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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

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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.

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

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

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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 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, the use of parenteral depot-contraceptives during the 6 months before the study began, specified concurrent diseases, vaginal bleeding of unknown origin, and a history of migraine accompanying menstruation. All participants gave informed consent prior to their participation in the trial.

Starting on the first day of withdrawal bleeding period, the participants received either 23 or 21 tablets of 20 μg ethinyl estradiol/75 μg gestodene followed either by 5 or by 7 placebos. The study medications were supplied in calendar packs. If a participant missed the scheduled intake time, she was instructed to take the tablet until up to 12 h after the scheduled time. All deviations from the specified intake regimen were recorded daily in a diary designed for this purpose.

Before treatment began, the participants underwent a thorough medical and gynecological examination including cervical cytology by the Papanicolaou method and exclusion of pregnancy. Also in the Netherlands and Germany, routine laboratory examinations (liver enzymes, hematologic parameters, lipids, creatinine, bilirubin, alkaline phosphatase, total protein and electrolytes) were carried out by vention and Diagnosis, Leiden; Germany: LKF, Laboratorium für Klinische Forschung, Lise-Meitner-Str. Kiel, Germany).

The participants were questioned about their cycle length and withdrawal bleeding patterns before being admitted to the study. Cycle control parameters, blood pressure, and body weight were recorded during the pretreatment cycle, treatment Cycles 3 and 7, and in the follow-up phase of the study. In the follow-up phase the participants were requestioned about their general health during the treatment phase. 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 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. The null hypothesis that the probability of the occurrence of at least

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 α 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 α 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 comedication 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 regime, n = 361 (2516 cycles)]. The demographic characteristics of both treatment groups were well matched at baseline, as shown in Table 1.

Table 1
Demographic characteristics at baseline

	23-day regimen (n = 395)	21-day regimen (n = 411)
Mean age (years)	25.2	25.2
[range]	[18–35]	[15–35]
Mean weight (kg)	64.0	64.5
[range]	[42–95]	[42–94]
Mean height (cm)	168.6	168.6
[range]	[149–195]	[152–186]
Smoking prevalence (% of subjects)	23.5	28.0
Prior OC use (% of subjects)	47.3	49.9
Subjects with regular cycles (%)	95.7	95.6
Median menstrual duration (days)	5	5
[range]	[1–11]	[2–10]

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 β-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-

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