Open, multicenter comparison of efficacy, cycle control, and tolerability of a 23-day oral contraceptive regimen with 20 μg ethinyl estradiol and 75 μg gestodene and a 21-day regimen with 20 μg ethinyl estradiol and 150 μg desogestrel

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Abstract

This prospective, open, randomized study was conducted to compare the contraceptive reliability, cycle control, and tolerability of a 23-day regimen with 20 μg ethinyl estradiol (EE) and 75 μg gestodene (GSD) and a 21-day regimen with 20 μg EE and 150 μg desogestrel (DSG). Participants took either 23 tablets with active substances plus 5 placebo tablets (23-day EE/GSD) or 21 tablets with active substances followed by 7 days without pill-taking (21-day EE/DSG). Contraceptive efficacy, cycle control, and tolerability were evaluated over a period of seven cycles. Efficacy data gathered from 5967 treatment cycles (23-day EE/GSD: 2975 cycles; 21-day EE/DSG: 2992 cycles) were obtained from 890 participants (445 in each group).

Both preparations proved to be effective contraceptives and provided good cycle control. No pregnancy during treatment was recorded. This resulted in a study Pearl Index of 0.0 for both treatments. For 23-day EE/GSD, 32.4% of participants reported at least one intracyclic bleeding episode during Cycles 2–4 (primary target) compared to 31.5% for 21-day EE/DSG. In the 23-day EE/GSD group, intracyclic bleeding episodes were reported by 48.8% of the participants in Cycle 1 but in only 15.1% in Cycle 7, and in the 21-day regimen group by 43.4% in Cycle 1 and only 14.2% in Cycle 7. Overall, intracyclic bleeding was reported in 20.9% of cycles for both treatments.

A greater number of 23-day EE/GSD participants had shorter withdrawal bleeding periods than with 21-day EE/DSG. In significantly (p < 0.0001) more cycles in the 23-day EE/GSD group participants reported withdrawal bleeding periods that lasted only 1–4 days compared to the 21-day EE/DSG group. For the majority of the treatment cycles, the median number of bleeding days in the 23-day EE/GSD group was 4 days and in the 21-day EE/DSG 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 EE/GSD: 6.1%; 21-day EE/DSG: 5.6%). No serious vascular adverse events were reported. More than 82% in the 23-day EE/GSD group and 79% in the 21-day EE/DSG group 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 compared to baseline. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Oral contraceptives; Ethinyl estradiol; Gestodene; Desogestrel cycle control; 23-day regimen

1. Introduction

In the past few years, extensive clinical data have been collected on low-dose oral contraceptives (OCs) containing 20 μg ethinyl estradiol (EE), particularly in combination with gestodene (GSD) [1–5]. Despite some initial doubts about reducing the estrogen dose to this level, it has become an established fact that 20 μg EE, in combination with GSD, desogestrel, or levonorgestrel, provides effective contraceptive protection [1–3, 6–8]. 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 application regimen could be one approach to reduce the frequency of intracyclic bleeding. In the present study, we investigated the effect the prolongation of treatment from 21 to 23 days while shortening the hormone-free interval from 7 to 5 days had 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 [9].

2. Materials and methods

In the present study, we compared contraceptive efficacy, cycle control, and tolerability of a 23-day regimen with 20 μg EE and 75 μg GSD and a 21-day regimen with 20 μg EE and 150 μg desogestrel (DSG). The study was conducted as a phase III, multicenter, double-blind, randomized, study in six European countries over a period of seven treatment cycles. This prospective study was carried out from August 1994 to December 1997 at 67 centers in Austria, Belgium, France, Italy, Switzerland, and United Kingdom. The study protocol was reviewed and approved by all appropriate ethics committees.

The investigators recruited a total of 1,059 healthy, 18–35-year-old participants to the study, who requested contraception for at least 7 months. A total of 890 participants (5,967 treatment cycles) provided data for the efficacy analysis. New OC users and participants who wanted to change their OC regimen (switchers) were included in the study. The switchers had to observe at least one OC-free wash-out cycle prior to intake of study medication. Other exclusion criteria were the established OC intake contraindications, vaginal bleeding of unknown origin, and a history of contraceptives during the preceding treatment cycles which 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 6 through cycle day 23 for 23-day EE/GSD and between cycle day 4 through cycle day 21 for 21-day EE/DSG. 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 menstruation 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.
hypothesis that the probability of the occurrence of at least one intracyclic bleeding episode under the 23-day regimen 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 planned to be 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 the post-study 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 1101 participants randomized, 1059 received medication as either 23-day EE/GSD: (n = 526, 3241 cycles) or 21-day EE/DSG: (n = 533, 3312 cycles). Major protocol violations such as not meeting inclusion criteria (age $\geq 40$ 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 169 volunteers. The data from these participants were only included in the ITT analysis. The data from 890 participants were included in the VC analyses (23-day EE/GSD: n = 445, 2975 cycles; 21-day EE/DSG: n = 445, 2992 cycles). The demographic characteristics of both treatment groups were well matched at baseline, as shown in Table 1.

### 3.1. Contraceptive efficacy

No pregnancies, neither method nor participant failures, were reported in either group. Based on these data, study Pearl Indexes of 0.0 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 32.4% for 23-day EE/GSD and 31.5% for 21-day EE/DSG (Fig. 1). This difference (0.9%) was not significant ($p = 0.6404$). The cumulative intracyclic bleeding rates for Cycles 2–7 and 1–7 were similar (Fig. 1).

![Fig. 1. Any intracyclic bleeding (% of participants; 23-day EE/GSD: n = 418; 21-day EE/DSG: n = 417).](image-url)
As the trial progressed, the percent of 23-day EE/GSD participants with any intracyclic bleeding decreased from 48.8% in Cycle 1 to 15.1% in Cycle 7, and for 21-day EE/DSG participants from 43.4% to 14.2%, respectively (Fig. 2). Overall, in 20.9% of cycles in both treatment groups, intracyclic bleeding was reported. The results for spotting were very similar to those for any intracyclic bleeding: 19.6% (23-day EE/GSD) and 20% (21-day EE/DSG) of all cycles were affected.

In each treatment cycle, a greater number of 23-day EE/GSD participants had shorter withdrawal bleeding periods, lasting 1–4 days, than in the 21-day EE/DSG group. At baseline (pretreatment cycle), 35.2% (23-day EE/GSD) and 34.1% (21-day EE/DSG) 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 62% in the 23-day EE/GSD group during treatment (Fig. 3). Short withdrawal bleeding periods (1–4 days) were reported in 58.1% cycles treated with the 23-day EE/GSD and in 43.2% of the cycles treated with the 21-day EE/DSG. An exploratory analysis of the data showed that this difference was significant (p <0.0001). 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 in the 23-day EE/GSD group and 5 in the 21-day EE/DSG group (Fig. 5). Both treatments relieved symptoms of dysmenorrhea: 52.2% (23-day EE/GSD) and 48.7% (21-day EE/DSG) of participants with dysmenorrhea at baseline showed improvement.

3.3. Tolerability

A total of 272 participants discontinued the study (23-day EE/GSD, n = 145 (27.6%); 21-day EE/DSG, n = 127; 23.8%) for various reasons. Thirty-two (6.1%) 23-day EE/GSD and 30 (5.6%) 21-day EE/DSG 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 EE/GSD and 21-day EE/DSG group were headache (16.3% vs. 15.8%, respectively), breast tension (8.3% vs. 6.6%, respectively), and nausea (5.3% in both groups). Other adverse events occurred in less than 5% of participants.

Four serious nonvascular adverse events were documented for 23-day EE/GSD and three for 21-day EE/DSG. One case (dermoid cyst of the ovary) was considered as unlikely to be drug related by the investigator, and all others were considered as not related.

The mean study group blood pressure values (systolic: 115 mm Hg; diastolic: 71 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 EE/GSD 10.3%, 21-day EE/DSG 9.0%; diastolic: 23-day EE/GSD 6.3%, 21-day EE/DSG 6.0%) than those with a decrease of >10 mm Hg (systolic: 23-day EE/GSD 8.2%, 21-day EE/DSG 8.1%; diastolic: 23-day EE/GSD 3.2%, 21-day EE/DSG 5.4%).

Body weight remained constant throughout the trial for most participants in both treatment groups. More than 82% (23-day EE/GSD) and 79% (21-day EE/DSG) of the participants in both groups either maintained their initial 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 20 μg EE/75 μg GSD and the 21-day 20 μg EE/150 μg DSG preparations provide reliable contraception and good cycle control. A large data pool that is available for 21-day regimens of EE/GSD and EE/DSG substantiates these findings [1–3,5,8].

Pregnancies were not reported in this study, resulting in an uncorrected study Pearl Index of 0.0 for both treatment
Table 2

Percentages of subjects experiencing various adverse events for the first time during treatment (at least once)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>23-day EE/GSD (n = 526)</th>
<th>21-day EE/DSG (n = 533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16.3</td>
<td>15.8</td>
</tr>
<tr>
<td>Breast tension</td>
<td>8.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Depressive moods</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Change of libido</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Acne</td>
<td>2.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Edema</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Varicose complaints</td>
<td>0.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

groups. 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 23-day EE/GSD versus a 21-day regimen with EE/GSD were reported by Spona et al. [9]. He found superior ovarian suppression with the 23-day EE/GSD 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 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 bleeding incidences for both regimens were equally low, we found that withdrawal bleeding periods were shorter with the 23-day EE/GSD. Significantly (p <0.0001) more cycles with short withdrawal bleeding periods of 1–4 bleeding days were reported for the 23-day EE/GSD compared to the 21-day EE/DSG. In the majority of the 23-day EE/GSD treatment cycles, the median number of bleeding days was 4 and in the 21-day EE/DSG group it was 5. However, there were two variables making our treatment groups different: the duration of treatment and the progestin component. In a parallel study (data submitted for publication), we examined a 21- versus a 23-day EE/GSD preparation. The results were very similar to this study, indicating that the two different progestins were not a highly relevant factor for shortening withdrawal bleedings, but the different regimens were. We believe that the shorter withdrawal bleeding periods would be welcomed by users, most likely by those who suffer from heavy and profuse withdrawal bleeding periods. Additionally, blood loss is reduced and iron deficiency might be less frequent. Similar findings were reported by the Gestodene Study group 324 [10]. This group investigated a 24-day regimen with 15 μg EE/60 μg GSD compared to a 21-day regimen of 20 μg EE/150 μg DSG. 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. Thus, the Gestodene Study Group [10,11] also provided evidence that prolongation of length of intake might facilitate further EE and progesterone dose reductions.

Virtually no differences between treatment groups were found in the safety parameters measured in our study (i.e., gynecological status, blood pressure, body weight, and laboratory parameters). Overall, more than 82% (23-day EE/GSD) and 79% (21-day EE/DSG) 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 EE/GSD and the 21-day EE/DSG OC preparations provided reliable contraception, acceptable cycle control, and good tolerability. We found that the length of withdrawal bleeding period with 23-day EE/GSD was favorably shortened. The superior ovarian suppression of this regimen was investigated in another study [9]. 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


