Continuous Compared With Cyclic Oral Contraceptives for the Treatment of Primary Dysmenorrhea: A Randomized Controlled Trial

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Abstract

Objective—To estimate whether continuous OCP (oral contraceptive pills) will result in more pain relief in primary dysmenorrhea patients than cyclic OCP, which induces withdrawal bleeding with associated pain and symptoms.

Material and Methods—We conducted a double-blind, randomized controlled trial comparing continuous to a cyclic 21/7 OCP regimen (gestodene 0.075 mg and ethinyl estradiol 20 mcg) for 6 months in 38 primary dysmenorrhea patients. The primary outcome was the difference in subjective perception of pain as measured by the Visual Analog Scale (VAS) over the period of 6 months.

Results—Twenty-nine patients completed the study. In both groups, pain reduction measured by VAS declined over time and was significant at 6 months compared to baseline with no difference between groups. Continuous regimen was superior to cyclic regimen after one month (mean difference: -27.3; 95% CI: (-40.5,-14.2); p<0.001) and 3 months (mean difference: -17.8; 95% CI: (-33.4,-2.1); p=0.03) of treatment. Secondary outcomes noted no difference between groups in terms of menstrual distress as measured by the Moos Menstrual Distress Questionnaire. After 6

months, there was an increase in weight and decrease in systolic blood pressure in continuous compared with the cyclic group.

Conclusions—Both regimens of OCP are effective in the treatment of primary dysmenorrhea. Continuous OCP outperforms cyclic OCP in the short term, but this difference is lost after 6 months.

INTRODUCTION

Primary dysmenorrhea (PD) is the most common cause of pelvic pain in women. It is estimated that 50–90% of the female population suffers from this condition, and 10% are severely affected for 1–3 days a month as a consequence [1]. This has both psychological and economic impact, as the resulting absenteeism causes severe economic loss each month. In one study dysmenorrhea accounted for 600 million lost work hours and $2 billion annually in the U.S. [2].

PD is most commonly attributable to excess prostaglandin production at the time of menstruation. Prostaglandin overproduction causes abnormal uterine contractions and increased intrauterine pressure, vasoconstriction of small uterine vessels leading to decreased uterine blood flow, increased sensitivity of pain receptors and ischemia of the uterine muscle, which consequently contributes to pelvic pain [3, 4]. During uterine contractions, endometrial blood flow decreases, indicating that ischemia due to the hypercontractility is the primary cause of the pain [3, 5]. Preventing menstruation thus may be a viable treatment option.

Oral contraceptives (OCP) are frequently prescribed for this condition, but are not always effective [6]. We theorized that cyclic OCP which induces withdrawal bleeding occasionally allows the production of prostaglandins and persistent pain. Continuous OCP has not been studied as a primary treatment of PD, although recent studies show its superiority to cyclic regimens in the treatment of endometriosis [7–9]. We hypothesized that continuous administration of an OCP will result in more pain relief than a cyclic 21 days active pills and 7 days placebo pills administration in PD patients. We hypothesized secondarily that the differences in uterine artery pulsatility index (PI) measured by color Doppler ultrasound would be significant between treatment groups at the end of the trial period, compared to the beginning of the trial; and that the patient self-evaluation of menstrual symptoms as determined by a standardized questionnaire would be more favorable in the continuous group compared to the cyclic 21/7 regimen group.

MATERIAL AND METHODS

The study was approved by the Institutional Review Board at Penn State Hersey Medical Center and by the Ethics Comittee at Nova Gradiska General Hospital, in Croatia, where it was conducted. Subjects were recruited from the Ob/Gyn department at Nova Gradiska General Hospital, from January 2007 to May 2010. A number of women who participated in the study were presenting for their annual screening and complaining about dysmenorrhea, while others were refered to the clinic for evaluation of dymenorrhea. All subjects gave written informed consent.

We conducted a a double-blind, randomized controlled trial of two treatment regimens of a monophasic OCP (gestodene 0.075 mg /ethinyl estradiol 20 mcg) in 38 PD patients with an allocation ratio of 1:1. The randomization list was created by our biostatistician at Penn State (ARK), who send the list to the certified reasearch pharmacy in Croatia (Magdis, Sveta Nedjelja), who overencapsulated the OCP to blind the treatment, and then sent it to research site. In order to preserve the blinding, we overencapsulated the commercially purchased

intact gestodene 0.075 mg /ethinyl estradiol 20 mcg OCP, and identical-appearing placebo pills. Adherence was assessed with pill counts confirmed at each visit. The research pharmacy also kept the randomization list. Both participants and care providers in the study were blinded to the treatment. The patients were randomized into the study group of continuous OCP and control group of cyclic OCP based on a randomization table with block size of four known only by the biostatistician. Patients in the continuous group received 28 active pills (0.075 mg gestodene/20 μg EE, a monophasic OCP), while patients in the cyclic OCP group received 21 active pills and 7 placebo pills. Gestodene-containing oral contraceptives are currently not available in United States; however they are marketed in Croatia where the study was conducted (and we choose this as we wanted a low dose EE pill and this was the only 20 μg EE available in Croatia).

Inclusion Criteria

Subjects were in good health, their age was 18–35, and they had a history of PD (onset < 3 years after menarche). Subjects had regular (25–31 day) menstrual cycles for the three-month period preceding enrollment, with symptoms of moderate to severe PD during those cycles. The pain associated with PD was abdominal or pelvic, could radiate to the back and along the thighs, could begin up to one day before menses and last for the first three days of bleeding. The pain could be accompanied with systemic symptoms including nausea, vomiting, diarrhea, headache, fatigue, nervousness and dizziness.

Exclusion Criteria

Exclusion criteria were contraindications to OCP therapy (as described in the drug label), known or suspected secondary dysmenorrhea (major abdominal or pelvic surgery, endometriosis, pelvic inflammatory disease (PID), ovarian cysts, pathological vaginal secretion, chronic abdominal pain, inflammatory bowel disease, irritable bowel syndrome), concomitant treatment with OCPs, GnRH agonists and antagonists, antiandrogens, gonadotropins, and anti-obesity drugs, the use of contraceptive implants, injectable contraceptives or intrauterine devices (the washout period on all these medications was three months), smoking (because we were uncertain about the risk benefit of continuous OCP use in this population), migraine, increased severity of headaches, depression requiring hospitalization or associated with suicidal ideation during previous estrogen or OCP use, and known or suspected hypersensitivity to trial drug. Patients enrolled simultaneously into other investigative studies that require medications, or otherwise prevent compliance with the protocol were also excluded.

Study Visits

Patients had a screening visit, where inclusion and exclusion criteria were determined and informed consent signed; a randomization visit, and three study visits (after 1 month, 3 months and 6 months). At the screening visit, patients were asked to define pain they were feeling for the last three cycles, on a categorical scale presented, as none, mild, moderate or severe. They were allowed to participate in the study if they rated their pain as moderate or severe. The first two OCP boxes were dispensed at the randomization visit, and patients were advised to take one pill daily, and two pills if one day was missed, starting on first day of their next period.

At first study visit, scheduled between days 25–28 of the study, VAS scale and Moos Menstrual Distress Questionnaire (MMDQ) were administered for current bleeding, if it happened, and for previous bleeding, at days 1–4 of the study. Other visit were scheduled at days 53–56, 81–84, and 165–168 of the study. Subjects kept vaginal bleeding diaries that were reviewed at each study visit. On each page of the bleeding diary patients had three pictures of sanitary pads and three pictures of tampons (for analysis they were named

spotting, moderate, and heavy bleeding), indicating the amount of blood staining. They were ask to make a mark for each pad or tampon they have used, that had bloodstaining that is similar to that shown in the picture, underneath the appropriate picture and across from the correct date. Color Doppler ultrasound was also performed at each study visit, using an Aloka 2000 color Doppler ultrasound with 7.5 MHz vaginal transducer. The scanning technique was as follows: after excluding uterine and ovarian pathology with the conventional ultrasound, uterine arteries were visualized laterally in the transverse section of the cervicocorporeal junction. Measurements of the pulsatility index (PI= maximal systolic flow−minimal diastolic flow/meanflow) were made after at least three consecutive blood flow velocity waveforms were analyzed.

The primary outcome was the difference in subjective perception of pain as measured by the Visual Analog Scale (VAS) over the period of six months, while the secondary outcomes were the differences in menstrual related complaints as determined by MMDQ and in ultrasound parameters (endometrial thickness, uterine artery PI). The VAS is a validated pain scale [10], used widely in clinical trials assessing the intensity of pain, especially in trials with patients suffering from PD. The VAS uses an analog linear scale to assess pain intensity. The scale is 100 mm long; the extremes of the scale are to the left "no pain" and to the right "worst pain I have ever felt". A score itself is determined by measuring the distance from the left side of the scale to the point that the patient marked.

At baseline, at 3 months and 6 months, patients completed the MMDQ [11], a validated questionnaire of menstrual related complaints which is often used in the dysmenorrhea trials. In a questionnaire, patients are asked to quantify their symptoms related to the cycle, for four days before the current bleeding, for the time of the bleeding, and the rest of the cycle, describing it as 0 – No experience of symptom, 1 – Present, mild, 2 – Present, moderate, 3 – Present, strong, and 4 – Present, severe.

Sample Size and Data Analysis

A modified intention-to-treat (mITT) approach, defined prior to study initiation, was used for efficacy analyses. The pre-defined mITT approach included for analysis all subjects who took the medication they were randomized to and who recorded at least one primary outcome score post-dose. Baseline values were not imputed or carried forward. All analyses were performed using SAS statistical software (SAS Institute Inc., Cary, NC).

Linear mixed-effects models were fit to the data to assess between-group (treatment regimen) and within-group differences over time for all continuous outcomes [12]. The independent variables for these models were treatment regimen, time (month), and the interaction of treatment regimen and time. From these linear mixed-effects models that included the two main effects and their interaction, contrasts were constructed to assess changes from baseline to each specific post-randomization month to compare within and between the treatment regimens. The linear mixed-effects models used a spatial power law covariance structure to account for unequally spaced repeated measurements (i.e., visits) over time [13]. Poisson regression models were fit to assess differences in treatment regimens with respect to bleeding day outcomes, where bleeding days were represented as the total number of bleeding days over the 6 month study time interval. Effect sizes from the Poisson regression models were quantified using rate ratios [14] and 95% confidence intervals.

We estimated that 38 subjects would be needed to detect a 30 mm difference in VAS between the continuous and cyclic 21/7 OCP treatment regimens with 90% power using a two-sided test having a significance level of 0.05. The power calculation assumed a VAS

standard deviation of 25 mm and factored in an anticipated 15% subject drop-out for the
trial.

RESULTS

Forty three women were screened, 38 randomized, and 29 patients completed the study
(Figure 1). Three of the 38 randomized women never returned for a post-dose visit
assessment and therefore were excluded in the mITT analysis. Baseline descriptives are
presented in Table 1. There were no significant changes from baseline between the two
groups after 6 months of treatment for any of the following blood tests: bilirubin, alkaline
phosphatase, ALT, glucose, total cholesterol, LDL, HDL, triglycerides, TSH, T3, T4, BUN,
creatinine, and complete blood count.

Mean VAS score (SD) in the cyclic regimen was 64.4 (31.9) at screening visit, 19.0 (24.8)
after one month, and 5.2. (9.5) at the end of the study. Mean VAS score in the continuous
group was 75.6 (16.7) at screening visit, 3.1 (5.8) after one month, and 0.8 (1.4) at the end of
the study. In both groups pain reduction measured by VAS was significant compared to
baseline (Table 2). The continuous regimen was superior to the cyclic regimen when
comparing pain reduction after one and three months of treatment, and had marginal
statistical significance after six months of treatment (Figure 2).

The changes in MMDQ scores over time were the same for the continuous and cyclic group,
with no changes between the groups (Table 2). We did note significant increase in weight
and BMI, and decrease in systolic blood pressure at 6 months between the study groups (all
P < 0.05) (Table 3). There were no significant changes from baseline between the two
groups after 6 months of treatment for ovarian volume and endometrial thickness, nor for
uterine artery resistance and pulsatility indices (data not shown). Within both groups, there
was a signficant decrease in endometrial thickness after 6 months of treatment [continuous
-3.7 (-5.4,-2.0), p<.0001, and cyclic -3.4 (-5.2,-1.7), p=0.0002] with no difference between
treatments. We observed more bleeding and spotting days in continuous compared to cyclic
regimen over the period of 6 months, as shown in Table 4.

DISCUSSION

This is a randomized trial of continuous versus cyclic OCP in the treatment of primary
dysmenorrhea. Our results show that in healthy young women both regimens of OCP are
effective in the treatment of PD at 6 months, although the continuous OCP regimen is
superior in pain relief to cyclic OCP in the short term (up to 3 months), with no differences
in quality of life as determined by the Moos MDQ between groups. Further we noted in the
continuous group a greater weight gain, more bleeding/spotting day, but a decrease in
systolic blood pressure compared to the cyclic group.

Dysmenorrhea has been succesfully treated with OCP. Davis et al [15] assessed whether a
low-dose OCP is more effective than placebo treatment for dysmenorrhea pain in
adolescents, and reported that the mean MMDQ pain score was lower (less pain) in the OCP
group than the placebo group, comparable to our findings in both groups. Our findings are
also consistent with other studies of other gynecologic disorders with chronic pain. For
instance, several studies addressed the use of a continuous OCP regimen in patients with
endometriosis, which is associated with pelvic pain, dysmenorrhea, dyspareunia and
infertility [7–9]. They found less endometriosis-associated dysmenorrhea in the continuous
contraceptive groups, which is comparable to our findings. Kwiecien et al. [16] in a study of
bleeding patterns and patient acceptability of standard or continuous dosing regimens of a
low-dose OCP, looked into symptoms of menstrual pain. At the conclusion of the study,

subjects completed a satisfaction questionnaire, and significantly less menstrual pain was noted in the continuous group.

Under social, cultural, and religious influences, women have traditionally been prescribed OCP in a pattern of 21 days of active pills with seven days of inactive pills as a way of mimicking the natural menstrual cycle [17]. However, in dysmenorrhea patients, this may attenuate the full pain benefit of OCP. The continuous administration may reduce dysmenorrhea by eliminating withdrawal bleeding and associated uterine contractions, as well as by preventing rebound ovarian function during the pill free interval which may stimulate the growth of the endometrium [18]. Previous studies in other populations have shown greater satisfaction and quality of life with extended cycle regimens. [19–21]. A multicenter randomized trial [22] of an extended cycle OCP assessed patient satisfaction with the continuous regimen. Patients reported a preference for the reduced frequency of menstrual periods, and that they would prefer to have fewer menstrual periods following completion of the study.

We found no or only modest differences between the groups in premenstrual and intermenstrual symptoms that constitute the MMDQ, which is different from other studies [18, 23]. However, some studies did not find that OCP use alter the incidence or severity of premenstrual change in MMDQ [24]. The reason for this may be our small sample size, but also the subjective nature of the questionnaire.

Our patients in the continuous group gained weight, while patients in the cyclic group did not. We did not note this in our previous trial [18], and moreover a recent metaanalysis [25] did not find evidence to support a large weight change on OCP. Though this reflect improved appetite due to decreased pelvic pain, this may be a chance finding due to our small sample size, but also likely the consequence of weighing women when the two groups were in a different endocrinologic millieu [in the continuous group always on active pills, in the cyclic group on placebo pills (i.e.the last four days of each pill cycle)]. Women in the cyclic group had an increase in both systolic and diastolic blood pressure, which is expected, as OCP is associated with a small but significant increase in blood pressure. Recent studies [26, 27] confirmed this, but while this may be true for cyclic regimen of OCP, continuous regimens, as in our study, may not change blood pressure to the same degree [18, 28].

Although ultrasound has been the most important diagnostic tool in gynecology in the past decades, it has little value in the diagnosis of PD. Its main contribution in such patients is in excluding the patients with secondary dysmenorrhea by positively identifying endometriomas, uterine leiomyomas, adenomyosis, and other abnormalities. This was confirmed in this study, because the only significant change we observed was a change in endometrial thickness for both groups compared to baseline after six months of treatment, a common change in these studies [29, 30].

Women in our study reported more beeding days and more spotting on continuous regimen than previously reported [16]. However this was likely a minor distraction, without involvement of the myometrium and prostaglandin production, given the signficant reduction in VAS and the lack of difference in the quality of life as reported on the MMDQ. Further, there was no significant difference in the total number of moderate/heavy bleeding days in our study between regimens, although previously we noted fewer days [18]. However we were studying normal women and using a different OCP formulation.

In conclusion, patients with PD may benefit from continuous administration of OCP compared to cyclic OCP by a more rapid achievement in pain reduction. However, since PD therapy is a long-term therapy, and continuous regimen could be associated with unpleasant side-effects such as weight gain, women should be counseled about this. In the clinical

setting, they may be less tolerant to side effects, and thus discontinue the OCP. Further larger randomized trials are needed to establish the risk benefit ratio of longer use of extended cycle OCP regimens for PD.

Acknowledgments

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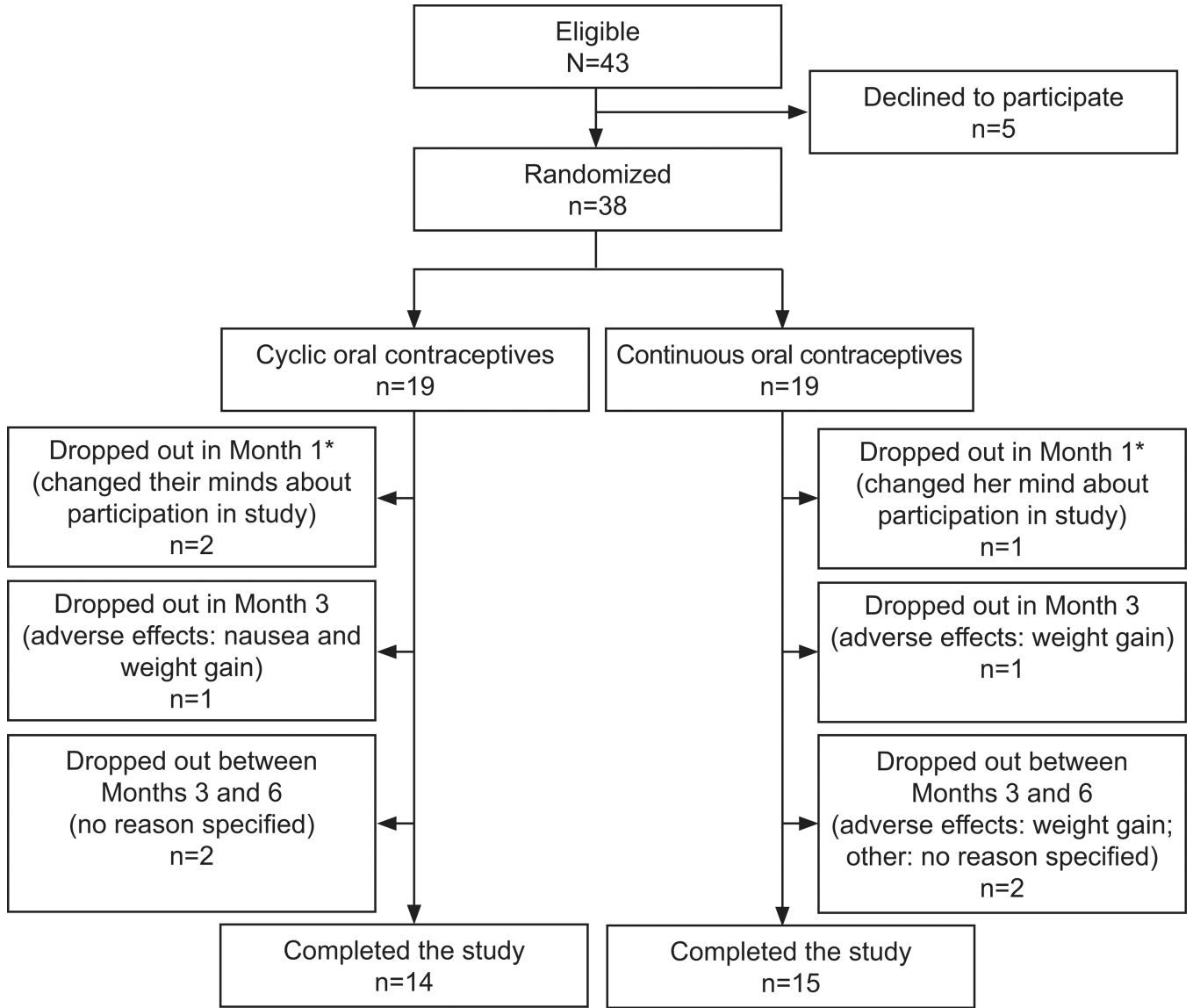
Figure 1.
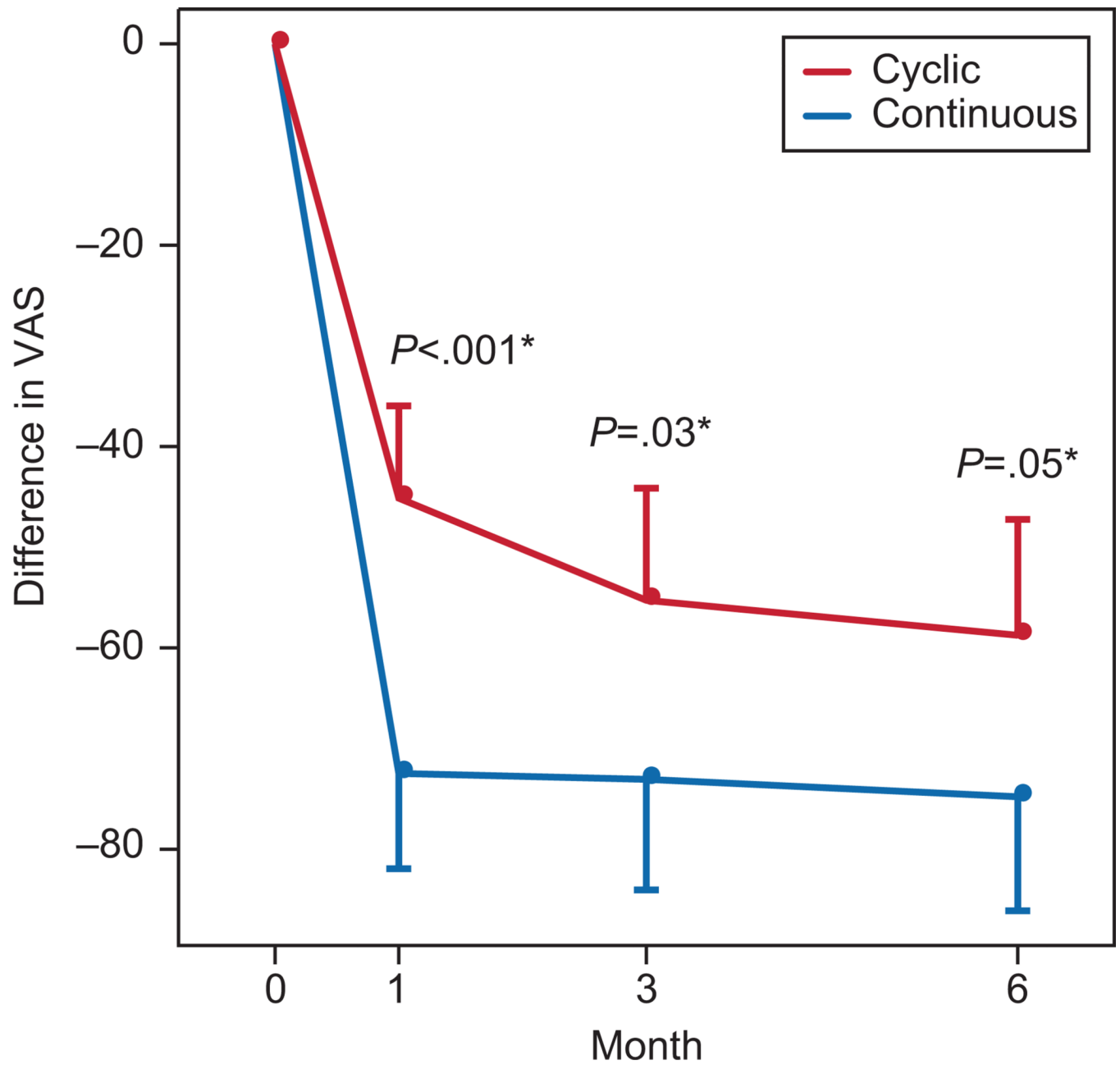Flow of participants through the study.

Figure 2.
Comparisons between the two groups in Visual Analogue Scores (VAS) at varying time points in the study.

Table 1

Baseline Characteristics of Patients by Treatment Regimen

	Continuous		Cyclic	
	n	Mean(SD)	n	Mean(SD)
Biometric				
Age (y)	18	20.7 (3.9)	17	21.1 (4.3)
Weight (kg)	18	57.9 (6.8)	17	55.9 (5.2)
BMI (kg/m^2)	18	20.7 (2.5)	17	20.3 (1.8)
Systolic blood pressure (mm Hg)	18	107.2 (6.7)	17	101.8 (8.1)
Diastolic blood pressure (mm Hg)	18	65.3 (6.1)	17	60.6 (7.5)
Liver profile				
Bilirubin (umol/L)	17	12.9 (3.8)	15	14.0 (9.2)
Alkaline phosphates (J/L)	16	57.4 (15.7)	14	52.9 (21.7)
ALT (J/L)	17	14.7 (4.7)	15	13.4 (4.4)
Glucose (nmol/L)	17	4.8 (0.4)	15	5.2 (0.9)
Lipid profile				
Total Cholesterol (nmol/L)	16	4.2 (1.1)	15	4.1 (0.9)
LDL (nmol/L)	16	2.5 (1.0)	13	2.1 (0.9)
HDL (nmol/L)	16	1.4 (0.3)	13	1.7 (0.4)
Triglycerides (nmol/L)	16	0.8 (0.2)	15	0.8 (0.3)
Renal profile				
BUN (umol/L)	13	246.2 (33.7)	15	202.2 (77.5)
Creatinine (umol/L)	17	81.7 (8.0)	15	80.9 (9.9)
CBC				
White blood cell (x10^9/L)	17	6.9 (2.2)	15	6.4 (1.9)
Hemoglobin (g/L)	18	134.1 (8.9)	15	129.8 (9.8)
Hematocrit (L/L)	18	0.4 (0.2)	15	0.4 (0.0)
Platelet count (x10^9/L)	18	262.3 (45.9)	15	244.4 (41.0)
Ultrasound parameters				
Endometrial thickness (mm)	16	7.2 (2.4)	14	6.8 (3.1)
Total ovarian volume (cm^3)	16	11.1 (5.4)	14	12.1 (7.0)

SD, standard deviation; BMI, body mass index; ALT, alanine transminase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BUN, blood urea nitrogen; CBC, complete blood count.

Table 2

Linear Mixed-Effects Model-Based Differences in Key Outcomes of Treatment Compared to Baseline by Treatment Group and Difference Between Groups

	Month	Continuous		Cyclic		Difference (Continuous-Cyclic)	
		Mean Change (95% CI)	P	Mean Change (95% CI)	P	Mean Change (95% CI)	P
Visual Analog Scale							
Degree of dysmenorrhea	1	-72.5 (-81.9,-63.0)	<.001	-45.1 (-54.3,-36.0)	<.001	-27.3 (-40.5,-14.2)	<.001
	3	-73.1 (-84.0,-62.1)	<.001	-55.3 (-66.4,-44.1)	<.001	-17.8 (-33.4,-2.1)	0.03
	6	-74.8 (-86.1,-63.5)	<.001	-58.7 (-70.3,-47.2)	<.001	-16.0 (-32.2,0.1)	0.05
MOOS Menstrual Distress Questionnaire							
T-Score Pain Scale (menstrual)	1	-8.0 (-16.7,0.7)	0.07	-4.5 (-12.9,4.0)	0.29	-3.5 (-15.6,8.6)	0.57
	3	-21.0 (-32.4,-9.7)	<.001	-18.5 (-30.0,-6.9)	0.002	-2.6 (-18.8,13.7)	0.76
	6	-23.0 (-35.4,-10.5)	<.001	-18.4 (-31.0,-5.9)	0.004	-4.5 (-22.2,13.2)	0.61
T-Score Pain Scale (premenstrual)	1	-2.5 (-8.0,2.9)	0.35	0.4 (-4.9,5.6)	0.89	-2.9 (-10.5,4.7)	0.45
	3	-6.2 (-14.1,1.6)	0.12	-3.4 (-11.3,4.5)	0.40	-2.8 (-14.0,8.3)	0.61
	6	-6.6 (-15.8,2.7)	0.16	-0.6 (-9.9,8.7)	0.89	-5.9 (-19.1,7.2)	0.37
T-Score Pain Scale (intermenstrual)	1	-6.1 (-12.9,0.8)	0.08	-5.7 (-12.3,1.0)	0.09	-0.4 (-9.9,9.2)	0.93
	3	-13.0 (-22.7,-3.3)	0.009	-10.5 (-20.4,-0.6)	0.04	-2.5 (-16.4,11.4)	0.72
	6	-14.3 (-25.7,-2.9)	0.01	-7.1 (-18.6,4.3)	0.22	-7.2 (-23.4,9.0)	0.38

Table 3

Linear Mixed-Effects Model-Based Differences in Safety Outcomes of Treatment Compared to Baseline and Difference Between Groups[*]

	Continuous		Cyclic		Difference (Continuous-Cyclic)	
	Mean Change (95% CI)	P	Mean Change (95% CI)	P	Mean Change (95% CI)	P
Weight (kg)	2.1 (1.1,3.1)	<.001	-0.2 (-1.3,0.8)	0.67	2.3 (0.8,3.8)	0.003
BMI (kg/m^2)	0.8 (0.4,1.1)	<.001	0.0 (-0.4,0.4)	0.92	0.7 (0.2,1.3)	0.01
Systolic blood pressure (mm Hg)	2.4 (-2.8,7.6)	0.35	10.5 (5.1,15.8)	<.001	-8.1 (-15.5,-0.6)	0.04
Diastolic blood pressure (mm Hg)	3.1 (-2.6,8.9)	0.27	11.0 (5.1,16.9)	<.001	-7.9 (-16.1,0.4)	0.06
Alkaline phosphatase (J/L)	-9.3 (-17.1,-1.5)	0.02	-7.6 (-15.9,0.7)	0.07	-1.7 (-13.1,9.7)	0.76
ALT (J/L)	2.8 (0.0,5.6)	0.05	1.7 (-1.5,4.8)	0.28	1.2 (-3.0,5.4)	0.57
Total cholesterol (nmol/L)	0.4 (0.2,0.7)	0.003	0.4 (0.1,0.7)	0.007	0.0 (-0.4,0.4)	0.96
HDL (nmol/L)	0.2 (0.0,0.3)	0.05	0.2 (0.1,0.4)	0.007	-0.1 (-0.3,0.1)	0.45
Triglycerides (nmol/L)	0.3 (0.1,0.5)	0.006	0.2 (-0.0,0.4)	0.07	0.1 (-0.2,0.4)	0.49

[*]
Only parameters with a significant difference compared to baseline or between groups. BMI, body mass index; ALT, alanine transminase; HDL, high-density lipoprotein.

Table 4

Differences in Vaginal Bleeding (Days) by Treatment Group Based on Poisson Regression Models

	Continuous	Cyclic	Continuous Compared With Cyclic	
	Mean (95% CI)	Mean (95% CI)	Rate Ratio (95% CI)	*P*
All bleeding (days)	58.2 (43.8,77.2)	33.7 (23.6,47.9)	1.7 (1.1,2.7)	0.02
Moderate-to-heavy bleeding (days)	16.7 (10.5,26.5)	17.6 (11.5,27.0)	0.9 (0.5,1.8)	0.87
Spotting (days)	41.5 (29.3,58.8)	16.0 (9.4,27.3)	2.6 (1.4,4.9)	0.003