*The European Journal of Contraception and Reproductive Health Care, 2014; 19: 321–339*

# Extended regimens of combined hormonal contraception to reduce symptoms related to withdrawal bleeding and the hormone-free interval: A systematic review of randomised and observational studies

Nicolás Mendoza*, Paloma Lobo†, Roberto Lertxundi‡, Marta Correa§, Esteban Gonzalez#, Alberto Salamanca^ and Rafael Sánchez-Borrego$

*Department of Obstetrics and Gynaecology, University of Granada, Spain, †Hospital Infanta Sofia, San Sebastián De Los Reyes, Madrid, Spain, ‡Clinica Euskalduna, Bilbao, Spain, §Hospital Universitario de Canarias, Tenerife, Spain, #Hospital Universitario de Albacete, Albacete, Spain, ^Hospital Universitario Virgen de las Nieves, Granada, Spain, and $Clínica Diatros, Barcelona, Spain



ABSTRACT

**Objective** To assess whether continuous and extended regimens (CRs/ERs) of combined hormonal contraceptives (CHCs) improve symptoms related to withdrawal bleeding or the hormone-free interval and to compare the efficacy, safety, and cost of CRs/ERs to those of conventional 28-day regimens.

**Study design** A literature search of the PubMed database was conducted for randomised clinical trials (RCTs) and observational studies published in any language between 2006 and 2013.

**Results** Sixteen RCTs and 14 observational studies evaluated issues related to our objectives. CRs/ERs, whose efficacy and safety were comparable to those described for conventional regimens, were preferred due to their improvement of symptoms related to withdrawal bleeding or the hormone-free interval and the lower costs resulting from the reduced incidence of these symptoms.

**Conclusion** The contraceptive efficacy and safety of CR/ER use of CHCs is at least equal to that of 28-days conventional regimens, and this use may have some cost savings. CRs/ERs are recommended for women willing to take a CHC for treatment of symptoms related to withdrawal bleeding or the hormone-free interval.

KEYWORDS Contraception; Combined hormonal contraceptives; Extended regimen; Continuous regimen; Withdrawal bleeding; Hormone-free interval

Correspondence: Nicolas Mendoza, MD, PhD, Maestro Montero, 21, 18004 Granada, Spain. Tel: +34 958 120 206. Fax: +34 958 818 277. E-mail: nicomendoza@telefonica.net


DOI: 10.3109/13625187.2014.927423

## INTRODUCTION

The first paper on the use of a combined oral contraceptive (COC) taken according to a time schedule different from the regular 28-days pill-driven cycle was published in 1977; it reported on the suitability of an 84/7 regimen of intake of a COC containing 50 μg ethinylestradiol (EE) and 250 μg lynestrenol over a period of one year. Eighty-two percent of the volunteers appreciated the reduction in the number of withdrawal bleeds and their accompanying symptoms, and many considered this alternate COC easier for compliance[1]. Since then, several continuous or extended regimens (CRs/ERs) for use of combined hormonal contraceptives (CHCs) have been developed, and these have shown similar rates of efficacy, safety, and compliance compared to the standard 28-day regimen; they indeed lessen the frequency and severity of symptoms related to the hormone-free period[2]. Although none of these methods are marketed in Spain, they can be simulated in clinical practice by extending the use of monophasic CHCs. Depending on how these drugs are administered orally, transdermally or vaginally, they can shorten or suppress the hormone-free interval.

In the Cochrane review of 2006[2], the variations in pill type and time-interval for continuous dosing made direct comparisons between regimens unfeasible, and the authors concluded that more attention towards participant satisfaction and menstruation-associated symptoms were needed. The present systematic review, which included studies published after 2006, assessed therefore whether CRs/ERs indeed improve the symptoms associated with withdrawal bleeding or the hormone-free interval, and have similar efficacy and safety profiles compared to those of conventional 28-day regimens.

### The meaning of 'extended' and 'continuous regimens'

Although there is no generally accepted definition, an *extended regimen* (ER) refers to the lengthening of the period of use of a CHC to many more days than in the conventional 21/7- or 24/4-day regimens, with either a fixed or a flexible schedule being applied[3]. In the studies analysed for this review, most of the ERs were scheduled for periods of use of the sex steroids that were multiples of 21 days. In flexible or adapted schedules, the users themselves control the occurrence of their withdrawal bleeding based on bleeding, sporting, working or social needs. In comparison, a *continuous regimen* (CR) refers to the uninterrupted use of CHC drugs without a hormone-free interval.

## METHODS

### Selection of studies

We searched the PubMed database for all articles (in any language) published in peer-reviewed journals since the Cochrane review of 2006[2] through to October 2013, using the search strategy described in Appendix A. Reference lists from papers identified by the search, as well as key reviews, were hand-searched to identify additional publications. Those that were in press in peer-reviewed journals and available online, ahead of publication, were also considered.

We included studies that looked at treatment or prevention of withdrawal bleeding-related symptoms[2] (Table 1). PICOS (population, interventions, comparators, outcomes, studies design) criteria were formulated a priori to guide the review's scope and the search procedure, selection and synthesis of the literature. The selection criteria were as follows: (population) patients of any age with symptoms related to menstruation or the hormone-free period; (intervention) treatment with CHC; (outcome) efficacy and safety; (study design) RCTs and observational studies; no language restrictions.

Full articles that met the inclusion criteria were reviewed in detail. Data items to be considered were discussed by the review authors and appear in Table 1. Three relevant reviews and other papers were used for reference list purposes. When some of this information was not available or insufficiently clear, we treated it as missing data.

### Assessment of study quality and data synthesis

We followed the PRISMA guidelines for systematic reviews[4]. Two authors (NM and PL) independently conducted the search and screened studies for inclusion, extracted and checked the data, and synthesised the findings. Four authors (NM, PL, RL and RSB) independently determined the adequacy of the studies' design and main methodological characteristics in order to ascertain the validity of the research.

**Table 1** Description of randomised controlled trials.

| *Reference* | *Randomisation* | *Participants* | *Intervention* | *Outcomes* |
|---|---|---|---|---|
| Edelman *et al.* 2006[6] | Double-blind.<br>Subjects were randomly assigned to 1 of the 4 active treatment arms using a simple computer-generated randomisation scheme. | 139 healthy women aged 18–49 years.<br>Exclusion criteria: Contraindication to HC use. | Four CR groups:<br>1. EE 20 μg/LNG 100 μg<br>2. EE 30 μg/LNG 100 μg<br>3. EE 20 μg/NETA 1 mg<br>4. EE 30 μg/NETA 1 mg.<br>180 days | Bleeding profiles. |
| Legro *et al.* 2007[7] | Computer-generated randomisation list using permuted-block randomisation. | 62 nonsmoking healthy women with normal menstrual cycles.<br>Exclusion criteria: Contraindication to HC use. | CR group: EE 20 μg/NETA 1 mg vs.<br>Cyclic group (21/7): EE 20 μg/NETA 1 mg.<br>168 days | Primary outcome: bleeding profiles.<br>Secondary outcomes: Ovarian and endometrial suppression and improved quality of life. |
| Sulak *et al.* 2008[8] | No information provided. | 65 healthy women aged 18–45 years.<br>Exclusion criteria: Contraindication to HC use, BMI >38, tobacco use >10 cigarettes/ day, antiretroviral therapy, use of oestrogen-containing products or phyto-oestrogens, a desire to become pregnant within one year. | Group 1: Instructed to replace the vaginal ring monthly on the same calendar day with no ring-free days vs.<br>Group 2: Same process, but if breakthrough bleeding/ spotting occurred for 5 days or more, they were to remove the ring for 4 days, and then reinsert it.<br>6 months | Bleeding profiles and symptoms. |
| Teichmann *et al.* 2009[9] | Phase 3, open-label, multicentre study at 44 European sites<br>Subjects were randomly assigned by the sponsor, using an interactive voice recognition system. The system provided a randomisation number (independent of the subject number) and corresponding treatment package number, which were relayed to the caller and later confirmed by facsimile. | 641 healthy women aged 18–49 years with normal menstrual cycles.<br>Exclusion criteria: Contraindication to HC use, abnormal laboratory- or clinical findings, smoking >14 cigarettes/ day if age 34 or older, human immunodeficiency virus seropositivity. | CR group: EE 20 μg/LNG 90 μg vs.<br>Cyclic group (21/7): EE 20 μg/LNG 100 μg.<br>1 year | Primary outcome: Safety and efficacy.<br>Secondary outcome: Bleeding profiles. |

(*Continued*)

**Table 1** Continued

| *Reference* | *Randomisation* | *Participants* | *Intervention* | *Outcomes* |
|---|---|---|---|---|
| Machado *et al.* 2010a[10], 2010b[11] | An open, computer-generated randomisation list. Multicentre. Allocation using sequentially numbered opaque envelopes which contained the randomisation number. The randomisation and the statistical analysis were done by an independent specialist unrelated to the study. | 78 healthy, sexually active women aged 18–35 years, BMI 19–30, a minimum of 8 years of schooling.<br>Exclusion criteria: Contraindication to HC use. | CR group: EE 30 µg/DRPS 3 mg vs.<br>Cyclic group (21/7): EE 30 µg/DRPS 3 mg.<br>168 days | Machado *et al.*[10]: Metabolic effects, including those on lipids and carbohydrates and coagulation indices.<br>Machado *et al.*[11]: Bleeding profiles and withdrawal bleeding-related symptoms. |
| Wiegratz *et al.* 2008[12], 2010a[13], 2010b[14] | Women were randomly assigned 1:1 using randomisation blocks of 4 by means of the software package SAS. The allocation was chronologically linked to the sequence of arrival. | 59 healthy women aged 18–40 years seeking contraception.<br>Exclusion criteria: Contraindication to HC use. | ER group (84/7): EE 30 µg/DNG 2 mg vs.<br>Cyclic group (21/7): EE 30 µg/DNG 2 mg.<br>1 year | Wiegratz *et al.*[12]: Haemostatic indices.<br>Wiegratz *et al.*[13]: Indices of carbohydrate metabolism.<br>Wiegratz *et al.*[14]: Serum lipids. |
| Wiegratz *et al.* 2011[15] | Phase 3, open, multicentre trial (51 active study centres in Germany). Women were randomly assigned 1:1 using randomisation blocks of 4 by means of the software package SAS. The allocation was chronologically linked to the sequence of arrival. | 1377 healthy women aged 18–40 years and not using drugs known to influence the effects of HC.<br>Exclusion criteria: Contraindication to HC use and active smokers > 30 years; for the remaining women, the daily cigarette consumption was restricted to 10 per day. | ER group (84/7): EE 30 µg/DNG 2 mg vs.<br>Cyclic group (21/7): EE 30 µg/DNG 2 mg.<br>1 year | Primary outcome: Bleeding profiles.<br>Secondary outcomes: Efficacy and safety. |
| Rad *et al.* 2011[16] | Randomised, open-label, multicentre, comparative sub-study of a larger phase 3 trial. | 147 healthy women aged 18–49 years. | CR: EE 20 µg/LNG 90 µg vs.<br>Cyclic group (21/7): EE 20 µg/LNG 100 µg<br>1 year | Haemostasis, lipids, carbohydrates, bone metabolism, and SHBG. |

| | | | | |
|---|---|---|---|---|
| Klipping *et al*. 2012a, 2012b[17,18] | The study consisted of two phases: a 1-year comparative phase where women were randomly allocated to receive HC administered as flexible, conventional or fixed extended regimen[17] and a 1-year safety extension phase during which the majority of women received the flexible regimen[18] | 1312 healthy women aged 18–35 years. Smokers could participate if aged 30 years or younger at baseline.<br>Exclusion criteria: Contraindication to HC use, BMI < 18 and > 30. | Conventional 24/4 regimen of EE 20 μg/DRSP 3 mg or one of the following treatment modalities:<br>• FR: 24–120 days´ active hormonal intake followed by 4-day tablet free interval<br>• Fixed extended:120 days' uninterrupted active hormonal intake followed by a 4-day tablet-free interval)<br>Duration: 1 year[17] and 2 years[18] | Klipping *et al*.[17]: Primary outcomes: bleeding profiles and efficacy.<br>Klipping *et al*.[18]: Long-term safety and tolerability. |
| Jensen *et al*. 2012[19] | Open-label, active-controlled, phase 3 study conducted at 84 centres in the USA. The randomisation sequence used SAS software. Subjects were assigned their randomisation numbers via an interactive voice response system upon initiation of screening procedures. | 2450 healthy women aged 18–45 years<br>Exclusion criteria: Contraindication to HC use. | Conventional 24/4 regimen of EE 20 μg/DRSP 3 mg or one of two variants of a FR of the same formulation:<br>• FR that required subjects to initiate 4-day tablet-free intervals after 3 days of breakthrough bleeding/ spotting.<br>• An alternative FR allowed subjects to initiate a 4-day tablet-free interval irrespective of the occurrence of bleeding.<br>1 year | Bleeding profiles, efficacy and safety. |

(*Continued*)

Table 1 Continued

| *Reference* | *Randomisation* | *Participants* | *Intervention* | *Outcomes* |
|---|---|---|---|---|
| Halbreich *et al*. 2012[19] | Multicentre, randomised, double-blind, placebo-controlled study. Randomisation was generated for double-blind treatment using a computerised randomisation/ enrollment system. | Healthy women aged 18–49 years who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria for premenstrual dysphoric disorder. | CR group: EE 20 μg/ LNG 90 μg vs. placebo. | Premenstrual dysphoric disorder. |
| Stephenson *et al*. 2013[20] | Allocation by computer-generated online randomisation using permuted blocks in a ratio of 1:1, once the participant was registered. | 503 healthy women aged 18–45 years. Exclusion criteria: Contraindication to HC use. | TR (daily pills until three consecutive days bleeding triggers a 3-day pill-free interval) vs. Conventional 21/7 (EE 30 μg/LNG 150 μg). 1 year | Continuation and satisfaction rates. |

DNG, dienogest; DRSP, drospirenone; EE, ethinylestradiol; ENG, etonogestrel; LNG, levonorgestrel; NETA, norethisterone acetate; BMI, body mass index; SHBG, sex hormone-binding globulin; HC, hormonal contraceptive; CR, continuous regimen; ER, extended cycle regimen; FR, flexible regimen; TR, tailored regimen.

Disagreements were resolved by discussion and consensus. When duplicates of a study were found, we selected the one which was more detailed or pieced together data from the multiple reports indicating the corresponding references.

Summary measures of association were not computed due to heterogeneity among studies with respect to study design, subject characteristics and outcomes.

## RESULTS

The literature search identified 219 studies, but the current systematic review was based finally on 29 publications from 2006 to 2013 involving 16 RCTs. Table 1 describes the RCTs[5–20] that were published since the last Cochrane systematic review in 2006[2]. As for RCTs included in that review, it was unusual for studies to describe allocation concealment, and with the exception of three papers[5,6,19], evaluators and participants were not double-blinded. However, the fact that the data were collected on a daily basis reduced the influence of performance bias.

Observational studies[21–34] which we also reviewed to measure safety and long-term efficacy, as well as the relief of symptoms associated with withdrawal bleeding, are summarised in Table 2.

Overall, this review shows that CRs/ERs are characterised by similar efficacy, safety, and compliance in comparison to conventional 28-day regimens. In addition, our findings suggest that women who experience symptoms associated with withdrawal bleeding and the hormone-free interval using conventional regimens may benefit from using a CR/ER approach (Tables 3 and 4).

## DISCUSSION

### Efficacy

Due to the heterogeneity and small sample size of the included studies, it was not possible to conduct a meta-analysis or to evaluate Pearl indices (PIs). Most authors reporting on RCTs included in this review did not calculate the PI, and most studies did not record pregnancy or serious adverse effects. The PI was determined in only four RCTs[14,16–18]. Of these, that by Klipping *et al.*[17] had the longest monitoring of participants (two years), with a PI of 0.64 (95% confidence interval [CI]: 0.28–1.26). We were able to confirm that the efficacy of CRs/ERs was not less than that of conventional 28-day cycles of CHCs, and data were also available showing that these regimens may improve follicular growth inhibition/suppression[35,36] and help prevent non-adherence (e.g., omission of pills, delayed patch replacement)[37]. The efficacy of the CR/ER was independent of the route of administration, and one recent RCT evaluating a CR of use of the vaginal ring[7] confirmed the Cochrane review data. In a recent retrospective US claims analysis, pregnancy rates were lower with ERs than with conventional cyclic regimens[38].

### Efficacy in reducing symptoms associated with withdrawal bleeding and the hormone-free interval

Women with premenstrual syndrome or symptoms related to the hormone-free interval when using conventional regimens were shown to benefit from switching to CR/ER, according to the RCTs[5–19,14,16,18] that assessed these regimens (Table 3), which confirms data from observational studies[23,25,27,31,32]. Upon reviewing observational studies where COCs containing chlormadinone acetate (CMA) were taken, Huber and co-authors proposed that this benefit could be due to an agonist effect of some of the drug metabolites on the GABA system[26].

Moreover, there was also a clear improvement in dysmenorrhoea by reducing the number of bleeding episodes[2]. When an ER was adhered to by women under 20 years of age for a duration of six months, the prevalence of dysmenorrhoea dropped by 56%, spending on painkillers by 75%, and work and school absenteeism by 92%[26].

Similarly, CR/ER had a favourable effect on headaches by reducing the number of hormone-free intervals and of withdrawal bleeds[31,32]. In a retrospective study, contraceptive vaginal ring users also less frequently suffered from migraine with aura related to the drop in plasma levels of sex steroids[34].

### Bleeding pattern

Although there are differences in the definition of bleeding patterns, most scholars use the World Health Organization (WHO) criteria, and all of the studies provided data on continuity. Overall, they indicated that the total number of days of bleeding was lower with CRs/

**Table 2** Description of observational studies.

| *References* | *Method* | *Participants* | *Intervention* | *Outcomes* | *Key results* |
|---|---|---|---|---|---|
| Foidart *et al.* 2006[21] | Prospective, multicentre, open, un-controlled study. | 177 healthy women aged 18–35 years. | ER: EE 30 μg/DRSP 3 mg. 126 days | Bleeding profile, acceptance and safety. A subset of 30 women underwent endometrial histology sampling after completion of the ER. | ER was safe, efficacious, well accepted and reduced bleeding. |
| Anderson *et al.* 2006[21] | Multicentre, open-label. | 1006 healthy women aged 18–40 years. | ER (84/7): EE 30 μg/LNG 150 μg followed by EE 10 μg for 7 days instead of placebo. 1 year | Efficacy and safety. | ER is effective, safe and well tolerated. |
| Sulak *et al.* 2006[23] Coffee *et al.* 2006[24] Sulak *et al.* 2007[25] | Open label single-centre prospective study. Prospective analysis of headaches. | 111 healthy women aged 18–40 years. | ER: EE 30 μg/DRSP 3 mg (168 days) vs. 21/7 cyclic of the same HC. 196 days | Bleeding patterns. Premenstrual-type symptoms and headaches. | Acceptable bleeding profile with a high continuation rate. ER led to a decrease in premenstrual-type symptoms. ER led to a decrease in headache severity along with improvement in work productivity and involvement in activities. |
| Huber *et al.* 2008[26] | Data from four prospective, non-interventional observational studies. | Nearly 50,000 women. | The studies documented use of four, six and 12 treatment cycles of the 28-day conventional regimen, as well as extended cycle regimens. EE 30 μg/CMA 2 mg according to gynaecologists' usual practice. | Emotional well-being and mood swings. | EE/CMA improves symptoms of depressive mood. |

| | | | | | |
|---|---|---|---|---|---|
| Anderson *et al.* 2008[27] | Multicentre, open-label. | 1006 healthy women aged 18–40 years. | ER (84/7): EE 30μg/LNG 150 μg.<br>1year | Efficacy and safety. | ER is effective, safe and well tolerated. |
| Archer *et al.* 2009[28] | Open-label. | 37 healthy women aged 18–35 years. | CR: EE 20 μg/LNG 90 μg.<br>84 days | Ovarian activity and safety. | The CR completely inhibited ovulation, with little evidence of follicular development and with rapid return of ovulation after stopping treatment. |
| Kroll *et al.* 2010[29] | Phase 3, multicentre, open-label, single treatment study. | 1249 healthy women aged 18–40 years. | ER (84/7): EE 20 μg/LNG 100 μg followed by EE 10 μg instead of placebo.<br>1 year | Efficacy and safety. | ER is effective, safe and well tolerated. |
| Seidman 2010[30] | Single-centre prospective study. | 137 healthy women aged 18–40 years. | ER (84/7): EE 30 μg/DRSP 3 mg vs. 21/7 of the same HC.<br>168 days | Bleeding patterns, menstrual symptoms and quality of life. | The ER satisfied most participants, and reduced the number of bleeding days and menstruation-related symptoms compared to 21/7 cycles. |
| Anthuber *et al.* 2010[31] | Prospective, observational, non-interventional, multicentre 'Teenager in Non-Interventional Study'. | 7462 healthy women ≤ 20 years. | EE 30μg/CMA 2 mg:<br>ER (42/7) vs. 21/7 of the same HC.<br>6 months | Cycle disorders, dysmenorrhoea, skin problems, efficacy and tolerability in young women. | ER had a significantly beneficial effect on cycle disorders, dysmenorrhoea and skin disorders, and confirmed the good efficacy and tolerability. |
| Göretzlehner *et al.* 2011[32] | Pooled analysis of 3 non-interventional, observational studies. | 625 healthy women (mean ± SD age 24.9 ± 9.0 years). | ER (84/7): EE 30 μg/CMA 2 mg.<br>6 months | Cycle-dependent symptoms. | ER reduced cycle-related complaints and was very well tolerated. |

(*Continued*)

Table 2 Continued

| *References* | *Method* | *Participants* | *Intervention* | *Outcomes* | *Key results* |
|---|---|---|---|---|---|
| Guazzelli *et al.* 2012[33] | Single-centre prospective study. | 150 healthy women aged 18–39 years. | ER: 84 days followed by a 7-day pause: vaginal ring (EE 15 μg/ENG 120 μg) vs. COC (EE 30μg/DSG 150 μg).<br>1 year | Lipid metabolism. | The steroids released by the ring had the same effects on the lipid metabolism and lipoprotein levels seen with oral or parenteral routes. |
| Calhoun *et al.* 2012[34] | Retrospective database series. | 23 women with menstrual migraine | Vaginal ring (EE 15 μg/ ENG 120 μg): CR (8 women) or ER (84/7 with use of a transdermal E2 patch during those 7 days; 15 women).<br>Mean observation of 7.8 months | Frequency of migraine aura and prevention of menstruation-related migraine. | Both the CR and the ER with the contraceptive vaginal ring reduced the frequency of migraine with aura and suppressed menstruation-related migraine. |

CMA, chlormadinone acetate; DRSP, drospirenone; EE, ethinylestradiol; ENG, etonogestrel; LNG, levonorgestrel; NETA, norethisterone acetate; HC, hormonal contraceptive; COC, combined oral contraceptive; E2, 17β-oestradiol; CR, continuous regimen; ER, extended cycle regimen; FR, flexible regimen.

Editor's note (J. J. Amy): The studies by Sulak et al. 2006 (ref 23), Coffee et al. 2006 (ref 24) and Sulak et al. 2007 (ref 25) apparently concerned a single study sample of 111 women. The findings of the aforementioned investigators could have been reported in a single paper.

**Table 3** Efficacy in treating symptoms related to withdrawal bleeding and hormone-free intervals.

| *Reference* | *Symptoms recorded* | *Intervention* | *Results* |
|---|---|---|---|
| Edelman *et al.* 2006[6] | Subjects were asked to make a daily notation in their calendars (yes/no) regarding the occurrence or absence of headache, nausea, bloating, acne, mood disorders/depression, breast tenderness, dysmenorrhoea and other events. | Four CRs:<br>1. EE 20 μg/LNG 100 μg<br>2. EE 30 μg/LNG 100 μg<br>3. EE 20 μg/NETA 1 mg<br>4. EE 30 μg/NETA 1 mg. | No differences between these four regimens. |
| Legro *et al.* 2008[7] | Moos Menstrual Distress Questionnaire (behavioural, psychological, and physical changes in response to withdrawal bleeding-related symptoms) | CR vs conventional (21/7) with EE 20 mg/NETA 1 mg. | CR was associated with less dysmenorrhoea ($p < 0.01$) and with improvements in behaviour ($p < 0.04$) during the period prior to scheduled bleeding. |
| Machado *et al.* 2010[10] | Acne, dysmenorrhoea, headache, breast swelling, mastalgia, nausea, irritability, oedema, increased appetite.<br>The symptoms were evaluated by means of a score reflecting their intensity (0 = absent; 1 = mild; 2 = moderate; and 3 = intense). | CR vs conventional (21/7) with EE 30 μg/DRSP 3 mg. | Dysmenorrhoea, headache, mastalgia, acne, nausea, oedema and increased appetite improved significantly with CR. |
| Sulak *et al.* 2008[8] | Daily diary of symptoms (occurrence and degree of bleeding, pelvic pain, headaches, depression, anxiety, and irritability). | CR vs conventional (21/7) with vaginal contraceptive ring. | CR with the vaginal ring reduced the frequency and the intensity of bleeding episodes and of pelvic pain. |
| Wiegratz *et al.* 2011[15] | Headache, breast pain. | ER (84/7) vs conventional (21/7) with EE 30 μg/ DNG 2 mg. | ER was an effective and mostly well tolerated option for women who needed or wished to omit the pill-free interval. |
| Klipping *et al.* 2012[17,18] | Mild abdominal/pelvic pain, mild backache, impairment of daily activities, confinement to bed for part of a single day, interference with leisure activities. | FR vs conventional (24/4) vs. ER (120/4) with EE 20 μg/DRSP 3 mg. | No differences between groups with respect to withdrawal bleeding-related problems. |

HC, hormonal contraceptive; CR, continuous regimen; ER, extended cycle regimen; FR, flexible regimen; EE, ethinylestradiol; LNG, levonorgestrel; NETA, norethisterone acetate; DRSP, drospirenone; DNG, dienogest.

**Table 4** Bleeding profiles in randomised controlled trials.

| *Reference* | *Switchers/starters* | *Definition of bleeding profile* | *Intervention* | *Results* |
|---|---|---|---|---|
| Edelman *et al.* 2006[6] | Switchers (3 months) | Subjective ordinal scale of bleeding intensity: 0 = no bleeding; 1 = spotting; 2 = slight bleeding; 3 = moderate bleeding; and 4 = heavy bleeding. | Four CRs:<br>1. EE 20 μg/LNG 100 μg<br>2. EE 30 μg/LNG 100 μg<br>3. EE 20 μg/NETA 1 mg<br>4. EE 30 μg/NETA 1 mg. | Patients in the 20NETA and 30NETA arms had significantly more days of amenorrhoea than those in the 30LNG arm in the second 90 days ($p < 0.001$).<br>The 30LNG group reported more spotting days than the 20NETA group over the entire study period ($p < 0.001$) and the 30NETA group for the second 90 days ($p < 0.001$).<br>Only a small number of bleeding days were reported with no differences between groups. |
| Legro *et al.* 2008[7] | Switchers | Subjective ordinal scale of bleeding intensity: 0 = no bleeding; 1 = spotting; 2 = slight bleeding; 3 = moderate bleeding; and 4 = heavy bleeding. | CR vs conventional (21/7) with EE 20 mg/NETA 1 mg. | There was no statistically significant difference in the number of total bleeding days between groups, but moderate/heavy bleeding was significantly more frequent with the cyclical regimen (mean 11.0 d [SD 8.5] vs.CR 5.2 d [SD 6.8]; $p < 0.005$), with, in both groups, a decrease over time. |
| Sulak *et al.* 2008[8] | Switchers (2 months) | Subjective ordinal scale of bleeding intensity: 0 = no bleeding; 1 = spotting; 2 = slight bleeding; 3 = moderate bleeding; and 4 = heavy bleeding. | CR vs conventional with vaginal contraceptive ring. | Most patients had no to minimal bleeding during CR use, with group 2 experiencing a statistically greater percentage of days without breakthrough bleeding or spotting (95%) compared with group 1 (89%) ($p = 0.016$). Instituting a 4-day hormone-free interval was more ($p < 0.001$) effective in resolving breakthrough bleeding/spotting than CR ring use. |

| | | | | |
|---|---|---|---|---|
| Teichmann *et al.* 2009[9] | Starters | Standard definitions provided by the WHO. | CR (EE 20 μg/LNG 90 μg) vs. conventional (21/7) with EE 20 μg/LNG 100 μg. | The percentage of women who achieved amenorrhoea during each 28-day pill pack increased: 40% at pill pack 7, 53% at pill pack 13. The percentage of women with no bleeding (with or without spotting) was 50%, 69% and 79% at pill packs 3, 7 and 13, respectively. |
| Machado *et al.* 2010[10] | Starters | Subjective ordinal scale of bleeding intensity: 0 = no bleeding; 1 = spotting; 2 = slight bleeding; 3 = moderate bleeding; and 4 = heavy bleeding. | CR vs conventional (21/7) with EE 30 μg/DRSP 3 mg. | Amenorrhoea increased with CR; 62.2% of women with CR use were amenorrhoeic at the end of treatment (95% CI: 46.6–77.8%). |
| Wiegratz *et al.* 2011[15] | Switchers | Bleeding/spotting episode was defined as the number of days with bleeding/spotting preceded and followed by at least 2 bleeding-free days. | ER (84/7) vs conventional (21/7) with EE 30 μg/DNG 2 mg. | In the ER group, the total number of days with bleeding progressively decreased over time, and overall, the volunteers had fewer days with bleeding/spotting compared to those treated conventionally. Intracyclic bleeding was more frequent in the ER group, although its frequency considerably diminished over time. |
| Klipping *et al.* 2012[17,18] | Starters | Standard definitions provided by the WHO. | FR vs conventional (24/4) vs. ER (120/4) with EE 20 μg/DRSP 3 mg. | Over the full 2 years of the study, the FR was associated with the lowest mean number of bleeding/spotting days. |
| | Switchers | | | Serious AEs occurred in 3.0%, 1.4% and 3.3% of women receiving the FR, conventional and fixed ER, respectively. No unexpected effects on endometrium, hormone levels, lipids, haemostasis or metabolic indices were observed with any of the three regimens. |

(*Continued*)

Table 4 Continued

| *Reference* | *Switchers/starters* | *Definition of bleeding profile* | *Intervention* | *Results* |
|---|---|---|---|---|
| Jensen *et al.* 2012[19] | Starters | Standard definitions provided by the WHO | Conventional (24/4) vs FR with EE 20 μg/DRSP 3 mg. variants of a FR:<br>• FR that required subjects to initiate 4-day tablet-free intervals after 3 days of breakthrough bleeding/spotting.<br>• An alternative FR allowed subjects to initiate a 4-day tablet-free interval irrespective of the occurrence of bleeding. | Over 1 year, subjects in the FR group experienced significantly fewer bleeding/spotting days than those in the conventional group. |
| Stephenson *et al.* 2013[20] | Mostly switchers | Subjective ordinal scale of bleeding intensity: 0 = no bleeding; 1 = spotting; 2 = slight bleeding; 3 = moderate bleeding; and 4 = heavy bleeding. | TR (daily pills until three consecutive days bleeding triggers a 3-day pill-free interval) vs. conventional 21/7 (EE 30 μg/LNG 150 μg). | Incidence, duration and intensity of bleeding episodes were significantly lower in the TR group.<br>Continuation rates and satisfaction were similar. |

AE, adverse effect; CI, confidence interval; CR: continuous regimen; ER: extended cycle regimen; FR: flexible regimen; TR: tailored regimen; EE, ethinylestradiol; LNG, levonorgestrel; NETA, norethisterone acetate; DRSP, drospirenone; DNG, dienogest.

ERs. Although there was an increase in breakthrough bleeding (BTB) during the first months of use, its frequency and intensity subsequently decreased over time.

BTB constitutes the main complaint related to CR/ER, and several measures have been proposed to treat this problem[39]. In this respect, a large group of women highly rated their ability to control bleeding according to their sporting activities, work, and social needs. This advantage is the main justification for adopting a flexible or adapted ER which, in addition, will also reduce the frequency of BTB[17,18,20]. To experience less BTB when relying on a CR/ER, one can advantageously observe a four-day hormone-free interval, when BTB occurs, followed by the resumption of treatment, as suggested by a recent systematic review, although this recommendation was based on data from a single RCT[40].

It should be noted that studies which assessed satisfaction of users of CRs/ERs showed that satisfaction was higher when the number of bleeding episodes of any type decreased.[5,6,9,14,17, 18,20] In this regard, participants in the study by Stephenson *et al.*[20], who were mostly young, nulliparous women with little prior experience of hormonal contraception, valued particularly the advantages and disadvantages of the ER they had newly adopted, primarily those relating to BTB and the possibility of eliminating the symptoms associated with withdrawal bleeds and hormone-free periods. This study also evaluated issues related to the ease of use and reached the interesting conclusion that women generally need time to adjust to any modality of CR/ER[41].

Reducing the frequency and intensity of the bleeding episodes is a strategy used to treat women with heavy menstrual bleeding (HMB), anaemia, and endometriosis. In the case of HMB, the 2006 Cochrane review[2] showed conflicting results, and also recent RCTs have taken into consideration the number of bleeds rather than their intensity. Most studies have brought to light that the frequency of bleeding was lower and the amenorrhoea rate was higher in CR/ER users; two of these studies[6,20] also showed that the intensity of bleeding was greater with conventional regimens (Table 4). Canadian guidelines actually recommend CR/ER for women with HMB or blood dyscrasias[42].

In some prospective studies and RCTs, CRs/ERs have been found to alleviate the symptoms of endometriosis by reducing the number of bleeding episodes, especially after surgery[43,44].

In this regard, the levonorgestrel releasing-intrauterine system (LNG-IUS) is an alternative to CRs/ERs of CHC use for women experiencing problems around the period of the menstruation (when having spontaneous cycles) or during the hormone-free interval (when on a CHC), mainly related to bleeding or pain; however, its effect on the premenstrual syndrome remains uncertain. In fact, the LNG-IUS could be considered as the first-line therapy for dysmenorrhoea and heavy menstrual bleeding whereas CRs/ERs of CHC should be preferred for prevention of other menstruation- or withdrawal bleeding-related problems such as, for instance, the premenstrual syndrome and cyclic headaches[45].

### Other non-contraceptive benefits

The risk of endometrial cancer is reduced in users of a CHC with a residual protective effect after discontinuation. It is unlikely that CRs/ERs would alter this benefit, considering the results of endometrial biopsies[28,29]. Moreover, the reduction in ovarian cancer risk was shown to be independent of the regimen used[46].

Few investigators have assessed acne reduction with CR/ER. One ER of daily intake of 30 μg EE and 2 mg chlormadinone acetate appeared to have been associated with a reduction in the severity of acne after six months[31,32]. Investigators evaluating a pill containing 30 μg EE and 2 mg DNG reported that the level of sex hormone-binding globulin (SHBG) had risen whereas that of testosterone had dropped, as is seen with conventional regimens[47].

### Acceptability

No differences were found comparing CRs/ERs to conventional regimens with regard to other side effects such as mastalgia, nausea and weight changes. Women using a CR/ER are exposed to more days of hormonal treatment, yet the low incidence of side effects would require the assessment of thousands of users to identify differences between regimens in this respect. Therefore, regulatory agencies still maintain the contraindications, warnings, or precautions associated with conventional regimens.

### Endometrial effects

It appears that CRs/ERs are safe with regard to the endometrium, as histological examinations, as a rule, detect an inactive endometrium in such patients. The absence of regular shedding causes an increase in neither endometrial thickness nor in the risk of

hyperplasia, as confirmed in several studies evaluating endometrial biopsies of women relying on a CR/ER. Three of the papers concerned, pertaining to one RCT[48] and two observational studies[28,32] were published after the most recent Cochrane review[2].

### Return to fertility

The few studies that evaluated this have shown a rapid return to fertility after discontinuation of CR/ER of intake of a COC[24,44]. As with conventional regimens, the mean time to withdrawal bleeding after CR/ER was 32 days, and 99% of women have a spontaneous menstruation (or pregnancy) within three months of leaving the CR/ER[49].

### Thrombotic risk

There are no data on record to evaluate whether the risk of thrombosis rises due to the adoption of a CR/ER. Although it is possible that extending the number of days with hormone exposure would increase this risk, pharmacokinetic studies indicate that this risk depends on the daily dose and the nature of the steroids, rather than the duration of use[50]. In fact, the incidence of thrombotic events described in studies subsequent to the review published in 2006[2] is similar to that reported for conventional regimens. Some studies have shown that changes in several coagulation- and fibrinolysis indices in users of a CR/ER were similar to those observed with conventional regimens[10,11,24]. Recently, the European Pharmacovigilance Risk Assessment Committee (PRAC), upon completion of a review of the thrombotic effects of CHCs, issued a statement that there should be no reasons for suspending treatment in users not presenting certain risk factors[51].

### Cardiovascular disease

The increased risk of experiencing a myocardial infarction or stroke with a CHC appears to be related to thrombotic mechanisms, especially in women over 35 years of age and those who smoke[52]. In the studies included in this review an increased risk of myocardial infarction or stroke was not observed in users of any CR/ER. Moreover, investigations concerning the effects of CRs/ERs on blood pressure and lipid- or carbohydrate metabolism revealed no differences in comparison to the conventional regimen or according to the route of administration[2,10–12,28].

### Cancer

An association between cervical cancer and use of CHCs has been observed. This risk augments over time with use, possibly due to increased viral expression through hormone-sensitive elements found in viral genomes[53].

Data about breast cancer risk indicate a slightly greater risk among current users of COCs, an effect which disappears 5–10 years after stopping[54]. In an *in vitro* study, comparing the effects of different steroids and regimens, no increased risk of breast cancer following treatment with any of the studied drugs was observed[55].

### Cost-effectiveness analysis

Monthly bleeds may affect health, as well as psychological and social functioning, regardless of whether they are caused by physiological endometrial shedding at menstruation or CHC deprivation. They could also have an economical impact due to the cost of feminine hygiene products, medical consultations for premenstrual- or menstruation-related symptoms and drug consumption in response to such symptoms.

A large, matched cohort study demonstrated that a diagnosis of idiopathic HMB is associated with significant resource use, direct medical-, and indirect work loss cost burden[56]. We should also mention the cost of work- and school absenteeism for women and girls concerned. However, at present, there is insufficient evidence to determine whether any specific CHC or regimen is more efficient than any other in reducing such costs. CHCs administered via the transdermal and vaginal routes are more expensive than COCs. According to the 2007 Canadian consensus[42], the ER was associated with a greater reduction in the consumption of hygiene products than conventional CHC-driven cycles. In particular, a reduction in drug consumption was related to the less frequent bleeding episodes and the reduced work/school absenteeism; the greater number of days of pill intake did not lead to an increase in the global cost of extended/continuous regimens[31].

## CONCLUSIONS

The contraceptive efficacy and safety of CR/ER use of CHCs is at least equal to that of 28-days conventional regimens. Currently, there are no guidelines regarding the optimal modality of CHC administration. Individualisation of treatment is paramount, and we suggest considering the cultural background and personal preferences of each patient when helping her decide on the number and timing of bleeding episodes. In addition, CR/ER uses of CHCs reduce the symptoms associated with withdrawal bleeds or the hormone-free period and the costs related to these.

Changes in the attitudes of women using CHC methods are encouraging, but it is also advisable to change the attitudes of health professionals regarding the use of CHCs.

## ACKNOWLEDGEMENTS

This article has been translated and corrected by American Journal Experts.

***Declaration of interest:*** Authors NM, PL, RL, MC, and RSB have participated in conferences, symposiums, and studies sponsored by various pharmaceutical companies.

The authors alone are responsible for the content and the writing of the paper.

This study benefited from an educational grant from the *Fundación Española de Contracepción*.



## REFERENCES

1. Loudon NB, Foxwell M, Potts DM, *et al.* Acceptability of an oral contraceptive that reduces the frequency of menstruation: The tri-cycle pill regimen. *BMJ* 1977;2:487–90.
2. Edelman A, Gallo MF, Nichols MD, *et al.* Continuous versus cyclic use of combined oral contraceptives for contraception: Systematic Cochrane review of randomized controlled trials. *Hum Reprod* 2006;21:573–8.
3. Sánchez-Borrego R. Ciclo prolongado/continuado. [Extended or continuous cycle.] *Progr Obstet Ginecol* 2010;53:89–93. [In Spanish]
4. PRISMA – Transparent reporting of systematic reviews and meta-analyses. The PRISMA statement. Accessed 31 March 2014 from: http://www.prisma-statement.org/statement.htm
5. Edelman AB, Koontz SL, Nichols MD, Jensen JT. Continuous oral contraceptives: Are bleeding patterns dependent on the hormones given? *Obstet Gynecol* 2006;107:657–65.
6. Legro RS, Pauli JG, Kunselman AR, *et al.* Effects of continuous versus cyclical oral contraception: A randomized controlled trial. *J Clin Endocrinol Metab* 2008;93:420–9.
7. Sulak PJ, Smith V, Coffee A, *et al.* Frequency and management of breakthrough bleeding with continuous use of the transvaginal contraceptive ring: A randomized controlled trial. *Obstet Gynecol* 2008;112:563–71.
8. 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;80:504–11.
9. Machado RB, De Melo NR, 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;81:215–22.
10. Machado RB, de Melo NR, Maia H Jr, Cruz AM. Effect of a continuous regimen of contraceptive combination of ethinylestradiol and drospirenone on lipid, carbohydrate and coagulation profiles. *Contraception* 2010;81:102–6.
11. Wiegratz I, Stahlberg S, Manthey T, *et al.* Effects of conventional or extended-cycle regimen of an oral contraceptive containing 30 mcg ethinylestradiol and 2 mg dienogest on various hemostasis parameters. *Contraception* 2008;78:384–91.
12. Wiegratz I, Stahlberg S, Manthey T, *et al.* Effects of combined oral contraceptive ethinylestradiol (30 microg) and dienogest (2 mg) on carbohydrate metabolism during 1 year of conventional or extended-cycle use. *Horm Metab Res* 2010;42:358–63.
13. 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.
14. Wiegratz I, Stahlberg S, Manthey T, *et al.* Effect of extended-cycle regimen with an oral contraceptive containing 30 mcg ethinylestradiol and 2 mg dienogest on bleeding patterns, safety, acceptance and contraceptive efficacy. *Contraception* 2011;84:133–43.
15. Rad M, Kluft C, de Kam ML, *et al.* Metabolic profile of a continuous versus a cyclic low-dose combined oral contraceptive after one year of use. *Eur J Contracept Reprod Health Care* 2011;16:85–94.
16. 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, randomized, controlled study. *J Fam Plann Reprod Health Care* 2012;38:73–83.
17. 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 randomized, controlled, multicentre study. *J Fam Plann Reprod Health Care* 2012;38:84–93.
18. Jensen JT, Garie SN, 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;86:110–8.
19. 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;79:350–5.
20. 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;88:523–31.
21. Foidart JM, Sulak PJ, Schellschmidt I, Zimmermann D. The use of an oral contraceptive containing ethinylestradiol and drospirenone in an extended regimen over 126 days. *Contraception* 2006;73:34–40.
22. Anderson FD, Gibbons W, Portman D. Safety and efficacy of an extended-regimen oral contraceptive utilizing continuous low-dose ethinyl estradiol. *Contraception* 2006;73:229–34.
23. Sulak PJ, Kuehl TJ, Coffee A, Willis S. Prospective analysis of occurrence and management of breakthrough bleeding during an extended oral contraceptive regimen. *Am J Obstet Gynecol* 2006;195:935–41.
24. Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: Comparison of a 21/7 and extended regimen. *Am J Obstet Gynecol* 2006; 195:1311–9.
25. Sulak P, Willis S, Kuehl T, *et al*. Headaches and oral contraceptives: Impact of eliminating the standard 7-day placebo interval. *Headache* 2007;47:27–37.
26. Huber J, Heskanp ML, Schramm. Effect of an oral contraceptive with chlormadinone acetate on depressive mood. *Clin Drug Invest* 2008;28:783–91.
27. Anderson FD, Feldman R, Reape K. Endometrial effects of a 91-day extended-regimen oral contraceptive with low-dose estrogen in place of placebo. *Contraception* 2008;77:91–6.
28. Archer DF, Kovalevsky G, Ballagh SA, *et al*. Ovarian activity and safety of a novel levonorgestrel/ethinyl estradiol continuous oral contraceptive regimen. *Contraception* 2009;80:245–53.
29. 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;81:41–8.
30. Seidman D, Yeshaya A, Ber A, *et al*. A prospective follow-up of two 21/7 cycles followed by two extended regimen 84/7 cycles with contraceptive pills containing ethinyl estradiol and drospirenone. *IMAJ* 2010;12:400–5.
31. Anthuber S, Schramm G, Heskamp ML. Six-month evaluation of the benefits of the low-dose combined oral contraceptive chlormadinone acetate 2mg/ethinylestradiol 0,003mg in young women. *Clin Drug Investig* 2010;30:211–20.
32. Göretzlehner G, Waldmann-Rex S, Schramm G. Extended cycles with the combined oral contraceptive chlormadinone acetate 2mg/ethinylestradiol 0,003mg. *Clin Drug Investig* 2011;31:269–77.
33. Guazzelli CA, Barreiros FA, Barbosa R, *et al*. Extended regimens of the contraceptive vaginal ring versus hormonal oral contraceptives: Effects on lipid metabolism. *Contraception* 2012;85:389–93.
34. Calhoun A, Ford S, Pruitt A. The impact of extended-cycle vaginal ring contraception on migraine aura: A retrospective case series. *Headache* 2012;52:1246–53.
35. Birtch RL, Olatunbosun OA, Pierson RA. Ovarian follicular dynamics during conventional vs. continuous oral contraceptive use. *Contraception* 2006;73:235–43.
36. Kallio S, Puurunen J, Ruokonen A, *et al*. Antimüllerian hormone levels decrease in women using combined contraception independently of administration route. *Fertil Steril* 2013;99:1305–10.
37. Zapata LB, Steenland MW, Brahmi D, *et al*. Effect of missed combined hormonal contraceptives on contraceptive effectiveness: A systematic review. *Contraception* 2012;87:685–700.
38. 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;89:25–7.
39. 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;79:350–5.
40. Godfrey EM, Whiteman MK, Curtis KM. Treatment of unscheduled bleeding in women using extended- or continuous-use combined hormonal contraception: A systematic review. *Contraception* 2013;87:567–75.
41. Graham CA, Panicker S, Shawe J, Stephenson J. Women's experiences with tailored use of a combined oral contraceptive: A qualitative study. *Hum Reprod* 2013;28: 1620–5.
42. Guilbert E, Boroditsky R, Black A, *et al*. Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception, 2007. *J Obstet Gynaecol Can* 2007;29 (Suppl 2):S1–32.

43. Vercellini P, Crosignani P, Somigliana E, *et al*. 'Waiting for Godot': A common sense approach to the medical treatment of endometriosis. *Hum Reprod* 2011;26:3–13.
44. Vlahos N, Vlachos A, Triantafyllidou O, *et al*. Continuous versus cyclic use of oral contraceptives after surgery for symptomatic endometriosis: A prospective cohort study. *Fertil Steril* 2013;100:1337V42.
45. Leminen H, Heliövaara-Peippo S, Halmesmäki K, *et al*. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on premenstrual symptoms in women treated for menorrhagia: Secondary analysis of a randomized controlled trial. *Acta Obstet Gynecol Scand* 2012;91:318–25.
46. Huber JC, Bentz EK, Ott J, Tempfer CB. Non-contraceptive benefits of oral contraceptives. *Expert Opin Pharmacother* 2008;9:2317–25.
47. Sänger N, Stahlberg S, Manthey T, *et al*. Effects of an oral contraceptive containing 30 mcg ethinyl estradiol and 2 mg dienogest on thyroid hormones and androgen parameters: Conventional vs. extended-cycle use. *Contraception* 2008;77:420–5.
48. Johnson JV, Grubb GS, Constantine GD. Endometrial histology following 1 year of continous daily regimen of levonorgestrel 90 μg/ethinylestradiol 20 μg. *Contraception* 2007;75:23–6.
49. Davis AR, Kroll R, Soltes B, *et al*. Occurrence of menses or pregnancy after cessation of a continuous oral contraceptive. *Fertil Steril* 2008;89:1059–63.
50. Lidegaard Ø, Nielsen LH, Skovlund CW, *et al*. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ* 2011;343:d6423.
51. EMA's Pharmacovigilance Risk Assessment Committee (PRAC). Accessed 11 October 2013 from: http://www.ema.europa.eu
52. Lidegaard Ø, Løkkegaard E, Jensen A, *et al*. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;366:2257–66.
53. Appleby P, Beral V, Berrington de González A, *et al*. for the International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptives: Collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007;370:1609–21.
54. Cibula D, Gompel A, Mueck AO, *et al*. Hormonal contraception and risk of cancer. *Hum Reprod Update* 2010;16:631–50.
55. Merki-Feld GS, Seeger H, Mueck AO. Proliferative effects of estradiol or ethinylestradiol-progestogen combinations on human breast cancer cells in an intermitted and a long-term regimen. *Horm Metab Res* 2012;44:415–21.
56. Jensen JT, Lefebvre P, Laliberte F, *et al*. Cost burden and treatment patterns associated with management of heavy menstrual bleeding. *J Womens Health (Larchmt)* 2012; 21:539–47.



## APPENDIX A: SEARCH STRATEGY

((hormonal[All Fields] AND ('contraceptive agents'[Pharmacological Action] OR 'contraceptive agents'[MeSH Terms] OR ('contraceptive'[All Fields] AND 'agents'[All Fields]) OR 'contraceptive agents'[All Fields] OR 'contraceptives'[All Fields])) OR (('vagina'[MeSH Terms] OR 'vagina'[All Fields] OR 'vaginal'[All Fields]) AND ('contraceptive agents'[Pharmacological Action] OR 'contraceptive agents'[MeSH Terms] OR ('contraceptive'[All Fields] AND 'agents'[All Fields]) OR 'contraceptive agents'[All Fields] OR 'contraceptives'[All Fields])) OR (('administration, cutaneous'[MeSH Terms] OR ('administration'[All Fields] AND 'cutaneous'[All Fields]) OR 'cutaneous administration'[All Fields] OR 'transdermal'[All Fields]) AND ('contraceptive agents'[Pharmacological Action] OR 'contraceptive agents'[MeSH Terms] OR ('contraceptive'[All Fields] AND 'agents'[All Fields]) OR 'contraceptive agents'[All Fields] OR 'contraceptives'[All Fields])) OR ('contraceptives, oral'[Pharmacological Action] OR 'contraceptives, oral'[MeSH Terms] OR ('contraceptives'[All Fields] AND 'oral'[All Fields]) OR 'oral contraceptives'[All Fields] OR ('oral'[All Fields] AND 'contraceptives'[All Fields])))) OR ((hormonal[All Fields] AND ('contraception'[MeSH Terms] OR 'contraception'[All Fields])) OR (('vagina'[MeSH Terms] OR 'vagina'[All Fields] OR 'vaginal'[All Fields]) AND ('contraception'[MeSH Terms] OR 'contraception'[All Fields])) OR (('administration, cutaneous'[MeSH Terms] OR ('administration'[All Fields] AND 'cutaneous'[All Fields]) OR 'cutaneous administration'[All Fields] OR 'transdermal'[All Fields]) AND ('contraception'[MeSH Terms] OR 'contraception'[All Fields])))) AND (extended[All Fields] OR continuous[All Fields] OR flexible[All Fields] OR tailored[All Fields]) AND ((Clinical Trial[ptyp] OR Comparative Study[ptyp]) AND hasabstract[text] AND '2003/11/20'[PDat] :'2013/11/16'[PDat] AND 'humans'[MeSH Terms] AND 'female'[MeSH Terms] AND ('adolescent'[MeSH Terms] OR 'adult'[MeSH Terms]))