

### Extended and Continuous Combined Contraceptive Regimens for Menstrual Suppression

#### **PRÉCIS**

Alterations of the customary 28-day combined contraceptive regimen can be used to reduce or eliminate monthly bleeding.

#### **ABSTRACT**

Many women have medical indications for menstrual suppression or a personal preference to reduce or eliminate monthly bleeding, which can be achieved with extended and continuous regimens of combined estrogen and progestin contraceptives. Combined contraceptives are traditionally administered in a 28-day cycle with 21 days of a contraceptive pill, vaginal ring, or transdermal patch followed by a hormone-free interval that is usually 7 days. During the hormone-free interval, women either take a placebo pill or do not use their combined contraceptive method. Hormone-related symptoms are higher during the hormone-free interval than the days when the contraceptive is used. Alterations of the standard 28-day cyclic regimen for menstrual suppression include decreasing the frequency of the hormone-free interval, thus extending the time between withdrawal bleeding episodes (extended use), and eliminating the hormone-free interval altogether (continuous use). This article reviews menstrual suppression indications and physiology. Research demonstrating that the effectiveness, safety, and side effects of oral, vaginal, and transdermal extended and continuous regimens are comparable to cyclic regimens is summarized. Findings from studies of women's and health care providers' attitudes toward menstrual suppression are also reviewed. Important topics to include in evidence-based counseling for extended and continuous combined contraceptive use are presented.

#### **KEYWORDS**

Contraception, ovulation inhibition, drug administration schedule, menstrual cycle, patient satisfaction, attitude of health personnel, patient education



#### INTRODUCTION

Frequent menstruation is a relatively new phenomenon. It has been estimated that modern women experience 3 times the number of menstrual cycles per lifetime than did pre-agricultural women.<sup>1,2</sup> Approximately 450 menses can be anticipated in modern Western women due to earlier menarche, later childbearing, lower parity, shorter periods of breastfeeding, and later menopause.<sup>2</sup>

Monthly menstruation is perceived by some as a "natural" state necessary for cleansing the system. Monthly menses may also be seen as a symbol of femininity, fertility, and youth. Practically speaking, monthly menses is a sure sign that a woman is not pregnant and provides reassurance of fertility potential and reproductive health.

The customary 21/7 cycle, which includes 21 days of active estrogen and progestin pills followed by 7 days of placebo pills, originated with John Rock and Gregory Pincus, co-inventors of the first oral contraceptive pill.<sup>3</sup> Although Pincus stated as early as 1958 "a cycle of any desired length could presumably be produced," the end product was a 28-day cycle with a placebo week during which bleeding occurs. The placebo week technically induces withdrawal bleeding from the lack of exogenous hormones though this bleeding is commonly referred to as menses.

There was no scientific evidence that the 21/7 cycle was best; rather, mimicking the native menstrual cycle was intended to increase acceptance of combined oral contraceptives. The high hormone doses in early pills could cause significant symptoms, many of which were similar to pregnancy, such as nausea, vomiting, and breast tenderness. Monthly bleeding reassured women they were not pregnant and alleviated concerns about long-term adverse effects of the pill.<sup>4</sup> Rock and Pincus also hoped the monthly cycle of the pill would lead to the Pope to approve its use by Catholics, which did not come to fruition.<sup>3</sup>

Cyclic, Extended, and Continuous Combined Contraceptive Regimens

Cyclic combined contraceptive regimens are the traditional 28-day cycles with 21 days of a combined estrogen and progestin contraceptive pill, vaginal ring, or transdermal patch followed by a hormone-free interval that is usually 7 days. During the hormone-free interval, women either take a placebo pill or do not use their combined contraceptive method. Extended regimens observe the hormone-free interval less



frequently than every month, usually 3 to 4 times a year. Continuous regimens omit the hormone-free interval entirely.

Extended and continuous regimens have been reported in the literature since the 1970s,<sup>5</sup> and clinicians have long advised women they could "bicycle" or "tricycle" pills by taking multiple packages in a row without a hormone-free interval. The US Food and Drug Administration (FDA) first approved dedicated products for extended and continuous regimens in 2003 (Seasonale) and 2007 (Lybrel) respectively.<sup>6</sup> Combined oral contraceptives approved and packaged for extended and continuous use are listed in Table 1. Other combined oral contraceptives, the contraceptive vaginal ring, and the transdermal contraceptive patch can also be used off-label in extended and continuous regimens. Studies have shown that extended and continuous combined contraceptive regimens are as effective at preventing pregnancy as cyclic regimens, and there is some evidence to suggest extended and continuous contraceptive regimens may be more effective at preventing pregnancy than 21/7 regimens by blunting the pituitary-ovarian axis response during the hormone-free interval and reducing or eliminating breakthrough ovulation.<sup>7-9</sup>

<<FOR TYPESETTER, PLEASE INSERT TABLE 1 ABOUT HERE>>

#### **Indications for Menstrual Suppression**

There are many indications for menstrual suppression in women and adolescents. 4,10 Menses-related conditions such as dysmenorrhea, menorrhagia, abnormal uterine bleeding, premenstrual syndrome, premenstrual dysphoric disorder, and menstrual migraines, can be treated with extended or continuous regimens. Certain medical conditions, such as endometriosis, anemia, bleeding disorders, and developmental delay, are also reasons for frequency reduction or elimination of menses. Other indications include relief of perimenopausal symptoms, convenience, travel (eg, honeymoons, vacations, business meetings), and military deployment. Last, and importantly, menstrual suppression is indicated for women whose preference is not to menstruate monthly.

**Physiology of Menstrual Suppression** 



It is important for clinicians and women to understand why it is safe to reduce or eliminate menses with extended or continuous use of combined contraceptives when oligomenorrhea and amenorrhea are considered pathologic findings that warrant evaluation and possibly treatment. Many women who infrequently or never menstruate have an interruption of the hypothalamic-pituitary-ovarian axis that results in anovulation. Conditions that can cause anovulation include polycystic ovary syndrome, hyperthyroidism or hypothyroidism, uncontrolled diabetes mellitus, eating disorders, hyperprolactinemia, medications (eg, antiseizure drugs, antipsychotics), and being at either end of the reproductive years (ie, postmenarche, perimenopause). 11 With persistent anovulation, endometrial hyperplasia can develop because the proliferation of the endometrium that occurs during the follicular phase is not opposed by the progesterone that is normally produced in the luteal phase. However, when combined contraceptives are used, the endometrium is atrophic so hyperplasia does not occur. The reduction or elimination of menses with extended or continuous use of combined contraceptives is an expected outcome of exogenous hormone administration, rather than an indication of a pathologic process that is causing anovulation and potential health risks.

# EFFECTIVENESS, SAFETY, AND SIDE EFFECTS OF CYCLIC, EXTENDED, AND CONTINUOUS REGIMENS OF COMBINED ORAL CONTRACEPTIVES Withdrawal Symptoms with the Cyclic Regimen

In 2000, Sulak et al published a landmark study that investigated hormone-related symptoms during the active-pill and hormone-free intervals in 262 women taking combined oral contraceptives  $^{12}$ . Women who had no prior use, were restarting use, or had been taking combined oral contraceptives for 12 months or longer participated in the study. All participants used a daily diary to record symptoms. Pelvic pain (70% vs 21%, P<.001), headaches (70% vs 53%, P<.001), breast tenderness (38% vs 16%, P<.001), and bloating or swelling (58% vs 19%, P<.001) were all significantly worse during the 7-day hormone-free interval when compared with the 21-day active-pill interval. The use of pain medications was also significantly increased during the



hormone-free interval (69% vs 43 %, *P*<.001).<sup>12</sup> These hormone withdrawal symptoms can be severe in some women.<sup>13</sup>

#### **Extended Regimens**

In 2001, Miller et al published a 2-year study comparing cyclic 28-day versus extended 49-day regimens. A Ninety women were randomly assigned to a combined oral contraceptive (30 mcg ethinyl estradiol + 300 mcg norgestrel) with either 21/7 or 42/7 cycles over 4 84-day reference periods; 53 women completed the study. During the study, women kept diaries on bleeding, pill taking, and symptoms. The mean number of bleeding days was significantly lower with the extended regimen compared to the cyclic regimen (*P*=<.001 for first and fourth reference periods, *P*=.05 for second reference period, *P*=.03 for third reference period). The mean number of spotting days was similar for both regimens (*P*>.05 for all 4 reference periods). Overall, there were no significant differences in amenorrhea, frequent menses, or prolonged menses. Days of hygiene product use over the year of the study were significantly lower for women on the extended regimen (28-day=53.5, 49-day=27.3, *P*<.001). Women in the 49-day group had significantly lower median headache symptom scores than women in the 28-day group. Breast tenderness, cramping, weight, and method satisfaction scores did not differ significantly.

Another randomized controlled trial compared the safety and efficacy of 4 91-day cycles with 13 28-day cycles in 682 women of whom 432 completed the study. <sup>15</sup> The extended-cycle regimen consisted of 84 continuous days of the combined oral contraceptive (30 mcg ethinyl estradiol + 150 mcg levonorgestrel) followed by a 7-day placebo interval. Over the course of the study, participants used an electronic diary to report symptoms and pill taking. In addition, endometrial biopsies were performed on a subset of patients to assess endometrial changes. A total of 7 patients became pregnant during the study: 4 of 456 (0.9%) in the 91-day cycle group and 3 of 226 (1.3%) in the 28-day cycle group. With each successive cycle, days of breakthrough bleeding as well as the onset and duration of breakthrough bleeding decreased in the 91-day cycle group. By the last extended cycle (cycle 4), breakthrough bleeding was comparable between the 91-day cycle group and the 28-day cycle group. The median number of days of withdrawal bleeding per cycle was also similar for the 2 groups. <sup>15</sup> A



subset (n=50) of the women who received up to 4 cycles of the 91-day cycle had endometrial biopsies before and after therapy. No hyperplasia or significant pathology was noted. The endometrium quickly reverted to normal cyclic changes after discontinuation of the extended regimen suggesting extended use of combined contraceptives has no adverse effect on the endometrium.

An open-label, single-treatment study of 1249 women reported similar results for an extended 91-day cycle (20 mcg ethinyl estradiol + 100 mcg levonorgestrel) utilizing 7 low-dose ethinyl estradiol pills (10 mcg each) rather than a hormone-free interval.<sup>18</sup> Use of low-dose estrogen pills in lieu of a hormone-free interval has also been shown to improve the bleeding profile, decrease the number of developing follicles, and possibly reduce headaches compared to the 91-day cycle utilizing a hormone-free 7-day interval.<sup>19,20</sup>

While most studies of extended regimens have been 2 years or shorter, Davis et al followed women who had been in 1-year continuous regimen trials<sup>16,21</sup> for 4 years (N=320, n=85 for full 4 years).<sup>22</sup> The incidence of commonly reported adverse effects (eg, headache, metrorrhagia, dysmenorrhea) was not significantly higher during the extended study compared to the initial trials. Complete blood count, serum chemistry, lipid profile, and urinalysis values remained the same or only changed minimally. Blood pressure was stable. Median rates of unscheduled bleeding or spotting (outside of the hormone-free interval) declined over the duration of the study.<sup>22</sup>

Multiple other studies have confirmed extended regimens of combined oral contraceptives improve hormone-withdrawal symptoms and are well tolerated and safe. <sup>21,23-30</sup> An analysis of 1736 women using a 91-day regimen (20 mcg ethinyl estradiol + 100 mcg levonorgestrel) found contraceptive efficacy was not reduced in women who were overweight or obese. <sup>31</sup> In addition, a pharmacokinetic study confirmed that extended use of ethinyl estradiol and levonorgestrel does not result in additional accumulation of these hormones in the body compared to cyclic regimens. <sup>32</sup> Other studies have demonstrated lipid profiles, hemostasis variables, thyroid hormones, and androgen parameters are similar with extended and cyclic regimens. <sup>33-35</sup>

#### **Continuous Regimens**



In 2003, Kwiecien et al published a trial in which 32 women were randomized to 168 days without a pill-free interval (continuous) or 6 28-day cycles (cyclic) using a combined oral contraceptive (20 mcg ethinyl estradiol + 100 mcg levonorgestrel); 28 women completed the study.<sup>36</sup> A daily diary was maintained by participants evaluating adverse side effects of headache, bloating, breast tenderness, nausea, depression, premenstrual syndrome, and menstrual pain. The diary also tracked bleeding events in 3 categories: none, spotting, or required sanitary protection. The women on the continuous regimen had fewer total bleeding days than the women in the 28-day cycle group (25.9 vs. 34.9); however, this result was not statistically significant. Women on the continuous regimen reported significantly fewer bleeding days that required protection than women on the cyclic regimen (18.4 vs. 33.8, P < .01). Both groups reported a high level of satisfaction with side effects and bleeding. Overall, women in the continuous group reported fewer days of bloating (0.7 vs. 11.1, P = .04) and menstrual pain (1.9 vs. 13.3, P < 0.01) than the cyclic group. Other side effects were reported infrequently with no significant difference between groups. The women on the continuous regimen underwent endometrial stripe measurements, which were all within normal range. No endometrial biopsies were needed. 36

Later in 2003, Miller et al reported a study in which 79 women were randomized to 28-day cycles or continuous use of a combined oral contraceptive (20 mcg ethinyl estradiol + 100 mcg levonorgestrel) for 12 cycles; 60 women completed the study. The 2 groups did not have a significant difference in total spotting days, and the median number of spotting days in the continuous group declined over time (9.0 in cycles 1-3 vs 1.5 in cycles 10-12) while there was little change in the cyclic group (6.0 in cycles 1-3 vs 5.0 in cycles 10-12). Weight, hemoglobin, and diastolic blood pressure did not differ significantly between the two groups at the study's completion, but the continuous group had a slightly lower systolic blood pressure than the cyclic group (107.9 vs. 115.6, P=.02). No significant differences were found in method satisfaction scores and reported breast tenderness or nausea.

Since those trials, multiple other studies have found continuous combined oral contraceptive regimens are effective for preventing pregnancy and hormone-withdrawal symptoms, well-accepted with adequate counseling, and safe. 38-47 Return to fertility



after discontinuation is rapid. 48,49 Continuous regimens have been found to have similar effects on lipids, carbohydrates, and coagulation factors as cyclic 28-day regimens. 50

### VAGINAL AND TRANSDERMAL OPTIONS FOR EXTENDED AND CONTINUOUS REGIMENS

#### Contraceptive vaginal ring

The etonogestrel/ethinyl estradiol contraceptive vaginal ring (NuvaRing) was approved by the FDA in 2001 and is worn for 3 weeks of continuous use followed by 1 ring-free week during which withdrawal bleeding occurs. In 2005, Miller et al published a trial in which 429 women were randomized to a 28-day (21/7), 49-day (42/7), 91-day (84/7) or 364-day cycle of the vaginal ring; 289 women completed the entire year of the study. <sup>51</sup> Although all 4 regimens were acceptable to women, higher rates of study completion were reported for the shorter cycles (77% for 28-day cycle, 72% for 49-day cycle, 62% for 91-day cycle, 59% for 364-day cycle). Women who had the longer cycles had fewer total bleeding days but more spotting days (defined as bleeding requiring 1 or less pad or tampon for the day) than women with shorter cycles. In another study in which 62 women completed one year of 91-day cycles, the total number of scheduled and unscheduled bleeding days decreased over the course of the study. <sup>52</sup>

One trial assessed continuous use of the vaginal ring in 65 women who completed 6 months of use. <sup>53</sup> Participants changed rings monthly based on evidence from a pharmacokinetic study that the ring is effective for 35 days. <sup>54</sup> One group was advised that if they had breakthrough bleeding, they should to remove the ring for 4 days then reinsert it. The other group was instructed to continuously use the ring with no ring-free days. Women following the 4-day ring-free protocol had a greater proportion of days without breakthrough bleeding than women who had no ring-free days (95% vs 89%, P=.016).

Extended use of the vaginal ring does not change blood pressure significantly.<sup>55</sup> The vaginal ring has been shown to have no effect on carbohydrate metabolism in both cyclic and extended regimens and is therefore safe and effective for use in women with diabetes.<sup>56,57</sup> Lipid metabolism and lipoprotein levels were similar in women using 84/7 extended regimens of the vaginal ring or combined oral contraceptives.<sup>58</sup>



#### Transdermal contraceptive patch

The norelgestromin/ethinyl estradiol transdermal contraceptive patch (Ortho Evra) was approved for contraceptive use in the United States in 2001. The cyclic patch regimen consists of 3 weekly patch applications followed by a patch-free week when withdrawal bleeding occurs. A randomized trial of the transdermal contraceptive patch in 239 women compared an 84/7 extended regimen to the approved 21/7 regimen.<sup>59</sup> The extended regimen consisted of weekly patch application for 12 consecutive weeks followed by a patch-free week. Overall, women were very satisfied in both the extended and cyclic use groups, and the difference in reported adverse events was not statistically significant. The women in the extended regimen group had fewer median bleeding days than did the women in the cyclic use group (6 vs 14, *P*<.001). Similarly, bleeding and spotting episodes were also reduced in the women in the extended regimen group (2 vs 3, *P*<.001). There was no significant difference in the number of bleeding or spotting days between the 2 groups (14 vs 16, *P*=.407).<sup>59</sup>

### ATTITUDES OF WOMEN AND HEALTH CARE PROVIDERS TOWARD MENSTUAL SUPRESSION

Two national surveys of women aged 18 to 40 years were conducted by the Association of Reproductive Health Professionals (ARHP) in 2003 prior to approval of a dedicated product for extended or continuous regimens (N=1470)<sup>60,61</sup> and in 2005 (N=1021).<sup>62</sup> Few women reported they enjoy their menses in some way (16% in 2003 vs 8% in 2005). The majority of women viewed menses as something they just have to put up with (75% in 2003 vs 77% in 2005). In 2003, half of women believed it is necessary to have a monthly menses; one-third disagreed or strongly disagreed. When asked how often they would menstruate if they had a choice, the largest proportion chose never (32% in 2003 vs 40% in 2005). Less than one-quarter (22% in 2003 and 2005) chose monthly. Most women had not heard of menstrual suppression (73% in 2003 vs 55% in 2005). The participants in the 2 studies were not the same thus the results cannot be directly compared, but the findings suggest increased awareness of menstrual suppression. Concerns about menstrual suppression in the 2005 survey included long-term health effects (89%), side effects (88%), that it is unnatural not to have a menses



(66%), that it could affect future fertility (58%), and that it would be too expensive (57%).<sup>62</sup>

In a study of 100 female college students, 89% had heard of menstrual suppression. <sup>63</sup> Primary sources of information about menstrual suppression were media (64%), physicians (18%), and friends (16%). Only one-third (33%) of participants were willing to suppress their menses, but two-thirds (68%) said they would be willing if there were no side effects. Interestingly, women who reported positive menstrual cyclerelated changes were more willing to suppress menstruation than women who did not report positive changes. <sup>63</sup>

The 2003 ARHP survey also had 512 health care provider participants, the majority of whom were nurse practitioners (76%).<sup>60,61</sup> Only 7% of respondents felt monthly menstruation was physically necessary. Most of the respondents had heard about menstrual suppression with extended combined oral contraceptive regimens (81% of health care providers vs 27% of women), and half (52%) had prescribed extended regimens. Issues that were rated as extremely important influences on the decision to prescribe extended regimens included long-term health effects (91%), future fertility (86%), side effects (83%), and cost (42%).

A 2004 survey was conducted with physicians who care for adolescents (N=222); 55% of respondents were pediatricians and 34% were gynecologists.<sup>64</sup> The majority of the physicians reported prescribing extended regimens of combined hormonal contraceptives (90%). Patient preferences to induce amenorrhea for a specific event (82%) or have fewer menses (72%) were more common reasons for prescribing extended regimens than medical indications (eg, menorrhagia 68%, dysmenorrhea 65%, endometriosis 62%).<sup>64</sup>

A 2005 survey assessed the extended regimen attitudes, knowledge, and prescribing habits of 211 physicians in Oregon; 44% were obstetrician-gynecologists and 56% were family medicine physicians.<sup>65</sup> Three-quarters of the physicians reported prescribing extended regimens of combined oral contraceptives often (23.5%) or sometimes (50.5%). Most respondents disagreed monthly withdrawal bleeds are essential for women on cyclic regimens (mean 1.47 on 5-point Likert scale: 1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree).<sup>65</sup>



Two surveys of a variety of health care providers, including physicians, nurse practitioners, nurse-midwives, and physician assistants were conducted in 2004 (N=551)<sup>66</sup> and 2008 (N=799).<sup>67</sup> The goal of the studies was to determine attitudes and prescribing preferences of providers regarding extended regimens of combined oral contraceptives. Most respondents had prescribed extended combined oral contraceptive regimens in their practices (82% in 2004 vs 92% in 2008). Those who prescribed extended regimens were asked if they did so frequently (29% in 2004 vs 54% in 2008), occasionally (45% in 2004 vs 31% in 2008), or rarely (24% in 2004 vs 7% in 2008). A minority of participants felt monthly bleeding on a cyclic regimen is necessary and has health benefits (12% in 2004 vs 9% in 2008). While the participants in the 2 studies were not the same and thus cannot be directly compared, these differences in prescribing over time suggest increasing acceptance of novel contraceptive prescribing regimens in the United States.<sup>66,67</sup>

### EVIDENCE-BASED COUNSELING FOR EXTENDED AND CONTINUOUS CONTRACEPTIVE REGIMENS

Women need to understand the menstrual cycle as well as the mechanisms of action, safety, advantages, and disadvantages of contraceptive methods. This information may be particularly important for women to feel secure with regimens other than the customary 21/7 cycle. A list of important topics when counseling women about extended and continuous use of combined contraceptives is provided in Box 1.

<<FOR TYPESETTER: PLEASE INSERT BOX 1 ABOUT HERE>>

#### Safety

Dozens of studies that have in total included thousands of participants have confirmed the safety of extended and continuous combined contraceptive regimens. 

14-53, 55-59

Studies have documented no harmful effects on the uterus or endometrium. Blood pressure measurements and laboratory findings were not different between groups of women using cyclic regimens and extended or continuous regimens. Return to fertility



after extended or continuous hormonal regimens has been found to be the same as return to fertility after cyclic regimens.

#### **Advantages**

Many menstrual-related and medical conditions can be alleviated by extended and continuous regimens. Side effects associated with combined contraceptives tend to occur during the hormone-free interval. Use of extended and continuous regimens can reduce or eliminate the hormone-free interval and decrease side effects such as bloating, headaches, and breast tenderness. The cost of hygiene products is also reduced, and women's lives are less interrupted by menses.

#### **Disadvantages**

Although total bleeding days are reduced with postponement or elimination of withdrawal bleeding in extended and continuous regimens, the number of spotting days often increases. This irregular bleeding will usually decrease with time as the body adjusts to a new hormone balance. It may also be helpful to take a 3 to 4-day hormone-free interval if breakthrough bleeding persists. <sup>53,68,69</sup> There is a need to remember a new schedule such as when to take pills or change the ring or patch. This is especially true for off-label use because product packaging will not include instructions for extended or continuous regimens. Women who have an unintended pregnancy while using an extended or continuous regimen may find it more difficult to detect early pregnancy because they do not bleed monthly so cannot use missed menses as a sign of pregnancy. Despite menstrual suppression, other symptoms of pregnancy (eg, breast tenderness, nausea, fatigue) will still be present. If a woman is particularly concerned about pregnancy, a pregnancy test should be performed. Last, some extended or continuous regimens may be more costly, and insurance may not cover extra pill packs, rings, or patches.

#### CONCLUSION

Given the evidence that most combined contraceptive side effects occur during hormone-free intervals and that there is no medical indication for periodic withdrawal bleeding, requiring a monthly hormone-free interval is unnecessary. For many women, reduction or elimination of the discomforts, costs, and medical conditions from



unnecessary bleeding episodes is desirable. Continuous or extended use of combined contraceptives is evidence-based practice and should be offered as an option to all women who are interested in hormonal contraception.



### Author Manuscript

#### **REFERENCES**

- **1.** Eaton SB, Pike MC, Short RV, et al. Women's reproductive cancers in evolutionary context. *Q Rev Biol.* Sep 1994;69(3):353-367.
- **2.** Thomas SL, Ellertson C. Nuisance or natural and healthy: should monthly menstruation be optional for women? *Lancet*. Mar 11 2000;355(9207):922-924.
- 3. Gladwell M. John Rock's Error. *The New Yorker*. 2000(March 13, 2000).
- **4.** Nelson A. New low-dose, extended-cycle pills with levonorgestrel and ethinyl estradiol: an evolutionary step in birth control. *International journal of women's health*. 2010;2:99-106.
- **5.** Loudon NB, Foxwell M, Potts DM, Guild AL, Short RV. Acceptability of an oral contraceptive that reduces the frequency of menstruation: the tri-cycle pill regimen. *British medical journal*. Aug 20 1977;2(6085):487-490.
- **6.** Cremer M, Phan-Weston S, Jacobs A. Recent Innovations in Oral Contraception. *Semin Reprod Med.* 13.04.2010 2010;28(02):140,146.
- 7. Willis SA, Kuehl TJ, Spiekerman AM, Sulak PJ. Greater inhibition of the pituitary--ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. *Contraception*. Aug 2006;74(2):100-103.
- **8.** Birtch RL, Olatunbosun OA, Pierson RA. Ovarian follicular dynamics during conventional vs. continuous oral contraceptive use. *Contraception*. Mar 2006;73(3):235-243.
- **9.** Shrader SP, Dickerson LM. Extended- and Continuous-Cycle Oral Contraceptives. *Pharmacotherapy*. 2008/08/01 2008;28(8):1033-1040.
- **10.** Gold MA, Duffy K. Extended cycling or continuous use of hormonal contraceptives for female adolescents. *Curr Opin Obstet Gynecol*. Oct 2009;21(5):407-411.
- **11.** Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and management of abnormal uterine bleeding in premenopausal women. *American family physician*. Jan 1 2012;85(1):35-43.
- **12.** Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. *Obstetrics and gynecology*. Feb 2000;95(2):261-266.
- **13.** Nelson AL. Communicating with patients about extended-cycle and continuous use of oral contraceptives. *J Womens Health (Larchmt)*. May 2007;16(4):463-470.
- **14.** Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. *Obstetrics and gynecology.* Nov 2001;98(5 Pt 1):771-778.
- **15.** Anderson FD, Hait H. A multicenter, randomized study of an extended cycle oral contraceptive. *Contraception.* Aug 2003;68(2):89-96.
- **16.** Anderson FD, Feldman R, Reape KZ. Endometrial effects of a 91-day extended-regimen oral contraceptive with low-dose estrogen in place of placebo. *Contraception*. 2008;77(2):91-96.
- **17.** Anderson FD, Hait H, Hsiu J, Thompson-Graves AL, Wilborn WH, Williams RF. Endometrial microstructure after long-term use of a 91-day extended-cycle oral contraceptive regimen. *Contraception.* Jan 2005;71(1):55-59.
- **18.** Kroll R, Reape KZ, Margolis M. The efficacy and safety of a low-dose, 91-day, extended-regimen oral contraceptive with continuous ethinyl estradiol. *Contraception*. 2010;81(1):41-48.
- **19.** Vandever MA, Kuehl TJ, Sulak PJ, et al. Evaluation of pituitary-ovarian axis suppression with three oral contraceptive regimens. *Contraception*. 2008;77(3):162-170.
- **20.** Kaunitz AM, Portman DJ, Hait H, Reape KZ. Adding low-dose estrogen to the hormone-free interval: impact on bleeding patterns in users of a 91-day extended regimen oral contraceptive. *Contraception*. 2009;79(5):350-355.
- 21. Anderson FD, Gibbons W, Portman D. Safety and efficacy of an extended-regimen oral contraceptive utilizing continuous low-dose ethinyl estradiol. *Contraception*. Mar 2006;73(3):229-234.



### Author Manuscript

- **22.** Davis MG, Reape KZ, Hait H. A look at the long-term safety of an extended-regimen OC. *Journal of Family Practice*. 2010;59(5):E9-E13.
- 23. Sulak PJ, Cressman BE, Waldrop E, Holleman S, Kuehl TJ. Extending the duration of active oral contraceptive pills to manage hormone withdrawal symptoms. *Obstetrics and gynecology*. Feb 1997;89(2):179-183.
- **24.** Sulak PJ, Kuehl TJ, Ortiz M, Shull BL. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. *Am J Obstet Gynecol.* Jun 2002;186(6):1142-1149.
- **25.** Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. *Am J Obstet Gynecol*. Nov 2006;195(5):1311-1319.
- **26.** Coffee AL, Sulak PJ, Kuehl TJ. Long-term assessment of symptomatology and satisfaction of an extended oral contraceptive regimen. *Contraception*. 2007;75(6):444-449.
- **27.** Edelman A, Gallo MF, Nichols MD, Jensen JT, Schulz KF, Grimes DA. Continuous versus cyclic use of combined oral contraceptives for contraception: systematic Cochrane review of randomized controlled trials. *Hum Reprod.* Mar 2006;21(3):573-578.
- **28.** Sillem M, Schneidereit R, Heithecker R, Mueck AO. Use of an oral contraceptive containing drospirenone in an extended regimen. *The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception.* Sep 2003;8(3):162-169.
- **29.** Wiegratz I, Stahlberg S, Manthey T, et al. Effect of extended-cycle regimen with an oral contraceptive containing 30 mcg ethinylestradiol and 2 mg dienogest on bleeding patterns, safety, acceptance and contraceptive efficacy. *Contraception*. Aug 2011;84(2):133-143.
- **30.** Anderson FD, Gibbons W, Portman D. Long-term safety of an extended-cycle oral contraceptive (Seasonale): a 2-year multicenter open-label extension trial. *Am J Obstet Gynecol.* Jul 2006;195(1):92-96.
- **31.** Westhoff CL, Hait HI, Reape KZ. Body weight does not impact pregnancy rates during use of a low-dose extended-regimen 91-day oral contraceptive. *Contraception*. Mar 2012;85(3):235-239.
- **32.** DiLiberti CE, O'Leary CM, Hendy CH, Waters DH, Margolis MB. Steady-state pharmacokinetics of an extended-regimen oral contraceptive with continuous estrogen. *Contraception*. 2011;83(1):55-61.
- **33.** Wiegratz I, Stahlberg S, Manthey T, et al. Effects of an oral contraceptive containing 30 mcg ethinyl estradiol and 2 mg dienogest on lipid metabolism during 1 year of conventional or extended-cycle use. *Contraception*. Jan 2010;81(1):57-61.
- **34.** Wiegratz I, Stahlberg S, Manthey T, et al. Effects of conventional or extended-cycle regimen of an oral contraceptive containing 30 mcg ethinylestradiol and 2 mg dienogest on various hemostasis parameters. *Contraception*. 2008;78(5):384-391.
- **35.** Sanger N, Stahlberg S, Manthey T, et al. Effects of an oral contraceptive containing 30 mcg ethinyl estradiol and 2 mg dienogest on thyroid hormones and androgen parameters: conventional vs. extended-cycle use. *Contraception*. Jun 2008;77(6):420-425.
- **36.** Kwiecien M, Edelman A, Nichols MD, Jensen JT. Bleeding patterns and patient acceptability of standard or continuous dosing regimens of a low-dose oral contraceptive: a randomized trial. *Contraception.* Jan 2003;67(1):9-13.
- **37.** Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. *Obstetrics and gynecology.* Apr 2003;101(4):653-661.
- **38.** Reid RL, Fortier MP, Smith L, Mirkin S, Grubb GS, Constantine GD. Safety and bleeding profile of continuous levonorgestrel 90 mcg/ethinyl estradiol 20 mcg based on 2 years of clinical trial data in Canada. *Contraception*. Dec 2010;82(6):497-502.



### Author Manuscript

- **39.** Machado RB, de Melo NR, Maia H, Jr. Bleeding patterns and menstrual-related symptoms with the continuous use of a contraceptive combination of ethinylestradiol and drospirenone: a randomized study. *Contraception.* Mar 2010;81(3):215-222.
- **40.** Teichmann A, Apter D, Emerich J, et al. Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. *Contraception*. Dec 2009;80(6):504-511.
- **41.** Legro RS, Pauli JG, Kunselman AR, et al. Effects of continuous versus cyclical oral contraception: a randomized controlled trial. *The Journal of clinical endocrinology and metabolism*. Feb 2008;93(2):420-429.
- **42.** Freeman EW, Halbreich U, Grubb GS, et al. An overview of four studies of a continuous oral contraceptive (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg) on premenstrual dysphoric disorder and premenstrual syndrome. *Contraception*. May 2012;85(5):437-445.
- **43.** Halbreich U, Freeman EW, Rapkin AJ, et al. Continuous oral levonorgestrel/ethinyl estradiol for treating premenstrual dysphoric disorder. *Contraception.* Jan 2012;85(1):19-27.
- Johnson JV, Grubb GS, Constantine GD. Endometrial histology following 1 year of a continuous daily regimen of levonorgestrel 90 micro g/ethinyl estradiol 20 micro g. *Contraception*. Jan 2007;75(1):23-26.
- **45.** Sulak P, Willis S, Kuehl T, Coffee A, Clark J. Headaches and oral contraceptives: impact of eliminating the standard 7-day placebo interval. *Headache*. Jan 2007;47(1):27-37.
- **46.** Foidart JM, Sulak PJ, Schellschmidt I, Zimmermann D. The use of an oral contraceptive containing ethinylestradiol and drospirenone in an extended regimen over 126 days. *Contraception.* Jan 2006;73(1):34-40.
- **47.** Shulman LP. The use of triphasic oral contraceptives in a continuous use regimen. *Contraception.* Aug 2005;72(2):105-110.
- **48.** Archer DF, Kovalevsky G, Ballagh SA, Grubb GS. Ovarian activity and safety of a novel levonorgestrel/ethinyl estradiol continuous oral contraceptive regimen. *Contraception*. Sep 2009;80(3):245-253.
- **49.** Barnhart K, Mirkin S, Grubb G, Constantine G. Return to fertility after cessation of a continuous oral contraceptive. *Fertility and sterility*. May 2009;91(5):1654-1656.
- **50.** Machado RB, de Melo NR, Maia H, Jr., Cruz AM. Effect of a continuous regimen of contraceptive combination of ethinylestradiol and drospirenone on lipid, carbohydrate and coagulation profiles. *Contraception*. Feb 2010;81(2):102-106.
- **51.** Miller L, Verhoeven CH, Hout J. Extended regimens of the contraceptive vaginal ring: a randomized trial. *Obstetrics and gynecology.* Sep 2005;106(3):473-482.
- **52.** Guazzelli CAF, Barreiros FA, Barbosa R, Araújo FFd, Moron AF. Extended regimens of the vaginal contraceptive ring: cycle control. *Contraception*. 2009;80(5):430-435.
- Sulak PJ, Smith V, Coffee A, Witt I, Kuehl AL, Kuehl TJ. Frequency and management of breakthrough bleeding with continuous use of the transvaginal contraceptive ring: a randomized controlled trial. *Obstetrics and gynecology*. Sep 2008;112(3):563-571.
- **54.** Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. *Clinical pharmacokinetics*. Sep 2000;39(3):233-242.
- **55.** Barreiros FA, Guazzelli CAF, Barbosa R, de Assis F, de Araújo FF. Extended regimens of the contraceptive vaginal ring: evaluation of clinical aspects. *Contraception*. 2010;81(3):223-225.
- **56.** Grodnitskaya EE, Grigoryan OR, Klinyshkova EV, Andreeva EN, Melnichenko GA, Dedov II. Effect on carbohydrate metabolism and analysis of acceptability (menstrual cycle control) of extended regimens of the vaginally inserted hormone-releasing system 'NuvaRing' as compared with the standard 21/7 regime in reproductive-age women with type 1 diabetes mellitus. *Gynecological Endocrinology*. 2010;26(9):663-668.



### Author Manuscript

- **57.** Guazzelli CA, Barreiros FA, Torloni MR, Barbieri M. Effects of extended regimens of the contraceptive vaginal ring on carbohydrate metabolism. *Contraception*. Mar 2012;85(3):253-256.
- **58.** Guazzelli CA, Barreiros FA, Barbosa R, Torloni MR, Barbieri M. Extended regimens of the contraceptive vaginal ring versus hormonal oral contraceptives: effects on lipid metabolism. *Contraception.* Apr 2012;85(4):389-393.
- Stewart FH, Kaunitz AM, LaGuardia KD, et al. Extended Use of Transdermal Norelgestromin/Ethinyl Estradiol: A Randomized Trial. *Obstetrics & Gynecology*. 2005;105(6):1389-1396 1310.1097/1301.AOG.0000160430.0000161799.f0000160436.
- ARHP. Menstruation and Mentrual Suppression: What Women and Health Care Providers Really Think. 2003; <a href="http://www.arhp.org/Publications-and-Resources/Studies-and-Surveys/2003-Menstruation-Survey">http://www.arhp.org/Publications-and-Resources/Studies-and-Surveys/2003-Menstruation-Survey</a>. Accessed December 29, 2011, 2011.
- Andrist LC, Arias RD, Nucatola D, et al. Women's and providers' attitudes toward menstrual suppression with extended use of oral contraceptives. *Contraception*. 2004;70(5):359-363.
- ARHP. Menstruation and Menstrual Suppression Survey. 2005;
  <a href="http://www.arhp.org/Publications-and-Resources/Studies-and-Surveys/Menstruation-and-Menstrual-Suppression-Survey">http://www.arhp.org/Publications-and-Resources/Studies-and-Surveys/Menstruation-and-Menstrual-Suppression-Survey</a>. Accessed December 29, 2011, 2011.
- Rose JG, Chrisler JC, Couture S. Young women's attitudes toward continuous use of oral contraceptives: the effect of priming positive attitudes toward menstruation on women's willingness to suppress menstruation. *Health care for women international*. Aug 2008;29(7):688-701.
- **64.** Gerschultz KL, Sucato GS, Hennon TR, Murray PJ, Gold MA. Extended cycling of combined hormonal contraceptives in adolescents: physician views and prescribing practices. *J Adolesc Health*. Feb 2007;40(2):151-157.
- **65.** Frederick CE, Edelman A, Carlson NE, Rosenberg KD, Jensen JT. Extended-use oral contraceptives and medically induced amenorrhea: attitudes, knowledge and prescribing habits of physicians. *Contraception.* Oct 2011;84(4):384-389.
- **66.** Sulak PJ, Buckley T, Kuehl TJ. Attitudes and prescribing preferences of health care professionals in the United States regarding use of extended-cycle oral contraceptives. *Contraception.* Jan 2006;73(1):41-45.
- **67.** Seval DL, Buckley T, Kuehl TJ, Sulak PJ. Attitudes and prescribing patterns of extended-cycle oral contraceptives. *Contraception*. Jul 2011;84(1):71-75.
- **68.** Sulak PJ, Kuehl TJ, Coffee A, Willis S. Prospective analysis of occurrence and management of breakthrough bleeding during an extended oral contraceptive regimen. *Am J Obstet Gynecol*. Oct 2006;195(4):935-941.
- **69.** Jensen JT, Garie SG, Trummer D, Elliesen J. Bleeding profile of a flexible extended regimen of ethinylestradiol/drospirenone in US women: an open-label, three-arm, active-controlled, multicenter study. *Contraception*. Aug 2012;86(2):110-118.



Table 1. Combined oral contraceptives approved for extended and continuous regimens

Active ingredients and	Brand Name	Generic Names	Regimen
daily dosage			
Levonorgestrel	Seasonale	Introvale,	84 active pills/7
150mcg/ethinyl		Jolessa,	placebo pills
estradiol 30 mcg		Quasense	
tablets			
Levonorgestrel 150	Seasonique	Amethia,	84 active pills/7 low-
mcg/ethinyl estradiol		Camrese	dose estrogen pills
30 mcg tablets and			
ethinyl estradiol 10			
mcg tablets			
Levonorgestrel 100	LoSeasonique	Amethia Lo,	84 active pills/7 low-
mcg/ethinyl estradiol		Camrese Lo	dose estrogen pills
20 mcg and ethinyl			
estradiol 10 mcg			
tablets			
Levonorgestrel 90	Lybrel	Amethyst	28-day packs with
mcg/ethinyl estradiol			no hormone-free
20 mcg tablets			interval



Box 1. Key points for counseling women considering extended and continuous use combined contraceptive regimens

- Preventing ovulation is the primary mechanism of action of all combined contraceptive regimens (cyclic, extended, and continuous)
- Monthly bleeding episodes with combined contraceptives are not menses but instead are withdrawal bleeding designed to mimic the timing of normal menstrual cycles
- There is no scientific evidence that monthly bleeding while on combined contraceptives is necessary
- Extended and continuous use of combined contraceptives reduce and eliminate monthly withdrawal bleeding respectively; this is an expected outcome of these regimens and does not represent pathology
- Menstrual blood does not "build up" with extended or continuous use of combined contraceptives; the endometrium is atrophic with all combined contraceptive regimens
- Unpredictable breakthrough bleeding may occur with extended or continuous use of combined contraceptives; this is similar to cyclic regimens
- No harmful effects have been documented specific to extended and continuous regimens; risks are similar to those with cyclic use
- Fertility will return on discontinuation of extended and continuous regimens as it does with cyclic contraceptive use
- Extended and continuous regimens can treat menses-related conditions and reduce contraceptive side effects
- Women may find having fewer or no menses more convenient
- Contraceptive costs may be higher with extended and continuous regimens, but less sanitary products will be needed
- Provide a detailed schedule for the selected regimen, especially when hormonefree days occur, if at all