Extended Use of Transdermal Norelgestromin/Ethinyl Estradiol: A Randomized Trial

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OBJECTIVE: To compare bleeding profiles and satisfaction among women using a norelgestromin/ethinyl estradiol (E2) transdermal contraceptive patch in an extended regimen to those among women using a traditional 28-day patch regimen.

METHODS: Healthy, regularly menstruating women (N = 239) were randomly assigned (2:1 ratio) to receive the norelgestromin/ethinyl E2 transdermal patch in an extended regimen (weekly application for 12 consecutive weeks, 1 patch-free week, and 3 more consecutive weekly applications, n = 158) or a cyclic regimen (4 consecutive cycles of 3 weekly applications and 1 patch-free week, n = 81). Subjects recorded bleeding data daily and completed satisfaction questionnaires. Subjects and investigators provided overall assessments of the regimens.

RESULTS: Extended use of the norelgestromin/ethinyl E2 transdermal patch resulted in fewer median bleeding days (6 compared with 14, $P < .001$), bleeding episodes (1 compared with 3, $P < .001$), and bleeding or spotting episodes (2 compared with 3, $P < .001$) compared with cyclic use during days 1–84; median numbers of bleeding or spotting days were similar between regimens (14 compared with 16, $P = .407$) during this time. Extended use delayed median time to first bleeding to 54 days compared with 25 days with cyclic ($P < .001$). Subjects were highly satisfied with both regimens. Although not statistically significant, slightly more adverse events were reported with the extended than with the 28-day regimen.

CONCLUSION: Compared with cyclic use, extended use of the norelgestromin/ethinyl E2 transdermal patch delayed menses and resulted in fewer bleeding days. This regimen may represent a useful alternative for women who prefer fewer episodes of withdrawal bleeding. (Obstet Gynecol 2005;105:1389–96. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

Combined estrogen plus progestin contraceptives have traditionally been administered in cycles of 21 days of active hormone followed by a 7-day hormone-free interval that results in withdrawal bleeding in most women. Use of extended regimens (ie, administration of active hormones for an interval > 21 days) of combined oral contraceptives is common among women wishing to delay or prevent withdrawal bleeding for reasons such as athletic participation or vacation.[1–4] In addition to the convenience of reducing the frequency of withdrawal bleeds, elimination of the hormone-free interval reportedly reduces many menstrual-related symptoms (eg, headaches, dysmenorrhea) that occur at a greater frequency during the hormone-free interval than during the rest of the cycle.[1–6]

Many women prefer extended hormonal contraceptive regimens over traditional cyclic regimens.[7] Extended regimens are well tolerated and efficacious for the prevention of pregnancy and reduction in menstrual-related symptoms.[3,5,6,8] The traditional oral contraceptive cycle of 21 days of active pills and 7 days of inactive pills is not based on evidence of superiority and may have important disadvantages for some women. Many of the cyclic symptoms that women complain of occur during the hormone-free period.[6] Hence, for some women, reducing the number of days off active hormones may provide a significant benefit. In addition, it

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may be easier for some women to implement and adhere to extended regimens.

However, one of the side effects reported with extended regimens is breakthrough bleeding or spotting.[3,8–11] Compared with cyclic regimens, extended oral contraceptive use may be associated with an increased incidence of breakthrough bleeding and spotting, especially during the first few months.[3,5,12–14] Experience with a 91-day oral contraceptive extended regimen product indicates that bleeding and spotting decrease with repeated 91-day cycles. However, during the first 84 days, 65% of the extended users, compared with 38% of the cyclic users, experienced seven or more days of unscheduled bleeding and spotting (Seasonale package insert, available at www.seasonale.com, retrieved March 2, 2005).

ORTHO EVRA transdermal system (Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ), is a combined hormonal contraceptive system containing 6.0 mg of the progestin norelgestromin (the primary active metabolite of norgestimate) and 0.75 mg of the estrogen ethinyl estradiol (E2). The 20-cm^2 patch delivers 150 μg/day norelgestromin and 20 μg/day ethinyl E2 to the systemic circulation, and is approved as a cyclic regimen of 3 consecutive 7-day patches followed by 1 patch-free week.[15–17] The current trial compared the bleeding profiles of extended and cyclic regimens of the norelgestromin/ethinyl E2 transdermal patch and evaluated investigator and subject overall assessments and subject satisfaction with each regimen.

MATERIALS AND METHODS

Healthy, regularly menstruating females (N = 239) aged 18 to 45 years (nonsmokers if aged 35 years or older) at 9 clinical research sites were randomly assigned in a 2:1 ratio to receive an extended or cyclic regimen of the norelgestromin/ethinyl E2 transdermal system. The computer-generated randomization list was prepared by Ortho-McNeil Pharmaceutical, Inc. before the study to assign subjects to treatment within centers and by permuted blocks of size 6. Extended regimen subjects applied 1 patch weekly for 12 consecutive weeks (84 days) followed by 1 week (7 days) without patch application (patch-free) and then 3 final weeks (21 days) of weekly patch applications, for a total of 112 days. The last treatment cycle was included to determine the duration of menses in the extended regimen group and to allow a transition back to cyclic contraception (Fig. 1). Cyclic regimen subjects used patches for 4 consecutive 28-day cycles (112 days), applying 1 patch weekly for 3 weeks (21 days) followed by 1 patch-free week (7 days).

The study was approved by the institutional review board at each site. Procedures were conducted according to Good Clinical Practice, the Declaration of Helsinki of 1975 as revised in 1983, and current International Conference on Harmonization guidelines. Signed written informed consent was obtained from all subjects before any protocol-specific procedures were completed.

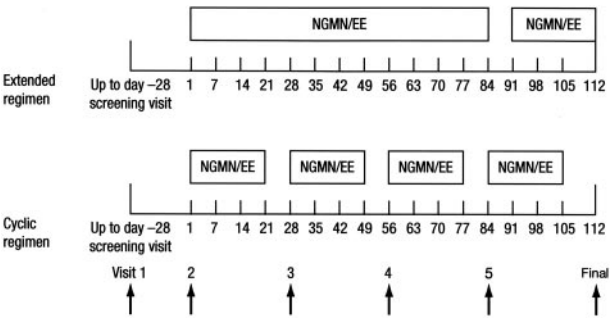

Fig. 1. Diagram of study design. Arrows indicate study visits.

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The last term pregnancy had to have been completed at least 42 days before screening, and there had to have been at least 1 normal menstrual period since pregnancy. Women agreed not to use any other steroid hormone therapy except topical corticosteroids, if needed, during the trial.

Exclusion criteria included history or presence of any disorder contraindicating steroid hormonal therapy, history of dermal hypersensitivity, and treatment with an extended regimen of an oral contraceptive within the 3 months before screening. Although weight heavier than 198 pounds is a precaution in the prescribing information for the norelgestromin/ethinyl E2 transdermal system (due to decreased contraceptive efficacy compared with that in women < 198 pounds), it is not a contraindication, and it was not a criterion for exclusion from the study, because increased risk of pregnancy is not a deterrent to use. Enrollment of women heavier than 198 pounds was left to the discretion of the physician and subject.

Subjects were instructed to record bleeding and headache data in a diary booklet at home every day starting on day 1 (defined as the first day of patch application), including days of patch use, and the number of tampons, pads, or panty liners used. They were also to record the presence or absence of headache along with headache characteristics, such as nausea or sensitivity to light. Diaries were collected by clinic personnel and reviewed with the subject at each visit. Detailed results of analyses of data regarding headaches, collected as described above, are reported elsewhere (LaGuardia K, Fisher AC, Bainbridge JD, LoCoco JM, Friedman AJ. Suppression of estrogen-withdrawal headache with extended transdermal hormonal contraception. Fertil Steril, in press).

Study participants underwent medical history review, physical examination, including breast and pelvic examination, and hemoglobin and hematocrit testing at enrollment and study completion. A cervical Pap test was performed at the screening visit. Vital signs and body weight were measured, and a urine pregnancy test was performed at each visit. Adverse events reported by subjects were recorded at each visit.

The primary endpoint of the study was total bleeding or spotting days during the primary reference period, days 1–84. Secondary endpoints included headache frequency and overall subject and investigator assessment. The number of bleeding–spotting days, bleeding–spotting episodes, bleeding days, bleeding episodes, percent of subjects with amenorrhea, time to first bleeding or spotting, time to first bleeding during the 84-day interval, and the duration of menses at the conclusion of the 84-day interval were evaluated. Secondary reference periods of 56 days and 28 days were also analyzed, because results at each of these 28-day intervals allow comparisons of bleeding characteristics of extended use with those of cyclic use, which is typically administered every 28 days. Bleeding profiles were summarized using the World Health Organization (WHO) reference period methodology.[18,19] Definitions, adapted from the WHO, for the bleeding data analyses are shown in the box.

Definitions Used for Bleeding Diary Analysis

Bleeding	Vaginal bleeding that required sanitary protection of at least one pad or tampon
Spotting	Vaginal bleeding that did not require sanitary protection (panty liner use was acceptable)
Bleeding day	Day on which bleeding occurred
Spotting day	Day on which spotting alone occurred; if spotting and bleeding occurred on the same day, it was recorded as a bleeding day
Bleeding-free day	Day on which neither bleeding nor spotting occurred, bounded by bleeding/spotting days
Bleeding/spotting episode	Any set of one or more consecutive bleeding or spotting days, bounded by bleeding-free days
Bleeding episode	Any set of one or more consecutive bleeding days, bounded by bleeding-free days
Amenorrhea	No bleeding or spotting occurring during the entire reference period

The initial bleeding episode for each subject was excluded from all bleeding profile summaries, because the first day of menses was the first day of study medication. At the 4 visits during treatment, each subject completed a questionnaire containing items evaluating overall satisfaction (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied) and bleeding (heavier than before, about the same as before, lighter than before, haven't bled). At the final visit, investigators and subjects provided an "overall assessment of the study drug regimen" (excellent, good, fair, or poor).

Statistical analyses of the bleeding profile were conducted for both an intent-to-treat and a perfectly compliant completer population. The intent-to-treat population included all randomly assigned subjects who applied study drug and for whom postrandomization data were available. The perfectly compliant completer population, a subgroup of the intent-to-treat population, was defined for extended regimen subjects as a patch on every day (through day 84), with no patch on for more than 7 days, and for cyclic regimen subjects as a patch on the first 21 days of each cycle and no patch on the subsequent 7 days of each cycle (through day 84), with no patch on for more than 7 days. Except for the variables of duration of menses and overall satisfaction at day 84, which required that subjects complete the treatment period, the intent-to-treat results are presented. The intent-to-treat and the perfectly compliant completer groups yielded bleeding profiles that were comparable. The safety evaluable population included all subjects who applied a patch and had at least 1 safety assessment after baseline (n = 235). The incidence of adverse events was evaluated in this population.

The Mann–Whitney *U* test was used to compare possible differences between the treatment regimens in

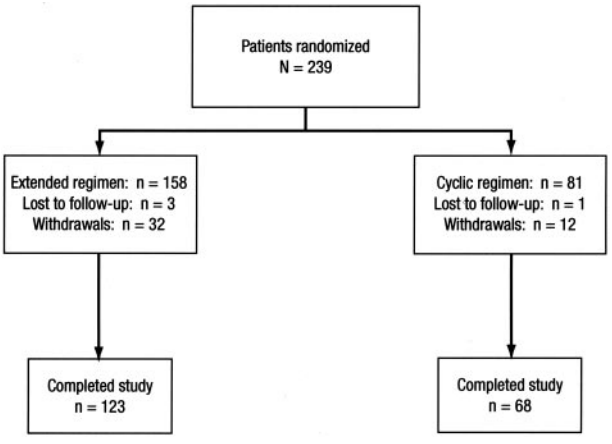

Fig. 2. Flow of patients through the trial.
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Table 1. Reasons Cited for Withdrawal Prior to Study Completion for Subjects Assigned to Extended or Cyclic Regimens of Norelgestromin/Ethinyl Estradiol

	Norelgestromin/Ethinyl Estradiol Contraceptive Regimen	
Reason for withdrawal	Extended (n = 155)	Cyclic (n = 80)
Limiting adverse event*	16 (10)	4 (5)
Lost to follow-up	3 (2)	3 (4)
Subject choice	4 (3)	3 (4)
Protocol violation	1 (1)	1 (1)
Bleeding	6 (4)	0 (0)
Other	2 (1)	1 (1)

Values are n (%).

* Limiting adverse events (those that led to study discontinuation) for the extended regimen group were application site reaction, breast discomfort (defined as "exacerbated breast tenderness, breast tenderness, and exacerbation of breast tenderness"), depression, emotional lability, esophageal stricture, headache, hypertension, migraine, nausea, urticaria, and vomiting. For the cyclic group, they were breast pain (defined as "sharp breast pains and mastalgia"), dizziness, emotional lability, hypertension, nausea, sweating, and vomiting. Subjects could have discontinued due to 1 or more adverse events.

the bleeding profile variables (including duration of menses), the overall satisfaction and bleeding questionnaire, and the overall assessments by the subject and investigator. Fisher exact test was used to compare the proportions of subjects in the treatment regimens for categorical demographic variables, adverse events, and the variable "no bleeding days." The *t* test was used for continuous demographic variables. Time to first bleeding or spotting, time to first bleeding, and time to discontinuation due to bleeding were summarized by Kaplan-Meier estimates, with the statistical significance of treatment group differences assessed by the log-rank test. The perfect compliance rate per 28-day reference period for the 2 groups was compared with generalized estimating equation methodology, using Proc GENMOD from SAS 9.1 (SAS Institute Inc., Cary, NC).

The sample size was chosen to detect, at the 5% significance level with 80% power, a 5-day difference during the 84-day reference period in the mean total number of bleeding or spotting days, assuming a standard deviation of 12 days. All statistical tests were performed at a 2-tailed, 5% level of significance.

RESULTS

This study was initiated on May 30, 2002, and completed on March 13, 2003. Two hundred thirty-nine subjects were randomly assigned to extended regimen norelgestromin/ethinyl E2 (n = 158) or cyclic regimen norelgestromin/ethinyl E2 (n = 81) (Fig. 2). Four subjects (3 extended, 1 cyclic) either never received the drug or were lost to follow-up with no information after randomization. Of those 235 women with information after randomization, 191 (81%) completed the study: 123 of 155 (79%) assigned to the extended regimen and 68 of 80 (85%) assigned to the cyclic regimen. Reasons cited for withdrawal before study completion and adverse events that led to discontinuation are outlined in Table 1. The demographic and baseline characteristics of the

Table 2. Demographics and Baseline Characteristics of Subjects Assigned to Extended or Cyclic Regimens of Norelgestromin/Ethinyl Estradiol

	Norelgestromin/Ethinyl Estradiol Contraceptive Regimen	
	Extended (n = 155)	Cyclic (n = 80)
Mean age [y (± SD)]	29.1 (± 6.2)	28.0 (± 5.9)
Race (%)		
White	54	61
Hispanic or Latina	24	20
African American	18	10
Asian	3	5
Other	1	4
Smoker (%)	12	13
Mean height [cm (± SD)]	163.8 (± 6.8)	164.0 (± 7.1)
Mean weight [kg (± SD)]	70.1 (± 16.0)	67.2 (± 14.0)
Mean body mass index [kg/m^2 (± SD)]	26.2 (± 6.0)	25.0 (± 5.1)
Previous hormonal contraceptive use* (%)		
Fresh start	43	45
Direct switch	45	49
Indirect switch	11	6
Unknown	1	0

SD, standard deviation.

* "Fresh start" means subject took no hormonal contraceptive for more than 60 days before screening, "Direct switch"means subject switched from another form of hormonal contraceptive to study contraceptive within 10 days before screening, and "Indirect switch" means subject switched from another form of hormonal contraceptive to study contraceptive between 11 and 60 days before screening.

Table 3. Bleeding Profile Information for Intent-to-Treat Subjects (Excluding Initial Bleeding Days) Assigned to Extended or Cyclic Regimens of Norelgestromin/Ethinyl Estradiol

	Norelgestromin/Ethinyl Estradiol Contraceptive Regimen		
	Extended (n = 155)	Cyclic (n = 80)	*P*
Day 1 to day 84			
Median bleeding-spotting days	14	16	.407
Median bleeding-spotting episodes	2	3	< .001
Median bleeding days	6	14	< .001
Median bleeding episodes	1	3	< .001
Amenorrhea (%)	12	1	< .003
Day 1 to day 56			
Median bleeding-spotting days	6	10	.009
Median bleeding-spotting episodes	1	2	< .001
Median bleeding days	1	9	< .001
Median bleeding episodes	0.5	2	< .001
Amenorrhea (%)	28	1	< .001

study groups were statistically comparable (Table 2). Subjects were generally compliant with patch application. Perfect compliance by 28-day reference periods over the initial 84 days was numerically higher in the extended regimen group compared with the cyclic regimen group (85% compared with 78%, $P = .322$). Relatively few patches were reported as having fallen completely off (approximately 3% of patches per 28-day reference period).

For the primary reference period, days 1–84, there was no significant difference between the extended and cyclic regimens in the median number of bleeding or spotting days (Table 3). However, there were significant differences in bleeding or spotting episodes, bleeding days, bleeding episodes, and incidence of amenorrhea during this time. During days 1–56, all bleeding variables were significantly lower in the extended compared with the cyclic regimen group. For those subjects who received the extended regimen, the incidence of amenorrhea was over twice as great during days 1–56 (28%) as it was during days 1–84 (12%).

The median time to first bleeding was 54 days for the extended regimen group and 25 days for the cyclic regimen group ($P < .001$; Fig. 3). The extended regimen group had significantly ($P < .001$) fewer bleeding days per 28-day interval than the cyclic group through day 84. The median number of bleeding days in the extended regimen group was 0, 0, and 2 for the 28-day intervals of days 1–28, 29–56, and 57–84, respectively, whereas the median number of bleeding days in the cyclic regimen group was 4, 6, and 5 for the same intervals (Fig. 4). Overall, in each 28-day interval studied, the extended regimen group had fewer bleeding days but more spotting days than the cyclic regimen group. In general, the differences between the 2 groups were most apparent through 56 days of use. The mean duration of menses, measured using the first menstrual cycle for the extended regimen group and the third menstrual cycle for the cyclic regimen group, was significantly longer in the extended regimen group than in the cyclic regimen group (6.9 compared with 5.2 days, $P < .001$).

Overall satisfaction, evaluated on day 84, was similar between groups; 86.3% (107/124) of subjects in the extended regimen group and 88.6% (62/70) of subjects in the cyclic group were very or somewhat satisfied. Subjects in the extended regimen group indicated a perception of lighter or no bleeding flow compared with their pretreatment menstrual flow. On day 84, 35% (43/124) of the subjects in the extended regimen group reported that they had not bled, compared with 3% (2/70) of cyclic subjects.

For the overall global assessment of the study drug regimen, ratings of "excellent" or "good" were given by 87% (70/80) and 79% (122/155) of subjects in the cyclic and extended treatment regimens, respectively,

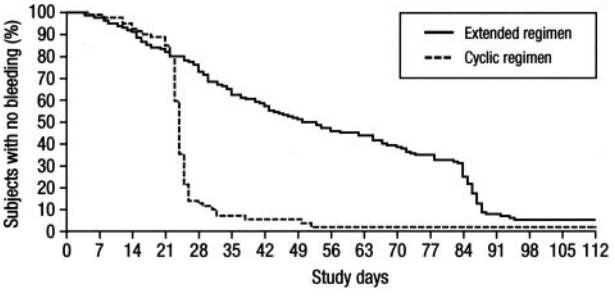

Fig. 3. Kaplan-Meier analysis of time to first bleeding for the extended and cyclic regimens. Data collected during the first week (during menses) were excluded; hence, the study started with 100% of subjects with no bleeding. Median day: extended, 54; cyclic, 25 ($P < .001$).

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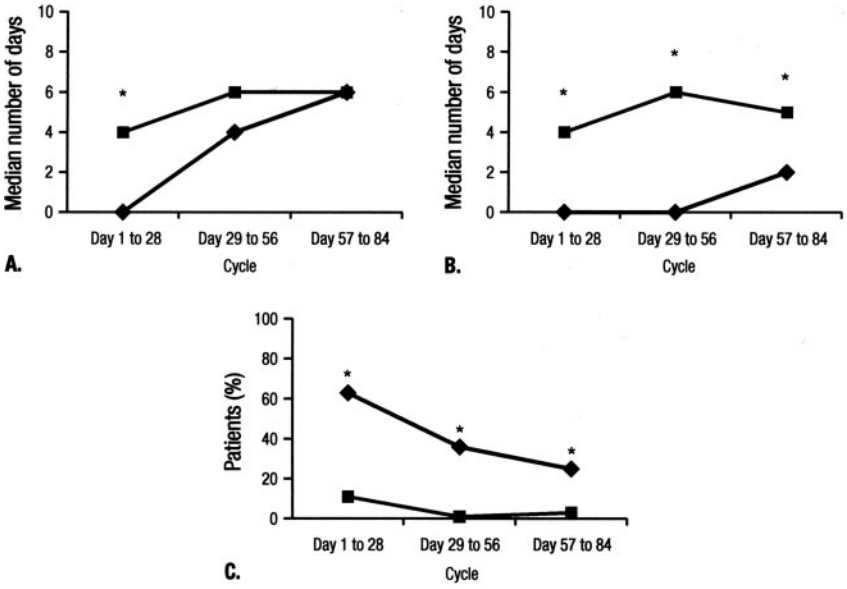

Fig. 4. Median bleeding or spotting days **(A)**, median bleeding days **(B)**, and incidence of amenorrhea **(C)** for extended (*black line with diamonds*) (n = 155) and cyclic (*black line with squares*) (n = 80) regimens, by cycle. *$P < .001$.

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($P = .111$). The investigators cited the treatment regimen as "excellent" or "good" in 86% (69/80) of subjects in the cyclic regimen group, compared with 79% (123/155) of subjects in the extended regimen group ($P = .217$).

Both regimens of norelgestromin/ethinyl E2 were well tolerated. The adverse event profiles were similar with respect to the types of adverse events. Adverse events that occurred with an incidence of at least 5% for either regimen included application site reaction, upper respiratory tract infection, breast discomfort, headache, nausea, vaginitis, and emotional lability (Table 4). Although not statistically significant, there were more reports of headache, nausea, and breast discomfort in the extended group compared with the cyclic group. A total of 20 subjects, 16 (10%) in the extended group and 4 (5%) in the cyclic group, discontinued the study due to adverse events (Table 1). Six (4%) subjects in the extended regimen group discontinued due to bleeding; no subject in the cyclic regimen group discontinued due to bleeding. In the extended regimen group, the mean time to discontinuation due to bleeding was 107 days, and no subjects discontinued due to bleeding before day 62.

One pregnancy occurred during the study in a subject assigned to the extended regimen. The pregnancy was discovered at the final clinic visit (day 112), and the subject subsequently had a spontaneous pregnancy loss later, at approximately 8 weeks gestation. An ultrasound indicated a blighted ovum. This was the only serious adverse event that occurred during the study. Changes in hemoglobin and hematocrit levels from baseline to the end of the study were small and clinically insignificant in both groups. Changes in vital signs from baseline to the end of the study were also unremarkable. Mean body weight changes in both treatment groups were small (.35 ± 2.31 kg in the extended regimen group and .47 ± 2.22 kg in the cyclic regimen group).

Table 4. Adverse Events That Occurred With an Incidence of at Least 5% in Either Extended or Cyclic Regimen Norelgestromin/Ethinyl Estradiol Subjects

	Norelgestromin/Ethinyl Estradiol Contraceptive Regimen		
Adverse Event	Extended (n = 155)	Cyclic (n = 80)	*P**
Application site reaction	28 (18)	12 (15)	.589
Upper respiratory tract infection	21 (14)	9 (11)	.684
Breast discomfort	23 (15)	5 (6)	.058
Headache	18 (12)	3 (4)	.054
Nausea	16 (10)	4 (5)	.220
Vaginitis	10 (7)	5 (6)	1.000
Emotional lability	8 (5)	3 (4)	.754

Values are n (%).

* *P* values were calculated using the Fisher exact test.

DISCUSSION

Based on results of a search of publications from the years 1995 through 2005 included in the National Library of Medicine's PubMed database (search terms: continuous use OR extended use AND contraceptive NOT replacement NOT postmenopausal; limitation: clinical trials; no language limitation), this randomized clinical trial comparing extended use of the norelgestromin/ethinyl E2 transdermal patch to cyclic use is one of the largest on extended regimen use of approved cyclic regimens published to date. In addition, it is the first such trial using a transdermal mode of hormonal delivery. The purpose of this trial was to examine the efficacy and safety of an extended regimen of the norelgestromin/ethinyl E2 transdermal system over an 84-day period. Extended use resulted in fewer median bleeding days, bleeding episodes, and bleeding or spotting episodes, a greater incidence of amenorrhea during this period, and subject satisfaction that was similar to that seen with cyclic use.

The Kaplan-Meier analysis of the bleeding data shows a significantly longer median time to first bleeding (54 days compared with 25 days) among the extended users as compared with the cyclic users (Fig. 3). The advantage of the time to first bleeding analysis is that it provides an understandable interpretation of regimen performance. If the objective of an extended regimen is to delay menses, knowing how long a patient can reliably delay bleeding is a key determinant of regimen acceptability and provides a meaningful definition to the concept of "delaying menses." Time to first bleeding analyses have been done for a few oral contraceptives.[20,21]

The norelgestromin/ethinyl E2 transdermal system was assessed over fixed periods of time in this study. However, it should also be possible to apply this contraceptive system in a flexible manner to accommodate changes in a woman's social or personal activities. Although the present study demonstrated a median delayed time to first bleeding of 54 days, some women may choose to delay menses through 8 continuous patch-weeks, whereas others may choose a different duration, such as 6 continuous patch-weeks. This ability to accommodate variable regimens provides a flexible approach to extended contraception.

Although the extended regimen users reported more breast discomfort, headache, and nausea than the cyclic users, the overall adverse event profile was favorable. Only 1 serious adverse event, a spontaneous pregnancy loss, occurred during this study. The discontinuation rate due to adverse events was low, and most discontinuations occurred late in the study, indicating that both regimens were well tolerated overall. Given the recent approval of an extended oral contraceptive, the scientific community will likely follow safety and efficacy data closely. The higher incidence of adverse event reports of breast discomfort, nausea, and headaches seen in the extended group may represent an estrogenic effect in some women. It is also possible that women assigned to use the "new" extended regimen were more aware of and more likely to report common side effects than were women using the more common monthly regimen.

A limitation of this study is that its relatively short treatment duration did not allow a determination of the long-term efficacy, tolerability, and safety of the extended regimen. Any pregnancies or serious adverse events that may occur beyond 84 days of continuous transdermal norelgestromin/ethinyl E2 use require further study in a long-term usage trial. In addition, the relatively small size of the population studied makes any generalization about efficacy or safety difficult.

In summary, extended-regimen dosing with the norelgestromin/ethinyl E2 transdermal patch was effective for delaying menses and was associated with reports of high satisfaction, low adverse events, and few discontinuations due to bleeding.

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APPENDIX

The following investigators comprised the ORTHO EVRA Extended Regimen Study Group:

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