



## Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception, 2007

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THE SOCIETY OF OBSTETRICIANS  
AND GYNAECOLOGISTS OF CANADA  
LA SOCIÉTÉ DES OBSTÉTRICIENS  
ET GYNÉCOLOGUES DU CANADA

# Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception, 2007

This consensus guideline has been reviewed and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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**Key Words:** Extended or continuous hormonal contraception, extended or continuous oral contraception, extended vaginal ring, continuous or extended contraceptive patch, continuous or extended combined contraceptives, continuous or extended transdermal hormonal contraception, monophasic, multiphasic, administration, dosage, therapeutic use, efficacy, effectiveness, side effect, adverse event, irregular bleeding and spotting, irregular bleeding, endometriosis, pelvic pain, dyspareunia, dysmenorrhea, uterine leiomyoma, hemorrhagic diatheses, hormone withdrawal symptoms, perimenopause, dysfunctional uterine bleeding, menorrhagia, menometrorrhagia, headaches, migraine, cost-effectiveness, cost-savings, economics

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## Abstract

**Objective:** To serve as a guideline for health care providers on the use of continuous and extended combined hormonal contraception regimens, to prevent pregnancy, and to delay menses that affect health-related quality of life.

**Options:** All combined hormonal contraceptive methods available in Canada that may be used in a continuous or extended regimen are reviewed, and the implications are discussed.

**Outcomes:** Efficacy of cited regimens and assessment of their side effects, patient safety, medical usage and non-contraceptive benefits, cost-effectiveness, and availability in Canada. Indications for patient counselling are also provided

**Evidence:** Medline, PubMed, and Cochrane Database were searched for articles published in English between 1977 and May 2007. Relevant publications and position papers from appropriate reproductive health and family planning organizations were also reviewed.

**Values:** The quality of evidence is rated using the criteria described by the Canadian Task Force on Preventive Health Care (Table 1).

**Benefits, harms, and costs:** The guideline is intended to help reduce unintended pregnancies and improve health-related quality of life in women who find their menses problematic. Increased awareness and empowerment of women, their partners, and health care professionals will improve their ability to make appropriate choices between continuous or extended and cyclic usage of these regimens.

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## Summary Statements and Recommendations

### Chapter 1: Definition and Scope

No statements or recommendations.

### Chapter 2: Background

#### Statement

Personal, religious, and cultural beliefs may affect women's attitudes towards bleeding and menstruation. (III)

**Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care**

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

\*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.<sup>172</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.<sup>172</sup>

**Recommendation**

1. Health care providers should enquire about individual preferences and respect these preferences when counselling on the use of continuous or extended combined hormonal contraceptive regimen. (III-A)

**Chapter 3: Current Usage****Statements**

Continuous or extended combined hormonal contraception is commonly used to various degrees worldwide. (III)

Given the choice, many women in all age groups would consider using continuous or extended combined hormonal contraception. (III)

**Recommendation**

2. Health care providers should be aware of the option of using continuous or extended combined hormonal contraception and consider offering it to women for contraception, medical reasons, and personal preferences. (III-A)

**Chapter 4: What Is Used?****Statements**

A number of currently available combined hormonal contraceptives, originally designed for cyclic use, have been studied using a range of continuous or extended regimens. (I)

A few dedicated continuous or extended combined hormonal contraceptive products have been studied in a variety of regimens. (I)

A number of physicians currently counsel women about how to use combined hormonal contraceptives in continuous or extended regimens. (III)

A number of women currently use combined hormonal contraceptives in continuous or extended regimens for their own convenience, at their own discretion. (III)

**Chapter 5: Efficacy and Adherence****Statement**

Continuous or extended combined hormonal contraceptive regimens are as effective as cyclic regimens in preventing pregnancy. (I)

**Chapter 6: Side Effects****Statements**

A continuous or extended combined hormonal contraceptive regimen compared with a cyclic regimen will result in fewer total bleeding days. (I)

The frequency of unscheduled bleeding and/or spotting with a continuous or extended combined hormonal contraceptive regimen is similar to that of a cyclical regimen (I) and reduces over time with both regimens. (II-2)

Some trials on continuous or extended combined oral contraceptive regimens showed evidence of lower frequency of side effects such as headaches, genital itch, bloating, and menstrual pain than cyclic regimen, but others showed no difference. (I)

**Recommendation**

3. Women using continuous or extended combined hormonal contraceptive regimens should be counselled about expected bleeding patterns. (I-A)

**Chapter 7: Medical/Non Contraceptive Usage****Statements**

In women with surgically proven endometriosis, continuous or extended combined hormonal contraceptives administered for six months are shown to be effective in reducing the frequency and the intensity of dysmenorrhea, deep dyspareunia, and non-menstrual pelvic pain over this period. (I)

Many women with abnormal uterine bleeding, including bleeding related to uterine fibroids, may benefit from menstrual suppression

with continuous or extended combined hormonal contraceptive regimens. (III)

Women with hemorrhagic diatheses may consider continuous or extended administration of combined hormonal contraceptives in order to decrease monthly withdrawal bleeding. (III)

Women experiencing hormonal withdrawal symptoms such as nausea, vomiting, breast tenderness, bloating, swelling, and mood changes during the hormone-free interval while using cyclic combined hormonal contraceptives, may benefit from continuous or extended combined hormonal contraceptive regimens. (II-2)

Menstrual migraine and headaches may improve with continuous or extended combined hormonal contraceptive regimens. (III)

Women in the perimenopause with problematic bleeding and vasomotor symptoms may benefit from continuous or extended combined hormonal contraceptive regimens rather than cyclic regimens because of the elimination of the hormone-free interval. (III)

## Chapter 8: Patient Safety

### Statements

The short-term safety of continuous or extended combined hormonal contraceptive regimens is similar to that of cyclic regimens. (III)

Direct evidence on long-term safety of continuous or extended combined hormonal contraceptive regimens is currently unavailable. (III)

The extensive body of data on the long-term safety of combined oral contraceptives over the past 50 years is reassuring. If there is a

greater risk associated with long-term use of continuous or extended combined hormonal contraceptive regimens than with long-term use of cyclic regimens, it is likely to be minimal. (III)

## Chapter 9: Cost-Effectiveness

### Statements

Continuous or extended use of combined hormonal contraceptive regimens is associated with significantly less menstrual-hygiene product consumption than cyclic regimens. (I)

Provided that the total annual cost of hormonal contraception remains lower than the total annual cost of menstrual-related products and medications, continuous or extended use regimens are a cost saving for the individual compared with cyclic regimens. (III)

From a societal perspective, there may be cost savings with continuous or extended combined hormonal regimens in terms of reduced absenteeism and doctor visits for menstruation-related complaints. However, the magnitude of these savings is uncertain and likely to be low. (III)

### Recommendation

4. The annual cost of dedicated products for continuous or extended hormonal regimens should be similar to that for cyclic regimens. (I)

## Chapter 10: Patient Education

No statements or recommendations.

## Definition and Scope

Suppression of menstruation has been the subject of many scientific articles and ensuing debate. Although pregnancy and menopause are the two natural states that suppress menstruation, many hormonal products can achieve this effect. The progestin-only contraceptive depot medroxyprogesterone acetate has the well known side-effect of amenorrhea.<sup>1</sup> Reduction of menstrual flow and possibly amenorrhea are also side-effects of the levonorgestrel-releasing intrauterine system.<sup>2</sup> These two products are notably used in a continuous fashion (12 weeks for DMPA and 5 years for LNG-IUS). Since their usage is discussed in the Canadian Contraception Consensus,<sup>3-5</sup> this consensus guideline does not address them.

This consensus guideline describes the use of combined hormonal contraception for pregnancy prevention and suppression or postponement of menses that affect health-related quality of life. Combined hormonal contraception can be delivered orally, transdermally, or vaginally, and any of these delivery methods can be used in continuous or extended regimens.<sup>6-8</sup>

Although no official definition exists, extended use usually refers to use of ChCs with planned hormone-free intervals (up from 2 contiguous cycles),<sup>9</sup> and continuous use of ChCs usually refers to uninterrupted use without hormone-free intervals.

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### Abbreviations Used in This Guideline

AUB	abnormal uterine bleeding
BMD	bone mineral density
C/E	continuous and/or extended
CHC	combined hormonal contraception
ChC	combined hormonal contraceptive
COC	combined oral contraception
CoC	combined oral contraceptive
DMPA	depot medroxyprogesterone acetate
DSG	desogestrel
DUB	dysfunctional uterine bleeding
EE	ethinyl estradiol
HIV	human immunodeficiency virus
HPV	human papillomavirus
LNG	levonorgestrel
LNG-IUS	levonorgestrel intrauterine system
MI	myocardial infarction
NGM	norgestimate
Patch	contraceptive transdermal patch
PID	pelvic inflammatory disease
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
RCT	randomized controlled trial
Ring	contraceptive vaginal ring
VTE	venous thromboembolism

# Background

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In 1960, the Food and Drug Administration approved the introduction of the first combined oral contraceptive into the United States. John Rock and his collaborator, Gregory Pincus, faced the dual challenges of developing a safe and effective method of preventing unwanted pregnancy that would reassure women, and convincing the Roman Catholic Church that the pill exerted its beneficial effects through a “natural” process. Rock is said to have argued that the pill, by regulating menstruation, allowed women to use the rhythm method as a means to space their children.<sup>10</sup> Thus, more by happenstance than by some dictum of science, the pill was introduced in packs with three weeks of active medication followed by one week without exogenous hormones, during which a “normal seeming” menstruation would occur. Indeed in 1958, Pope Pius XII approved Rock’s pill concept for Catholics as long as its contraceptive effects were “indirect.”

We now have a better understanding of how hormonal contraception works and of how its hormonal effects differ from the typical endogenous hormone production during a woman’s natural reproductive life. In years past and in cultures where women still cannot avail themselves of the benefits of modern contraception, a typical woman would be exposed to variable estrogen levels and cyclic bursts of progestin following ovulation until such time as she became pregnant, often in her mid teens. When a woman’s reproductive years were marked by repeated episodes of pregnancy and lactation, from her early teens until her mid forties, she could expect to experience no more than 150 ovulatory cycles in her lifetime.<sup>11</sup> Earlier menarche, delayed first birth, low parity, late menopause, and as many as 450 ovulatory cycles and menstrual periods differentiate contemporary women from their predecessors.<sup>12</sup> By reducing the frequency of ovulation, thinning the endometrium, decreasing exposure to estrogen and obstetrical morbidity through pregnancy prevention, and alleviating several menstrual symptoms, hormonal contraception has had an impressive impact on the lives and health of women.

The concept of C/E use of CHC is not new, having been reported in the scientific literature for the first time in 1977.<sup>13</sup> It is likely that its clinical usage predates this report. In fact, for many years, physicians have prescribed CHC in a C/E fashion for contraception, medical reasons (menstrual disorders, endometriosis, etc.), and women’s preference (vacations, sports,

special events, etc.).<sup>14</sup> Today, using hormonal contraception in a C/E fashion to suppress menstruation is an increasingly popular option among women.

When considering this option, it must be remembered that perceptions of menstruation vary in different cultures and that menstruation may be an event that has social, cultural, and psychological implications. These perceptions may be positive or negative and will influence the attitudes of women—and their partners—to changes in bleeding patterns resulting from the use of hormonal regimens and C/E regimens. Menstruation may be perceived as an occasion of rest and gathering with other women, as well as a sign of femininity, fertility, youth, or purification of the body; but it may also be associated with vulnerability and pollution, and with attitudes of disgust and shame.<sup>15</sup> In some societies, negative perceptions are the basis for restricting women’s religious, social, and domestic activities while they are menstruating. According to the World Health Organization, “*A woman has two perceptions of bleeding: one from her actual experience and the other from her position as a member of society which has attached certain meanings to menstruation.*”<sup>15</sup> So although some women may prefer to have fewer menstruations, other women may prefer to have regular menses.

Most clinicians have been or will be approached by women asking about menstrual suppression with C/E CHC. In addition, clinicians may identify women who may obtain health benefits from it. For these reasons, the Society of Obstetricians and Gynaecologists of Canada has produced guidelines to address the topic of C/E hormonal contraception. Current trends in the use of CHC regimens will be reviewed, as will the products that can be used, the efficacy of these products in achieving menstrual suppression and contraception, side-effect profile, medical indications, the safety of such usage, the cost-effectiveness of these regimens, and the education women should receive before using such regimens.

## Statement

Personal, religious, and cultural beliefs may affect women’s attitudes towards bleeding and menstruation. (III)

## Recommendation

1. Health care providers should enquire about individual preferences and respect these preferences when counselling on the use of continuous or extended combined hormonal contraceptive regimen. (III-A)

# Current Usage

Melissa Mirosh, MD, FRCSC

## **PREVALENCE OF CONTINUOUS COMBINED HORMONAL CONTRACEPTIVE USE**

A few international studies have tried to estimate the prevalence of C/E ChC use. One study from Australia,<sup>16</sup> which surveyed 158 female patients and 20 health care providers, found that 22% of patients had ever used ChCs to extend their cycle, and 45% of the providers had prescribed ChCs for this use. In the Netherlands, 1301 Dutch women were interviewed about C/E use.<sup>17</sup> Sixty-nine percent of teens and 63% of women aged 25 to 34 had ever used this method to postpone menses. In the United States, a Harris Interactive telephone poll conducted in 2005 for the Association of Reproductive Health Professionals<sup>18</sup> gathered data from 1021 women. Forty-five percent of them had heard of menstrual suppression, but only 7% had ever used birth control to stop periods.

## **WOMEN'S ATTITUDES TO CONTINUOUS COMBINED HORMONAL CONTRACEPTIVE USE AND MENSTRUAL SUPPRESSION IN GENERAL**

Although information about women's attitudes towards menstrual suppression has been available for almost 30 years,<sup>13</sup> there has been renewed interest of late. In a recent survey of 1195 German women aged 15 to 49 years,<sup>19</sup> 26% to 35% wished to have monthly menses and 37% to 46% preferred amenorrhea, mostly because of fewer menstrual complaints and improved quality of life. The women's concerns regarding menstrual suppression included fear of pregnancy and infertility, side effects, and "not being natural."<sup>19</sup> In one US study,<sup>20</sup> 59% of women were interested in menstruating less often, and one third would consider a method that caused amenorrhea. Fifty-six percent of the women interviewed would be interested in bleeding anywhere from every three months to not at all.<sup>20</sup> Younger women showed a preference for bleeding every three months, but as women approached the perimenopause, their preference was for amenorrhea.<sup>21</sup>

Adolescents have also shown significant interest in having more control over their menstrual cycles. In surveys of 310 German<sup>19</sup> and 322 Dutch<sup>17</sup> adolescents aged 15 to 19 years, 27% and 44% respectively would prefer to menstruate every three months or less, and 41% and 26% respectively would prefer amenorrhea.

Women's social, cultural, and religious backgrounds will influence, positively or negatively, how women—and their partners—accept the changes in menstrual flow caused by C/E

ChC. Certain religious groups consider intermittent or unpredictable bleeding is unacceptable, making continuous ChC regimens less desirable. For Brazilian women, although it is regarded as a nuisance, menstruation is thought to reflect youth, health, fertility, and being a female.<sup>22</sup> One study showed that many women in Nigeria, South Africa, and China have a strong wish to menstruate, as they feel it "cleanses bad blood" and tells them they are not pregnant.<sup>23</sup> For women using contraception without their partner's knowledge, having a monthly bleed allows them pregnancy protection but conceals their use of birth control.<sup>23</sup>

## **PHYSICIANS' ATTITUDES TO CONTINUOUS COMBINED HORMONAL CONTRACEPTIVE USE**

In 2002, the Association of Reproductive Health Professionals and the National Association of Nurse Practitioners in Women's Health surveyed their annual meeting registrants (N = 117)<sup>24</sup>; 77% indicated that they prescribed C/E CoC regimens. Two years later, in a survey of US health care providers attending medical conferences,<sup>25</sup> 87% felt C/E ChC regimens should be routinely offered, and 82% had already recommended them. Only 12% thought regular withdrawal bleeding had health benefits, and 83% felt there was no added risk to C/E ChC use compared with regular cyclic CoC use.<sup>25</sup> These beliefs also extended to health care providers who treat adolescents. An online survey of physicians working in adolescent medicine showed that 90% prescribed extended cycles of hormonal contraception to adolescents, and 33% said extended cycles made up more than 10% of their total ChC prescriptions.<sup>26</sup> In another survey,<sup>20</sup> 44% of the providers felt menstrual suppression was a good idea, but only 22% had actually provided that service to patients. Both patients and providers felt that further research was needed to examine the long-term risks and side effects of C/E ChC use.<sup>20</sup>

### **Statements**

Continuous or extended combined hormonal contraception is commonly used to various degrees worldwide. (III)

Given the choice, many women in all age groups would consider using continuous or extended combined hormonal contraception. (III)

### **Recommendation**

2. Health care providers should be aware of the option of using continuous or extended combined hormonal contraception and consider offering it to women for contraception, medical reasons, and personal preferences. (III-A)

## What Is Used?

Erica Weir, MD, MSc, FCFP

Continuous and extended regimens of a variety of monophasic and multiphasic CoCs have been studied.<sup>6,13,27-40</sup> Table 2 lists the RCTs designed to evaluate C/E use of CHC and describes the EE and progestin doses and types of ChCs used. Tables 3 and 4 show the CoCs currently available for cyclic use in Canada and the dedicated products available in the United States for C/E use, respectively. Table 5 shows products currently available in Canada for transdermal and vaginal administration of CHC. The studies show that hormonal contraceptive products used in C/E administration are distinguished not by their formulation but by the way they are prescribed (i.e., the number of consecutive days the hormones are taken before an HFI is introduced).

The number of days of consecutive use has been studied. Most are multiples of the conventional “21 days” (e.g., 42, 63, 84, 126 days), followed by a conventional seven-day

HFI.<sup>13,27,28,30-33,39</sup> Most of the studies span a year, with follow-up of selected cohorts for an additional year or two. A few RCTs have evaluated the C/E use of COC for 168 or 336 consecutive days, without a seven-day HFI.<sup>6,34,38,40</sup> The rationale for the length of the seven-day HFI appears to be arbitrary, and some evidence indicates that shorter HFIs, such as four days, might be acceptable,<sup>35</sup> as might replacing the HFI with a progestin-free interval and maintaining the intake of a small amount of estrogen.<sup>40</sup>

There is limited evidence on the use of triphasic CoCs in a C/E regimen<sup>28,37</sup> and no RCT. A 1987 cohort study comparing monophasic and triphasic CoCs in a continuous regimen examined the risk of breakthrough bleeding and/or spotting in women, over a single period of 42 days.<sup>28</sup> A more recent retrospective chart review described use of a continuous triphasic CoC regimen for a median of 237 days (8 cycles) in 43 women.<sup>37</sup>

**Table 2. Randomized control trials on continuous or extended combined oral contraception use**

Study	Continuous CHC Regimen (C/E)	Cyclic 21/7 Regimen (C)	Sample size		Duration	Completion rate %	EE dose	Progestin dose and type
			C/E	C				
Cachrimanidou 1993 <sup>30</sup>	63/7	Y	198	96	12 months	58 (C/E) 76 (C)	30 µg	150 µg DSG
Miller & Notter 2001 <sup>32</sup>	42/7	Y	46	44	336 days	63 (C/E) 54.5 (C)	30 µg	300 µg Norgestrel
Anderson & Hait 2005 <sup>33</sup>	84/7	Y	456	226	12 months	59.4 (C/E) 71.2 (C)	30 µg	150 µg LNG
Kwiecien & Edelman 2003 <sup>34</sup>	168	Y	16	16	168 days	87 (C/E) 87 (C)	20 µg	100 µg LNG
Miller & Hugues 2003 <sup>6</sup>	336	Y	39	40	336 days	82 (C/E) 72 (C)	20 µg	100 µg LNG
Stewart & Kaunitz 2005 <sup>7</sup> (Contraceptive patch)	84/7	Y	158	81	84 days	77.8 (C/E) 84 (C)	20 µg	150 µg Norelgestromin
Miller & Hout 2005 <sup>8</sup> (Contraceptive vaginal ring)	42/7	Y	A 107	D 108	12 months	A 72 (C/E)	15 µg	120 µg Etonorgestrel
	84/7		B 105	B 62 (C/E)				
	364		C 109	C 59 (C/E) D 77 (C)				

(C): cyclic regimen; Y: yes

**Table 3. Combined oral contraceptive products available in Canada**

Phase	Product	Estrogen	Progestin
Monophasic	Allesse	20 µg EE	0.10 mg LNG
	Minestrin	20 µg EE	1.00 mg norethindrone acetate
	Loestrin	30 µg EE	1.50 mg norethindrone acetate
	Demulen	30 µg EE	2.00 mg ethynodiol diacetate
	Marvelon	30 µg EE	0.15 mg DSG
	Min-Ovral	30 µg EE	0.15 mg LNG
	Ortho-Cept	30 µg EE	0.15 mg DSG
	Yasmin	30 µg EE	3.00 mg drospirenone
	Brevicon 0.5/35	35 µg EE	0.50 mg norethindrone
	Brevicon 1/35	35 µg EE	1.00 mg norethindrone
	Cyclen	35 µg EE	0.25 mg norgestimate
	Ortho 1/35	35 µg EE	1.00 mg norethindrone
	Ortho 0.5/35	35 µg EE	0.50 mg norethindrone
	Diane-35	35 µg EE	2.0 mg cyproterone acetate
	Lo-Femenol	30 µg EE	0.3 mg norgestrel
	Ovral	50 µg EE	0.5 mg norgestrel
	Ortho-Novum 1/50	50 µg mestranol	1.00 mg norethindrone
	Norinyl	50 µg mestranol	1.00 mg norethindrone
	Biphasic	Synphasic	35 µg EE
0.50 mg (12 tablets)			
Triphasic	Tri-Cyclen-LO	25 µg EE	1.00 mg (9 tablets)
			norgestimate
			0.180 mg (7 tablets)
			0.215 mg (7 tablets)
			0.250 mg (7 tablets)
			DSG
			0.100 mg (7 tablets)
	Linessa	25 µg EE	0.125 mg (7 tablets)
			0.150 mg (7 tablets)
			DSG
	Triquilar	30 µg EE (6 tablets)	LNG
			40 µg EE (5 tablets)
			0.050 mg (6 tablets)
	Triphasil	30 µg EE (6 tablets)	0.075 mg (5 tablets)
			40 µg EE (5 tablets)
			0.125 mg (10 tablets)
	Ortho 7/7/7	35 µg EE	LNG
0.05 mg (6 tablets)			
0.075 mg (5 tablets)			
Tri-Cyclen	35 µg	0.125 mg (10 tablets)	
		norethindrone	
		0.50 mg (7 tablets)	
		0.75 mg (7 tablets)	
Tri-Cyclen	35 µg	1.00 mg (7 tablets)	
		norgestimate	
		0.180 mg (7 tablets)	
Tri-Cyclen	35 µg	0.215 mg (7 tablets)	
		0.250 mg (7 tablets)	

**Table 4. Combined oral contraceptive products dedicated for extended/continuous regimen**

Phase	Regimen	Product	Estrogen	Progestin
Monophasic	Extended use 84 days 7 day HFI	*Seasonale	30 µg EE	0.15 mg LNG
Monophasic	Continuous use 365 days	Anya	20 µg EE	0.090 mg LNG
Monophasic	Extended use 84 days followed by 7 days of 10 g EE (i.e., no HFI)	*Seasonique	30 µg EE 10 µg EE)	0.15 mg LNG

\* Not available in Canada

**Table 5. Transdermal and vaginally delivered hormonal contraceptive products available in Canada**

Route	Phase	Product	Estrogen	Progestin
Dermal	Monophasic	Evra	0.6 mg EE (20 µg daily)	6 mg norelgestromin (150 µg daily)
Vaginal	Monophasic	NuvaRing	2.6 mg EE (15 µg daily)	etonogestrel 11.4 mg (120 µg daily)

Different routes for delivering CHC in a C/E regimen have also been studied. One RCT compared a continuous contraceptive patch regimen (weekly application of the patch for 12 weeks, 1 patch-free week) with a cyclic patch regimen.<sup>7</sup> Another RCT randomized 429 women to one of four regimens over 365 days using the contraceptive vaginal ring: 3, 6, 12 or 51 weeks of continuous use followed by 1 ring-free week<sup>8</sup> (results of these studies are presented thereafter shown in Table 2).

Evidence from the field suggests that many health care providers, particularly obstetricians and gynaecologists and those in family planning, are responding to women's requests and have adopted C/E CHC in their practice. In 2002, the survey of the American Association of Reproductive Health Professionals and the National Association of Nurse Practitioners in Women's Health<sup>24</sup> showed that the most commonly prescribed regimen among their respondents was 63 active pills followed by a seven-day HFI. According to a more recent survey of health care providers,<sup>25</sup> the most commonly prescribed regimen was a 84-day active pill use period followed by a seven-day HFI.

Overall, the literature suggests that available orally, transdermally, and vaginally administered ChCs, including those originally designed for cyclic use, can be and are being administered in a variety of C/E regimens. The literature suggests that no single regimen is most effective and that a variety of regimens can be administered according to patient/provider preference.

**SOGC Clinical Tip**

The length of the C/E combined hormonal contraceptive ChC regimen can be altered, depending on the experience of side effects.

**SOGC Clinical Tip**

All currently available sub 50µg EE contraceptives (oral [monophasic or multiphasic], transdermal, vaginal) can be used in a continuous C/E regimen.

**SOGC Clinical Tip**

The length of the C/E combined hormonal contraceptive ChC regimens should be administered according to the preference of the woman or the provider.

### Statements

A number of currently available combined hormonal contraceptives, originally designed for cyclic use, have been studied using a range of continuous or extended regimens. (I)

A few dedicated continuous or extended combined hormonal contraceptive products have been studied in a variety of regimens. (I)

A number of physicians currently counsel women about how to use combined hormonal contraceptives in continuous or extended regimens. (III)

A number of women currently use combined hormonal contraceptives in continuous or extended regimens for their own convenience, at their own discretion. (III)

# Efficacy and Adherence

Marie-Soleil Wagner, MD, MSc, FRCSC

Interpretation of studies on efficacy of adherence to C/E ChC regimens may be limited by a few factors: use of different regimens (route of administration, dose, type of progestins, and duration), small sample sizes, and non-optimal completion rates.

## EFFICACY

### Continuous or Extended Use of Combined Oral Contraceptives

In RCTs comparing the C/E CoC administration with the conventional 28-day cycle CoC administration, pregnancy rates were similar with both regimens,<sup>6,30,32-34</sup> except in one study.<sup>41</sup> In this study, where both regimens were used intravaginally, four pregnancies were recorded, all in the 28-day cycle regimen (OR 0.1; 95% CI 0.0-1.0).<sup>9,41</sup> The retrospective chart review on continuous triphasic CoC regimens did not report any pregnancy.<sup>37</sup>

Many clinicians think that C/E CoC regimens have the potential to increase contraceptive efficacy. This view is partly supported by studies demonstrating that reduction of the HFI or addition of estrogen during this period achieves greater ovulation suppression, making it a more “forgiving” regimen.<sup>42-45</sup> It has also been shown that ovulation was more effectively suppressed with continuous CoC administration than with conventional 28-day cycle CoC administration.<sup>4,46,47</sup> One recent RCT compared follicular and endometrial development during 84-day continuous CoC administration and conventional 28-day cycle CoC administration.<sup>46</sup> In the continuous CoC group, statistically fewer ovarian follicles developed, and no apparition of dominant follicles was noted. The endometrial thickness did not differ between the two regimens.

### Continuous or Extended Use of the Contraceptive Patch and the Vaginal Ring

One RCT compared a continuous patch regimen with a conventional 28-day cycle patch regimen. The only pregnancy in this study occurred with the continuous regimen.<sup>7</sup> One RCT compared the use of three C/E ring regimens (49, 91, and 364-day regimens) with the conventional 28-day ring regimen.<sup>8</sup> One pregnancy was reported,

occurring with the 91-day regimen (the woman lost her vaginal ring and did not notice it).

Studies on the effect of the contraceptive patch or vaginal ring on follicular suppression have been done only with conventional 28-day regimens. One study showed that the use of a contraceptive patch suppressed follicular development more effectively than conventional 28-day cycle CoC administration, even after incorrect dosing.<sup>48</sup> Another study showed that the vaginal ring was effective in suppressing ovulation up to five weeks after its insertion.<sup>49</sup>

## ADHERENCE

### Continuous or Extended Use of Combined Oral Contraceptives

Unintended pregnancies often occur as a result of inconsistent use of CoC.<sup>50,51</sup> In a cohort study of CoC adherence,<sup>52</sup> 22.5% of the women reported having missed at least one pill during one cycle, and 42% of these omissions occurred at the beginning of a new cycle. Contributing to physicians’ positive attitude towards C/E CoC regimens, this cohort study<sup>52</sup> also showed that pill omissions were lower with C/E CoC regimens than with the conventional 28-day cycle CoC regimens. By removing the need for women to make the transition between packs of pills, C/E CoC regimens may be easier to follow and may result in higher efficacy.<sup>53,54</sup> However, in three RCTs on C/E CoC regimens,<sup>6,32,33</sup> although definitions of adherence varied among studies, there was no statistical difference in women’s adherence between C/E CoC regimens and 28-day regimens.<sup>9</sup>

Lack of adherence also relates to discontinuation rate. In RCTs comparing continuous CoC regimens with conventional 28-day CoC regimens, completion rates varied from 59.4% to 87% for C/E CoC regimens and from 54.5% to 87% for 28-day CoC regimens.<sup>6,30,32-34</sup> In one RCT,<sup>33</sup> the overall discontinuation rate was significantly lower with the 28-day regimen (28.8%) than with the continuous CoC regimen (40.6%).<sup>9</sup> Otherwise, there was no statistical difference in overall discontinuation rates between C/E CoC regimens and 28-day regimens.<sup>9</sup> Most reasons for discontinuation were related to side effects, primarily irregular bleeding and/or spotting.

### **Continuous or Extended Use of the Contraceptive Patch and the Vaginal Ring**

The continuation rates reported in the RCT on the contraceptive patch<sup>7</sup> were 79% for the extended patch regimen and 85% for the 28-day patch regimen.

In the RCT comparing various contraceptive vaginal ring regimens,<sup>8</sup> the continuation rate of the 91-day regimen was similar to that of the 364-day regimen, and both were significantly lower than those of the 49- and 28-day cycle regimens. The main difference in continuation rates between these regimens was related to a higher percentage of irregular bleeding and spotting in the groups with the highest discontinuation rates.

### **Statement**

Continuous combined hormonal contraceptive regimens are as effective as cyclic regimens in preventing pregnancy. (I)

#### **SOGC Clinical Tip**

In combined hormonal contraception CHC users, frequent lack of adherence may lead to increased failure. Use of C/E combined hormonal contraception CHC may be more “forgiving” about missed combined hormonal contraceptives ChCs because of the absence of a cyclic HFI.

# Side Effects

Sari Kives, MD, FRCSC

Marie-Soleil Wagner, MD, MSc, FRCSC

## **BLEEDING AND SPOTTING**

All cyclic ChC regimens are associated with unscheduled bleeding and/or spotting, which typically improves or resolves with persistent use. This is also true for C/E CHC. A systematic review of the literature identified seven RCTs (Table 2) that compared bleeding patterns, as their primary outcome, in cyclic and continuous ChC users. However, these studies differed in cycle length, type of ChC (progestin and estrogen dose), route of administration (i.e., pill, patch, or ring), and analysis of bleeding. All studies defined “spotting” as any bloody vaginal discharge that does not require sanitary protection and “bleeding only” as any bloody vaginal discharge requiring sanitary protection. Additionally, bleeding and/or spotting can occur at any time, including during the HFI.

### **Continuous or Extended Use of Combined Oral Contraceptives**

#### **Bleeding-only days**

The rates of bleeding-only days were consistently reduced with all continuous CoC regimens. The mean number of bleeding-only days was significantly less in the C/E CoC groups than in the cyclic groups (6.4 vs. 10.9 days over an 84-day cycle<sup>32</sup> and 18.4 vs. 33.8 days over a 168-day cycle<sup>34</sup>). In two additional studies, the median number of bleeding-only days was also significantly reduced with the C/E CoC regimens compared with cyclic regimens<sup>9</sup> (16 vs. 40 days over a 364-day reference period,<sup>33</sup> and 3 vs. 10 days over a first 84-day reference period<sup>6</sup>). This statistically significant reduction in the number of bleeding-only days persisted throughout the study periods and often decreased over time.<sup>6,32</sup> Amenorrhea rates were also increased with C/E CoC regimens.<sup>6,33</sup>

By reducing or eliminating the week of withdrawal bleeding, C/E CoC regimens were associated with a decrease in bleeding-only days and increase in amenorrhea rates, regardless of the type of CoC or the C/E CoC regimen chosen.

#### **Bleeding and spotting days**

All studies failed to show any significant difference in the mean or the median number of spotting days or bleeding and/or spotting days between C/E and cyclic regimens. The mean number of spotting days was similar for both schedules over an 84-day reference period (49-days =  $3.7 \pm 3.6$  and 28-days =  $4.8 \pm 3.8$ ),<sup>32</sup> and the mean number of bleeding and/or spotting days was also similar for both regimens over a 168-day reference period (C/E =  $25.9 \pm 29.2$  and 28-days =  $34.9 \pm 16.9$ ).<sup>34</sup> The mean number of bleeding and/or spotting days remained approximately the same throughout the study periods in these studies.<sup>32,34</sup> In two additional studies, the median number of bleeding and/or spotting days was also found to be similar for continuous and cyclic CoC regimens: nine days versus six days over an 84-day cycle for spotting days<sup>6</sup> and 35 days versus 53 days over a 364-day reference period for bleeding and/or spotting days.<sup>33</sup> In these studies, the number of bleeding and/or spotting days decreased with each successive cycle.<sup>6,33</sup> Spotting was initially increased (although not significantly) with the C/E CoC regimen but this effect gradually decreased over time.<sup>6,33</sup>

Cachrimanidou et al. also found that unscheduled bleeding and/or spotting were significantly more frequent with extended regimens than with cyclic regimens and that they decreased over time.<sup>30</sup>

Rates of bleeding and spotting appeared similar for continuous and cyclic regimens. C/E regimens did not seem to aggravate this common side effect of CoCs.

### **Continuous or Extended Use of the Contraceptive Patch and the Vaginal Ring**

#### **Bleeding-only days**

An extended patch regimen resulted in significantly fewer median bleeding days than a cyclic patch regimen (6 vs. 14 days) over an 84-day period.<sup>7</sup> Amenorrhea rates were also greater (12% vs. 1%) with the extended patch regimen.<sup>7</sup> The median number of bleeding-only days varied from 0 days to 4 days for various extended ring regimens, compared with 7.5 days for a 28-day ring regimen, over the first

91-day study period.<sup>7,8</sup> This reduction in median number of bleeding-only days persisted through the one-year study with all three extended ring regimens.<sup>8</sup>

### **Bleeding or spotting days**

The C/E patch regimen showed no significant difference in the median number of bleeding and/or spotting days compared with the cyclic group (14 vs. 16 days) over an 84-day cycle.<sup>7</sup> Compared with the 28-day standard ring regimen, the 49-day extended ring regimen showed a mean decrease of 2% in bleeding and/or spotting days, whereas the 91-day and 364-day extended ring regimens increased the number of bleeding and/or spotting days by 3.5% and 7.1%.<sup>8</sup> More women discontinued the ring for unacceptable bleeding and/or spotting with the extended regimens than with the conventional cyclic regimen.<sup>8</sup>

Rates of bleeding and/or spotting appear similar for C/E and cyclic patch regimens. Rates of bleeding and/or spotting slightly increase when the ring is used for C/E regimens of 91 days and 364 days compared with 28-day or 49-day regimens.<sup>8</sup> The 28-day ring regimen has been demonstrated to result in significantly less irregular bleeding than cyclic CoCs.<sup>55,56</sup> Future studies could compare C/E use with ring or patch versus COC.

### **Management of Bleeding and/or Spotting With Continuous or Extended Regimens**

Regardless of the regimen of CHC, bleeding and/or spotting in the first three months is extremely common. If bleeding and/or spotting persist, other causes of bleeding should be ruled out (pregnancy, non-compliance, cervical infection, smoking, malabsorption, and use of concomitant medications), and a thorough questionnaire on daily compliance could be done.<sup>4</sup> If bleeding and/or spotting persist, after a minimum of 21 days of ChC use, women may consider a short break of a maximum of three to seven days. A small RCT with extended CoC users demonstrated greater improvement in bleeding and/or spotting in women who were asked to stop CHC for a three-day HFI than in those who did not stop (29/30 vs. 17/33 with no persistent bleeding and/or spotting).<sup>36</sup> Doubling up on the pill to resolve bleeding and/or spotting episodes is not suggested, as it maintains the same EE/progestin ratio and may, in fact, increase this side effect. Suggestions developed in the Canadian Contraception Consensus for the resolution of bleeding and/or spotting during cyclical use of CHC can also be followed.<sup>4</sup>

### **OTHER SIDE EFFECTS**

Nausea, vomiting, breakthrough bleeding and spotting, headaches, bloating or swelling, and breast tenderness are common side effects reported with CoC use.<sup>55,57,58</sup>

Comparisons of C/E ChC regimens and conventional 28-day regimens regarding side effects have many limitations. The evaluation of side effects is not uniform among studies, and not all same side effects are reported in all studies. The results are inconsistent between studies, and some studies report data on adverse events rather than side effects per se, with no statistical comparison. Since side effects are often secondary objectives, estimates of magnitude are also often not reported.

### **Continuous or Extended Combined Oral Contraceptive Use**

#### **Headaches**

In an RCT of a 30 µg EE and 150 µg DSG COC in a C/E 63-day regimen compared with a conventional 28-day regimen, the frequency of headache was significantly lower with the extended regimen.<sup>30</sup> Another RCT of a 30 µg EE and 300 µg norgestrel CoC administered in a C/E 49-day regimen compared with a conventional 28-day regimen found significantly fewer severe headaches in the C/E regimen group.<sup>32</sup> Two other RCTs reported fewer headaches with the C/E CoC regimen, but no statistical comparison was available.<sup>6,33</sup> One RCT of a 20 µg EE and 100 µg LNG CoC administered in a C/E 168-day regimen compared with a 28-day regimen reported no significant difference of headache frequency between the groups.<sup>33</sup>

#### **Miscellaneous side effects**

In an RCT of a 20 µg EE and 100 µg LNG CoC administered in a continuous 168-day regimen compared with a 28-day regimen, the frequency of bloating and menstrual pain were significantly lower with the continuous regimen, but there was no significant difference between the groups regarding breast tenderness, nausea, depression, and PMS symptoms.<sup>33</sup> Another RCT of a 20 µg EE and 100 µg LNG CoC in a continuous 336-day regimen compared with a 28-day regimen reported that abdominal pain occurring at least once a month was significantly less common/less commonly reported in the continuous group (26%) than in the cyclic group (72%).<sup>6</sup> This study showed no difference for breast tenderness and nausea, but fewer mood changes in the C/E group. A third RCT of a 30 µg EE and 300 µg norgestrel CoC in a C/E 49-day regimen compared with a 28-day regimen, women in the C/E group reported significantly less severe genital itch.<sup>32</sup> There was no statistically significant difference between the groups for breast tenderness, cramping, and tiredness.<sup>32</sup> Another RCT of a 30 µg EE and 150 µg DSG CoC in a C/E 63-day regimen compared with a 28-day regimen reported no statistically significant difference between the groups for symptoms such as nervousness, nausea, dizziness, and depression.<sup>30</sup> Finally,

one observational study of a 30 µg EE and 3 mg drospirinone CoC in a C/E regimen of 42 to 126 days compared with a 28-day cycle regimen demonstrated a significant improvement of dysmenorrhea, swelling of the extremities, and breast tenderness with the C/E regimen.<sup>59</sup> Both regimens improved skin problems and bloating.<sup>59</sup>

### Weight changes

In an RCT comparing the vaginal administration of 50 µg of EE and 250 µg of LNG CoC in a one-year continuous regimen with a 28-day cycle regimen,<sup>41</sup> the weight gain was significantly less with the continuous regimen (0.4 kg vs. 1.2 kg). No significant weight differences between C/E CoC regimens and conventional 28-day cycle regimen were reported in other RCTs,<sup>6,30,32,33</sup> which is congruous with the Cochrane Review showing no association between CoC use and weight.<sup>60</sup> In one study, both regimens, cyclic and C/E, decreased body weight.<sup>59</sup>

### Continuous or Extended Contraceptive Patch and Ring Use

The only available study comparing a C/E patch regimen with a conventional 28-day patch regimen was an RCT designed to evaluate the bleeding profiles<sup>7</sup> and headache<sup>61</sup> frequency. Slightly more adverse events, such as breast discomfort, nausea, vaginitis, and emotional lability were observed with the C/E patch regimen; however, there was no statistically significant difference between the two regimens.<sup>7</sup> Mean headache days roughly doubled in both regimens during the patch-off weeks compared with the patch-on weeks. The headache rate during patch-on weeks in both regimens decreased significantly over the 16-week study.<sup>61</sup>

The RCT comparing three C/E vaginal ring regimens with a conventional 28-day ring regimen reported that the frequency of breast tenderness, weight changes, headaches, and mood changes were similar in the groups.<sup>8</sup> Breast complaints were more frequent with the 364-day regimen than with the 28-day cycle regimen (no statistical comparison available).<sup>8</sup>

### Statements

A continuous or extended combined hormonal contraceptive regimen compared with a cyclic regimen will result in fewer total bleeding days. (I)

The frequency of unscheduled bleeding and/or spotting with a continuous or extended combined hormonal contraceptive regimen is similar to that of a cyclical regimen (I) and reduces over time with both regimens. (II-2)

Some trials on continuous or extended combined oral contraceptive regimens showed evidence of lower frequency of side effects such as headaches, genital itch, bloating, and menstrual pain than cyclic regimen, but others showed no difference. (I)

### Recommendation

3. Women using continuous or extended combined hormonal contraceptive regimens should be counselled about expected bleeding patterns. (I-A)

#### SOGC Clinical Tip

The side-effect profile with C/E ChC regimens is not worse than with cyclic regimens and may be better.

#### SOGC Clinical Tip

If irregular bleeding and/or spotting persist with the use of any C/E ChC regimen, rule out pregnancy, non-compliance, cervical infection, smoking, malabsorption, and use of concomitant medications.

#### SOGC Clinical Tip

Women will be more likely to accept irregular persistent bleeding and/or spotting if they are informed about it before the initiation of C/E ChC. A three-day HFI should be considered. After a three-day HFI, if the woman uses CoCs, she must take the next pill of her pack, if the woman uses the patch or the ring, she must use a new patch or a new ring.

# Medical/Non-Contraceptive Usage

Richard Boroditsky, MD, FRCSC

Mathieu Leboeuf, MD, FRCSC

This section addresses medical conditions in which menstrual suppression or postponement of menses may be beneficial. There are three main reasons to use C/E CHC aside from contraception: suppression of menstrual-cycle-related symptoms and hormone withdrawal symptoms, suppression of vasomotor symptoms in the HFI during the perimenopause, and failure of cyclical use of CHC for the treatment of conditions such as endometriosis, abnormal uterine bleeding linked to fibroids, or hemorrhagic diatheses.

## ENDOMETRIOSIS

Endometriosis can cause chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. The growth of endometriotic lesions is estrogen-dependent, and the suppression of ovarian steroid production may lead to the regression of these lesions.<sup>62</sup> The suppression of ovarian estrogen synthesis by CHC may reduce the local estrogenic effect. In addition, EE has less estrogenic and proliferative activity than estradiol.<sup>63</sup> An RCT showed a significant reduction of dysmenorrhea, deep dyspareunia, and non-menstrual pelvic pain scores after six months of C/E COC (EE 20 µg and DSG 150 µg) compared with cyproterone acetate in women with surgically proven endometriosis.<sup>64</sup> A prospective cohort study also showed a significant reduction of dysmenorrhea with C/E COC in women with surgically proven endometriosis that did not respond to cyclical use of COC (both were EE 20 µg and DSG 150 µg).<sup>65</sup> The long-term effectiveness of CHC in alleviating pelvic pain in endometriosis patients has not been evaluated.

## ABNORMAL UTERINE BLEEDING

The SOGC Clinical Practice Guidelines for the Management of Abnormal Uterine Bleeding define abnormal uterine bleeding as changes in frequency of menses, duration of flow, or amount of blood loss.<sup>66</sup> Dysfunctional uterine bleeding is defined by the same guidelines as a diagnosis of exclusion when there is no pelvic pathology or underlying medical cause.<sup>66</sup> DUB is typically characterized by heavy

prolonged flow with or without breakthrough bleeding. It may occur with or without ovulation.

Cyclic use of CHC is an effective treatment of DUB.<sup>67,68</sup> Since the total number of bleeding days is reduced when C/E CoC regimens are used (as stated in Chapter 6), patients with DUB may benefit from menstrual suppression caused by such regimens, when treatment has failed or when it is the patient's preference. However, no studies are available concerning C/E CHC for the treatment of DUB.

In women with symptomatic leiomyomas, a 12-month treatment with COC decreased the duration of menstrual flow and increased hematocrit by decreasing uterine blood flow and suppressing the endometrium.<sup>69</sup> No increase in uterine size was noted in this study. Current users of COC were also found to be at reduced risk of uterine leiomyoma, confirmed by ultrasound or hysterectomy.<sup>70</sup> However, there are no studies of the usage of C/E CHC in women with symptomatic leiomyomas.

## HEMORRHAGIC DIATHESSES

Women with hemorrhagic diatheses such as afibrinogenemia, factor XII deficiency, von Willebrand's disease, or factor IX deficiency may benefit from C/E CHC because it will prevent heavy and prolonged menstruation, as well as withdrawal bleeding. However, the only available data are case reports. For example, in a young woman with afibrinogenemia, prolonged and excessive menstrual bleeding was stopped by continuous use of CoCs containing EE 30 µg and LNG 150 µg.<sup>71</sup> The SOGC Clinical Practice Guidelines on Gynaecological and Obstetric Management of Women with Inherited Bleeding Disorders suggests considering C/E CHC in women with anemia and in those who experience a hemodynamic challenge with menses.<sup>72</sup>

## **HORMONE WITHDRAWAL SYMPTOMS**

Hormone withdrawal symptoms such as nausea, vomiting, breast tenderness, bloating, swelling, headaches, unscheduled bleeding and spotting, and mood changes may affect up to 70% of women during the HFI while taking cyclical COC.<sup>57</sup> In a retrospective study conducted to evaluate the acceptability of a shortened HFI (3–4 days instead of the traditional 7 days), 82% of subjects reported an improvement of their quality of life, mostly due to an improvement in their menstrual-associated symptoms.<sup>35</sup> Moreover, continuous COC administration for 6 to 12 weeks followed by a seven-day HFI lowered by 74% the hormone withdrawal symptoms experienced by women already taking COC.<sup>73</sup>

Decreasing estrogen levels immediately before and during spontaneous menses can lead to menstrual migraines in susceptible women secondary to an estrogen withdrawal effect on the cerebral vasculature.<sup>74,75</sup> There is also a select group of high-risk women who tend to have exacerbation of seizures, asthma, and even coronary spasm just before or during menses.<sup>76–78</sup> Migraine attacks occurring during the HFI in women using cyclical CoC regimens may be aggravated by a decline of the EE levels.<sup>79</sup> An open-label single-centre prospective study showed that during the first 28 days of an extended placebo-free regimen of oral contraceptives, daily headache scores decreased compared with those of the previous 21-day active/seven-day placebo cycle.<sup>80</sup> The difference on a daily basis persisted throughout the remainder of the 168-day regimen and was significantly reduced among the group with higher total headache scores.<sup>80</sup> More studies are needed to confirm the efficacy of C/E combined hormonal contraception for these problems.

## **PREMENSTRUAL DYSPHORIC DISORDERS**

There are no RCTs of C/E ChC use for the treatment of premenstrual dysphoric disorder. One comparative prospective study assessed the incidence and severity of PMDD in women using a 168-day continuous CoC regimen compared with a 28-day regimen<sup>81</sup>: the continuous regimen led to a significant decrease in premenstrual symptoms compared with the cyclic regimen. Women with PMDD also showed a significant improvement of their symptoms while using a CoC containing 20 µg EE and drospirone 3 mg administered for 24 days followed by a four-day HFI.<sup>82</sup> In contrast, a prospective cohort study demonstrated that conventional cyclical administration of COC (with a 7-day HFI) improved PMDD only to a small extent.<sup>83</sup>

## **THE PERIMENOPAUSE**

The perimenopausal transition is characterized by fluctuating hormone levels, irregular menstrual cycles, and the onset of symptoms such as hot flashes and insomnia that may increase in number and severity as menopause approaches. The irregular bleeding patterns and the vasomotor symptoms can both be well controlled with CHC. The usual cyclic and continuous combined hormone replacement regimens may not suppress ovulation and may not improve an abnormal bleeding pattern if the woman continues to ovulate. CHC is more useful in this situation and can be effective in relieving menopausal symptoms. One study of a CoC containing 20 µg EE has been shown to provide effective contraception, reduce menstrual cycle irregularity, decrease bleeding, and provide relief from menopausal symptoms.<sup>84</sup> Perimenopausal women taking a CoC may experience a return of symptoms during the HFI, and supplementation during that time with a low dose of estrogen may be helpful. Alternatively, CoCs taken continuously may have a number of advantages as described above,<sup>85</sup> as well as decreasing menopausal symptoms. It should be noted that as age increases, the desire to avoid regular menses increases, and up to two thirds of women aged over 50 years do not want to bleed at all.<sup>19</sup> Abnormal uterine bleeding, which occurs frequently in perimenopause, may then be reduced or prevented by the use of C/E CHC once intrauterine and endometrial pathology has been ruled out. Many therapeutic interventions, such as hysteroscopic or global endometrial ablation, and hysterectomy could be avoided.

### **Statements**

In women with surgically proven endometriosis, continuous or extended combined hormonal contraceptives administered for six months are shown to be effective in reducing the frequency and the intensity of dysmenorrhea, deep dyspareunia, and non-menstrual pelvic pain over this period. (I)

Many women with abnormal uterine bleeding, including bleeding related to uterine fibroids, may benefit from menstrual suppression with continuous or extended combined hormonal contraceptive regimens. (III)

### **SOGC Clinical Tip**

For women in the perimenopausal transition who may be ovulating, C/E CHC is preferred to hormonal replacement therapy for controlling problematic bleeding and vasomotor symptoms.

Women with hemorrhagic diatheses may consider continuous or extended administration of combined hormonal contraceptives in order to decrease monthly withdrawal bleeding. (III)

Women experiencing hormonal withdrawal symptoms such as nausea, vomiting, breast tenderness, bloating, swelling, and mood changes during the hormone-free interval while using cyclic combined hormonal contraceptives, may benefit from continuous or extended combined hormonal contraceptive regimens. (II-2)

Menstrual migraine and headaches may improve with continuous or extended combined hormonal contraceptive regimens. (III)

Women in the perimenopause with problematic bleeding and vasomotor symptoms may benefit from continuous or extended combined hormonal contraceptive regimens rather than cyclic regimens because of the elimination of the hormone-free interval. (III)

# Patient Safety

Robert Reid, MD, FRCSC

The recent introduction of “new” C/E ChC regimens onto the North American market has brought this approach under scrutiny as the lay public, special interest groups, the media, and government regulatory agencies have entered the discussion about the wisdom and safety of menstrual suppression.<sup>86</sup> Before revising specific data on safety, it is important to understand how federal regulatory agencies determine whether a new drug or a new drug regimen is safe enough to allow on the market.

Typically a company wishing to launch a new product will investigate the drug and its actions in several phases: phase 1: pharmacology and toxicology; phase 2: effectiveness and safety in a small number of subjects; phase 3: full scale clinical trials to evaluate effectiveness and safety in specific populations. The idea to use an existing product for a new indication often emerges from investigator sponsored clinical trials when it appears that a new use may be medically helpful for a specific condition or patient population. If a beneficial effect is confirmed and the drug manufacturer decides to seek formal approval for the new indication, they must demonstrate the efficacy and safety of the new application in phase 3 clinical trials.

Pre-marketing studies testing medication for a young, generally healthy population can look only for indicators of short-term benefits or harms. Studies of one to two years can give a good indication whether the drug has any early side effects (e.g., headache, nausea) or any adverse effects of the kind that may occur at any time after a treatment is started (e.g., venous thromboembolism). Phase 3 trials on C/E CoC regimens<sup>87,88</sup> have evaluated laboratory parameters such as liver and kidney function tests, clotting factors, and lipids and have revealed no clinically significant differences between C/E CoC regimen and cyclic CoCs, and no increase in the risk for any short-term adverse events such as VTE.

Phase 3 trials cannot reliably predict the outcomes of diseases that have lag times between exposure and disease that might be several decades (e.g., cancer), and diseases that are rare in the population under study (e.g., stroke, myocardial infarction). However, new products could never enter the marketplace if complete assurance of long-term safety were a pre-marketing requirement. In the absence of long-term

safety data, regulatory agencies have to make a best estimate of the likely balance of benefits and risks on the basis of known class effects of the drug and potential surrogate markers for disease, although these markers often correlate poorly with clinical events.<sup>89</sup> Health Canada acknowledges the fact that long-term risks of new products are best evaluated in phase 4 studies through post-marketing surveillance.<sup>90</sup>

There is no long-term follow-up of C/E ChC use beyond two years. However, there is an extensive body of data on the long-term safety of CoCs, which have been in use for over 50 years, and these data may apply to C/E ChC.

## SAFETY OF MENSTRUAL SUPPRESSION

### Is the Absence of Monthly Bleeding Safe?

The answer to this question lies in the understanding of the physiology of menstruation.<sup>91</sup> The endometrium responds to estrogen production from the developing ovarian follicle by thickening to create a lush responsive uterine lining in anticipation of pregnancy. Ovulation, in turn, results in production of progesterone that acts upon the endometrial lining to give it the secretory characteristics necessary to support and nourish the early pregnancy. If a pregnancy does not ensue, ovarian progesterone production falls and endometrial prostaglandins are released. The rhythmic contraction of endometrial vessels that this triggers causes endometrial self-destruction and shedding in preparation for another attempt to recreate a fertile environment for the next ovulation.

From a teleological point of view menstruation can be seen as an attempt to eliminate an endometrium that has passed its prime in order to allow restoration of a new receptive uterine lining in time for the next possible opportunity for implantation and pregnancy. When the endometrium fails to develop because of the lack of hormonal stimulation (such as during lactation) or in response to continuous suppression by the progestin component of ChC, there is no role for menstruation.

### Is Menstruation Necessary?

There is no evidence that any form of toxin is eliminated through menstruation as some opponents of menstrual

**Table 6. Odds ratio for achieving pregnancy in different time intervals after pill discontinuation according to years of prior OC use**

Years of OC use	> 5	3–4	1–2	< 1	Never
OR for conception	1.00	0.71	0.52	0.46	0.67
Trend 33.24 ( $P < 0001$ ) <sup>94</sup> Adapted from Farrow et al. <sup>96</sup>					

suppression have suggested. As the onset of pelvic inflammatory disease is more likely to be during or shortly after menstruation, it is likely that the presence of “old” blood and dying endometrial fragments, the loss of the cervical barrier created by progestin-thickened cervical mucus, and the denuded endometrial lining create an environment favourable to ascending infection and PID.<sup>92</sup>

Although it has been suggested that “physiologic anemia” resulting from menstruation may slow down the progression of renal and cardiovascular diseases in women, overall, anemia is associated with increased mortality and morbidity. A recent review concluded that even though women have physiologic adaptations that allow them to better tolerate lower hemoglobin levels, correction of anemia improves clinical outcomes.<sup>93</sup>

### Does Menstrual Suppression Adversely Affect Future Fertility?

If menstruation is a time when cervical infection is more likely to ascend, causing tubal disease,<sup>54</sup> and if retrograde menstruation is one purported factor in the development of pelvic endometriosis,<sup>94</sup> then it follows that fewer menstrual cycles in her lifetime may make a woman less likely to develop PID or endometriosis. Similarly, chronic anovulation associated with polycystic ovary syndrome if left unchecked can result in ovarian hyperthecosis and hyperandrogenism that may increase ovarian resistance to any subsequent attempts to induce ovulation. Hormonal contraception, by suppressing gonadotrophic stimulation of the ovary, can minimize ovarian androgen production, allowing easier ovulation induction when pregnancy is desired.

An American study showed that women with ovulatory infertility were more likely to be past CoC users.<sup>95</sup> However, after confounding factors were controlled for, this association was not significant (OR 1.2; 95% CI 0.7–1.9); irregular cycles and polycystic ovary syndrome are common reasons for prescribing CoCs. Another prospective study<sup>96</sup> of 8497 British CoC users found that these women had high pregnancy rates that mimicked those in the normal population.<sup>96</sup> All women conceived rapidly, and the shortest “time to

conception” was in those with the longest past exposure to CoCs (see Table 6).

### Does Menstrual Suppression Increase the Risk of Unrecognized Pregnancy and Possible Teratogenesis?

Although many women report that the presence of monthly menstruation is important to reassure them that they are not pregnant, there is evidence that absence of menstruation in C/E ChC regimens increases the risk of inadvertent pregnancy. In theory, the use of C/E ChC regimens should create a greater window of “forgiveness” for missed pills (see Chapter 5). The only shortcoming is that C/E regimens may mask an unplanned pregnancy because of ongoing amenorrhea (see Chapter 10).

There is no evidence for teratogenesis with presently marketed ChCs and no reason to believe that C/E regimens would change that finding. Though some newer cyclic pills contain progestins with anti-androgenic properties that might theoretically interfere with genital development in the male fetus, this has not been reported.

### Does Menstrual Suppression Increase the Risk of Osteoporosis and Fracture?

Estrogen is known to be associated with bone formation<sup>97</sup> and its deficiency increases the remodelling rate and the volume of bone resorbed, leading to decreased bone mineral density and risk of osteoporosis.<sup>98–100</sup> Use of DMPA, which induces menstrual suppression in 55% to 60% of women after 12 months of use, has been associated with a decrease in BMD.<sup>101</sup> In recent years, therefore, there has been considerable concern that long-term exposure to progestin-based contraception might result in an increased prevalence of osteoporosis and resultant fractures.<sup>102</sup>

Recent systematic reviews of both progestin-only contraception<sup>103</sup> and COC<sup>104,105</sup> have concluded that there is insufficient evidence that either results in clinically significant loss of BMD or increased fracture risk. Both the World Health Organization and the Society of Obstetricians and Gynaecologists of Canada have issued statements indicating that the benefits of these contraceptive methods

**Table 7. Total estrogen exposure over one year for different marketed oral contraceptives compared to newer extended cycle regimens.**

Name of the COC	Type of regimen	Dose of EE
Alesse	Cyclic	5460 µg
Anya	Continuous	7300 µg
Marvelon, Min-ovral, Yasmin, Orthocept, LoEstrin	Cyclic	8190 µg
Cyclen and Ortho 1/35 or Ortho 0.5/35	Cyclic	9555 µg
Seasonale	Continuous	10 080 µg
Ovral, Ortho Novum1/50	Cyclic	13 650 µg

outweigh any possible risks for most women.<sup>101,106</sup> No evidence is available on the effect of C/E CHC on BMD.

### **HEALTH RISKS ASSOCIATED WITH CONTINUOUS OR EXTENDED COMBINED HORMONAL CONTRACEPTION USE**

Concerns about the health risks associated with taking C/E CHC are expressed because of the increased doses of hormones taken annually. No direct evidence on the risks associated with long-term use of C/E CHC is available. The data reflect what is true of the cyclic use of ChCs.

Rates of cardiovascular diseases increase with age and are associated with several factors other than CHC.<sup>107,108</sup> This is also true of cancers occurring in women.<sup>109</sup>

#### **Is There Reason to Believe That Continuous or Extended Combined Hormonal Contraception Use Will Increase the Risk of Cardiovascular Diseases?**

##### **Venous thromboembolism**

Venous thromboembolism is known to be increased in women on CoCs; however, the absolute risk is very small (1–2/10 000 users per year).<sup>110</sup> There is a greater risk for VTE soon after the CoC is started than there is with longer term use,<sup>111</sup> suggesting that initial exposure to COC may unmask women with pre-existing thrombophilias. The procoagulant effects of CHC take four weeks to return to normal, so there is no reason to think that the one week break from exogenous hormonal exposure that occurs with cyclic regimens would have any beneficial effect—or conversely that C/E exposure would be harmful.

##### **Myocardial infarction**

A prospective cohort study involving 17 032 CoC users in the UK revealed that there was a fourfold increase in the risk of MI (but not angina) only in women who were heavy smokers at the time of entry into the study.<sup>112</sup> Since baseline rates for MI are very low in young women using CoCs, the

authors reported that this would mean one additional MI among every 1060 heavy cigarette smokers who choose to use COC. To minimize this risk, current national guidelines suggest that physicians should encourage women who want to use the pill to stop smoking and should not prescribe CHC for smokers over age 35.<sup>4</sup> In non-smokers there appears to be no increased risk for MI. Indeed, the Women's Ischemia Syndrome Evaluation (WISE) Study<sup>113</sup> recently reported that menopausal women who were past CoC users had lower severity scores on quantitative angiographic assessment for coronary artery disease than did women who had never used COC.

#### **Is There Reason to Believe That Continuous or Extended Combined Hormonal Contraception Use Will Increase the Risk of Stroke?**

Whether there is an increased risk of stroke with the use of modern low-dose ChC is debatable.<sup>114</sup> A threefold increased risk of ischemic stroke in COC users was reported in a study, which, because baseline rates of stroke are so low in this age group, translated into one additional stroke for every 5880 pill users.<sup>112</sup> Others have not found any association.<sup>115</sup> A more recent systematic review concluded that the “association . . . (between oral contraceptive use and stroke) . . . is tenuous at best and perhaps non-existent.”<sup>114</sup> This probably reflects the fact that total exposure to estrogen in modern low-dose CoCs is less than that from endogenous production for most women.<sup>92</sup> Even the use of C/E COC has not increased total estrogen exposure above that associated with many CoCs used in the past 50 years (Table 7).

The absolute risks for all types of cardiovascular risk in women on CHC are small, especially when compared with the risks associated with pregnancy. Given that one alternative to the effective use of contraception is pregnancy, the risks of cardiovascular events due to use of CHC can be put into perspective by contrasting them with those of

**Table 8. Cardiovascular risks of oral contraceptive use compared with risks associated with other reproductive health circumstances**

Venous thromboembolism risk	
in young women (< 35y)	1/10 000
on OC	2–3/10 000
in pregnancy	
10–12/10 000	at term
200–400/10 000	immediately postpartum
Myocardial infarction risk	
in young women	0.1/10 000
on OC	0.2/10 000
in pregnancy	0.62/10 000
Stroke risk	
in young women	1/10 000
on OC	1/10,000
in pregnancy	3–4/10 000

Adapted from: Salonen Ros H et al.<sup>167</sup> Petitti DB et al.<sup>168,169</sup> James AH et al.<sup>170</sup> Baillargeon JP. et al.<sup>171</sup>

pregnancy<sup>117</sup> (Table 8). Concerning the contraceptive transdermal patch, there is no evidence that the concerns about the patch prescribed in the US apply to the patch prescribed in Canada, because of the lower EE content in the Canadian patch. There is also no reason to suspect that C/E CHC would alter the low cardiovascular risks noted with current low-dose ChCs.

### Is There Reason to Believe That Continuous or Extended Combined Hormonal Contraception Use Will Increase the Risk of Cancer?

The overall risk of death from cancer is low in comparison with other causes of death. Yet cancer remains in the forefront of public awareness because of successful awareness campaigns. Comparative charts showing absolute risks of death from different causes by decade help to put cancer deaths into perspective.<sup>118,119</sup>

#### Endometrial cancer

Because of their dominant progestational effect on endometrial development, CoCs have been shown to reduce the risk of endometrial cancer by as much as 50% after five years of use.<sup>120–124</sup> This beneficial effect increases with increasing duration of use and persists for years after discontinuation of the CoC. It is also present in DMPA users.<sup>125</sup> Continuous or extended CHC is unlikely to alter this benefit. One recent RCT compared endometrial development during C/E CoC administration for 84 days and conventional 28-day cycle CoC administration and did not find any difference between the two regimens.<sup>46</sup>

A prospective study among users of a continuous daily regimen of a CoC containing 20 µg EE and 90 µg LNG showed that endometrial biopsies performed at the end of a one-year follow-up showed no malignancy or hyperplasia.<sup>126</sup> Endometrial biopsies performed in ring users were also reassuring.<sup>127</sup>

#### Ovarian cancer

Ovarian cancer risk is reduced by 50% after five years of CoC use and by as much as 80% after 10 years of use.<sup>128</sup> This beneficial effect persists for up to 20 years after discontinuation of CoCs and is seen with both older higher dose pills and new lower dose pills<sup>129</sup> and with DMPA.<sup>130</sup> This beneficial effect is also seen in women with BRCA gene mutations, and use of CoCs is therefore recommended as chemoprevention of ovarian cancer in such individuals.<sup>131–133</sup> C/E CHC is unlikely to change this benefit.

#### Cervical cancer

Cervical cancer has now been clearly linked to infection with oncogenic strains of human papillomavirus. Some past studies have indicated an increased risk for development of invasive cervical cancer in long-term users of CoCs even after controlling for the fact that hormonal contraception users are less likely to use barrier protection.<sup>134</sup> In a meta-analysis of 28 cohort and case-control studies examining the relationship between invasive and in situ cervical cancer and CoC use, the overall relative risk (RR) was 1.1 (95% CI 1.1–1.2) for CoC use of less than five years, 1.6 (95% CI 1.4–1.7) for five to nine years' use, and 2.2 (95% CI 1.9–2.4)

for 10 or more years' use.<sup>135</sup> The reason for this finding remains obscure, although the possibility that CHC could increase HPV viral expression through hormone responsive elements on the viral genome has been considered.<sup>136</sup> The National Cancer Institute in the US subsequently conducted a large scale randomized trial to evaluate the association between the use of CoCs and cervical intraepithelial neoplasia 3 (CIN3) in women positive for oncogenic HPV DNA.<sup>137</sup> Rigorous methodology employed dual HPV DNA testing, intensive follow-up including colposcopic examinations, and rigorous pathologic review. These investigators concluded that CoCs had little or no impact on having an oncogenic HPV infection or on the development of CIN3.<sup>137</sup>

The role of CHC, administered either cyclically or continuously, in cervical cancer remains controversial. Safer sexual practices, regular condom use, and cervical cancer screening are efficient strategies to reduce this risk.

### Breast cancer

Several studies have found that use of CoCs by women under age 20 years may increase the relative risk of breast cancer.<sup>138,139</sup> The absolute risk of breast cancer in this population is very low, suggesting that the population impact of this will remain small. Published data are presently insufficient to indicate that exogenous hormones increase the risk of steroid hormone receptor positive tumours,<sup>140</sup> although recent research indicates that new, lower estrogen CoCs may carry lower risk for breast cancer in young women.<sup>141</sup>

To examine the relationship between CoC use and breast cancer in greater detail, a reanalysis of all published data in the world was conducted in 1996. This collaborative reanalysis examined the results of 54 studies conducted in 25 countries and included 53 297 women with breast cancer and 100 239 controls.<sup>142</sup> The effect of COC on breast cancer risk was very small and not influenced by duration of use. These findings were confirmed in 2002, when a large retrospective study failed to find any association between past use of oral contraceptives and breast cancer.<sup>143</sup>

Although some have suggested that women with a positive family history of breast cancer and those with a known BRCA gene mutation should not use hormonal contraception for fear of increasing their risk of breast cancer, recent evidence suggests that use of CoCs in this population has minimal impact on breast cancer risk<sup>143</sup> and may actually be associated with a reduced risk<sup>132</sup> while at the same time reducing the risk of concomitant ovarian cancer.<sup>133</sup> Currently, CoC therapy is recommended as one option for chemoprevention of ovarian cancer in those at high risk because of genetic predisposition.<sup>131</sup>

Absolute risk of breast cancer is low in women of reproductive age. Breast cancer risk with cyclic COC is also very low. Although studies on long-term effect of C/E ChC use on breast cancer are not available, current expertise suggests that the risk of breast cancer with C/E ChC use will not be significantly different from that with cyclic ChC use.

### Is There Reason to Believe That Continuous or Extended Combined Hormonal Contraception Use Will Increase Mortality?

Two large cohort studies have examined overall mortality in women who used CoCs compared with non-users. The Oxford Family Planning Study<sup>144</sup> evaluated the records of 17 032 women aged 25 to 39 at entry and found no increase in overall mortality among former CoC users. The Royal College of General Practitioners' oral contraception study<sup>145</sup> examined 1599 deaths and reported no increase in overall mortality odds ratio (OR) 1.0 (95% CI 0.9–1.1) with a decrease in deaths due to ovarian cancer OR 0.2 (95% CI 0.1–0.8), an increase in deaths due to cardiovascular disease OR 1.9 (95% CI 1.2–3.1), and increase in deaths due to cervical cancer OR 2.5 (95% CI 1.1–6.1). These studies were both initiated at a time when hormone dosage in CoCs was twofold to threefold higher than at present. This risk is not expected to be significantly different with C/E ChC use.

### **SOGC Clinical Tip**

The Society of Obstetricians and Gynaecologists of Canada (SOGC) defines use of low-dose ChCs as use of ChCs containing less than 50 µg of EE per day. Total estrogen exposure over one year with any low dose C/E ChC regimen falls into this SOGC definition (Table 7).

### **SOGC Clinical Tip**

Health care providers wonder whether or not a greater exposure to EE over one year relates to a greater number of side effects. Although uncertain, studies do not indicate that side effects are made worse with C/E ChC regimens, and, in fact, such regimens may decrease some of these side effects.

### **Statements**

The short-term safety of continuous or extended combined hormonal contraceptive regimens is similar to that of cyclic regimens. (III)

Direct evidence on long-term safety of continuous or extended combined hormonal contraceptive regimens is currently unavailable. (III)

The extensive body of data on the long-term safety of combined oral contraceptives over the past 50 years is reassuring. If there is an greater risk associated with long-term use of continuous or extended combined hormonal contraceptive regimens than with long-term use of cyclic regimens, it is likely to be minimal. (III)

# Cost-Effectiveness

Edith Guilbert, MD, MSc, FCFP

James Trussell, PhD

As seen previously, monthly hormonal fluctuations and withdrawal bleeding may be associated with significant adverse health effects, short-term disability, and negative consequences. Of reproductive age women, 10% to 52% report menorrhagia,<sup>146–148</sup> 50% of teenage school girls present primary dysmenorrhea,<sup>149</sup> and 12% to 20% of adult women describe their menstrual pain as severe and incapacitating.<sup>146,147,150,151</sup> In a representative Canadian sample of women 18 years and over, primary dysmenorrhea was identified in 60% of women, 60% of whom described their pain as moderate to severe<sup>151</sup>; no Canadian data are available for menorrhagia.

The impact of menstrual disorders on women's lives, on medical services, and on society is of notice. Data from the National Hospital Ambulatory Medical Care Survey from 1992 to 1994<sup>152</sup> showed that women of reproductive age made an average of 1.4 million visits each year to emergency departments for gynaecologic disorders, which is an average annual rate of 24.3 visits per 1000 women. Gynaecologic visits accounted for 6.3% of all visits to emergency departments, and menstrual disorders prompted 12% of the total gynaecologic visits. According to two studies,<sup>153,154</sup> women who had a heavier menstrual flow were at least 1.45 times more likely to use health care services than women who had a lighter or normal flow and 72% as likely to be in the work force. This translated into a 6.9% reduction in employment associated with heavier bleeding and an estimated loss of wages of US \$1692 per year. Women with primary dysmenorrhea also reported limitation of their activities in 51% of the cases, and 17% missed school or work because of it.<sup>151</sup> Women using COC reported significantly fewer absences from work or school than non-users.<sup>155,156</sup>

From a societal perspective, economic models assessing direct and indirect costs of contraceptive use over five years show that, regardless of the payment mechanism, cyclical use of CoCs is cost-effective compared with no method, use of natural or barrier methods, or tubal ligation.<sup>157–159</sup> Costs of pregnancy resulting from contraceptive failure and direct costs of the method account for 80% of the total costs associated with the use of COC.<sup>159</sup> Costs linked to side effects, complications, non-contraceptive benefits, and other health factors related to oral contraceptive use have a very small and limited impact on overall cost-effectiveness measurements.<sup>157,159</sup>

From the individual cost-effectiveness perspective, an RCT<sup>32</sup> showed that, over one year, the total number of days requiring menstrual-hygiene product use was significantly less with C/E CoC use than with cyclic use (27.3 vs. 53.5 days,  $P < 0.001$ ). Over one year, the cost of menstrual-hygiene products was an average of US \$17.54 for women with a 49-day cycle compared with US \$41.45 for women with a 28-day cycle ( $P < 0.001$ ). In another study using economic models,<sup>160</sup> a trimonthly regimen of COC was cost-effective only when CoCs were inexpensive, and menstrual-hygiene product use was higher. However, several factors, such as not considering the decreased use of analgesics and iron supplements during menses, the increase in productivity, and the qualitative benefits in lifestyle, limited the accuracy of this study. An extensive cost and threshold analysis (numerous factors considered)<sup>161</sup> found that under base-case assumptions, the cost of one oral contraceptive pill was low and was identical for both regimens and that trimonthly COC reduced menstrual-hygiene product use by 50%, and C/E CoC use appeared cost-effective.

These studies suggest that C/E CoC use is cost-effective for women because of decreased use of menstrual-hygiene products. However, this is true only if the cost of the contraceptive method remains low. From a societal perspective, C/E ChC use might be cost-effective if it proved to be more efficient than cyclic use in preventing pregnancy, if the cost of the method were kept low, and if it were associated with greater productivity.

## Statements

Continuous or extended use of combined hormonal contraceptive regimens is associated with significantly less menstrual-hygiene product consumption than cyclic regimens. (I)

Provided that the total annual cost of hormonal contraception remains lower than the total annual cost of menstrual-related products and medications, continuous or extended use regimens are a cost saving for the individual compared with cyclic regimens. (III)

From a societal perspective, there may be cost savings with continuous or extended combined hormonal regimens in terms of reduced absenteeism and doctor visits for menstruation-related complaints. However, the magnitude of these savings is uncertain and likely to be low. (III)

## Recommendation

4. The annual cost of dedicated products for continuous or extended hormonal regimens should be similar to that for cyclic regimens. (I)

# Patient Education

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In the absence of contraindications,<sup>162</sup> C/E ChC may be considered for any woman who, for medical reasons, contraceptive purposes, or personal preference, may benefit from this regimen. Counselling for patients on C/E ChC may vary, depending on the indication for using it. Counselling should be tailored to the women, with consideration being given to their cultural or religious beliefs and their expectations of how C/E ChC may or may not benefit them.

## WHAT TO COVER WITH YOUR PATIENT WHEN PRESCRIBING

- Determine if there are any contraindications to ChC.<sup>162</sup> Women with contraindications to ChC are not appropriate candidates for C/E ChC regimens.
- Explain which delivery methods of ChC may be used (oral, transdermal, vaginal).
- Explain the overall concept of C/E ChC and discuss the difference between cyclic and C/E regimens.
- Address possible misperceptions about C/E use (see “Myths”).
- Discuss the advantages and disadvantages of C/E ChC regimens.

### Advantages

- Decreased incidence of menstrual symptoms, for example, dysmenorrhea,<sup>64,65</sup> menorrhagia, menstrual migraines,<sup>30,32,61</sup> PMS.<sup>81</sup>
- Fewer symptoms that are seen in the HFI associated with cyclic use.<sup>35,73</sup>
- More convenient for some women.
- Possibly better compliance and possible increase in contraceptive efficacy.
- Fewer bleeding days<sup>7–9,32–34,163</sup> and thus lower cost of menstrual-hygiene supplies.<sup>31</sup>

### Disadvantages

- Side-effect profile (similar to or better than cyclic use).<sup>6,30,32,33,59</sup>
- Unscheduled bleeding and spotting may occur.<sup>8,30,33</sup>

- Possible delay in recognition of pregnancy (although not teratogenic if inadvertently taken during pregnancy).
- Although short-term safety is documented (up to 2 years),<sup>87,88</sup> evidence for long-term safety is not available.
- Cost of medications.

## Initiation of an Continuous or Extended Use Hormonal Contraceptive Regimen

- Decide what ChC method will be used (CoC, patch, ring). Any CoC can be used in a C/E regimen.
- Discuss when to have an HFI, if at all.
- Discuss possible side-effects, including unscheduled bleeding and/or spotting.
- C/E ChC may start at any time in the cycle provided pregnancy can be excluded (“Quick Start”). If using a Quick Start method,<sup>164–166</sup> back-up contraception should be used for at least seven days.
- In general, a minimum of 21 consecutive days of hormonal contraception (pill, patch, or ring) should be taken before an HFI. At no time should the HFI exceed seven days.
- As with all contraceptive methods, the use of condoms is recommended to provide protection against sexually transmitted infections and HIV.

## What to Do if Unscheduled Bleeding or Spotting Occurs

Unscheduled bleeding or spotting may occur, particularly in the first months of use.

If this occurs, a woman can (a) continue to use the contraceptive method or (b) take a three- to seven-day HFI and then restart ChC.

A small RCT found that if bleeding persisted for more than seven days, an HFI of three days was more effective in resolving bleeding or spotting than continuation of active pills. A minimum of 21 consecutive days of ChC is suggested before an HFI. Doubling up of CoCs to manage bleeding or spotting in patients on a continuous regimen is not suggested. If the bleeding and/or spotting continue

beyond a few months, a health care provider may need to rule out other possible etiologies.

### When to Contact a Health Care Provider

- For side effects such as sudden onset severe headache, leg pain, chest pain, abdominal pain, or loss of vision.
- If heavy vaginal bleeding occurs.
- If nausea, vomiting, bloating, or mood changes persist beyond the first three months of use.
- If pregnancy is suspected.

### What to Do in the Event of Missed Contraception

Continuous or extended use of CHC is considered to be the use of active hormones for more than 21 consecutive days. When CHC is taken in a continuous or extended fashion, the HFI is omitted. When there is no HFI, there is no hormone break to allow the rebound of the hypothalamic-pituitary-ovarian axis and thus no signal to drive ovarian follicular growth. Therefore, a patient on a C/E ChC regimen would have to miss seven consecutive days of active hormones before the suggestions about missed hormonal contraceptives used for cyclic CHC would apply.

During C/E ChC, omission of CHC can occur either because of problem in compliance or because of a planned HFI when bleeding or spotting is persistent.

The following recommendations, based on longevity of sperm in female reproductive tract, apply to women using a C/E ChC regimen who have unprotected intercourse in the three days before or during missed contraception.

- If omission occurs within the first two weeks of C/E ChC use, apply the rules related to omission in the first two weeks for cyclic use.
- If omission of C/E ChC occurs on more than seven consecutive days (it equals extending the HFI), take emergency contraception as soon as possible and reinitiate the use of the continuous regimen as if it were a “new” start.
- Omission of C/E ChC occurring on seven consecutive days or less is safe provided that the woman has been taking ChC for at least 21 consecutive days.
- After an omission of C/E ChC of seven consecutive days or less, any new omission within the next 21 days must follow the rules related to omission for cyclic use.

### MYTHS

#### Taking continuous or extended contraception will . . .

#### . . . affect my future fertility.

Women who use continuous or extended combined hormonal contraception can expect their fertility potential to return to their previous level immediately the pills are discontinued.

#### . . . cause more side effects.

The side effects from using continuous or extended combined hormonal contraception are similar to those seen with cyclic use and may improve over time. Some women using continuous or extended combined hormonal contraception have reported a decrease in bloating, headaches, dysmenorrhea, and menorrhagia.

#### . . . cause a build-up of menstrual blood.

Combined hormonal contraceptive methods cause the endometrium to become very thin, especially with continuous or extended use. As a result, there is no significant amount of tissue to shed and no build-up of menstrual blood.

#### . . . not provide good birth control.

Continuous or extended combined hormonal contraceptive regimens have a failure rate equivalent to typical cyclic regimens. The elimination of the pill-/ring-/patch-free interval, which is a main source of patient error, is likely to be “forgiving.”

#### . . . not be normal or “natural”: women should bleed every 28 days.

The normal menstrual cycle ranges from 21 to 35 days in length and may change from month to month, as well as during a woman’s reproductive lifetime. It is normal not to bleed when pregnant or breastfeeding, when using progestin-only contraception (such as DMPA or LNG IUS), or when using continuous or extended combined hormonal contraception. In these cases, the lining of the uterus does not grow, so there is nothing to shed, and no menses are required.

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