FERTILITY AND STERILITY®
VOL. 72, NO. 1, JULY 1999

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

CONTRACEPTION

Effect of 21-day and 24-day oral contraceptive regimens containing gestodene (60 μg) and ethinyl estradiol (15 μg) on ovarian activity

Helen Sullivan, M.D., Hilary Furniss, M.B., Ch.B.,* Jurgen Spona, Ph.D.,† and Max Elstein, M.D.**

University of Manchester, Manchester, United Kingdom and Ludwig Boltzmann Institute for Experimental Endocrinology, University of Vienna, Vienna, Austria

Objective: To compare ovulation inhibition and ovarian activity with 21-day and 24-day regimens of a low-dose combined oral contraceptive (COC) containing 60 μg of gestodene and 15 μg of ethinyl estradiol.

Design: Interventional observational study.

Setting: Reproductive medicine unit.

Patient(s): Fifty-eight healthy volunteers aged 18–35 years.

Intervention(s): Ovarian activity was monitored every other day with the use of ultrasound to measure the diameters of follicle-like structures and blood samples to measure serum concentrations of 17β-E_2 and progesterone. Subjects were observed for five cycles: pretreatment and posttreatment control cycles and three cycles in which the COC was administered for either 21 or 24 days of each cycle.

Main Outcome Measure(s): Occurrence of ovulation and evidence of ovarian activity.

Result(s): The study was completed by 27 (90%) of the 30 subjects who received the 24-day regimen and by 24 (79%) of the 28 subjects who received the 21-day regimen. Ovulation was inhibited in all cycles in the 24-day group and in 74 of 75 cycles in the 21-day group. Luteinized unruptured follicles were seen in no cycles with the 24-day regimen and in 6 (8%) of 75 cycles with the 21-day regimen. Mean ovarian follicular development and serum 17β-E_2 and progesterone levels were lower in the 24-day group.

Conclusion(s): The 24-day regimen is an innovative strategy for maintaining effective ovulation inhibition at ultra-low doses of contraceptive steroids. (Fertil Steril® 1999;72:115–20. ©1999 by American Society for Reproductive Medicine.)

Key Words: Combined oral contraceptive, gestodene, ovulation inhibition, ultrasound

Received November 10, 1998; revised and accepted February 26, 1999.

Supported by Wyeth-Ayerst Research, Paris, France.

Reprint requests: Helen Sullivan, M.D., Department of Obstetrics, Gynaecology and Reproductive Healthcare, University of Manchester, Manchester, United Kingdom (FAX: 44-161-276-6134).

* Department of Obstetrics, Gynaecology and Reproductive Healthcare, University of Manchester.

† Department of Obstetrics and Gynaecology, Ludwig Boltzmann Institute for Experimental Endocrinology, Division of Cellular Endocrinology, University of Vienna, Vienna, Austria.

0015-0282/99/$20.00
PII S0015-0282(99)00205-8

Successive reductions in the estrogen and progestin doses have improved the risk-to-benefit ratio of combined oral contraceptives (COCs) (1, 2). Further reductions in the estrogen dose in combination with the lowest effective doses of the newer progestins have yet to be fully explored.

Preparations that contain 20 μg of ethinyl estradiol (EE) appear to suppress ovulation consistently in a traditional 21-day active pill regimen with a 7-day pill-free interval when combined with 150 μg of desogestrel or 75 μg of gestodene (3, 4). However, follicular development and circulating E_2 levels are greater during the pill-free interval compared with preparations that contain 30 μg of EE (5). This finding suggests that pill omission might lead more readily to ovulation and contraceptive failure (3). Reduction of the pill-free interval to 5 days with a preparation that contains 20 μg of EE and 75 μg of gestodene is associated with reduced ovarian activity compared with a conventional regimen with a 7-day pill-free interval (6). This finding suggests that a reduced pill-free interval may improve the margin of contraceptive safety with the use of low-dose preparations in susceptible women.

We examined the effects of further reductions in the estrogen and progestin doses on ovarian activity using an ultra–low-dose COC with 15 μg of EE and 60 μg of gestodene and a regimen with a 4-day pill-free interval. These

doses of EE and gestodene were investigated because, even with an extra 4 days of active treatment in each 28-day cycle, they represented a significant dose reduction compared with preparations that contain 20 μg of EE and 75 μg of gestodene.

MATERIALS AND METHODS

Two open-label studies were conducted in healthy women to assess the effects on ovarian activity of COC regimens of 21 and 24 days of treatment in each 28-day cycle with formulations that contained 60 μg of gestodene and 15 μg of EE. A randomized, double-blind design was not considered feasible. There would have been logistical problems in investigating this number of volunteers in one study in a relatively small reproductive medicine unit. We also believed, on the basis of our experience, that it would be apparent to the investigators which regimen each woman was taking. Because of the intensity of the schedule of visits (>70 in 5 months), we believed that an open, candid approach would enhance our relationship with the volunteers needed to perform such a study.

The studies were conducted according to the Declaration of Helsinki guidelines and with the approval of our institutional review board. Written informed consent was obtained from all participants.

Study Subjects

Healthy women who were 18–35 years old, were within 20% of the upper limit of normal weight, and smoked <10 cigarettes per day were eligible to participate in the study. All subjects had three regular (25- to 31-day) menstrual cycles before the start of the pretreatment cycle. All subjects were required to use a medically acceptable nonhormonal form of contraception during the study.

Subjects were excluded from the study if they had a history of or the presence of any medical condition known to be a risk factor for adverse events associated with COCs. Women who had a history of previous failure of an OC, a serious adverse experience with previous OC use, or undiagnosed genital bleeding within the previous 6 months also were excluded. No subject was allowed to use any other hormone or any other concomitant medication that could interfere with study assessments. All women had normal routine blood tests and cervical smear test results at the start of the study. Only women who ovulated in the pretreatment control cycle were eligible to start treatment. Three subjects in the 21-day group and one in the 24-day group failed to fulfill entry requirements.

Study Design

Each subject was scheduled to be monitored over five cycles: a pretreatment cycle to establish ovulation, three treatment cycles, and a posttreatment cycle to document the return of ovulation. The treatment for each subject was a COC that contained 60 μg of gestodene and 15 μg of EE given either for 21 days with a 7-day pill-free interval or for 24 days with 4 days of placebo tablets, in each 28-day cycle. Treatment was started on the first day of menstruation. Compliance was assessed from the diary cards kept by the subjects. No woman omitted a pill for longer than 24 hours in either study. At the start of each cycle, the weight and blood pressure of each subject was checked.

TABLE 1

Grading scale for ovarian activity.

Grading scale	Diameter of follicle-like structure (mm)	Level of E_2 (pg/mL)	Level of progesterone (ng/mL)
1 (no activity)	≤10		
2 (potential activity)	>10–<13		
3 (nonactive follicle-like structure)	≥13	<30	
4 (active follicle-like structure)	≥13	≥30	≤1.6
5 (luteinized unruptured follicle)	≥13	≥30	>1.6
6 (ovulation)	≥13	≥30	>1.6

Note: Table adapted from Fitzgerald et al. (3).

Ovarian Activity

The primary outcome measure was ovarian activity, which was determined by ultrasound observation of follicle-like structures and by hormone assays of serum E_2, progesterone, FSH, and LH. Ultrasound and hormone assessments were made every 2 days during the five cycles. Ovarian activity was graded according to the scale (Table 1) reported by Fitzgerald et al. (3).

Ovulation was defined as the presence of a follicle-like structure that was >13 mm in diameter and ruptured within 48 hours combined with serum 17β-E_2 and progesterone concentrations of >30 pg/mL and >1.6 ng/mL, respectively, in the same cycle. The definition of a luteinized unruptured follicle was the same, except that there was no evidence of follicle rupture on ultrasound examination.

Ultrasound Examination

The diameters of right and left ovarian follicle-like structures were measured by 5-MHz transabdominal or transvaginal ultrasound transducers and an Ultramark 4 Plus ultrasound machine (Advanced Technology Laboratories, Bothwell, WA). For each subject, the same method of ultrasound examination was used throughout the study. The diameters of follicle-like structures were calculated as the mean of three ultrasound measurements taken in two different planes.

Hormone Assays

The blood collected for measurement of hormone concentrations was centrifuged and the serum frozen. Analysis was performed in batches, one cycle at a time, under the

TABLE 2

Details of the radioimmunoassays used and their sensitivities.

Hormone measured	Manufacturer	Sensitivity*
E_2	Diagnostic Products Corporation, Los Angeles, CA	4.84 ± 3.83 pg/mL
Progesterone	Diagnostic Products Corporation, Los Angeles, CA	0.02 ± 0.01 ng/mL
FSH	Behring Institute, Marburg, Germany	0.184 ± 0.009 IU/L
LH	Sorin, Saluggia, Italy	0.38 ± 0.54 IU/L

* Sensitivity is defined as the concentration at 95% of the binding at the minimum detectable dose/binding at zero concentration.

direction of one of the investigators (J.S.) at a central laboratory in Vienna, Austria. Samples were sent to the laboratory to be assayed in batches, one cycle at time. Table 2 shows details of the RIAs used. Intra-assay and interassay coefficients of variation were 5%–9%.

Cervical Mucus

Cervical mucus hostility was assessed (7) when the ultrasound examination suggested ovarian activity. This was done because adjuvant contraceptive mechanisms are most important when the risk of breakthrough ovulation is greatest. Mucus was not collected in the presence of vaginal bleeding.

Cycle Control Assessments

Subjects noted the timing and intensity of all vaginal bleeding in a diary. A cycle was classified as "normal" if the onset of the withdrawal bleed did not extend beyond 7 days after ingestion of the last active pill and there was no breakthrough bleeding or spotting during the rest of the cycle. Bleeding intensity was rated using the following scale: 0 = none, 1 = spotting (very slight breakthrough bleeding that did not require sanitary protection), 2 = light, 3 = moderate, and 4 = heavy.

RESULTS

The baseline demographic characteristics of the women who started each study are shown in Table 3. The study was completed by 24 (79%) of 28 subjects in the 21-day group and by 27 (90%) of 30 subjects in the 24-day group. Four women in the 21-day group and 3 in the 24-day group discontinued their participation after starting treatment, for reasons not related to use of the COC. Only completed cycles are included in the analysis.

There were no serious adverse events, and the most commonly reported minor side effects were headache, abdominal pain, and breast pain. No clinically significant changes from baseline blood pressure, weight, or laboratory values were reported.

TABLE 3

Baseline demographic characteristics of 58 healthy volunteers.

Characteristic	Study group: 21-day regimen (n = 28)	Study group: 24-day regimen (n = 30)
Mean (±SD) age in years (range)	29.6 ± 3.6 (23.0–35.0)	28.5 ± 3.7 (22.0–35.0)
Mean (±SD) weight in kilograms (range)	63.4 ± 9.4 (48.0–87.5)	63.0 ± 7.3 (48.0–85.0)
No. (%) of patients with indicated parity		
0	7 (25)	12 (40)
1	7 (25)	10 (33)
2	14 (50)	7 (23)
3	0 (0)	0 (0)
4	0 (0)	1 (3)

Effects on Ovulation and Cervical Mucus Assessment

A total of 84 cycles were completed in the 24-day group and 75 in the 21-day group. Ovulation was inhibited in all cycles in the 24-day group and in 74 of 75 cycles in the 21-day group. The one ovulation that occurred was atypical but fulfilled the grading classification primarily on the basis of ultrasound findings. However, the maximum progesterone level was 6 ng/mL, which was not sustained.

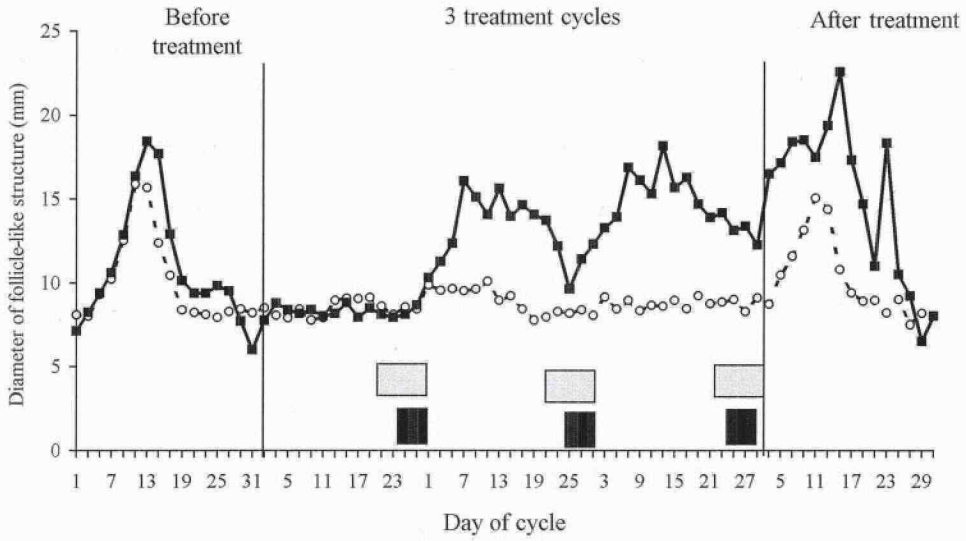
Luteinized unruptured follicles were seen in no cycles with the 24-day regimen and in six cycles with the 21-day regimen; all of them occurred in treatment cycles 2 and 3. One woman had luteinized unruptured follicles in two cycles. The mean maximum progesterone level observed in these luteinized unruptured follicle cycles was 6.4 ng/mL (range, 2.42–12.32 ng/mL). The mean maximum diameter of the follicle-like structures measured was 29 mm, but there was no evidence of follicular rupture.

The mean (±SD) maximum cervical score in the control cycles for the women who took the 21-day preparation was 10.9 ± 1.8; in the treatment cycles studied, it was reduced to 6.8 ± 1.6. For the women who took the 24-day preparation, the mean (±SD) maximum cervical score was 10.6 ± 1.9 in the control cycles and 4.1 ± 1.1 in the treatment cycles.

In the posttreatment cycle, ovulation was observed in all subjects with the 24-day regimen and in 18 of 24 subjects with the 21-day regimen. The other 6 women all had luteinized unruptured follicle cycles.

FIGURE 1

Mean diameter of largest follicle-like structure with 21- and 24-day regimens. ■, 7-day pill-free interval; ■, 4-day placebo-pill interval; --○--, 24-day; –■–, 21-day.



Effects on Ovarian Activity: Diameters of Follicle-like Structures and Levels of Ovarian Steroids

The mean diameters of the largest follicle-like structures of each subject at each assessment, for the two regimens, are shown in Figure 1. The mean diameter of the largest follicle-like structure for the 24-day regimen remained at <10 mm throughout the three treatment cycles. With the 21-day regimen, the mean diameter of the largest follicle-like structure rose to >13 mm in treatment cycles 2 and 3.

The mean serum 17β-E_2 concentrations are shown in Figure 2. In both groups, a reduction in mean levels occurred during the treatment cycles. The 17β-E_2 level remained at <50 pg/mL during treatment with the 24-day regimen but increased to >100 pg/mL during treatment cycles 2 and 3 with the 21-day regimen. Serum E_2 concentrations rose with both regimens during the pill-free interval. Mean progesterone levels remained at <1 ng/mL for both regimens. However, a slight rise in mean progesterone levels was seen in the women who took the 21-day preparation in treatment cycles 2 and 3 because of the luteinized unruptured follicles observed.

Levels of LH were suppressed during treatment, with only a small rise seen during the pill-free intervals. The mean levels during treatment were all <10 mIU/mL. There was little difference between the 21- and 24-day regimens. Concentrations of FSH were suppressed with active treatment. However, during each pill-free interval with both regimens, FSH rose to levels similar to those seen in the control cycles. There was better suppression with the 24-day regimen than with the 21-day regimen. However, there was marked variation between individuals, especially during the pill-free intervals.

Cycle Control

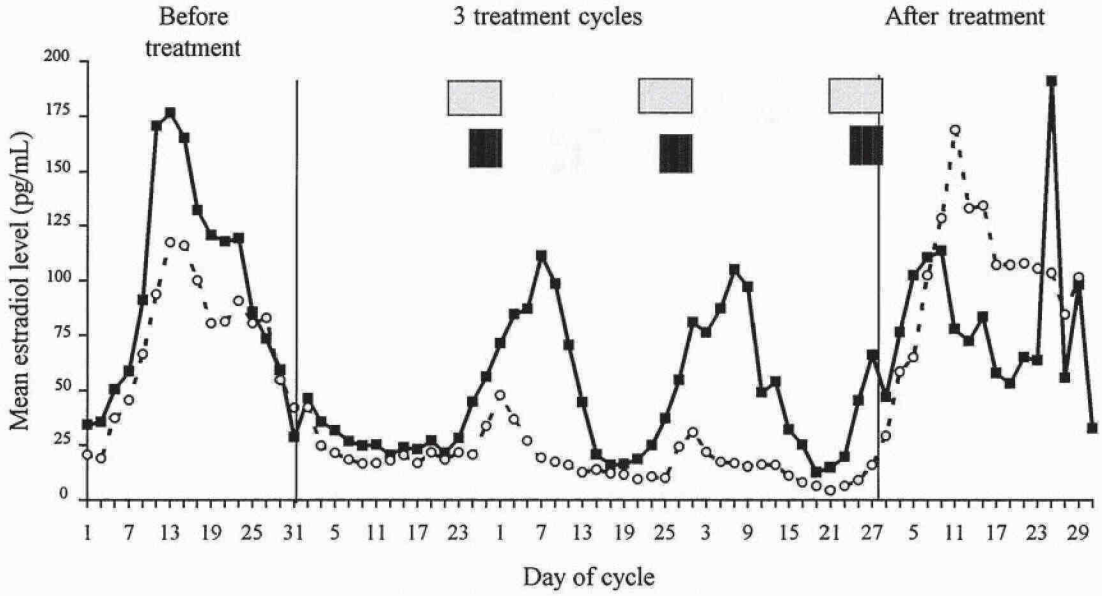
Overall, breakthrough bleeding that was more substantial than spotting occurred in 16 (21%) of 75 treatment cycles in the 21-day group and 35 (42%) of 84 treatment cycles in the 24-day group. By the third treatment cycle, breakthrough bleeding occurred in 6 (25%) of 24 subjects in the 21-day group and 12 (42%) of 28 subjects in the 24-day group. Three women in the 21-day group and 1 woman in the 24-day group failed to bleed in the 7 days after ingestion of the last active pill. The mean duration of withdrawal bleeding was 4 days in the 21-day group and 5 days in the 24-day groups. The median intensity of bleeding was light in both groups.

DISCUSSION

It is desirable to minimize the doses of estrogen and progestins in COCs to reduce the incidence of adverse events and side effects. There has been concern that reducing steroid doses might reduce the margin of contraceptive efficacy in susceptible individuals and lead to poorer cycle control (8). Combined oral contraceptives that contain 20 μg of EE and 75 μg of gestodene are known to inhibit ovulation effectively and to decrease cervical mucus scores (3, 9). Even with a 24-day regimen, a COC that contains 15 μg of EE and 60 μg of gestodene represents a 14% reduction in the total EE dose per cycle over 21-day regimens of OCs that contain 20 μg of EE and a 9% reduction in the total gestodene dose over OCs that contain 75 μg of gestodene.

FIGURE 2

Mean serum 17-β-E_2 concentration with 21- and 24-day regimens. ■, 7-day pill-free interval; ■, 4-day placebo-pill interval; --○--, 24-day; –■–, 21-day.



Reduction of the pill-free interval from 7 days to 5 days with a COC that contains 20 μg of EE and 75 μg of gestodene has been shown to be associated with better ovarian suppression as evidenced by reduced follicular development and lower serum 17β-E_2 concentrations (6). Extension of the pill-free interval has been shown to allow increased follicular development (10). The results of this study suggest that a 24-day regimen of a COC that contains 15 μg of EE and 60 μg of gestodene effectively inhibits ovulation. They also suggest that a 21-day regimen is less effective and may allow breakthrough ovulation in susceptible individuals. However, the adjunctive contraceptive mechanism of cervical mucus hostility is maintained.

Phase III studies were performed to investigate the efficacy of this ultra–low-dose COC with a 24-day regimen in a larger population. Two thousand twenty women who followed the regimen for 21,521 cycles showed a Pearl Index of 0.24 (11). This is comparable to that seen with COCs that contain 30 μg of EE and gestodene (12).

It has been established that maximum ovarian activity is seen at the end of the pill-free interval with COCs that contain 20 μg of EE (3). In our study of a COC that contains 60 μg of gestodene and 15 μg of EE, with a 21-day active treatment regimen, the standard 7-day pill-free interval allowed more time for follicles to develop, so the observed follicle diameters were larger and the 17β-E_2 concentrations were higher. In addition, the longer pill-free interval appeared to allow recruitment of a follicle to a size and stage of development that was suppressed more slowly and less profoundly by the commencement of steroid therapy. With the shorter 4-day pill-free interval and 24 days of active treatment per cycle, there was a reduced risk of breakthrough ovulation.

After treatment with the 24-day regimen, there was greater variation in the interval between cessation of active treatment and ovulation. Because of this variation, the mean E_2 level each day was lower. This could represent the relative susceptibility of individuals to breakthrough ovulation. This possibility currently is being explored.

A COC with an ultra-low dose of estrogen (15 μg) would be expected to cause somewhat more unscheduled vaginal bleeding than a COC with a higher dose of estrogen. Our data are consistent with this expectation. However, other studies (with similar higher-dose preparations) (13, 14) have reported incidences of breakthrough bleeding. The numbers of subjects in these studies are too small to assess cycle control, and more useful information is available from larger clinical studies (11).

The 60-μg dose of gestodene and 15-μg dose of EE in the COC used in this study are lower than those of any marketed formulation. The 24-day regimen is an innovative strategy to lower the total contraceptive dose while maintaining effective ovulation inhibition and tolerability.

Acknowledgments: The authors thank the volunteers, without whom the work would not have been possible. They also are grateful to the staff of the

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.