

Effects of Continuous *Versus* Cyclical Oral Contraception: A Randomized Controlled Trial

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Context: Continuous oral contraception may better suppress the ovary and endometrium, lending itself to the treatment of other medical conditions.

Objective: Our objective was to determine the effects of continuous vs. cyclical oral contraception.

Design: This was a randomized double-blind trial.

Setting: This trial was performed at an academic medical center in Pennsylvania.

Patients: A total of 62 healthy women with regular menses were included in the study.

Intervention: Cyclical oral contraception (21-d active/7-d placebo given for six consecutive 28-d cycles) vs. continuous (168-d active pill) therapy using a monophasic pill (20 µg ethinyl estradiol and 1 mg norethindrone acetate) was examined.

Main Outcome Measures: The primary outcome was vaginal bleeding, and secondary outcomes included hormonal, pelvic ultrasound, quality of life, and safety measures.

Results: There was no statistically significant difference in the number of total bleeding days between groups, but moderate/heavy bleeding was significantly greater with the cyclical regimen [mean 11.0 d (SD 8.5) vs. continuous 5.2 d (SD 6.8); $P = 0.005$], with both groups decreasing over time. Endogenous serum and urinary estrogens measured over six cycles were significantly lower ($P = 0.02$ and 0.04 , respectively) in the continuous group than the cyclical group. Women in the continuous group also had a smaller ovarian volume and lead follicle size over the course of the trial by serial ultrasound examinations. The Moos Menstrual Distress Questionnaire showed that women on continuous therapy had less associated menstrual pain ($P = 0.01$) and favorable improvements in behavior ($P = 0.04$) during the premenstrual period.

Conclusions: Continuous oral contraception does not result in a reduction of bleeding days over a 168-d period of observation but provides greater suppression of the ovary and endometrium. These effects are associated with improved patient symptomatology.

The cyclical administration of oral contraception with a pill-free interval sprang from the dogma of its developers (1). Dogma dictated a 28-d cycle to reassure the patient that she was not pregnant and society (at a time when contraception was illegal in many of the U.S. states and countries, and proscribed by

multiple religious authorities), that this medication was a natural menstrual cycle regulator (2). This pill-free interval has been associated with increased and even rebound ovarian activity (3, 4), which may predispose to user and method contraceptive failure (failure to reinstitute the pill and/or inadequate suppression of

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Abbreviations: BMI, Body mass index; CI, confidence interval; E1G, estrone 3-glucuronide; HDL-C, high-density lipoprotein cholesterol; OCP, oral contraceptive pill; PdG, pregnanediol 3-glucuronide.

the reawakened hypothalamic-pituitary axis after the pill-free interval), although pregnancy rates have been similar in randomized trials comparing continuous and cyclical methods (5). Breakthrough bleeding defined as unpredictable bleeding during hormonal contraception has been linked to decreased quality of life and satisfaction with treatment. Continuous administration of the oral contraceptive pill (OCP) or extended cycles beyond the traditional 21-d treatment period are commonly used because of their putative beneficial effect on vaginal bleeding, ovarian suppression, and quality of life (5).

Because ovarian sex steroids or their fluctuation are implicated in the pathophysiology of many medical conditions, the OCP is also used for a number of noncontraceptive indications, including the treatment of acne (6), hirsutism (7), premenstrual syndrome (8), endometriosis (9), dysmenorrhea (10), and menstrual disorders such as polycystic ovary syndrome (11). Increased efficacy of a continuous regimen may improve care for these disorders. However, there are few adequately designed and blinded trials to establish the risk benefit ratio of continuous *vs.* cyclical administration, or to elucidate the mechanisms of breakthrough bleeding (5). We conducted this study to test the hypothesis that a low-dose OCP given continuously provides fewer bleeding days, greater ovarian and endometrial suppression, and improved quality of life compared with a traditional cyclical OCP.

Subjects and Methods

Design and setting

We conducted a 168-d randomized double-blind trial of two methods of oral contraception in healthy women at the Pennsylvania State College of Medicine in Hershey, Pennsylvania.

Participants

The Investigational Review Board at the M.S. Hershey Medical Center approved this study, and all subjects gave written informed consent. We studied 62 nonsmoking women in good health, with normal menstrual cycles 21–35 d in length in three menstrual cycles before enrollment, and off of confounding medications, including hormonal contraceptives, for at least 3 months. We excluded women with a contraindication to OCP use: clotting disorders, neoplasia, diabetes, vascular disease, migraines, hyperlipidemia, hypertension, or renal/hepatic disease through history or evaluation at the screening visit (12) (Fig. 1).

Randomization and interventions

During the screening visit, subjects were examined and completed the Moos Menstrual Distress Questionnaire (Form C) to obtain baseline measures of quality of life during a spontaneous menstrual cycle with premenstrual, menstrual, and intermenstrual components (13, 14). Each subject was given a bleeding diary at the initial visit to record daily symptoms and bleeding on a subjective ordinal scale: 0, no bleeding; 1, spotting; 2, light bleeding; 3, moderate bleeding; and 4, heavy bleeding. They began their daily bleeding diaries and urine collections on the first day of their subsequent period and began testing their urine for an LH surge on the seventh day of this untreated cycle to schedule an endometrial biopsy 7–12 d later (15).

The second visit consisted of a fasting phlebotomy for endocrine, metabolic, safety parameters, transvaginal sonogram, and biopsy. Ovarian size was obtained by measuring the largest plane of the ovary in two perpendicular dimensions and then rotating the vaginal probe 90° and

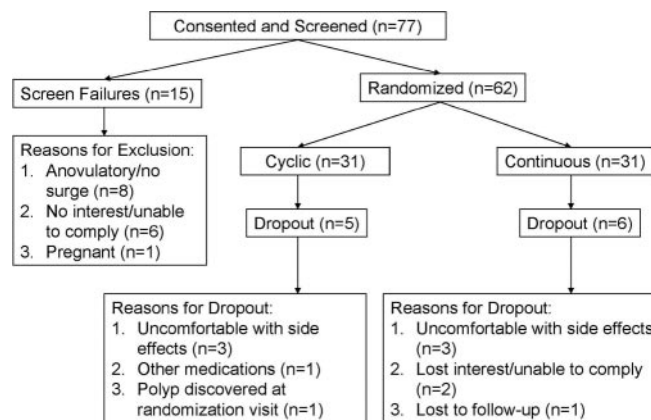


FIG. 1. Flow chart of subjects in the study.

obtaining a third measurement. The volume of the ovary was calculated using the formula for a prolate ellipsoid (length \times height \times width $\times \pi/6$) (16). A two-layer, maximum endometrial thickness was measured in the sagittal plane. An endometrial biopsy was performed using a 3-mm suction curette (Cooper Surgical, Trumbull, CT) (15). Subjects were instructed to collect daily 10 cc of the first morning urinary void, transfer to labeled tubes, and store this frozen until it was collected at the next monthly visit.

Subjects were randomly assigned at the second visit to a treatment group by a computer-generated list using permuted-block randomization, in which the block size ($n = 6$) was known only to the biostatistician (A.R.K.). Subjects in the continuous group received 4-wk cycles of 28 active pills (20 μ g ethinyl estradiol/1 mg norethindrone acetate), whereas subjects in the cyclical group received 21 active pills of the same formulation (20 μ g ethinyl estradiol/1 mg norethindrone acetate), followed by seven placebo pills. Subjects and investigators were blinded by over-encapsulating the pills during the fourth week of the cycle and repackaging into 28-d dispensing packs. Pills were begun on the first Sunday after menses.

Follow-up

Subjects were seen once a cycle during the third week of the 28-d pill cycle, such that both groups were on active medication. We queried for adverse events, performed a pill count and a limited physical examination, collected bleeding diaries and daily urines, dispensed medication, obtained blood for study parameters, and performed a sonogram. All subjects were compliant with their treatment regimens based on the monthly pill count. In addition, we repeated the Moos Questionnaire and endometrial biopsy between pill d 18 and 21 of the sixth cycle, during active OCP therapy for both groups. Subjects were instructed to base the phases of the menstrual cycle on the standard 28-d pill cycle, with menses possibly occurring during the fourth week of pills. The subjects continued the remainder of their medication and their urines for that cycle, which were collected at the subsequent closeout visit.

Outcomes

We assayed serum for sex steroids and gonadotropins each visit, and insulin, glucose, lipid profile, and SHBG at baseline and closeout as previously reported (17–19). There is no cross-reactivity in our serum assay between ethinyl estradiol and the estradiol antibody we use to measure estrogen up to 20 ng/ml ethinyl estradiol added, nor is there cross-reactivity between serum norethindrone and the progesterone antibody we use to measure progesterone when up to 1 μ g/ml norethindrone is added.

Urinary estrone 3-glucuronide (E1G) and pregnanediol 3-glucuronide (PdG) were measured in triplicate using competitive double-antibody time-resolved fluoroimmunoassays previously described (20), and values were divided by urinary creatinine concentrations to standardize

for urine flow rate (21). All assays had a method coefficient of variation less than or equal to 10% (17, 18, 22).

We did not perform cross-reactivity studies of norethindrone acetate and ethinyl estradiol in the urine because most of norethindrone acetate and ethinyl estradiol are excreted in the urine as conjugates. Given the large number of these metabolites and the vagaries as to what all the metabolites are, we realized we would derive far better information by conducting a “functional” test of cross-reactivity than to try to identify and test all the OCP steroid metabolites *in vitro*. Thus, we compared E1G and PdG levels during the weeks on OCP steroids *vs.* the placebo week; steady-state elimination half-lives for these OCP steroids are relatively

short: 19 h for ethinyl estradiol, and 13 h for norethindrone acetate. The endocrine profiles clearly reveal that there is undetectable or no cross-reactivity of the OCP steroids or their metabolites with the E1G and pregnanediol-3 α -glucuronide assays (23).

Given the large number of daily urines collected, we selected 10 subjects from each treatment group for the measure of urinary assays based on the completeness of their urinary collection. There were no significant differences in age and body mass index (BMI), as well as in baseline sex steroids, lipids, or glycemic parameters between these two groups. Subsequent analysis of results showed no difference in any of the reported outcomes between the group selected for urine studies ($n = 20$) and the

TABLE 1. Baseline characteristics of the treatment groups

	Cyclical (n = 31)		Continuous (n = 31)	
	Mean (sd)	Range	Mean (sd)	Range
Biometric				
Age (yr)	27.5 (4.7)	20.0–34.0	26.9 (5.6)	18.0–36.0
Weight (kg)	67.7 (13.9)	47.7–107.3	74.3 (20.3)	49.1–118.6
BMI (kg/m ²)	25.0 (4.6)	19.4–37.4	26.9 (7.3)	18.7–44.7
Diastolic (mm Hg)	73.0 (8.0)	61.0–89.0	74.2 (7.4)	59.0–90.0
Systolic (mm Hg)	114.6 (12.5)	97.0–146.0	117.6 (10.6)	92.0–135.0
Hematological				
Hemoglobin (g/dl)	13.3 (0.9)	11.0–15.1	13.3 (0.7)	12.0–15.1
Hematocrit (%)	38.6 (2.5)	33.1–44.4	39.0 (1.8)	35.8–43.4
Reproductive hormones (serum)				
SHBG (nmol/liter)	134.9 (51.7)	60.0–267.0	140.3 (64.1)	29.0–288.0
Testosterone (ng/dl)	27.3 (16.3)	14.0–98.0	28.2 (14.0)	14.0–63.0
Estradiol (pg/ml)	92.8 (41.4)	18.0–185.0	98.6 (27.0)	40.0–147.0
Progesterone (ng/ml)	11.3 (5.9)	0.5–20.4	10.3 (6.7)	0.3–25.0
LH (mIU/ml)	6.6 (7.9)	1.0–38.0	5.3 (6.0)	1.0–25.0
FSH (mIU/ml)	6.1 (2.3)	1.0–10.0	5.5 (2.4)	2.0–12.0
TSH (μ IU/ml)	2.0 (2.5)	0.4–14.0	1.6 (0.6)	0.5–2.9
Metabolic (fasting)				
Glucose (mg/dl)	74.5 (4.5)	65.0–83.0	76.1 (7.4)	64.0–97.0
Insulin (μ IU/ml)	15.3 (5.8)	7.0–31.0	16.6 (9.2)	6.0–54.0
Total cholesterol (mg/dl)	162.4 (28.7)	109.0–237.0	164.6 (35.5)	107.0–265.0
HDL-C (mg/dl)	56.4 (11.2)	34.0–84.0	53.9 (10.7)	34.0–87.0
LDL-C (mg/dl)	91.1 (27.5)	52.0–169.0	93.3 (31.9)	34.0–177.0
Triglycerides (mg/dl)	74.5 (28.0)	45.0–164.0	87.4 (50.4)	37.0–257.0
Ultrasound				
Left ovarian volume (cm ³)	8.9 (4.9)	2.5–27.0	11.8 (15.0)	3.0–83.6
Right ovarian volume (cm ³)	10.9 (19.4)	3.4–114.8	10.8 (8.7)	4.2–46.3
Total ovarian volume (cm ³)	19.8 (19.5)	6.5–121.4	21.9 (17.4)	7.5–95.1
Left ovary largest follicle (mm)	6.9 (3.8)	3.0–21.0	8.0 (5.0)	2.5–21.5
Right ovary largest follicle (mm)	6.2 (3.1)	3.0–17.5	8.9 (7.3)	2.0–36.0
Either ovary largest follicle (mm)	7.5 (4.1)	3.0–21.0	9.9 (7.1)	3.0–36.0
Endometrial thickness (mm)	8.9 (3.4)	5.0–16.0	10.4 (3.0)	6.0–18.0
Moos Menstrual Distress Premenstrual Questionnaire T scores^a				
Pain scale	44.2 (12.9)	34.8–87.6	47.8 (13.0)	34.8–76.3
Water retention scale	47.1 (15.3)	32.0–98.3	47.2 (12.1)	32.0–76.2
Autonomic reactions scale	47.0 (11.3)	43.2–87.0	46.8 (8.1)	43.2–69.5
Negative affect scale	41.7 (8.9)	34.4–68.6	48.3 (15.0)	34.4–93.0
Impaired concentration scale	44.0 (10.1)	40.3–90.1	43.6 (6.1)	40.3–65.2
Behavior change scale	44.2 (13.0)	39.5–103.1	47.0 (12.6)	39.5–85.8
Arousal scale	39.1 (10.0)	34.7–79.8	46.2 (16.1)	34.7–88.8
Control scale	46.1 (12.0)	43.7–103.5	44.7 (3.8)	43.7–60.8

Means (sd). Conversion to Systeme International units: glucose \times 0.0551 (mmol/liter), insulin \times 7.175 (pmol/liter), testosterone \times 4.467 (nmol/liter), estradiol \times 3.671 (pmol/liter), progesterone \times 3.18 (nmol/liter), cholesterol \times 0.0259 (nmol/liter), and triglycerides \times 0.0113 (nmol/liter). LDL-C, Low-density lipoprotein-cholesterol.

^a The Moos Menstrual Distress Questionnaire contains eight scales with multiple items. The three somatic scales are pain (muscle stiffness, headache, cramps, backache, fatigue, general aches, and pains), water retention (weight gain, skin blemish or disorder, painful or tender breasts, swelling), and autonomic reactions (dizziness, faintness, cold sweats, nausea, vomiting, hot flashes). There are three scales capturing mood and behavioral changes: negative affect (loneliness, anxiety, mood swings, crying, irritability, tension, feeling sad or blue, restlessness); impaired concentration (insomnia, forgetfulness, confusion, poor judgment, difficulty concentrating, distractible, minor accidents, poor motor coordination); and behavior change (poor school or work performance, take naps, stay in bed, stay at home, avoid social activities, decreased efficiency). Of the two remaining scales, one measures arousal (affectionate, orderliness, excitement, feelings of well-being, bursts of energy, activity), and the other control (feelings of suffocation, chest pains, ringing in the ears, heart pounding, numbness, tingling, blind spots, fuzzy vision).

remaining group ($n = 42$) (data not shown). These data indicate that the subset was representative of the overall group.

We measured E1G in every daily sample in both groups. In the continuous group, we measured PdG in every other daily sample, and in the cyclical group, we measured PdG in every other daily sample collected on d 1–14 of the OCP cycle, and in every daily sample collected on d 15–28. We followed the same measurement scheme for the full 6 months of the trial. We determined suspected ovulation using a modification of Kassam *et al.* (24) by noting a sustained increase of more than or equal to 3-fold over baseline for more than or equal to three consecutive samples, rather than more than or equal to 3 consecutive days because sampling was typically every other day.

The endometrial tissue specimen obtained was fixed in 10% buffered formalin and paraffin embedded before sectioning (25). Each tissue specimen was distributed to a single gynecological pathologist (R.J.Z.), who was blinded to the subject, the day on which the specimen was obtained, and to the treatment group. Secretory endometrium was determined by the criteria of Noyes *et al.* (26).

The Moos Menstrual Questionnaire is a 47-item self-report inventory for measuring cyclical perimenstrual symptoms (13). Each item is rated on a five-point ordinal scale from zero (no experience of symptom) to four (present, severe). The T score expresses scale scores in comparison with the normative sample. T scores have a mean of 50 and a SD of 10. For this questionnaire, higher T scores are interpreted as more severe symptoms within a scale.

Statistical analysis

The study opened to accrual in February 2002 and completed enrollment in February 2005. The primary outcome for this study was the number of vaginal bleeding days over the 168-d trial. We assumed a dropout rate of 20% and that an absolute difference in means of three vaginal bleeding days (SD 3.5) between the two groups was an adequate difference to effect positively the lifestyle of women, and, therefore, needed to enroll 62 subjects for the study to have a power of 80% for a two-sided test with a type I error rate of 0.05. Data were analyzed following an intention to treat principle using SAS software (9.1; SAS Institute Inc., Cary, NC).

For the primary outcome, a two-sample *t* test was used to estimate the difference in the mean number of vaginal bleeding days over the 168-d trial between the two treatment groups. As a secondary analysis, a Poisson regression model was fit to the primary outcome. This model allowed us to adjust for the varying follow-up for the number of days the subjects remained enrolled in the trial due to dropout before study completion. To assess vaginal bleeding days per visit as another secondary analysis, generalized estimating equations using a log link were used to fit a polynomial Poisson regression model to the number of vaginal bleeding days over time (27). The generalized estimating equations methodology accounts for the correlation induced by repeated measurements per subject.

Polynomial mixed-effects regression models, adjusted for the baseline measurement, were fit to continuous secondary outcomes to compare the two treatment groups (28). The mixed-effects regression models are an extension of ordinary regression models that account for the within- and between-subject correlation inherent in longitudinal trials. Analysis of covariance models, adjusted for the baseline measurement, were used to compare the treatment groups for metabolic parameters. For urinary steroids, the trapezoidal rule was used to calculate the area under the curve per subject over the 168-d trial. The Wilcoxon-Mann-Whitney *U* test was used to compare the urinary steroid area under the curves between the two treatment groups.

Results

Subjects

The two groups were comparable at baseline (Table 1). Dropout rates were also comparable between groups (Fig. 1). The

majority of subjects were normal weight ($\text{BMI} < 27 \text{ kg/m}^2$, $n = 23$ cyclical and $n = 19$ continuous). Subjects were seen for the monthly visits as intended during the third week of active therapy [cyclical: (mean (SD)) 18.0 (1.3) *vs.* continuous: 18.5 d (1.6); $P = 0.14$].

Vaginal bleeding

We found no difference in overall bleeding between groups over the 168-d study period [cyclical mean 35.1 d (SD 15.8) *vs.* continuous 31.5 d (21.8); difference in means 3.7 d (95% confidence interval (CI) -6.2 to 13.6 d); $P = 0.46$]. This result was upheld when adjusting for the varying length of follow-up per subject using Poisson regression [rate ratio = 1.08 of overall bleeding rates for cyclical *vs.* continuous (95% CI 0.80–1.44); $P = 0.62$]. We did find a significant decrease in moderate/heavy bleeding days in favor of the continuous regimen [mean 11.0 d (SD 8.5) *vs.* continuous 5.2 d (6.8); difference in means 5.8 d (95% CI 1.8–9.7 d); $P = 0.005$]. This result also was upheld when adjusting for the varying length of follow-up per subject using Poisson regression [rate ratio = 2.04 of heavy/moderate bleeding rates for cyclical *vs.* continuous (95% CI 1.23–3.37; $P = 0.006$]. Bleeding decreased significantly over time in both groups (Fig. 2). However, bleeding patterns differed between groups, with a relatively constant rate for any given cycle day noted in the continuous group and increasing risk as the cycle progressed in the cyclical group (Fig. 3).

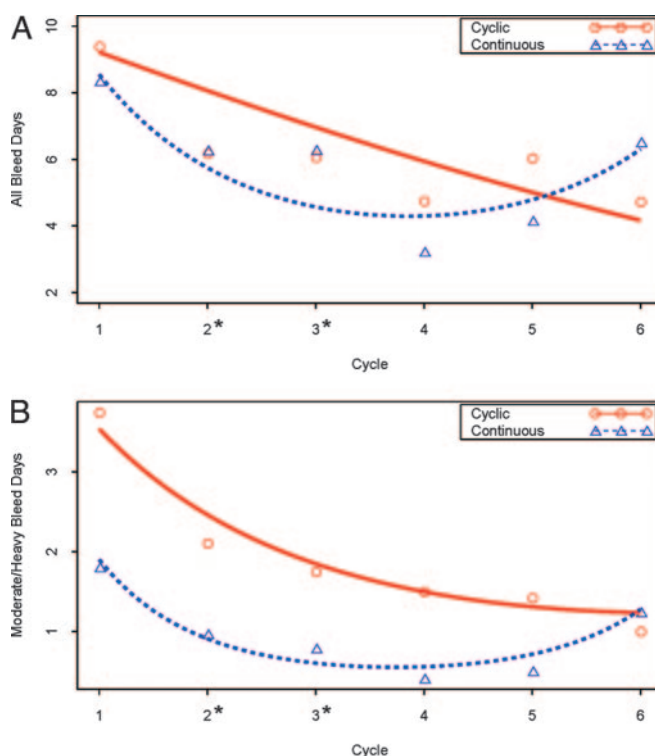


FIG. 2. Model-based effect of time (cycle) on bleeding by treatment group. A, Number of days of any bleeding per subject. B, Number of days of moderate/heavy bleeding per subject. Lines are the model-based regression estimates, and circles and triangles are the mean values at that visit per group. The asterisk at the x-axis indicates $P < 0.05$ between groups at that visit.

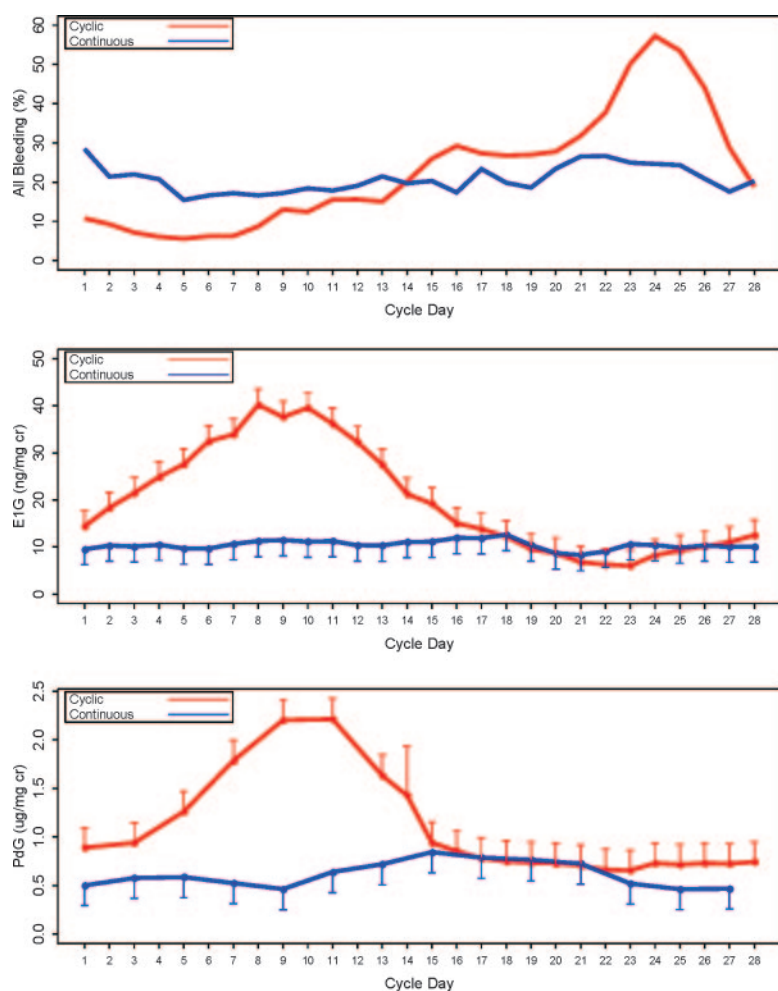


FIG. 3. Relationship between cycle day of vaginal bleeding, treatment group, and endogenous urinary sex steroids. *Top*, Percentage of patients with any bleeding by pill cycle day. All subjects averaged over the six cycles (model-based estimates to adjust for six cycles per subject). Mean (SE) urinary estrogen (E1G) (*middle*) and progestin (PdG) (*bottom*) metabolites by treatment group. Subset ($n = 20$) averaged over the six cycles (model-based estimates to adjust for six cycles per subject).

Sex steroids and gonadotropins

Urinary E1G and PdG levels varied according to treatment group (Fig. 3). We assessed integrated endogenous urinary sex steroid excretion over the length of the trial as a marker for overall end organ exposure during the trial. We found a significant increase in E1G in the cyclical group [cyclical 2922 (1635, 3241) ng/mg Cr median (25th percentile, 75th percentile) *vs.* continuous 1443 (591, 2227); $P = 0.04$] and a trend toward the same with PdG [cyclical 155 (118, 216) μ g/mg Cr *vs.* continuous 105 (68, 135); $P = 0.08$]. Based on a sustained increase in PdG, five women in the cyclical group had rebound ovarian function and suspected ovulation: one woman had one episode, three had two episodes, and one had four episodes. Thus, there were 11 suspected ovulatory cycles out of a total of 60 cycles for a rate of 18% in the cyclical group. In the continuous group, one woman had one episode. This distribution between the two groups approached statistical significance ($P = 0.054$).

We found a significant decrease from baseline in both groups in circulating testosterone and estradiol levels ($P < 0.001$) (Table 2), with a significantly greater suppression of

circulating estradiol levels at all time points after the second cycle on continuous treatment ($P < 0.05$) (Fig. 4). Testosterone levels plateaued by study midpoint after reaching the lower level of sensitivity for our testosterone assay (15 ng/dl) (18). Progesterone levels, obtained in the third pill week after the urinary increases in the first half of the pill cycle, were equally suppressed from baseline between groups.

Ultrasound findings

We found that the continuous group had a significantly greater decline in total ovarian volume ($P < 0.001$), and a smaller size of the largest follicle, both compared with baseline and to the cyclical group ($P = 0.01$) (Table 2 and Fig. 4). Total ovarian volume was significantly decreased compared with baseline in both groups after one treatment cycle and continued until the end of the fourth cycle in the cyclical group and throughout the full study period in the continuous group. Both groups experienced a decrease in the endometrial thickness compared with baseline ($P < 0.001$) (Table 2 and Fig. 4).

Menstrual quality of life

On the premenstrual Moos Questionnaire, the subjects in the continuous group reported significant improvements in pain ($P = 0.01$) and behavior change ($P = 0.04$) compared with the cyclical group. There were no differences between groups in the menstrual and intermenstrual cycle scales (data not shown).

Adverse events and histology results

There were no pregnancies or serious adverse events. Other adverse effects were comparable between groups except for increased breakthrough bleeding in the continuous group (22 *vs.* nine events in the cyclical group) ($P = 0.03$) (Table 3). Safety labs, including liver, renal, lipid, and blood count profiles, were normal and comparable during treatment with the exception of a comparatively significant increase from baseline in high-density lipoprotein-cholesterol (HDL-C) in the cyclical group compared to the continuous group ($P = 0.02$). The cyclical group also experienced a significant increase in hemoglobin and hematocrit compared with baseline ($P < 0.01$).

At the initial biopsy, we obtained tissue from 27 subjects in the cyclical group, and 24 had secretory histology, three had proliferative histology, and none had significant pathology. In the continuous group, tissue was obtained from 29 subjects, and 25 had secretory histology, three had proliferative histology, and one had simple endometrial hyperplasia. At the

TABLE 2. Changes from baseline at 6 months with between-groups comparison

	Cyclical	Continuous	Difference (cyclical-continuous)	
	Mean change (95% CI)	Mean change (95% CI)	Difference in mean change (95% CI)	P value
Biometric				
Weight (kg)	0.8 (−0.03, 1.7)	0.7 (−0.4, 1.8)	0.1 (−1.3, 1.5)	0.87
BMI (kg/m ²)	0.3 (0.02, 0.6)	0.3 (−0.1, 0.7)	0.05 (−0.5, 0.6)	0.85
Diastolic (mm Hg)	−0.1 (−2.8, 2.5)	0.9 (1.5, 3.2)	−1.0 (−4.5, 2.5)	0.58
Systolic (mm Hg)	−1.9 (−4.8, 1.0)	−0.9 (−4.0, 2.2)	−1.1 (−5.3, 3.2)	0.62
Hematological				
Hemoglobin (g/dl)	0.5 (0.2, 0.8)	0.2 (−0.1, 0.5)	0.3 (−0.1, 0.7)	0.19
Hematocrit (%)	1.3 (0.5, 2.2)	0.5 (−0.4, 1.3)	0.9 (−0.3, 2.1)	0.15
Reproductive hormones (serum)				
SHBG (nmol/liter)	72.4 (22.5, 122.4)	98.4 (49.4, 147.3)	−26.0 (−95.9, 44.0)	0.46
Testosterone (ng/dl)	−7.7 (−11.1, −4.3)	−9.9 (−11.8, −7.9)	2.2 (−1.7, 6.0)	0.27
Estradiol (pg/ml)	−57.0 (−73.4, −40.6)	−81.0 (−92.0, −70.0)	24.0 (4.4, 43.5)	0.02
Progesterone (ng/ml)	−9.9 (−10.5, −9.4)	−9.7 (−10.3, −9.1)	−0.2 (−1.1, 0.6)	0.59
LH (mIU/ml)	−2.4 (−3.6, −1.2)	−3.7 (−4.4, −2.9)	1.2 (−0.2, 2.6)	0.08
FSH (mIU/ml)	−0.01 (−1.3, 1.3)	−0.5 (−1.8, 0.8)	0.5 (−1.3, 2.3)	0.60
Metabolic (fasting)				
Glucose (mg/dl)	5.5 (2.4, 8.5)	3.4 (−0.04, 6.9)	2.0 (−2.6, 6.7)	0.38
Insulin (μIU/ml)	1.5 (−1.4, 4.3)	0.1 (−3.2, 3.3)	1.4 (−2.9, 5.7)	0.52
Total cholesterol (mg/dl)	21.8 (12.6, 31.1)	22.1 (12.7, 31.5)	−0.3 (−13.5, 12.9)	0.96
HDL-C (mg/dl)	4.4 (1.4, 7.4)	−0.6 (−3.6, 2.4)	5.0 (0.7, 9.3)	0.02
LDL-C (mg/dl)	14.0 (5.8, 22.1)	18.9 (10.6, 27.2)	−5.0 (−16.6, 6.7)	0.39
Triglycerides (mg/dl)	20.0 (6.4, 33.6)	17.0 (3.2, 30.9)	3.0 (−16.7, 22.7)	0.76
Ultrasound				
Left ovarian volume (cm ³)	−0.9 (−3.5, 1.8)	−4.7 (−7.2, −2.2)	3.8 (0.2, 7.5)	0.04
Right ovarian volume (cm ³)	−1.2 (−4.4, 2.0)	−5.4 (−6.6, −4.2)	4.2 (0.8, 7.6)	0.02
Total ovarian volume (cm ³)	−1.8 (−5.8, 2.2)	−10.4 (−12.9, −7.9)	8.6 (3.9, 13.3)	<0.001
Left ovary largest follicle (mm)	1.1 (−1.8, 4.0)	−0.8 (−4.3, 2.7)	1.9 (−2.6, 6.4)	0.40
Right ovary largest follicle (mm)	4.4 (1.2, 7.6)	−2.4 (−4.8, 0.04)	6.7 (2.8, 10.7)	0.001
Either ovary largest follicle (mm)	6.1 (2.1, 10.1)	−0.8 (−4.2, 2.6)	6.9 (1.7, 12.1)	0.01
Endometrial thickness (mm)	−5.4 (−6.4, −4.5)	−6.0 (−6.7, −5.2)	0.5 (−0.7, 1.7)	0.37
Moos Menstrual Distress Premenstrual Questionnaire T scores				
Pain scale	2.6 (−1.9, 7.1)	−5.8 (−10.3, −1.3)	8.4 (2.0, 14.7)	0.01
Water retention scale	−3.7 (−7.8, 0.5)	−7.0 (−11.2, −2.8)	3.3 (−2.6, 9.2)	0.26
Autonomic reactions scale	−0.7 (−4.5, 3.1)	−1.6 (−5.5, 2.2)	0.9 (−4.5, 6.4)	0.73
Negative affect scale	−2.3 (−6.2, 1.6)	−5.1 (−9.0, −1.1)	2.8 (−2.8, 8.4)	0.32
Impaired concentration scale	0.5 (−2.1, 3.1)	−0.02 (−2.6, 2.6)	0.6 (−3.1, 4.2)	0.76
Behavior change scale	1.4 (−1.5, 4.2)	−3.0 (−5.9, −0.1)	4.3 (0.3, 8.4)	0.04
Arousal scale	−2.3 (−5.8, 1.1)	−3.7 (−7.2, −0.3)	1.4 (−3.6, 6.4)	0.57
Control scale	2.4 (−1.5, 6.4)	1.2 (−2.7, 5.2)	1.2 (−4.4, 6.8)	0.67

Means (sd). Conversion to Systeme International units: glucose \times 0.0551 (mmol/liter), insulin \times 7.175 (pmol/liter), testosterone \times 4.467 (nmol/liter), estradiol \times 3.671 (pmol/liter), progesterone \times 3.18 (nmol/liter), cholesterol \times 0.0259 (nmol/liter), and triglycerides \times 0.0113 (nmol/liter). LDL-C, Low-density lipoprotein-cholesterol.

second biopsy, we obtained tissue on 26 subjects in the cyclical group, and nine had atrophy, inactive or inadequate endometrium, 12 showed OCP effect, and five had secretory histology. In the continuous group, we obtained tissue on 24 subjects, and 13 had atrophy, nine showed OCP effect, and two had secretory histology. These distributions in tissue histology at baseline and end of study were not statistically significantly different between treatment groups.

Discussion

The frequency of vaginal bleeding did not differ between the two regimens, although we noted less moderate to heavy bleeding in the continuous group, and both groups had less bleeding over time.

Endogenous ovarian function on OCP affected vaginal bleeding, though with varying effects depending on the treatment group. We provide two potential mechanisms for the observed breakthrough bleeding based on the treatment assignment: 1) rebound ovarian function and possibly ovulation that occurred mainly in the cyclical group; and 2) endometrial atrophy secondary to increased ovarian suppression that occurred more frequently in the continuous group. Women in the continuous group also demonstrated a greater decrease from baseline in circulating serum estradiol and integrated urinary estrogens, had smaller ovaries and lead follicles, and had fewer premenstrual impairments of their quality of life. Drawbacks of continuous therapy compared with cyclical include increased breakthrough bleeding, a failure to improve blood counts, small unfavorable changes in HDL-C, and no changes in quality of life measures over the bulk of the menstrual cycle.

TABLE 3. Adverse events by treatment group

Organ system	Adverse event	Cyclical (n = 31) total events (unique subjects)	Continuous (n = 31) total events (unique subjects)
Central nervous system	Bad dreams	0 (0)	1 (1)
	Mood swings	7 (5)	9 (7)
	Depression	2 (2)	7 (3)
	Fatigue	3 (3)	5 (4)
	Headache	9 (6)	9 (5)
	Vasovagal episode	0 (0)	1 (1)
	Hot flashes	0 (0)	1 (1)
	No sex drive	0 (0)	1 (1)
Endocrine metabolic	Hirsutism changes	0 (0)	1 (1)
	Acne changes	6 (3)	1 (1)
	Dry skin	0 (0)	2 (1)
Gastrointestinal	Nausea	9 (6)	5 (4)
	Weight gain	1 (1)	0 (0)
	Weight loss	1 (1)	0 (0)
	Diarrhea	4 (3)	0 (0)
	Cold sores	0 (0)	1 (1)
	Hemorrhoid	1 (1)	0 (0)
	Breakthrough bleeding or vaginal spotting	9 (7)	22 (13) ^a
	Cramps	9 (7)	7 (6)
Genitourinary	Dyspareunia	2 (1)	1 (1)
	Yeast infection	1 (1)	0 (0)
	Vaginal discharge	0 (0)	1 (1)
	Bloating	3 (1)	5 (3)
	Breast tenderness	5 (2)	3 (2)
	Breast lumps	1 (1)	0 (0)
	Back ache	0 (0)	1 (1)
	Asthma	1 (1)	1 (1)
Musculoskeletal	Flu symptoms	1 (1)	0 (0)
Respiratory	Coughing	0 (0)	1 (1)

^a Continuous vs. cyclical; *P* = 0.03 (rate ratio = 2.42; 95% CI 1.12, 5.26).

Rebound follicular development, which is more common in the cyclical group, tends to begin during the pill-free interval, and can lead to a peak in ovarian estrogen and progestin urinary metabolites 7–10 d into the next pill cycle, suggestive of ovulation. The increase in endogenous sex steroid levels is accompanied by a lower chance of bleeding in the cyclical group, and the decrease in these steroids over the next 7–10 d is associated with increased bleeding. This cycle within an artificial cycle is difficult to detect without detailed observations of the change in sex steroids that our frequently sampled urine specimens provided. Rebound ovarian function is common with cyclical regimens (~20% of cycles), and may involve both user and method lapses.

In the continuous group, greater endometrial suppression is suggested by the lower endogenous estrogen levels, the rapid reduction in endometrial thickness on ultrasound, and the trend toward posttreatment biopsies indicating atrophy and inactive endometrium. We attribute the increase in bleeding after the fourth cycle in the continuous group to increased endometrial atrophy due to the progressive loss of endogenous estrogen, which stabilizes the endometrium and prevents bleeding. It also suggests an endometrial atrophy threshold beyond which bleeding occurs. Our findings support an extended OCP regimen of 84 d, which may have less bleeding than longer cycles (168 d or beyond). Our study sought endometrial tissue on all participants, and not just subsets (29), with no adverse posttreatment endo-

metrial pathology in either group, upholding the safety of either regimen for the endometrium (30). The failure of 10–15% of the women to have a secretory endometrium at baseline is consistent with our earlier observations, which we attribute to false-positive LH surge testing (31), which is frequently noted in fertile women with regular menses (15).

We demonstrated no difference between regimens in the total number of bleeding days, consistent with both smaller (32) and larger studies (30). The latter study randomized 682 subjects to an open-label study of either 91-d cycles with 48.2 ± 44 (SD) total bleeding days (of 364 possible) *vs.* 50.8 ± 27.0 d in the 28-d cycle group. This study similarly found more breakthrough bleeding in the extended cycle group (37.6 ± 38.8 d *vs.* 18.3 ± 17.2 d). Our failure to note a significant treatment-related improvement in hemoglobin and hematocrit in the continuous group suggests that the vaginal bleeding is more than just spotting, though we did not attempt to quantify the bleeding beyond the subject's description of it. Our study did not detect any serious adverse events in either treatment group (nor was it powered to do so), but there is a theoretical increased risk of adverse events in the continuous group because they are exposed to 42 additional days of OCP over the six-cycle study period compared with the cyclical group.

Although the total number of bleeding days might not differ between treatment groups, the number of unanticipated bleeding

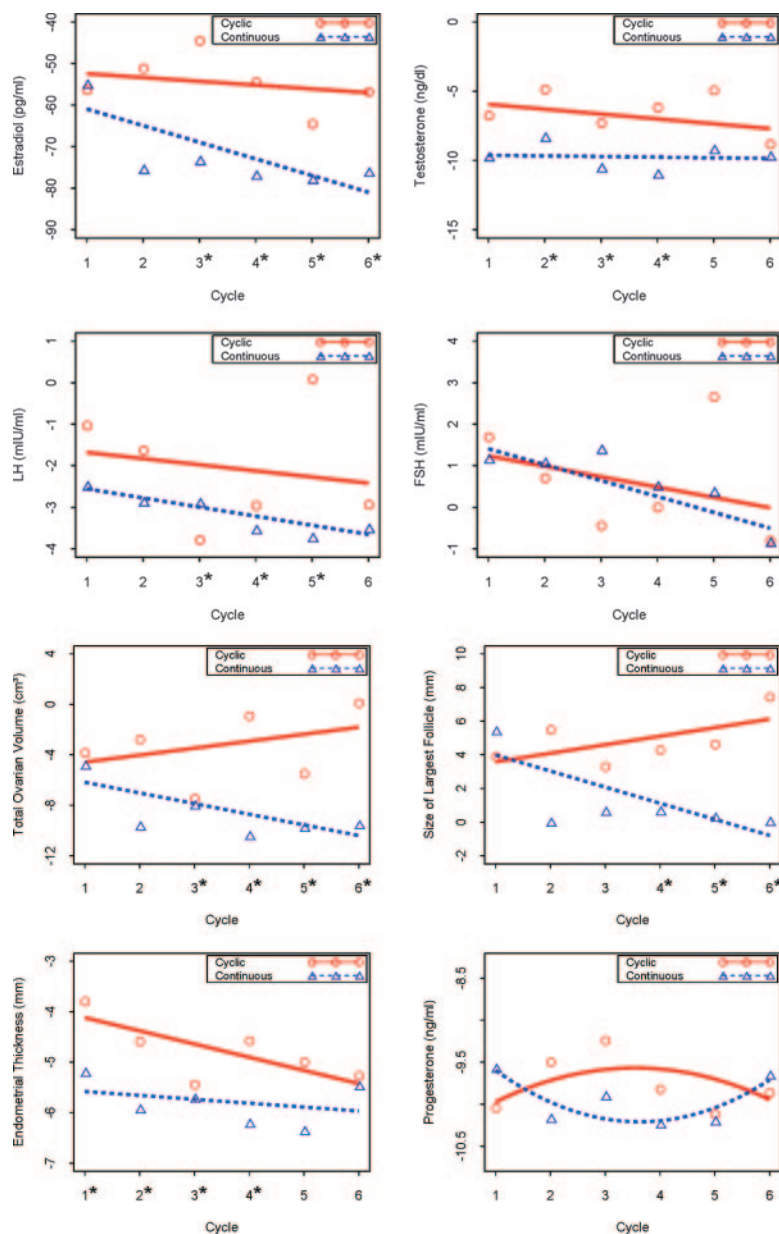


FIG. 4. Model-based change from baseline in serum sex steroids, gonadotropins, and ultrasound parameters by treatment cycle and treatment group. Lines are the model-based regression estimates, and circles and triangles are the mean values at that visit per group. The asterisk at the x-axis indicates $P < 0.05$ between groups at that visit.

days, *i.e.* the truly objectionable side effect, appears to be significantly greater in the continuous group, yet without adversely affecting quality of life. Furthermore, all bleeding diminishes over time for both groups, providing support for the adage to watch and wait when bleeding occurs early after the pill start, and not jump to another formulation. Our study also provides evidence that endogenous ovarian sex steroids influence bleeding, and, therefore, a rationale for exogenous steroid supplementation (and perhaps with low-dose estradiol and progesterone, both of which exist in micronized forms and can be given orally, to mimic endogenous ovarian function) from d 10–17 in the cyclical group and continuously in the continuous group to treat persistent breakthrough bleeding.

Quality of life measures are infrequently or superficially measured

in randomized trials of OCP regimens (5). Previous studies have used a visual analog scale to determine patient satisfaction (32) or a five-point ordinal scale, without detecting a difference between regimens (29, 33). We used the Moos Menstrual Distress Questionnaire, which has been validated for use in determining three subtypes (behavioral, psychological, and physical changes in response to menstrual symptoms) (34, 35), and has been used extensively in OCP trials (10, 36–39). Our study found significant differences between treatment groups during the premenstrual phase of the cycle, but not during the menstrual and intermenstrual phases of the cycle, which we attribute to the elimination of the pill-free interval in the continuous group and blurring of menstrual phases. Furthermore, we studied normal women, and greater differences in menstrual quality of life may be detected in symptomatic women with dysmenorrhea or the premenstrual syndrome (10).

The strengths of our study include the randomized double-blind design, intensive study of ovarian and endometrial function, and measure of menstrual quality of life. The weaknesses include the limited sample size, the select normal population we examined, and the focus on only one OCP formulation. We started low in terms of dose (given the longer sustained exposure per cycle), and it is possible that a pill containing a higher dose of estrogen, or another progestin may have had different effects. However, our choice was validated by a recent randomized trial that showed more bleeding with a higher estrogen dose (30 μ g ethinyl estradiol *vs.* 20 μ g) pill, and more bleeding with levonorgestrel as a progestin than norethindrone (40). Furthermore, our study focused on women with normal cycles and without significant medical problems. Bleeding patterns and other outcomes may vary for other women with men-

strual disorders, including oligomenorrheic women with polycystic ovary syndrome.

Our study provides solid physiological evidence for increased ovarian and endometrial suppression with continuous OCP, and the role of endogenous ovarian sex steroids on breakthrough bleeding. Although we detected no pregnancies, rebound ovulation with a 28-d cyclical regimen may be a concern for groups at higher risk for contraceptive failure (*e.g.* women with epilepsy on enzyme-inducing drugs) (41).

This study also provides a physiological rationale for continuous OCP use for noncontraceptive indications, in which additional suppression of the ovary and/or endometrium is desired. Further randomized trials of continuous regimens with uniform methodology are needed (42, 43), particularly

those evaluating effects on clinical endpoints in specific medical disorders and quality of life (44).

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