Original research article

Double-blind, multicenter comparison of efficacy, cycle control, and tolerability of a 23-day versus a 21-day low-dose oral contraceptive regimen containing 20 μg ethinyl estradiol and 75 μg gestodene

J. Endrikat a,* , M. Cronin a , C. Gerlinger a , A. Ruebig a , W. Schmidt b , B. Düsterberg a

a Schering AG, Müllerstr. 178, D-13342 Berlin, Germany
b Universitätskliniken des Saarlandes, Frauenklinik und Poliklinik, D-66421 Homburg/Saar, Germany

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Abstract

This prospective, double-blind, randomized study was conducted to compare the contraceptive reliability, cycle control, and tolerability of a 23-day versus a 21-day oral contraceptive regimen containing 20 μg ethinyl estradiol and 75 μg gestodene. Participants took trial medication daily for 28 days, either 23 tablets with active substances plus 5 placebo tablets or 21 tablets with active substances plus 7 placebo tablets. Contraceptive efficacy, cycle control, and tolerability were evaluated over a period of seven cycles. Efficacy data gathered from 4,878 treatment cycles (23-day regimen: 2,362 cycles; 21-day regimen: 2,516 cycles) were obtained from 703 participants (23-day regimen, n = 342; 21-day regimen, n = 361).

Both preparations proved to be effective contraceptives and provided good cycle control. One pregnancy because of method failure was recorded in each treatment group. This resulted in a study Pearl Index of 0.5 for each treatment. For the 23-day regimen, 36.0% of participants reported at least one intracyclic bleeding episode during Cycles 2–4 (primary target) compared to 37.1% in the 21-day regimen. In the 23-day regimen group, intracyclic bleeding episodes were reported by 42.4% of the participants in Cycle 1 but only in 14% in Cycle 7 and in the 21-day regimen group by 44.6% in Cycle 1 and only 17.3% in Cycle 7. Overall, intracyclic bleeding was reported in 21.9% of the 23-day regimen cycles and in 22.7% of the 21-day regimen cycles.

A greater number of 23-day regimen participants had shorter withdrawal bleeding periods than with the 21-day regimen. In significantly (p <0.0001) more cycles in the 23-day regimen group, participants reported withdrawal bleeding periods that lasted only 1–4 days compared to the 21-day regimen group. For the majority of the treatment cycles, the median number of bleeding days in the 23-day regimen group was 4 days and in the 21-day regimen group 5 days.

Both preparations were well tolerated and showed a similar adverse events pattern. The discontinuation rate because of adverse events was low (23-day regimen, 6%; 21-day regimen, 4%). No serious vascular adverse events were reported. More than 75% of the women in both groups either lost more than 2 kg of weight or did not gain weight during the study. The treatment effect on blood pressure was negligible. There were no appreciable changes in mean laboratory values over the course of the study. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

In the past few years, extensive clinical data has been collected on low-dose oral contraceptives (OCs) containing 20 μg ethinyl estradiol, particularly in combination with gestodene [1–5]. Despite some initial doubts about reducing the estrogen dose to this level, it has become an established fact that 20 μg ethinyl estradiol, in combination with gestodene, desogestrel, or levonorgestrel provides effective contraceptive protection [1–3,6,7]. Although the cycle control efficacy of these preparations has been questioned, clinical experience suggests that cycle control, particularly after an initial phase of adaptation, is generally acceptable. Nevertheless, innovations that optimize the cycle control of these low-dose preparations most likely will increase compliance and benefit users.

Modification of the dosage regimen could be one approach to reduce the frequency of intracyclic bleeding. In
the present study, we investigated the effect of prolongation of treatment from 21 to 23 days, while shortening the hormone-free interval from 7 to 5 days, on the length of withdrawal bleeding periods and on intracyclic bleeding rates. Moreover, we examined whether the reduction in hormone concentration fluctuations with this new regimen led to improvement in the general tolerability of the preparation. As shown in a previous study, the prolongation of the intake phase significantly increased the degree of suppression of ovarian follicle development and resulted in lower 17β-estradiol serum levels.

2. Materials and methods

In the present study, we compared contraceptive efficacy, cycle control, and tolerability of a 23-day versus a 21-day OC regimen containing 20 μg ethinyl estradiol/75 μg gestodene. The study was conducted as a phase III, multicenter, double-blind, randomized, study in three European countries over a period of seven treatment cycles. This prospective study was carried out from November 1994 to April 1998 at 32 centers in Denmark, the Netherlands, and Germany. The study protocol was reviewed and approved by all appropriate ethics committees.

The investigators recruited a total of 832 healthy 18–35 year old participants to the study, who requested contraception for at least 7 months. A total of 806 participants (4878 year old participants) to the study, who requested contraceptives during the 6 months before the study began, specified concurrent diseases, vaginal bleeding of unknown origin, and a history of dysmenorrhea were included in the study. The participants were questioned about their general health during the treatment cycles 3 and 7, and in the follow-up phase of the study. In the follow-up phase the participants were re-questioned about their general health during the treatment cycle. Medical and gynecological examinations, including a Papanicolaou smear and routine laboratory examinations, were repeated at the end of the study.

Bleeding patterns were documented by the participants throughout the study on a daily basis in individual diaries. If withdrawal bleeding failed to occur, a human chorionic gonadotropin (HCG) test was performed to exclude pregnancy before the treatment was continued. Pregnancies and all conditions during the preceding treatment cycles that might have impaired the reliability of contraceptive protection were noted.

Intracyclic bleeding during treatment Cycles 2–7 was defined as all vaginal bleeding occurring between cycle day 4 through cycle day 21 for 21-day regimen and between cycle day 6 through cycle day 23 for 23-day regimen. Therefore, the intracyclic bleeding assessment period was 17 days for both regimens. Intracyclic bleeding was assessed as either “spotting,” bleeding not requiring sanitary protection, or “normal/excessive breakthrough bleeding,” bleeding requiring sanitary protection. The incidence of spotting and normal/excessive breakthrough bleeding and the occurrence of amenorrhea (missed withdrawal bleeding) and dysmenorrhea were included in the efficacy analyses.

All unfavorable changes in the participant’s condition were defined as adverse events and were recorded. The protocol included a list of adverse events that required study withdrawal. These included pregnancy and any evidence for an increased thrombotic risk. Treatment compliance, including a record of missed tablets, was monitored on a menstrual chart and was assessed by the investigator at each of the planned study visits.

2.1. Statistical methods

Statistical analyses were performed on both the “intention-to-treat” (ITT) and the “valid case” (VC) populations. All randomized participants who took at least one dose of the study medication were included in all ITT population analyses. All of the data from volunteers who had a major protocol deviation were excluded from the VC population analyses.

The study primary target variable was the percent of participants who had at least one intracyclic bleeding episode from the 2nd to the 4th treatment cycle. The null hypothesis that the probability of the occurrence of at least one intracyclic bleeding episode under the 23-day regime is
not less than that under the 21-day regimen during the 2nd, 3rd, and 4th pill-taking cycles was tested against its alternative that this probability under the 23-day regimen is less than that under the 21-day regimen. The null hypotheses was tested by using a Fisher’s exact test at a significance level $\alpha$ of 5%.

The Pearl Index was calculated as 1300 times the number of pregnancies divided by the number of cycles. All pregnancies were included in the calculation, regardless of user failure. However, the study Pearl Indexes calculated should be interpreted with caution because the precision of the indexes is limited due to the sample size of the study.

Also, an exploratory test comparing the length of withdrawal bleeding periods for Cycles 1–6 was performed for the two treatment groups. Cycle 7 was excluded because start of poststudy medication prohibited correct determination of length of the last withdrawal bleeding period. For each participant the number of short withdrawal bleeding periods, i.e. those lasting 1–4 days, was determined. Because not all participants provided data for the same number of cycles, the percentage of cycles with short withdrawal bleeding periods was computed per participant. The null hypothesis that median of this variable is equal for the two regimens was tested against its alternative of inequality with a two-sided Wilcoxon rank sum test at a significance level $\alpha$ of 5%.

3. Results

Of the 832 participants randomized, 806 received medication as either a 23-day regimen ($n = 395$; 2533 cycles) or a 21-day regimen ($n = 411$; 2670 cycles). Major protocol violations, such as not meeting inclusion criteria (age >40 years, obesity, excessive smoking, incorrect wash-out cycle for women switching from another OC), prohibited co-medication intake or violation of the treatment schedule (irregular pill-intake) were recorded in 103 volunteers. The data from these participants were only included in the ITT analysis. The data from 703 participants were included in the VC analyses [23-day regimen, $n = 342$ (2362 cycles); 21-day regimen, $n = 361$ (2516 cycles)]. The demographic characteristics of both treatment groups were well matched at baseline, as shown in Table 1.

3.1. Contraceptive efficacy

In each treatment group, one participant became pregnant during the study medication phase. In the 23-day regimen group, one participant experienced vaginal bleeding and was hospitalized for evacuation. Fetal material was not found, but an “Arias-Stella-Phenomenon,” a histomorphological correlate typical either for an abortion or ectopic pregnancy, was described by the consulting pathologist. The participant’s ensuing $\beta$-HCG blood tests declined rapidly from 40 to 0 IU/L. The investigator evaluated the incident as a spontaneously reabsorbed ectopic pregnancy. Also, a participant in the 21-day regimen group became pregnant during the second treatment cycle. Both pregnancies were assessed as method failures. Based on this data, study Pearl Indices of 0.5 were calculated for each treatment.

3.2. Cycle control

Cycle control was good in both treatment groups. The cumulative percent of participants with any intracyclic bleeding episodes (spotting and/or breakthrough bleeding) from Cycle 2 to 4 (primary target) was 36.0% for the 23-day regimen and 37.1% for the 21-day regimen (Fig. 1). This difference (1.1%) was not significant ($p = 0.4055$). The cumulative intracyclic bleeding rates for Cycles 2–7 and 1–7 were similar (Fig. 1).

As the trial progressed, the percent of 23-day regimen participants with any intracyclic bleeding decreased from 42.4% in Cycle 1 to 14% in Cycle 7, and for the 21-day regimen participants from 44.6% to 17.3%, respectively (Fig. 2). Overall, in 21.9% of the 23-day regimen cycles and in 22.7% of the 21-day regimen cycles, intracyclic bleeding was reported.

The results for spotting were very similar to those for any intracyclic bleeding: 21.3% (23-day regimen) and 22% (21-day regimen) of all cycles were affected. In about 6% of all treated cycles in both groups, normal/excessive intracyclic bleeding was recorded.

In each treatment cycle, a greater number of 23-day regimen participants had shorter withdrawal bleeding periods, lasting 1–4 days, than in the 21-day regimen group. At baseline (pretreatment cycle), 42% of the participants in both treatment groups reported withdrawal bleeding periods that lasted between 1 and 4 days. The percent of participants with withdrawal bleeding periods that lasted 1–4 days increased to 60% in the 23-day regimen group during treatment (Fig. 3). Short withdrawal bleeding periods (1–4 days) were reported in 55.1% cycles treated with the 23-day regimen and in 43.2% of the cycles in the 21-day regimen. An exploratory analysis of the data showed that this differ-
The incidence of long withdrawal bleeding periods of >7 days or amenorrhea (0 days) was negligible in both groups (Fig. 4).

In the majority of the treatment cycles, the median number of bleeding days was 4 days in the 23-day regimen group and 5 days in the 21-day regimen group (Fig. 5).

Both treatments relieved symptoms of dysmenorrhea: 58.2% (23-day regimen) and 56% (21-day regimen) of participants with dysmenorrhea at baseline showed improvement.

3.3. Tolerability

A total of 113 participants discontinued the study (23-day regimen, n = 64; 21-day regimen, n = 49) for various reasons. Twenty-four (6%, 23-day regimen) and 16 (4%, 21-day regimen) participants discontinued the study because of adverse events (mainly headache, breast tension, and nausea). In addition to these events, other specific reasons for discontinuation included desire to have children, change of address, lack of efficacy, and loss to follow-up. The overall incidence of adverse events reported during the trial was low in both groups, as shown in Table 2. The most frequent events in the 23-day regimen and 21-day regimen group were headache (15.7% vs. 16.3%, respectively), breast tension (7% in both groups), and nausea (5.1% vs. 4.4%, respectively). Other adverse events occurred in less than 5% of participants.

In each treatment group, three serious (nonvascular) adverse events were reported. Only one case (spontaneously reabsorbed ectopic pregnancy) was considered by the investigator to be probably study drug related; all others were assessed by the investigators as not being related to the OC intake.

The mean study group blood pressure values (systolic: 117 mm Hg, diastolic: 72 mm Hg) did not noticeably change during treatment. However, slightly more participants had an increase of >10 mm Hg at the end of study (systolic: 23-day regimen 10.6%, 21-day regimen 11.4%; diastolic: 23-day regimen 8.1%, 21-day regimen 6.3%) than those with a decrease of >10 mm Hg (systolic: 23-day regimen 8.9%, 21-day regimen 8.5%; diastolic: 23-day regimen 6.3%, 21-day regimen 5.1%).

Body weight remained constant throughout the trial for
most participants in both treatment groups. More than 75% of the participants in both groups either maintained constant body weight (± 2 kg) or lost weight.

Neither appreciable changes in mean laboratory values over the course of the study nor remarkable differences in the laboratory values between the two treatment groups were found.

4. Discussion

These study results indicate that both the 23-day and the 21-day 20 μg ethinyl estradiol/75 μg gestodene regimens provide reliable contraception and good cycle control. A large data pool that is available for the 21-day regimen substantiates these findings [1–3,5].

In each treatment group, one pregnancy because of method failure was reported. This resulted in an uncorrected study Pearl Index of 0.5 for each treatment. It should be noted that the total number of cycles in this single study was only about one quarter of the number required to calculate a reliable estimate of the Pearl Index. However, interesting findings on ovulation inhibition of the 23-day versus the 21-day regimen were reported by Spona et al. [8]. He found superior ovarian suppression with the 23-day compared to the 21-day regimen. He claimed that shortening the pill-free interval could increase the contraceptive safety margin in women who use low-dose formulations. This slightly superior ovarian activity suppression might not be highly relevant for compliant users, but could be of particular importance for women who tend to miss at least two pills per cycle.

Although the intracyclic bleedings incidences for both regimens were equally low, we found that withdrawal bleeding periods were shorter with the 23-day regimen. Significantly (p <0.0001) more cycles where short withdrawal bleeding periods of 1–4 bleeding days were reported for the 23-day regimen compared to the 21-day regimen. In the majority of 23-day regimen treatment cycles, the median number of bleeding days was 4 days and in the 21-day regimen group 5 days. We believe that the shorter withdrawal bleeding periods would be welcomed by users, especially by those who suffer from heavy and profuse withdrawal bleeding periods. Additionally, blood loss is reduced

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**Fig. 3.** Percent of participants with 1–4 withdrawal bleeding days (23-day regimen: n = 321; 21-day regimen: n = 352).

**Fig. 4.** Length of withdrawal bleeding (% of Cycles 1–6) (23-day regimen: 2012; 21-day regimen: 2149).
and iron deficiency might be less frequent. Similar findings were reported by the Gestodene Study Group 324 [9]. This group investigated a 24-day regimen with 15 μg ethinyl estradiol/60 μg gestodene compared to a 21-day regimen of 20 μg ethinyl estradiol/150 μg desogestrel. Those findings also showed significantly shorter withdrawal bleeding period lengths, significantly lower bleeding intensity, and a significantly shorter time of onset of the withdrawal bleeding period in the pill-free interval with the prolonged intake regimen. Because the preparations used in that study were different in two variables (gestodene versus desogestrel, and 15 μg versus 20 μg ethinyl estradiol), it is difficult to assess the extent the prolongation of the intake regimen had on their results. Nevertheless, the Gestodene Study Group [9,10] provided evidence that prolongation of length of intake might facilitate additional ethinyl estradiol and progestin dose reductions.

Virtually no differences between treatment groups were found in the safety parameters measured in the study (i.e. gynecological status, blood pressure, body weight, and laboratory parameters). Overall, 75% of participants in both groups maintained their body weight or lost weight during the seven treatment cycles. Clinically relevant differences between the two regimens in the tolerability analysis were not found. Therefore the hypothesis that reduced hormone concentration fluctuations in the regimen with a shorter pill-free interval could improve tolerability was not substantiated. At the same time, obvious increases in the frequency of adverse events because of the prolongation of the intake phase were not found.

In conclusion, both the 23-day and the 21-day low-dose OC regimen (20 μg ethinyl estradiol/75 μg gestodene) provided reliable contraception, acceptable cycle control, and good tolerability. We found that the length of withdrawal bleeding period with the 23-day regimen was favorably shortened. The superior ovarian suppression of this regimen was investigated in another study [8]. Additional studies with prolonged intake regimens should examine whether this could be particularly advantageous for women who tend to miss tablet intake.

Overall, these results indicate that the development of prolonged intake regimens for OCs is a promising option to further improve the acceptance of this modern form of contraception.

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**References**


