A Prospective Follow-Up of Two 21/7 Cycles Followed by Two Extended Regimen 84/7 Cycles with Contraceptive Pills Containing Ethinyl Estradiol and Drospirenone

Daniel S. Seidman MD MMSc[1], Arie Yeshaya MD[1], Amos Ber MD[1], Ida Amodai MD[1], Itzhak Feinstein MD[1], Israelit Finkel MD[1], Nina Gordon MD[1], Noga Porat MD[1], Dganit Samuel MD[1], Einat Shiran-Makler MD[1] and Igal Wolman MD[2]

[1]Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, and [2]Department of Obstetrics and Gynecology, Sourasky Tel Aviv Medical Center, both affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Continuous use of combined oral contraceptives is currently attracting growing interest as a means of improving menstrual related symptoms and reducing the number of bleeding days.

Objectives: To evaluate bleeding patterns, menstrual symptoms and quality of life with an extended 84/7 oral contraceptive regimen versus 21/7 cycles.

Methods: In two consecutive run-in cycles, 30 µg ethinyl estradiol and 3 mg drospirenone tablets taken on days 1–21 were followed by a tablet-free period from days 22 to 28 of each cycle and then by two 84 day cycles of pill use with a 7 day tablet-free interval. The primary outcome was the total number of bleeding/spotting days. Secondary outcomes were severity of daily symptoms, general well-being determined by the PGWBI questionnaire, and overall treatment satisfaction.

Results: Of the 137 women invited to participate in the study 109 (aged 18–40 years) were enrolled. The number of bleeding days decreased by about one-third from a calculated 31.8 days of bleeding under a cyclic 21/7 regimen to an expected total of 21.8 days for the extended 84/7 regimen. The incidence of menorrhagia, intermenstrual bleeding, dysmenorrhea, abdominal bloating, breast tenderness, depressive moods and irritability – when compared at enrollment and at the end of the second extended study period – was significantly lower ($P < 0.005$) among women on the continuous pill regimen. The median (range) global PGWBI scores were not substantially different before and after the extended use cycles: 78.2 (39.1–96.4) and 77.3 (30.9–96.4), respectively. Body weight and skin condition also remained constant. At the completion of the study: 65.5% of the women were either highly satisfied (41.4%) or satisfied (24.1%) with the extended regimen.

Conclusions: The extended 84/7 regimen was found to be satisfactory for the majority of participants and was associated with a decrease in the number of bleeding days and an improvement in menstrual symptoms compared to 21/7 cycles.

IMAJ 2010; 12: 400–405

KEY WORDS: combined hormonal contraceptives, non-bleeding contraceptives, menorrhagia, continuous administration, spotting, menstrual symptoms

Extended use of combined oral contraceptives, omitting the hormone-free interval, has a favorable effect for many women by reducing the frequency of troublesome withdrawal bleeding [1]. It was shown to be associated with only slight breakthrough bleeding and relatively weak withdrawal bleeding episodes [1]. Continuous administration of combined oral contraceptives is, therefore, often recommended to women to avoid menstrual symptoms such as migraine headache [2], endometriosis-associated pelvic pain [3,4], premenstrual symptoms [5] and the inconvenience associated with menses [5,6]. Avoidance of these unpleasant symptoms may be a more powerful motivator for women to comply with oral contraceptives than the many known major health benefits, such as reduction in the risk of ovarian cancer. Few studies, however, have compared the safety, efficacy, side effects and potential advantages and disadvantages of continuous versus traditional administration of oral contraceptives [6-8]. Furthermore, an observational non-controlled study has suggested that women who took, continuously, a contraceptive pill containing 30 µg ethinyl estradiol combined with 3 mg drospirenone continuously for between 42 and 126 days seemed to have benefited from this progestin's anti-mineral corticoid activity (e.g., reduced breast tenderness, edema, bloating) and anti-androgenic activity (e.g., positive effects on the skin) [9]. Additional reports have shown that the continuous use of a 30 µg ethinyl estradiol and 3 mg drospirenone formulation over 126 days was safe, efficacious, well accepted by the users and resulted in a considerable reduction in bleeding [10,11].

A recent systematic Cochrane review of randomized controlled trials found that the contraceptive efficacy and compliance were similar for the continuous-use group versus the cyclic-use group [12]. The rate of discontinuation for any reason and specifically for bleeding problems was low in each group, and the participants reported high levels of satisfaction with both dosing regimens. Most studies found that bleeding patterns were either equivalent or improved with continuous-dosing regimens. For example, the continuous-dosing group in the study by Edelman et al. [12] had a greater reduction of menstrual-associated symptoms, including headaches, genital irritation, tiredness, bloating, and menstrual pain.

The authors of the Cochrane review commented that future studies on continuous or extended cycle use of combined oral contraceptives for contraception should choose a previously proven type of pill and dosing regimen while paying more attention to participant satisfaction and menstruation-associated symptoms. The aim of the present study was therefore to examine in a prospective manner the hypothesis that women taking combined oral contraceptives containing drospirenone, without a hormone-free interval for up to 84 days, have a favorable rate of side effects and bleeding days leading to improved quality of life and high satisfaction rates.

SUBJECTS AND METHODS

The purpose of this study was to evaluate bleeding patterns and acceptability of an extended 84/7 oral contraceptive regimen using a combined pill containing 30 μg ethinyl estradiol and 3 mg drospirenone taken for 84 continuous days during two consecutive cycles compared to two preceding 21/7 cycles using the same pills.

Nine outpatient gynecology clinics participated. Women between the age of 18 and 40 who requested oral contraceptive therapy, were willing and able to give informed consent, and had no medical contraindication to combined oral contraceptive therapy were invited to participate.

Each subject received, in two consecutive run-in cycles, an oral dose of 30 μg ethinyl estradiol and 3 mg drospirenone (Yasmin, Bayer Schering AG, Berlin, Germany) on days 1–21, followed by a tablet-free period from day 22 to 28 of each cycle. This was immediately followed by two extended cycles of 84 continuous days of pill administration with a 7 day tablet-free interval. The enrolled subjects received free oral contraceptives for the duration of the study (an unrestricted gift from Bayer Schering AG). They were all requested to return to the clinic after completion of the run-in cycles and after finishing the first and second extended cycles. The Institution Review Board of the Sheba Medical Center approved the study protocol and all participants signed a written informed consent.

The primary outcome was the total number of bleeding/spotting days during the 6 month course of treatment. The mean number of reported bleeding days was analyzed for each of the two extended treatment cycles and for the overall duration of the study. Secondary outcomes included the severity of selected daily symptoms and overall treatment satisfaction. The participants were also asked to describe their skin condition at enrollment, and any reported changes that occurred during the study phases were recorded. The somatic symptoms of the participants in the current study were rated every day, and changes in the total score served as a parameter to test the efficacy of the regimen.

The study women's mood state was assessed using the Psychological General Well-Being Index [13] before and after the extended-use cycles. The PGWBI is a brief self-administered questionnaire with 20 items rated on a six-point scale, where a higher score indicates a better quality of life and measures six mood states (anxiety, depressed mood, positive well-being, self-control, general health, vitality). The six mood states are scored as follows: 25 for anxiety, 20 for positive well-being and vitality, and 15 for the others. The PGWBI was completed by the patients themselves.

At enrollment, the women were provided with daily diaries and asked to document any occurrence of vaginal bleeding and side effects. Vaginal bleeding was categorized as either spotting or bleeding. Spotting was defined as a light flow that did not necessitate sanitary protection, and bleeding was defined as a heavier flow that did require sanitary protection. Subjects reporting bleeding were asked to classify it each day as light, moderate or heavy.

Participants were also asked to note any symptoms of headache, nausea, bloating, breast tenderness, irritability, depressive moods and menstrual pain, as well as any pills that were missed. They completed a satisfaction questionnaire at the conclusion of each extended-regimen cycle. Overall satisfaction with bleeding patterns and symptom severity were recorded on a 100 mm visual analog scale.

Data collection began at the time of study entry and was completed during clinic visits for all patients within 12 months. Cycle regularity, symptoms related to menstrual regularity, and associated medical problems and complications were recorded. This information was entered into a patient logbook and later transferred onto a computerized form. Study discontinuation, conception, and adverse events were noted. In the event of withdrawal from the study, the woman's accumulated data were analyzed up to that point.

STATISTICAL ANALYSIS

Our sample size was based on expected differences in the primary outcome of total bleeding days during extended pill use

PGWBI = Psychological General Well-Being Index

in comparison to a hypothetical period of six 21 day pill cycles. The statistical analysis was done with the chi-square or Fisher exact tests for categorical variables and the unpaired Student's *t*-test for continuous factors. A correlation between PGWBI scores, before and after the extended regimen, was performed using a Spearman correlation test. All the tests were two-sided. A P value of < 0.05 was accepted as significant.

RESULTS

Of the 137 women invited to participate in the study, 109 women consented and were enrolled from September 2004 through February 2006. Their mean ± SD age was 27.5 ± 5.3 years; 32 (29.4%) were multiparas and 77 (70.6%) were nulliparas. Most of them were white-collar workers (64.2%) and students (29.4%) and a few were manual workers (2.7%) or unemployed (3.7%). Almost one-third were married (30.3%) for a mean ± SD of 5.4 ± 3.5 years. About one-fourth were smokers (26.6%) who smoked a mean of 6.5 ± 4.4 cigarettes daily; only two were considered heavy smokers (>15 cigarettes a day). Prior use of oral contraceptives was reported by 39 subjects (35.8%) for a mean of 6.1 ± 4.4 years.

Sixty-eight of the 109 enrolled women (62.4%) completed the entire study protocol. The most common reasons given for discontinuation were loss of interest (8.3%), bleeding (6.4%), weight gain (6.4%), dissatisfaction with the study (5.6%), fear of participating in research (4.6%), and wishing to conceive (2.8%).

The number of bleeding days decreased by about one-third compared to the two run-in cycles [Table 1]. The calculation was based on the assumption that there would be 28.6 (4.4 x 6.5) days of withdrawal bleeding and 3.2 (0.5 x 6.5) days of breakthrough bleeding, yielding a total of 31.8 days of bleeding under a cyclic 21/7 regimen lasting for 182 days (i.e., during 6.5 cycles). This was compared to an expected total of 21.8 days of bleeding under a continuous regimen based on an average of the two extended cycles (totaling 182 days) with a mean of 9.7 (4.9 ± 4.8) days of withdrawal bleeding and 12.1 (7.0 ± 5.1) days of breakthrough bleeding.

The incidence of menorrhagia, intermenstrual bleeding, dysmenorrhea, abdominal bloating, breast tenderness, depressive moods and irritability – at enrollment compared with the end of the second extended study period – was significantly lower ($P < 0.005$) among women under the continuous pill regimen [Table 2]. There was no significant change in body weight during the study period: the mean weight of the cohort had been 60.0 ± 10.1 kg at enrollment, 60.3 ± 10.2 kg after the two run-in 21/7 day cycles, 60.7 ± 12.7 kg after the first extended contraceptive cycle, and 59.3 ± 16.6 kg after the second extended contraceptive cycle. However, while 20 of the participants gained 2 kg or more from enrollment to the completion of the study, only 11 women lost 2 kg or more during the same period. The participants' skin condition did not change markedly during the study period, with 84.7% reporting no difference, 9.7% reporting improvement and 5.6% reporting worsening, at the end of the study.

Table 1. Number of days of bleeding during the various phases of the study (run-in 21/7 cycles)

Duration of withdrawal bleeding (mean ± SD) (n=102)	4.4 ± 1.2 days
Breakthrough bleeding	
During the first 21 day cycle	5.8% (6/103)
During the second 21 day cycle	2.9% (3/103)
During both 21 day cycles	9.7% (10*/103)
Duration (average number of days)	0.5 ± 2.2 days
After first extended contraceptive cycle	
Duration of withdrawal bleeding (mean ± SD) (n=85)	4.9 ± 2.3 days
Breakthrough bleeding	52.8% (47/89)
Range	1–45 days
≥ 10 days	28.1% (25/89)
Mean ± SD of all patients (n=88)	7.0 ± 10.1 days
Mean ± SD of patients reporting breakthrough bleeding (n=47)	13.5 ± 10.5 days
After second extended contraceptive cycle	
Duration of withdrawal bleeding (mean ± SD) (n=68)	4.8 ± 1.6 days
Breakthrough bleeding	43.7% (31/71)
Range	1–49 days
≥ 10 days	18.3% (13/71)
Mean ± SD of all patients (n=71)	5.1 ± 9.5 days
Mean ± SD of patients reporting breakthrough bleeding (n=28)	12.4 ± 11.6 days

* One patient did not specify cycle

Seventy-three patients completed the PGWBI questionnaire. The median (range) global PGWBI scores were not substantially different before and after the extended-use cycles: 78.2 (39.1–96.4) and 77.3 (30.9–96.4) respectively. The scores for the six PGWBI mood states are presented in Table 3.

After the first extended contraceptive cycle, 44.8% of the women were highly satisfied and 28.7% were satisfied with the extended regimen. This high satisfaction rate was slightly less at the completion of the study: 65.5% of the women were either highly satisfied (41.4%) or satisfied (24.1%) with the extended regimen.

DISCUSSION

The present study has shown that the extended 84/7 use of combined oral contraceptives, omitting the hormone-free interval, has a favorable effect on several parameters. According to our results it substantially reduces the frequency of withdrawal bleeding, with a decrease of about one-third in the number of bleeding days compared to the two 21/7 run-in cycles. This regimen also reduced the amount of intermenstrual bleeding.

Bleeding patterns have been addressed in several studies [5,8,14-16], most of which showed no difference between groups, or less bleeding and/or spotting with continuous use of the contraceptives. Coutinho and co-authors [14] reported a mean of 10.7 fewer total bleeding days in the continuous group. Anderson and Hait [15] evaluated bleeding patterns over the entire 364 day study period and reported no significant difference between groups for the mean bleeding plus spotting days, although the continuous arm had fewer bleeding days. Cachrimanidou et al. [16] analyzed the bleeding pattern during the withdrawal week separately and found that it was decreased for the 70 day cycle compared to the 28 day cycle, but that the mean number of bleeding and spotting days was higher in the extended-cycle group. In a recent study, Legro and team [5] did not find any difference in the number of bleeding days between the continuous versus cyclic regimen, although they did observe that there were fewer moderate to heavy bleeding days.

A methodologic limitation of the present study is related to the fact that the two 21/7 cycles preceded the two extended 84/7 oral contraceptive cycles without a "washout period" between the two regimens. As it is well recognized that the number of bleeding days tends to decrease with duration of oral contraceptive use, this may have biased our findings to some extent. However, since our study population of young women was in constant need of a highly effective contraception, and considering the more limited compliance with backup methods (mainly the male condom), we were concerned that a prolonged "washout period" between the two study periods would expose the participants to an unacceptably high risk for unwanted pregnancies. Therefore, we decided that such a "washout period," although fulfilling an apparent methodologic need, would be unfeasible from an ethical point of view.

Dysmenorrhea, heavy bleeding, menorrhagia, abdominal bloating, breast tenderness, irritability and depressive mood were all less common in our study participants who followed the continuous pill regimen. Our search of the literature yielded only one randomized controlled trial that addressed menstrual pain, that of Kwiecien et al. [8] who showed that women in the continuous group are less likely to report menstrual pain. Cachrimanidou et al. [16] reported no improvement in dysmenorrhea.

Few studies have addressed the issue of continuous contraceptive use and other menstruation-associated symptoms. Our study findings showed an improvement in irritability and depression. Cachrimanidou et al. [16] reported a beneficial effect for headaches, but no improvement in any other menstruation-associated symptoms. Legro and colleagues [14] recently demonstrated that the continuous regimen is associated with improved premenstrual but not menstrual or intermenstrual related symptoms compared to a cyclic regi-

Table 2. Symptoms and side effects reported during the various phases of the study

	At enrollment		Start of first extended period		End of first extended period		End of second extended period	
Total no. of women	109		103		86		72	
Intensity of bleeding								
Weak	14	12.84%	24	23.30%	23	26.74%	28	38.89%*
Normal	64	58.72%	70	67.96%	52	60.47%	38	52.78%
Heavy	31	28.44%	9	8.74%	11	12.79%	6	8.33%*
Intermenstrual bleeding								
Yes	87	79.82%	13	12.62%	42	48.84%	31	43.06%*
No	22	20.18%	90	87.38%	44	51.16%	41	56.94%
Dysmenorrhea								
No	33	30.28%	60	58.25%	53	61.63%	48	66.67%*
Light	26	23.85%	36	34.95%	23	26.74%	19	26.39%
Strong	50	45.87%	7	6.80%	10	11.63%	5	6.94%*
Abdominal bloating								
No	48	44.04%	65	63.11%	59	68.60%	57	79.17%*
Light	32	29.36%	25	24.27%	16	18.60%	7	9.72%
Moderate	27	24.77%	12	11.65%	9	10.47%	7	9.72%
Strong	2	1.83%	1	0.97%	2	2.33%	1	1.39%
Breast tenderness								
No	64	58.72%	78	75.73%	65	75.58%	61	84.72%*
Light	26	23.85%	11	10.68%	11	12.79%	6	8.33%
Moderate	15	13.76%	6	5.83%	9	10.47%	5	6.94%
Strong	4	3.67%	8	7.77%	1	1.16%	0	0.00%
Edema								
No	101	92.66%	97	94.17%	80	93.02%	70	97.22%#
Light	5	4.59%	6	5.83%	3	3.49%	0	0.00%
Moderate	3	2.75%	0	0.00%	2	2.33%	2	2.78%
Strong	0	0.00%	0	0.00%	1	1.16%	0	0.00%
Depressive moods								
Never	69	63.30%	77	74.76%	70	81.40%	60	83.33%*
Rare	6	5.50%	10	9.71%	6	6.98%	4	5.56%
Occasionally	17	15.60%	10	9.71%	6	6.98%	6	8.33%
Often	17	15.60%	6	5.83%	4	4.65%	2	2.78%
Irritability								
Never	53	48.62%	68	66.02%	64	74.42%	57	79.17%*
Rare	5	4.59%	12	11.65%	9	10.47%	5	6.94%
Occasionally	21	19.27%	13	12.62%	9	10.47%	4	5.56%
Often	30	27.52%	10	9.71%	4	4.65%	6	8.33%

Statistical significance comparing the incidence of the symptoms and side effects at enrollment compared with the end of the second extended period.

* $P < 0.005$

Not significant

Table 3. Mood state as determined using the Psychological General Well-Being Index before and after the extended use cycles

	The median (range) adjusted PGWBI scores	
	Before extended cycles	**After extended cycles**
Anxiety	80.0 (24.0-100)	76.0 (32.0-100)
Depression	93.3 (46.7-100)	93.3 (46.7-100)
Well-being	65.0 (30.0-100)	70.0 (30.0-100)
Self-control	93.3 (26.7-100)	93.3 (46.7-100)
Global health	86.7 (40.0-100)	86.7 (46.7-100)
Vitality	70.0 (30.0-100)	70.0 (25.0-95.0)
Global	78.2 (39.1-96.4)	77.3 (30.9-96.4)

men. Coffee and associates [17] concluded that a continuous regimen of oral contraceptives diminishes premenstrual-like symptoms measured both by the S&W mood scale and the DSR 17 instrument, with the greatest improvement detected during the sixth month of continuous oral contraceptives.

Although oral contraceptives are thought to have an effect on skin condition [18], 85% of our subjects noticed no change: it reportedly deteriorated in 5% of them and improved in nearly 10%.

The most common reasons given for discontinuation were motivational (i.e., loss of interest, attitude towards study participation, and wishing to conceive). Side effects from the tablets themselves comprised a relatively minor reason for quitting (e.g., bleeding and weight gain – 6.4% each).

Two other important issues were addressed in the present study: weight gain and general well-being. Although it is commonly believed that the initiation of oral contraceptives may be followed by water retention and slight weight gain, no significant change in body weight was observed throughout the study period. We also prospectively evaluated menstrual symptoms following extended use of oral contraceptives and demonstrated that they seemed to improve with continuous dosing and that the user satisfaction rate was high.

It was recently suggested that since quality of life is one of the least explored factors in oral contraceptive users, more studies should investigate the impact of oral contraceptives on quality of life and general well-being in this overall healthy population [20]. The PGWBI is a well-recognized questionnaire of general well-being that was developed to provide an instrument for measuring subjective well-being or psychological distress [13]. It is widely used and well validated [21], having been validated in 32 languages, including Hebrew and Russian, both of which were used in the present study. The PGWBI was chosen as an especially suitable measure of subjective well-being and psychological distress since it covers relevant aspects of the emotional changes linked to hormonal fluctuations, such as depressive mood, anxiety, irritability and lack of energy. Two previous studies reported a beneficial effect on psychological general well-being, as measured by the PGWBI after six cycles of treatment with the same hormone combination used in the present study [19,20]. We assessed the psychological well-being by comparing PGWBI scores before and after the extended use cycles, but found no significant changes in the global, as well as six mood PGWBI scores. In conclusion, the findings of this study show that continuous contraceptive usage has several advantages over the cyclic regimen.

Acknowledgments:
We would like to thank Mrs. Pessia Perssi for her efforts as the research coordinator. Esther Eshkol is thanked for editorial assistance. This study was partially funded by an unrestricted research grant given by the Israeli subsidiary of Bayer Schering AG, Berlin, Germany.

Corresponding author:
Dr. D. Seidman
Dept. of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2697
Fax: (972-3) 604-4146
email: dseidman@tau.ac.il

References

1. Clarke AK, Miller SJ. The debate regarding continuous use of oral contraceptives. *Ann Pharmacother* 2001; 35: 1480-4.
2. MacGregor A. Migraine associated with menstruation. *Funct Neurol* 2000; 15: 143-53.
3. Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. *Fertil Steril* 2003; 80: 560-3.
4. Vercellini P, De Giorgi O, Mosconi P, Stellato G, Vicentini G, Crosignani PG. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. *Fertil Steril* 2002; 77: 52-61.
5. Legro RS, Pauli JG, Kunselman AR, et al. Effects of continuous versus cyclical oral contraception: a randomized controlled trial. *J Clin Endocrinol Metab* 2008; 93: 420-9.
6. Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. *Obstet Gynecol* 2001; 98: 771-8.
7. Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. *Obstet Gynecol* 2003; 101: 653-61.
8. 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* 2003 ;67: 9-13.
9. Sillem M, Schneidereit R, Heithecker R, Mueck AO. Use of an oral contraceptive containing drospirenone in an extended regimen. *Eur J Contrac Reprod Health Care* 2003; 8: 162-9.
10. Foidart JM, Sulak PJ, Schellschmidt I, Zimmermann D. Yasmin Extended Regimen Study Group. The use of an oral contraceptive containing ethinylestradiol and drospirenone in an extended regimen over 126 days. *Contraception* 2006; 73: 34-40.
11. Sulak PJ, Kuehl TJ, Coffee A, Willis S. Prospective analysis of occurrence and management of breakthrough bleeding during an extended oral contraceptive regimen. *Am J Obstet Gynecol* 2006; 195: 935-41.
12. 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 2006; 21: 573-8.

13. Dupuy HJ. The psychological general well-being (PGWB) index. In: Wenger NK, Mattson ME, Furberg CD, Elinson J, eds. Assessment of Quality of Life in Clinical Trials. New York, NY: Le Jacq Publishing Inc, 1984: 170-83, 353-6.
14. Coutinho EM, Barbosa IC, Zhi-Ping G, Shaaban MM, Aboul-Oyoon M, Aleem AH. Comparative study on intermittent versus continuous use of a contraceptive pill administered by vaginal route. *Contraception* 1995; 51: 355-8.
15. Anderson FD, Hait H. A multicenter randomized study of an extended cycle oral contraceptive. *Contraception* 2003; 69: 89-96.
16. Cachrimanidou AC, Hellberg D, Nilssen S, Waldenstrom U, Olssan SE, Sikstorm B. Long interval treatment regimen with a desogestrel-containing oral contraceptive. *Contraception* 1993; 48: 205-16.
17. Coffee AL, Huehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. *Am J Obstet Gynecol* 2006; 195: 1311-19.
18. Sabatini R, Orsini G, Cagiano R, Loverro G. Noncontraceptive benefits of two combined oral contraceptives with antiandrogenic properties among adolescents *Contraception* 2007; 76: 342-7.
19. Borges LE, Andrade RP, Aldrighi JM, et al. Effect of a combination of ethinylestradiol 30 microg and drospirenone 3 mg on tolerance, cycle control, general well-being and fluid-related symptoms in women with premenstrual disorders requesting contraception. *Contraception* 2006; 74: 446-50.
20. Apter D, Borsos A, Baumgartner W, et al. Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms. *Eur J Contracept Reprod Health Care* 2003; 8: 37-51.
21. Wiklund I, Holst J, Karlberg J. A new methodological approach to the evaluation of quality of life in postmenopausal women *Maturitas* 1992; 14: 211-24.