; acne; weight gain; breast tenderness; mastalgia; premenstrual symptoms; bloating; mood; sexuality; libido; sexual; dysfunctional uterine bleeding; menorrhagia; abnormal uterine bleeding; heavy menstrual bleeding; dysmenorrhoea; painful period; period pain; endometriosis; chocolate cyst; ovarian cyst; polycystic ovaries; morbidity; mortality; breast cancer; colon; cervical; death; long-term survival; outcomes. The search was limited to humans and to the English language.

RESULTS

Significance of the pill-free interval

The standard COC currently comes in packs of 21 hormonal or active pills, with or without seven placebo pills. The 7-day HFI produces a scheduled

bleed which can be reassuring for women as a signal of the absence of pregnancy, but plays no role in contraceptive efficacy. In fact, withdrawing the hormone for 7 days allows ovarian follicular development that may result in escape ovulation and unintended pregnancy,⁹ particularly if there is a delay in re-starting the next pill pack.¹⁰ Using high-resolution transvaginal ultrasonography (TVS) and measurement of blood levels of estradiol, follicular development due to loss of hypothalamo-pituitary suppression has been shown to occur as early as 3–4 days into the 7-day HFI.¹¹ As the hormonal content of the COC has been reduced over the past few decades, such pituitary-ovarian activity during the standard HFI, leading to follicular development and escape ovulation, has become more common¹² and this may be a particular concern in overweight and obese women.^{13 14}

However, although most women regard the monthly period as a fact of life, Thomas and Ellertson have questioned the general assumption that monthly menstruation is a 'natural' phenomenon. They argue that in hunter-gatherer times, women had as few as 50 menstruations per lifetime due to closely spaced pregnancies, prolonged breastfeeding and short lifespans; in contrast, the modern woman has approximately 450 bleeding episodes.⁸ There has been much debate in the wider scientific literature and the press about the role that 'incessant' ovulation plays in the reproductive lives of women in a modern industrialised society. Whilst offering no obvious benefits other than being part of the human reproductive process, ovulation and menstruation are responsible for the common problems of anaemia, dysmenorrhoea, mood changes, migraine and growth of fibroids.¹⁵ Further, it has been argued that as women have evolved away from the physiological 'norm' of continuous reproduction, they have been rendered more susceptible to reproductive cancers.¹⁶ The view that the COC may actually have a primary role in the prevention of cancers has gained popularity and in a powerful and well-argued article, the writer Malcolm Gladwell suggested that greater focus on the wider health benefits of the COC as they emerged might have helped it to gain greater acceptance in its early days.¹⁷

Continuous COC use

Whilst arguments against the need for either menstruation or an artificially induced scheduled bleed on the combined pill have gained wider acceptance more recently, manipulation of the pill-free interval has been clinically endorsed since the 1960s. To the surprise of many women, clinicians have, for many years, been regularly advising women on the off-label use of the COC to avoid bleeding during important life events such as honeymoons, business meetings and sports competitions.¹⁸ Continuous administration of COCs to abolish menstruation has also come to be

dissociated from the need for contraception and is instead accepted as treatment for gynaecological conditions such as endometriosis,¹⁹ dysmenorrhoea,²⁰ heavy menstrual bleeding (HMB) and menstruation-associated symptoms.^{21–22} It is often prescribed in the adolescent age group for the treatment of HMB, premenstrual symptoms, acne and hirsutism,²³ as well as in those with bleeding diatheses or catamenial seizures where avoidance of menstruation is indicated.²⁴ Extended regimens have also been tried in young women with cyclical behavioural problems such as self-mutilation and aggression, and in aiding personal hygiene in women with severe developmental or learning disabilities by the avoidance of menstrual bleeding.²⁵

Studies have documented the benefits of extended pill use in mature women with endometriosis, including relief from dysmenorrhoea and from pill-withdrawal migraines when compared with previous cyclical pill use,²⁶ and a reduction and delay of endometrioma recurrence after surgical excision.²⁷ The avoidance of menstruation through extended use of COCs for reasons of personal preference may have the additional benefits of improved compliance, greater user satisfaction, fewer menstrual symptoms, and less menstruation-related absenteeism from work or school.⁵

Benefits of extended COC use

Although traditional cyclical COC use is highly effective and safe, between one-third and two-thirds of women who wish to avoid pregnancy will stop the pill after 1 year, with irregular bleeding being one of the commonest causes.^{28–29} Numerous studies have aimed to determine more precisely the effects of extended COC use, in attempts to improve both contraceptive choice and continuation rates.^{12–30}

Avoidance of menstruation

Studies over the years have found that women are open to the concept of menstrual manipulation although there has been no large scale shift in prescribing practices to date. Over 35 years ago, Loudon *et al.* conducted a clinical trial of continuous pill use for 84 days, resulting in the reduction of the frequency of menstruation to once every 3 months. No pregnancies were reported and 82% of the participants welcomed the reduction in the number of periods, while 91% of the women completing the study refused to return to the standard way of pill-taking despite the advice of their clinicians.³¹ Another study conducted by den Tonkelaar *et al.*³² in the late 1990s, involving computer-assisted telephone interviewing of 1642 women, found that up to 80% of Dutch women were unhappy with their menstrual cycle and that most menstruating women preferred to have a bleeding frequency of less than once a month or never.

Based on findings from studies carried out in the Netherlands, Germany, France and Italy, a more recently published article argued that increasing numbers of Western European women either prefer to avoid periods altogether or would like to have a longer interval between periods.³³ However, a survey of Spanish women revealed a more conservative attitude, with 80.2% of the 588 surveyed considering menstruation to be a 'necessary natural event' and only 24.5% expressing an interest in an extended use COC regimen.³⁴ Interestingly, a survey of American female military personnel deployed to Iraq and Afghanistan found that in the face of problems like disposal of hygiene products, lack of privacy and the arduous nature of the work itself, 86% expressed a desire for mandatory education regarding extended pill use for all women joining the military.³⁵

Improvement in menstrual-related symptoms

As with the use of injectable contraceptives where amenorrhoea is common,^{36–37} research into the implications of extended COC use over the decades has revealed a reduction in menstrual-related symptoms and number of bleeding days, thus persuading both women and clinicians to move towards continuous pill regimens.^{36–38} Moreover, the majority of women in these studies expressed a preference for extended pill use despite the occurrence of unscheduled bleeding or spotting, based on an improvement in their quality of life.^{39–40}

Better efficacy

A study of 900 healthy women of reproductive age from Brazil, Egypt and China conducted in the early 1990s randomised women to either daily vaginal use of the contraceptive pill for 21 days with a 7-day break or to uninterrupted daily use of the pill by the vaginal route for 1 year. Continuous vaginal pill use was found to offer some advantage over cyclical vaginal use in terms of an increase in haematocrit and a difference in pregnancy rate between the two groups that was statistically significant ($p=0.048$).⁴¹

The first large-scale randomised controlled trial (RCT) of an extended-cycle COC [Seasonale®: 30 µg ethinylestradiol (EE)/150 µg levonorgestrel] in women up to the age of 40 years conducted in 2003 found that the extended-cycle regimen was both as safe and effective in preventing pregnancy as the 28-day control regimen. Participants were given either four 91-day cycles of extended-cycle regimen COC or 13 cycles of the conventional 28-day COC and were monitored daily for compliance and bleeding through the use of electronic diaries. It was found that patients on the extended-cycle regimen had a significant reduction in total days of scheduled bleeding/spotting compared to those on the conventional regimen. Although unscheduled bleeding was reported among the extended-cycle users, it decreased with each successive cycle of therapy and settled into a pattern

comparable to that reported by patients on the conventional regimen by the fourth extended cycle.⁴² Recent studies have shown no reduction in efficacy in obese or overweight women on extended-cycle COC.⁴³

A comprehensive review of the extended use of the COC also confirmed that its effects on metabolic and hormonal parameters as well as the endometrium were similar to those of cyclical use of the pill.⁴⁴ In a small trial conducted to follow ovarian follicular and endometrial development during and after conventional versus continuous regimens, 36 women were followed with high-resolution TVS. Overall, fewer follicles were noted during continuous COC use when compared to conventional use ($p=0.001$), while more dominant follicles (>10 mm) developed during conventional COC use with none noted during continuous COC use ($p=0.01$). Interestingly, all dominant follicles were initiated during the HFI.⁴⁵

Improved bleeding patterns and better compliance

One of the arguments put forward in favour of extended pill use is its ability to reduce the number of days of menstruation with consistent use.⁹ A Cochrane review of eight clinical trials of extended pill use concluded that continuous dosing of COCs was a reasonable approach when compared to traditional cyclic dosing as it had similar participant satisfaction, discontinuation rates (overall and for bleeding problems) and participant adherence while improving menstruation-associated symptoms and possibly bleeding patterns. However, none of the trials was large enough to provide data on differences in safety or contraceptive efficacy.⁴⁶

Many well-designed studies have shown that unscheduled bleeding tends to decrease with duration of continuous use of the COC.^{47–49} In a study conducted to assess the long-term efficacy and safety of a low-dose monophasic COC containing 0.02 mg ethinylestradiol and 2 mg chlormadinone acetate administered daily for 24 days followed by a 4-day placebo interval, only 52 of 1665 trial subjects (3.1%) terminated their trial participation due to bleeding irregularities.⁵⁰

Concerns relating to extended COC use

As with many innovative practices, the hormonal manipulation of the menstrual cycle, too, has attracted scepticism and concern, both among clinicians and pill-users. Currently, the American College of Obstetrics and Gynecology recommends continuous COC for menstrual suppression in the long term,⁵¹ while the Faculty of Sexual & Reproductive Healthcare has moved in the last 4 years from mentioning extended COC use as a possible option in the management of unscheduled bleeding⁵² to supporting the use of such regimens, albeit off licence.⁵³

Safety

The safety of continuous COC use has been demonstrated in many studies, with no changes in blood pressure or weight observed, and metabolic changes being comparable with those noted in patients on the standard arm.⁵⁴ Other well-designed RCTs have found no significant differences in the changes in haemostatic variables or in blood lipid or lipoprotein levels between the two groups.^{55 56} The use of a flexible extended regimen of EE/drospirenone (DRSP) over a study period of 2 years was shown to have an acceptable safety profile with no deaths reported and only four serious adverse events that were possibly related to the study medication: focal nodular hyperplasia, uterine leiomyoma and two cases of deep vein thrombosis. No statistically significant differences were noted in the lipid parameters, haemostatic variables or carbohydrate metabolism in comparison with the conventional regimen.⁵⁷

Return of fertility

Return of fertility following long-term continuous use of the COC has been another major concern, but results of studies have thus far been reassuring with an almost universal return to menses or commencement of pregnancy, with a median time to return to menses of 32 days.⁵⁸ This finding accords with a study of ovarian activity following a continuous COC regimen in which ovulation was documented by ultrasound and serum hormone levels within 3 weeks of stopping the pill in all but one of the 37 participants.⁵⁹ Recent reviews of return of fertility following extended and continuous COC use found no RCTs, but concluded from the available evidence that return to fertility after discontinuation of extended regimens is comparable to that following cyclic COC use.^{60 61}

Effects on endometrium

Concern about the possible effects of extended COC use on the uterus is commonly expressed by women. A review of a multi-centre non-blind trial comparing continuous COC use with traditional cyclical administration noted no cases of hyperplasia or malignancy.⁶² Other large well-designed studies of extended-cycle COC regimens confirmed that extended/continuous use is safe and does not lead to hyperplasia or other endometrial pathology after long-term use.^{63 64}

Irregular/unpredictable bleeding patterns

Unscheduled bleeding is a common adverse effect with extended-cycle COC regimens.^{65 66} However, this has been found to decrease with each successive cycle of extended pill use.⁴² Another large randomised, open-label, multicentre study across 44 clinical sites in Europe comparing safety and efficacy of continuous and cyclical use of COC confirmed a progressive increase in the percentage of women with no bleeding or spotting and amenorrhoea over one year.⁶⁷

Attitudes/concerns among clinicians

The personal use of extended COC regimens by female gynaecologists possibly dates back to the late 1960s. A recent survey in 2010 of female gynaecologists working in private practices and outpatient clinics in Germany ($n=2000$) and Austria ($n=500$) found that 97.1% had prescribed the extended COC regimen at some point, with 94% considering it safe and only 3% expressing concerns relating to effects on the breast, fertility and other adverse effects.⁷⁰ These results are in keeping with those of prospective, anonymous, written surveys conducted in 2004 and in 2011 to assess attitudes and patterns of health care providers in the USA prescribing COCs, which revealed an increasing tendency among clinicians to prescribe extended regimens.^{71–73} Equally, some clinicians have viewed this trend towards avoidance of menstruation with concern, as is clear from a systematic review of the literature on extended use of the COC up to 2003, the watershed year in which it was approved by the US FDA. It appeared that women on extended COC regimens tended to have more days of unscheduled bleeding as well as headaches, leading to higher discontinuation rates. The authors also sounded a warning regarding the lack of evidence with respect to the effects of extended COC use on breast tissue, breast density, endometrial safety and adolescent maturation and reproductive development and they were unable to locate any data on the return to reproductive function and fertility after extended COC use.⁷⁴

In contrast, a subsequent review of the literature on extended pill use in adolescents recommended that extended cycling should be considered an option for all young women on hormonal contraception, with no increase in clinical risk due to the additional hormonal exposure when compared with the traditional regimen.²⁴ This view is supported by the authors of another comprehensive review of menstrual manipulation, in which they caution clinicians against overestimating the risks of oral contraceptives and to instead “better educate themselves” regarding the safe use of this method to match individual needs.⁷⁵

There has thus been an ongoing debate on extended pill use, with providers expressing the need for more research on the long-term health effects and any effect on fertility of extended COC use.⁷⁶

Concerns in lay press

A study of popular press articles about menstrual suppression, described as a new and controversial health care option, analysed 22 American and Canadian articles relating to this topic, published before the FDA approval of extended COC use. The authors found that although the majority of women did eventually have fewer periods, they did not necessarily experience a relief of symptoms or fewer days of actual bleeding. Despite evidence that extended regimens

were safe and effective, they were sceptical about claims of a universal dislike of menstruation. Concern was expressed over the lack of information about possible long-term effects of menstrual suppression and skewed media coverage, which seemed heavily biased in favour of the elimination of the “inconvenient, bothersome, incapacitating and unnecessary” phenomenon called menstruation. The authors also called into question the ease with which extended pill use is recommended to all women as opposed to a judicious prescription for those with significant gynaecological problems such as endometriosis and premenstrual syndrome.⁷⁷

Newer options

Beginning with the tri-cycle regimen over 35 years ago, a large number of trials to date have explored extended COC use under various names including menstrual suppression, menstrual manipulation and menstrual reduction.⁷⁸ Supplementation of estrogen during the HFI is another option,⁷⁹ with the addition of low-dose estrogen in place of placebo improving the bleeding pattern in subsequent cycles.^{80 81}

Other options for extended COC use include use of higher-dose estrogen preparations⁸² and decreasing the duration of the HFI,⁸³ thus reducing the risk of escape ovulation in the event of missed pills.^{84 85} The continuous daily use of the COC in a 365-day regimen was also found to have a comparable efficacy and safety profile to conventional cyclical use. However unscheduled bleeding was more frequent, leading to a higher discontinuation rate.⁸⁶ Another option is a ‘woman-controlled’ or ‘tailored’ use of the COC, where a woman takes the pill daily until bleeding triggers a designated HFI.⁸⁷ The withdrawal bleed that occurs in the HFI seems to ‘discourage’ further irregular bleeding when the pill is restarted, leading to the desired combination of fewer withdrawal bleeds and less irregular bleeding. A recent RCT of standard versus tailored COC use revealed no significant difference in continuation or satisfaction rates at 1 year between the two regimens.³⁰ While a significant minority of women expressed a preference for regular menstrual periods in the recruitment phase, a qualitative sub-study noted high satisfaction with the reduced bleeding and relief over the medical sanctioning of extended pill use on the one hand, but a dislike of the unpredictability of bleeding and the worry that amenorrhoea might imply pregnancy on the other.⁸⁸ Another recent RCT of the use of EE/DRSP in a flexible extended regimen noted a reduced number of days of bleeding/spotting and fewer withdrawal bleed episodes over 1 year in comparison with a traditional 28-day regimen of the same COC.⁸⁹ The latest development in this field is the FDA approval in March 2013 of Quartette™, the first example of a new generation of extended oral contraceptives in a 91-day regimen, with the dose of estrogen increasing at three distinct points over the first 84 days

while the amount of progestogen remains the same; this is followed by 7 days of 10 µg estrogen alone. This particular regimen is thought to minimise unscheduled bleeding between scheduled withdrawal bleeds.⁹⁰ Yet another recent introduction is Flexyess[®], which contains 3 mg DRSP and 20 µg EE and has been licensed for use in a 'flexible extended' cycle oral contraceptive taken for between 24 and 120 days with a 4-day pill-free interval.⁹¹

DISCUSSION

The COC has been hailed as the greatest science and technology advance of the twentieth century,⁹² and it certainly had a dramatic effect on the lives of young women in the 1960s and early 1970s.⁹³ It led to an increase in the age at first marriage and helped women pursue education and training.⁹⁴ Fifty years on, what was once considered a novelty has become a way of life for millions of women, preventing an estimated 1.4 million unintended pregnancies and 600 000 abortions each year in the USA alone.⁹⁵ The benefits of extended pill use include better contraceptive efficacy, avoidance of scheduled bleeding and its attendant discomfort and expense, improvement in menstrual-related symptoms and bleeding patterns, all of which may result in better compliance. However, uncertainties remain about long-term safety, effects on the endometrium and return of fertility, with irregular bleeding patterns being an added inconvenience. From an individual perspective, it would appear that many women prefer to control when and whether they menstruate,⁹⁶ there being no physiological requirement for a monthly scheduled bleed in women who do not desire pregnancy.⁹⁷ Although slow in gaining acceptance and visibility among both clinicians and pill users, a growing base of scientific evidence points to the safety and efficacy of the avoidance of menstruation through extended pill use, which might well become the norm in years to come.

Acknowledgements The authors are grateful for the support of the Margaret Pyke Trust, which also contributes to the programme of reproductive health research at University College London.

Funding This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0906-11154). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. Trial co-ordination took place at University College London Hospitals, which receives a proportion of funding from the Department of Health's National Institute for Health Research Centres funding scheme.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Dhont M. History of oral contraception. *Eur J Contracept Reprod Health Care* 2010;15(S2):S12–S18.
- 2 Bitzer J. 50th Anniversary of the pill – what does this story teach us? *Eur J Contracept Reprod Health Care* 2010;15(S2):S6–S8.
- 3 Coutinho EM. To bleed or not to bleed, that is the question. *Contraception* 2007;76:263–266.
- 4 Sulak PJ, Scow RD, Preece C, *et al.* Hormone withdrawal symptoms in oral contraceptive users. *Obstet Gynecol* 2000;95:261–266.
- 5 Edelman AB, Gallo MF, Jensen JT, *et al.* Continuous or extended cycle versus cyclic use of combined oral contraceptives for contraception. *Cochrane Database Syst Rev* 2005;3:CD004695.
- 6 Szarewski A. Sisters doing it for themselves. *J Fam Plann Reprod Health Care* 2009;35:71–72.
- 7 Sucato GS, Gerschultz KL. Extended cycle hormonal contraception in adolescents. *Curr Opin Obstet Gyn* 2005;17:461–465.
- 8 Thomas SL, Ellertson C. Nuisance or natural and healthy: should monthly menstruation be optional for women? *Lancet* 2000;355:922–924.
- 9 Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. *Obstet Gynecol* 2003;101:653–661.
- 10 Mishell DR Jr. Rationale for decreasing the number of days of the hormone-free interval with use of low-dose oral contraceptive formulations. *Contraception* 2005;71:304–305.
- 11 Vandever MA, Kuehl TJ, Sulak PJ, *et al.* Evaluation of pituitary–ovarian axis suppression with three oral contraceptive regimens. *Contraception* 2008;77:162–170.
- 12 Sulak PJ. Continuous oral contraception: changing times. *Best Pract Res Clin Obstet Gynaecol* 2008;22:355–374.
- 13 Schlaff WD, Lynch AM, Hughes HD, *et al.* Manipulation of the pill-free interval in oral contraceptive pill users: the effect on follicular suppression. *Am J Obstet Gynecol* 2004;190:943–951.
- 14 Rible RD, Taylor D, Wilson ML, *et al.* Follicular development in a 7-day versus 4-day hormone-free interval with an oral contraceptive containing 20 mcg ethinyl estradiol and 1 mg norethindrone acetate. *Contraception* 2009;79:182–188.
- 15 Coutinho EM, Segal S. *Is Menstruation Obsolete: How Suppressing Menstruation Can Help Women Who Suffer From Anaemia, Endometriosis, or PMS*. Oxford, UK: Oxford University Press, 2000.
- 16 Eaton SB, Pike MC, Short RV, *et al.* Women's reproductive cancers in evolutionary context. *Q Rev Biol* 1994;69:353–367.
- 17 Gladwell M. Annals of Medicine: John Rock's Error. *The New Yorker*, 13 March 2000:52–63.
- 18 Nelson AL. Communicating with patients about extended-cycle and continuous use of oral contraceptives. *J Womens Health* 2007;16:463–470.
- 19 Guzick DS, Huang L, Broadman BA, *et al.* Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. *Fertil Steril* 2011;95:1568–1573.
- 20 Strowitzki T, Kirsch B, Elliesen J. Efficacy of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen in women with moderate-to-severe primary dysmenorrhoea: an open-label, multicentre, randomised, controlled study. *J Fam Plann Reprod Health Care* 2012;38:94–101.
- 21 Archer DF. Menstrual-cycle-related symptoms: a review of the rationale for continuous use of oral contraceptives. *Contraception* 2006;74:359–366.

- 22 Kaunitz AM. Menstruation: choosing whether . . . and when. *Contraception* 2000;62:277–284.
- 23 Omar H, Kives S, Lisa Allen L. Extended use of the oral contraceptive pill – is it an acceptable option for the adolescent? *J Pediatr Adolesc Gynecol* 2005;18:285–288.
- 24 Gerschultz KL, Sucato GS, Hennon TR, *et al.* Extended cycling of combined hormonal contraceptives in adolescents: physician views and prescribing practices. *J Adolesc Health* 2007;40:151–157.
- 25 Savasi I, Spitzer RF, Allen LM, *et al.* Menstrual suppression for adolescents with developmental disabilities. *J Pediatr Adolesc Gynecol* 2009;22:143–149.
- 26 Vercellini P, Frontino G, De Giorgi O, *et al.* Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhoea that does not respond to a cyclic pill regimen. *Fertil Steril* 2003;80:560–563.
- 27 Seracchioli R, Mabrouk M, Frasc C, *et al.* Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. *Fertil Steril* 2010;93:52–56.
- 28 Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. *Am J Obstet Gynecol* 1998;179:577–582.
- 29 WHO Task Force on Oral Contraceptives. A randomized double-blind study of six combined oral contraceptives. *Contraception* 1982;25:231–241.
- 30 Stephenson J, Shawe J, Panicker S, *et al.* Randomized trial of the effect of tailored versus standard use of the combined oral contraceptive pill on continuation rates at 1 year. *Contraception* 2013;88:523–531.
- 31 Loudon NB, Foxwell M, Potts DM, *et al.* Acceptability of an oral contraceptive that reduces the frequency of menstruation: the tri-cycle pill regimen. *Br Med J* 1977;2:487–490.
- 32 den Tonkelaar I, Oddens BJ. Preferred frequency and characteristics of menstrual bleeding in relation to reproductive status, oral contraceptive use, and hormone replacement therapy. *Contraception* 1999;59:357–362.
- 33 Aubeny E. Are monthly menstrual periods optional: a European perspective. *Reprod Health Matters* 2007;15:183–185.
- 34 Sánchez-Borrego R, García-Calvo C. Spanish women's attitudes towards menstruation and use of a continuous, daily use hormonal combined contraceptive regimen. *Contraception* 2008;77:114–117.
- 35 Powell-Dunford NC, Cuda AS, Moore JL, *et al.* Menstrual suppression for combat operations: advantages of oral contraceptive pills. *Womens Health Issues* 2011;21: 86–91.
- 36 National Institute for Health and Care Excellence. *Long-acting Reversible Contraception (CG30)*. <http://guidance.nice.org.uk/CG30> [accessed 2 September 2013].
- 37 Sulak PJ, Cressman BE, Waldor E, *et al.* Extending the duration of active oral contraceptive pills to manage hormone withdrawal symptoms. *Obstet Gynaecol* 1997;89:179–183.
- 38 Coffee AL, Kuehl TJ, Willis S, *et al.* Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. *Am J Obstet Gynecol* 2006;195:1311–1319.
- 39 Coffee AL, Sulak PJ, Kuehl TJ. Long-term assessment of symptomatology and satisfaction of an extended oral contraceptive regimen. *Contraception* 2007;75: 444–449.
- 40 Foidart JM, Sulak PJ, Schellschmidt I, *et al.* The use of an oral contraceptive containing ethinylestradiol and drospirenone in an extended regimen over 126 days. *Contraception* 2006;73:34–40.
- 41 Coutinho EM, O'Dwyer E, Barbosa IC, *et al.* Comparative study on intermittent versus continuous use of a contraceptive pill administered by vaginal route. *Contraception* 1995;51:355–358.
- 42 Anderson FD, Hait H, the Seasonale-301 Study Group. A multicenter, randomized study of an extended cycle oral contraceptive. *Contraception* 2003;68:89–96.
- 43 Westhoff CL, Hait HI, Reape KZ. Body weight does not impact pregnancy rates during use of a low-dose extended-regimen 91-day oral contraceptive. *Contraception* 2012;85:235–239.
- 44 Wright KP, Johnson JV. Evaluation of extended and continuous use oral contraceptives. *Ther Clin Risk Manag* 2008;4:905–911.
- 45 Birtch RL, Olatunbosun OA, Pierson RA. Ovarian follicular dynamics during conventional vs. continuous oral contraceptive use. *Contraception* 2006;73:235–243.
- 46 Edelman AB, Gallo MF, Jensen JT, *et al.* Continuous or extended cycle versus cyclic use of combined oral contraceptives for contraception. *Cochrane Database Syst Rev* 2005;3:CD004695.
- 47 Reid RL, Fortier MP, Smith L, *et al.* Safety and bleeding profile of continuous levonorgestrel 90 mcg/ethinylestradiol 20 mcg based on 2 years of clinical trial data in Canada. *Contraception* 2010;82:497–502.
- 48 Machado RB, de Melo NR, Hugo Maia H Jr. Bleeding patterns and menstrual-related symptoms with the continuous use of a contraceptive combination of ethinylestradiol and drospirenone: a randomized study. *Contraception* 2010;81:215–222.
- 49 Jensen JT, Garie SG, Trummer D, *et al.* 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.
- 50 Brucker C, Hedon B, The HS, *et al.* Long-term efficacy and safety of a monophasic combined oral contraceptive containing 0.02 mg ethinylestradiol and 2 mg chlormadinone acetate administered in a 24/4-day regimen. *Contraception* 2010;81:501–509.
- 51 American College of Obstetricians and Gynecologists. Practice Bulletin No. 110. Non-contraceptive uses of hormonal contraceptives. *Obstet Gynecol* 2010;115:206–218.
- 52 Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. *Management of Unscheduled Bleeding in Women Using Hormonal Contraception*. 2009. <http://www.fsrh.org/pdfs/UnscheduledBleedingMay09.pdf> [accessed 2 September 2013].
- 53 Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. *Combined Hormonal Contraception*. 2011. <http://www.fsrh.org/pdfs/CEUGuidanceCombinedHormonalContraception.pdf> [accessed 2 September 2013].
- 54 Machado RB, Fabrin P, Cruz AM, *et al.* Clinical and metabolic aspects of the continuous use of a contraceptive association of ethinyl estradiol (30 ug) and gestodene (75 ug). *Contraception* 2004;70:365–370.
- 55 Anderson FD, Gibbons W, Portman D. Long-term safety of an extended-cycle oral contraceptive (Seasonale): a 2-year multicenter open-label extension trial. *Am J Obstet Gynecol* 2006;195:92–96.
- 56 Wiegratz I, Stahlberg S, Manthey T, *et al.* Effects of an oral contraceptive containing 30 mcg ethinyl estradiol and 2 mg

- dienogest on lipid metabolism during 1 year of conventional or extended-cycle use. *Contraception* 2010;81:57–61.
- 57 Klipping C, Duijkers I, Fortier MP, *et al.* Long-term tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: results from a randomised, controlled, multicentre study. *J Fam Plann Reprod Health Care* 2012;38:84–93.
 - 58 Davis AR, Kroll R, Soltes B, *et al.* Occurrence of menses or pregnancy after cessation of a continuous oral contraceptive. *Fertil Steril* 2008;89:1059–1063.
 - 59 Archer DF, Kovalevsky G, Ballagh SA, *et al.* Ovarian activity and safety of a novel levonorgestrel/ethinyl estradiol continuous oral contraceptive regimen. *Contraception* 2009;80:245–253.
 - 60 Barnhart K, Mirkin S, Grubb G, *et al.* Return to fertility after cessation of a continuous oral contraceptive. *Fertil Steril* 2009;91:1654–1656.
 - 61 Barnhart KT, Schreiber CA. Return to fertility following discontinuation of oral contraceptives. *Fertil Steril* 2009;91:659–663.
 - 62 Wagstaff AJ. Continuous-use ethinylestradiol/levonorgestrel 20 µg/90 µg as an oral contraceptive. *Drugs* 2007;67:2473–2477.
 - 63 Anderson FD, Hait H, Hsiu J, *et al.* Endometrial microstructure after long-term use of a 91-day extended-cycle oral contraceptive regimen. *Contraception* 2005;71:55–59.
 - 64 Kroll R, Reape KZ, Margolis M. The efficacy and safety of a low-dose, 91-day, extended-regimen oral contraceptive with continuous ethinyl estradiol. *Contraception* 2010;81:41–48.
 - 65 Bednarek P. Continuous-use ethinylestradiol/levonorgestrel 20 µg/90 µg as an oral contraceptive. A viewpoint by Paula Bednarek. *Drugs* 2007;67:2478–2479.
 - 66 Davtyan C. Continuous-use ethinylestradiol/levonorgestrel 20 µg/90 µg as an oral contraceptive. A viewpoint by Camelia Davtyan. *Drugs* 2007;67:2478–2479.
 - 67 Teichmann A, Apter D, Emerich J, *et al.* Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. *Contraception* 2009;80:504–511.
 - 68 Kaneshiro B, Edelman A, Carlson N, *et al.* Treatment of unscheduled bleeding in continuous oral contraceptive users with doxycycline: a randomized controlled trial. *Obstet Gynecol* 2010;115:1141–1149.
 - 69 Kaneshiro B, Edelman A, Carlson NE, *et al.* A randomized controlled trial of subantimicrobial-dose doxycycline to prevent unscheduled bleeding with continuous oral contraceptive pill use. *Contraception* 2012;85:351–358.
 - 70 Wiegatz I, Galiläer K, Sängner N, *et al.* Prescribing preferences and personal experience of female gynaecologists in Germany and Austria regarding use of extended-cycle oral contraceptives. *Eur J Contracept Reprod Health Care* 2010;15:405–412.
 - 71 Sulak PJ, Terry Buckley T, Kuehl TJ. Attitudes and prescribing preferences of health care professionals in the United States regarding use of extended-cycle oral contraceptives. *Contraception* 2006;73:41–45.
 - 72 Seval DL, Buckley T, Kuehl TJ, *et al.* Attitudes and prescribing patterns of extended-cycle oral contraceptives. *Contraception* 2011;84:71–75.
 - 73 Frederick CE, Edelman A, Carlson NE, *et al.* Extended-use oral contraceptives and medically induced amenorrhea: attitudes, knowledge and prescribing habits of physicians. *Contraception* 2011;84:384–389.
 - 74 Hitchcock CL, Prior JC. Evidence about extending the duration of oral contraceptive use to suppress menstruation. *Womens Health Issues* 2004;14:201–211.
 - 75 Hicks CW, Rome ES. Menstrual manipulation: options for suppressing the cycle. *Clev Clin J Med* 2010;77:445–453.
 - 76 Andrist LC, Arias RD, Nucatola D, *et al.* Women's and providers' attitudes toward menstrual suppression with extended use of oral contraceptives. *Contraception* 2004;70:359–363.
 - 77 Johnston-Robledo I, Barnack J, Wares S. "Kiss Your Period Good-Bye": menstrual suppression in the popular press. *Sex Roles* 2006;54:353–360.
 - 78 Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. *Obstet Gynecol* 2001;98:771–778.
 - 79 Killick SR, Fitzgerald C, Davis A. Ovarian activity in women taking an oral contraceptive containing 20 µg ethinyl estradiol and 150 µg desogestrel: effects of low estrogen doses during the hormone-free interval. *Am J Obstet Gynecol* 1998;179:S18–S24.
 - 80 Kaunitz AM, Portman DJ, Hait H, *et al.* Adding low-dose estrogen to the hormone-free interval: impact on bleeding patterns in users of a 91-day extended regimen oral contraceptive. *Contraception* 2009;79:350–355.
 - 81 Reape KZ, DiLiberti CE, Hendy CH, *et al.* Effects on serum hormone levels of low-dose estrogen in place of placebo during the hormone-free interval of an oral contraceptive. *Contraception* 2008;77:34–39.
 - 82 Edelman AB, Koontz SL, Nichols MD, *et al.* Continuous oral contraceptives: are bleeding patterns dependent on the hormones given? *Obstet Gynaecol* 2006;107:657–665.
 - 83 Spona J, Elstein M, Feichtinger W, *et al.* Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception* 1996;54:71–77.
 - 84 Anttila L, Bachmann G, Hernádi L, *et al.* Contraceptive efficacy of a combined oral contraceptive containing ethinylestradiol 20 µg/drospirenone 3 mg administered in a 24/4 regimen: a pooled analysis of four open-label studies. *Eur J Obstet Gynecol* 2011. doi:10.1016/j.ejogrb.2010.12.037.
 - 85 Willis SA, Kuehl TJ, Spiekerman AM, *et al.* Greater inhibition of the pituitary–ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. *Contraception* 2006;74:100–103.
 - 86 Archer DF, Jensen JT, Johnson JV, *et al.* Evaluation of a continuous regimen of levonorgestrel/ethinyl estradiol: phase 3 study results. *Contraception* 2006;74:439–445.
 - 87 Read CM. New regimens with combined oral contraceptive pills – moving away from traditional 21/7 cycles. *Eur J Contracept Reprod Health Care* 2010;15(S2):S32–S41.
 - 88 Graham CA, Panicker S, Shawe J, *et al.* Women's experiences with tailored use of a combined oral contraceptive: a qualitative study. *Hum Reprod* 2013;28:1620–1625.
 - 89 Klipping C, Duijkers I, Fortier MP, *et al.* Contraceptive efficacy and tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomised, controlled study. *J Fam Plann Reprod Health Care* 2012;38:73–83.
 - 90 News Medical. FDA approves Teva's Quartette tablets for prevention of pregnancy. <http://www.news-medical.net/news/20130330/FDA-approves-Teva-Quartette-tablets-for-prevention-of-pregnancy.aspx?page=2> [accessed 2 September 2013].
 - 91 Percy L, Mansour D. Tailoring oral contraceptive pills to meet the needs of women. *J Fam Plann Reprod Health Care* 2013;39:237–240.

- 92 Oral contraceptives: the liberator. *The Economist* 1999;353:102.
- 93 Goldin C, Katz LF. Career and marriage in the age of the pill. *Am Econ Rev* 2000;90:461–465.
- 94 Goldin C, Katz LF. The power of the pill: oral contraceptives and women's career and marriage decisions. *J Polit Econ* 2002;110:730–770.
- 95 Aron J. Editorial: putting the pill to work. *Contraception* 2010;82:483–485.
- 96 Hall KS, Trussell J. Types of combined oral contraceptives used by US women. *Contraception* 2012;86:659–665.
- 97 Lin K, Barnhart K. The clinical rationale for menses-free contraception. *J Womens Health* 2007;16:1171–1180.

Faculty of Sexual and Reproductive Healthcare
of the Royal College of Obstetricians and Gynaecologists
27 Sussex Place
Regent's Park
London NW1 4RG
Website: www.fsrh.org

NOTICE TO TENDER

FSRH Clinical Effectiveness Unit

In April 2014, the Faculty of Sexual and Reproductive Healthcare (FSRH) will be advertising for applications to host and provide the Faculty's Clinical Effectiveness Unit (CEU) for the period starting 1 January 2015 for 3 years, renewable.

Organisations applying should have a proven track record in Sexual and Reproductive Healthcare (SRH), be closely linked to services providing clinical SRH care, be able to demonstrate a commitment to evidence-based medicine, and have experience of producing clinical guidance/standards.

The work of the CEU is central to the FSRH'S aims of advancing medical knowledge in SRH and promoting high standards of clinical practice. The Faculty has ambitious plans to increase its impact over the next few years, and an enhanced CEU will play a key role in delivering this impact to members and the wider public.

More information about the work of the current CEU can be found on the Faculty website (www.fsrh.org). To register interest in receiving the tender documents when they are published, please contact the Faculty Chief Executive (Jane Hatfield) on chiefexec@fsrh.org.