Oral Contraceptives for Dysmenorrhea in Adolescent Girls

A Randomized Trial

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Objective: To assess whether a low-dose oral contraceptive (OC) is more effective than placebo treatment for dysmenorrhea pain in adolescents.

Methods: This was a randomized, double-blind, placebo-controlled clinical trial of 76 healthy adolescents aged 19 years or younger reporting moderate or severe dysmenorrhea. Subjects were randomly allocated to receive either an OC (ethinyl estradiol [E2] 20 μg and levonorgestrel 100 μg) or a matching placebo for 3 months. Participants used their usual pain medications as needed during the trial. The main outcome measure was score on the Moos Menstrual Distress Questionnaire (pain subscale) for the third menstrual cycle on treatment. Secondary outcomes included pain intensity (rated 0 to 10), days of any pain, days of severe pain, hours of pain on worst day, and use of pain medications.

Results: The mean Moos Menstrual Distress Questionnaire pain score was lower (less pain) in the OC group than the placebo group (3.1, standard deviation 3.2 compared with 5.8, standard deviation 4.5, $P = .004$, 95% confidence interval for the difference between means 0.88–4.53). By cycle 3, OC users rated their worst pain as less (mean pain rating 3.7 compared with 5.4, $P = .02$) and used fewer pain medications than placebo users (mean pain pills used 1.3 compared with 3.7, $P = .05$). By cycle 3, OC users reported fewer days of any pain, fewer days of severe pain, and fewer hours of pain on the worst pain day than placebo users; however, these differences did not reach statistical significance.

Conclusions: Among adolescents, a low-dose oral contraceptive relieved dysmenorrhea-associated pain more effectively than placebo.

(Obstet Gynecol 2005;106:97–104)

Level of Evidence: I

Primary dysmenorrhea, defined as painful menstruation in the absence of organic pathology, is prevalent during adolescence. Most adolescent girls in varied populations report experiencing dysmenorrhea, and approximately 15% describe the pain as severe.[1] Morbidity due to dysmenorrhea represents a substantial public health burden. Based on estimates from the U.S. Census, approximately 2 million adolescents, or 15% of the total females aged 13–19 years, experience severe dysmenorrhea.[2] Ylikorkaland Dawood[3] estimated that dysmenorrhea is the single greatest cause of lost working hours and school absence in adolescent girls.

Dysmenorrhea may have a pronounced impact among adolescents due to undertreatment. In a national probability sample, Klein and Litt[4] reported that only 14% of U.S. adolescents with dysmenorrhea sought help from a physician, including only 29% of those reporting severe dysmenorrhea. Most adolescents who use pain medicine choose over-the-counter treatments such as nonsteroidal anti-inflammatory drugs. The efficacy of such medications in adolescents is not well-established because published clinical trials have largely been conducted in adult women.[5]

Oral contraceptives (OCs) are commonly used to treat dysmenorrhea, and both small laboratory studies and observational data suggest that OCs effectively reduce prostaglandin production and pain.[1] Few controlled trials, however, have examined the efficacy of

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Funding support by the National Institute of Child Health and Human Development grant number R03-HD39776-RCT. The views in this manuscript do not necessarily reflect those of the National Institute of Child Health and Human Development. Oral contraceptive and placebo pills were provided by Wyeth Pharmaceuticals, Collegeville, Pennsylvania.

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ISSN: 0029-7844/05

OCs for dysmenorrhea. A recent evidence review and meta-analysis by the Cochrane Collaboration[6] concluded that OCs may be more effective than placebo based on 5 controlled trials of OCs compared with placebo. The authors emphasized that these trials were of poor quality, were conducted more than 20 years ago, and only included high-dose OCs not currently in use.

Including adolescents in dysmenorrhea trials is especially important because dysmenorrhea is undertreated and leads to high morbidity in this group. Published data supporting a beneficial effect of OCs have largely been conducted in adult women, and such results may not be generalizable to adolescent girls. We conducted a randomized, placebo-controlled trial to examine the efficacy of a low-dose OC in treatment of dysmenorrhea among adolescent girls.

MATERIALS AND METHODS

This trial was conducted at a single academic medical center from August 2001 to November 2003, with approval from the medical center Institutional Review Board and Pediatric Institutional Review Board. Healthy adolescent girls aged 19 years or younger with moderate or severe dysmenorrhea were eligible to enroll. We used the Robinson modification of the Andersch scale to classify the severity of dysmenorrhea.[7] Using this scale, moderate dysmenorrhea indicates sometimes or always experiencing very painful menstrual cramps. Severe dysmenorrhea indicates sometimes or always cutting back on activities in addition to experiencing painful menstrual cramps. Other inclusion criteria were parental consent if aged younger than 18 years, English speaker, working telephone or pager, regular menstrual cycles for at least 1 year, and menstrual cycle length from 21 to 35 days. Exclusion criteria were a history of term pregnancy or possible current pregnancy, recent abortion or miscarriage followed by fewer than 3 menstrual cycles, history of pelvic pathology possibly related to dysmenorrhea, abnormal genital bleeding, or concurrent use of medications known to affect OC metabolism. Those interested in participating were explicitly asked about sexual activity, including vaginal intercourse. To be eligible, subjects had to be abstinent or established condom users. If an adolescent needed OCs for contraception, she was ineligible and was referred for family planning services.

We used print-based advertising for recruitment. This included postings at locations throughout the medical center, postings at college campuses, and advertisements in local newspapers. The postings and advertisements asked adolescents experiencing painful periods, or their mothers, to contact our research staff. We did not recruit directly from clinical settings where adolescents receive health care. We notified local physicians specializing in adolescent medicine about the study, and they subsequently referred 2 participants to our research staff. Finally, we encouraged those enrolled to refer friends or family members to the study.

After an initial telephone screening, the first visit was scheduled within 1 week of the last menstrual period to maximize recall of the most recent menses. A parent was required to attend the first visit for those adolescents aged younger than 18 years. In a few cases, the presence of a parent at the first visit became a difficult logistical issue. For these parents, we provided informed consent over the telephone and their daughters brought the signed parental consent form to the first visit.

We wished to avoid enrolling any adolescent having unprotected intercourse. As part of informed consent, the investigator emphasized that condom use was required if vaginal intercourse occurred during the study. Condoms were provided, if appropriate; use of emergency contraception was explained to all subjects. Participants were encouraged to call if they needed to start a contraceptive method, and all were provided with a 24-hour emergency pager number.

After giving informed consent, participants underwent a brief physical examination, including height, weight, and blood pressure measurements. A pelvic examination was not performed because we did not want to discourage enrollment by younger, virginal adolescents. The investigator then administered a demographic questionnaire, which included a detailed description of usual menstruation (during the last 4 months) and the most recent menstrual period. Menstrual characteristics included length of cycle, days of bleeding, days of any pain, days of severe pain, hours of pain on the most painful day, rating of worst pain on a 0 to 10 scale, use of nonpharmacologic and pharmacologic treatments for pain, occurrence of nausea, vomiting, or fainting with pain, and absence from work or school due to pain.

Subjects also completed 4 self-administered questionnaires. The first was the pain subscale of the Moos Menstrual Distress Questionnaire (MMDQ), form C.[8] The MMDQ pain subscale contains 6 items: muscle stiffness, headache, cramps, backache, fatigue, and general aches and pains. Participants rated each item as none, mild, moderate, strong, or severe (scored as 0, 1, 2, 3, and 4, respectively) for the most recent menstrual cycle. We chose the score on the MMDQ as the main outcome variable because this instrument is validated, reliable, and has been used to measure dysmenorrhea in adolescents.[8] As secondary hypotheses, we planned to explore the role of depression, self-esteem, and stress as potential modifiers of the

treatment and placebo effects. These were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D),[9] the Rosenberg Self-Esteem Scale,[10] and the Cohen Perceived Stress Scale.[11] All of these scales are reliable, valid, and have been extensively used in adolescent populations. Results of these subanalyses will be published elsewhere.

Next, participants were randomly assigned to receive either the OC (ethinyl E2 20 μg and levonorgestrel 100 milligrams) or a matching placebo. The oral contraceptives and placebos were prepared by the manufacturer in 28-day blister packs and appeared identical. The allocation sequence was generated using a random number table by an investigator who was not involved with the recruitment or enrollment of participants. The allocation ratio was 1:1. There were 2 stratification variables; severity of dysmenorrhea (moderate or severe) and age (younger than 18 years or 18 to 19 years). Within each of the 4 strata the block size was 4. To assess the efficacy of blinding, at the exit visit subjects were asked whether they thought they were assigned to the OC or placebo group.

After the investigator administered the first pill of the first pack, participants were advised to take 1 pill daily, 2 pills if 1 day was missed, and 2 pills for 2 days if 2 were missed. Participants were started on the treatment at the first visit regardless of cycle day; most were within the first 7 days of the menstrual cycle. Participants were advised to use their usual pain medications as needed. During the next 2 months, the study co-coordinator contacted participants by telephone after each menses for a brief interview regarding menstrual pain, medication use, and the need for contraception. Compliance with treatment was assessed by asking each participant if she missed or skipped any pills and by asking her to bring in the pill packs at the end of the study. An exit visit was scheduled during the week after the last day of the third menstruation. If no menstruation occurred by 2 weeks after the last dose of treatment, the participant was considered to have amenorrhea for that cycle. At the exit visit, participants underwent a physical examination (without a pelvic examination) and the MMDQ pain subscale and psychometric questionnaires were repeated. Participants received a modest stipend. All participants were offered referral for continuing treatment and additional diagnostic work-up if indicated.

The primary outcome was a comparison of mean MMDQ pain subscale scores between the OC and placebo groups for the third menstruation on treatment. In Moos' original published data from 839 women, the mean score on the MMDQ pain subscale was 18 (standard deviation [SD] $\pm$ 6.25) for the worst menstrual cycle.[12] This was based on a questionnaire scored using a 6-point scale from 1 to 6 for each item (possible score 0 to 36). In the modified, updated MMDQ questionnaire, each item is rated using a 5-point questionnaire from 0 to 4 for each item (possible score 0 to 24).[12] Because norms for the worst cycle have not been generated for the updated questionnaire, we calculated our sample size based on the scores and standard deviations for the updated questionnaires from our first 15 participants. This mean questionnaire score was 12.6 (SD $\pm$ 5.5).

We estimated that a 50% decrease in MMDQ scores in the OC group would be clinically meaningful, and that a 20% decrease would occur in the placebo group. To detect a difference at least this great with a power of 80% and an alpha of 5%, we would need 34 participants in each group. Based on published rates of OC discontinuation in adolescents (40%), we estimated that to achieve the desired sample size we would need to enroll 112 participants. The actual discontinuation rate was much lower than expected, thus enabling us to stop enrollment at 76 adolescents. Secondary outcomes included self-reported use of pain medication, rating of worst pain intensity (0 to 10 scale), hours of pain on the worst day, days of any pain, and days of severe pain.

All data entry and management were carried out with the investigators masked to treatment assignment. Additionally, the primary treatment effect analysis was performed while the investigator was still blind to treatment assignment. SPSS 10.0 (SPSS Inc., Chicago, IL) was used to perform the data analysis. The primary comparison, of third cycle MMDQ scores in the OC and placebo groups, was performed using an independent-samples Student *t* test using an intent-to-treat analysis. We also performed the primary comparison using a nonparametric test for ordinal data, the Mann-Whitney *U* test. Other analyses were performed using independent samples and paired samples Student *t* tests for continuous variables and Pearson χ^2 and odds ratio (OR) with associated 95% confidence intervals (CIs) for categorical variables where appropriate. We used repeated measures analysis of variance to examine effects over time within and between groups.

RESULTS

The flow of participants through the trial is shown in Figure 1. Among those eligible, the most common reason for nonparticipation was scheduling difficulty that interfered with the subject being able to attend the first visit with her parent. The second most common reason for nonparticipation was the adolescent's or parent's concern about side effects from OCs. Complete data were obtained for all participants except 2 (1 lost to follow-up and 1 pregnancy).

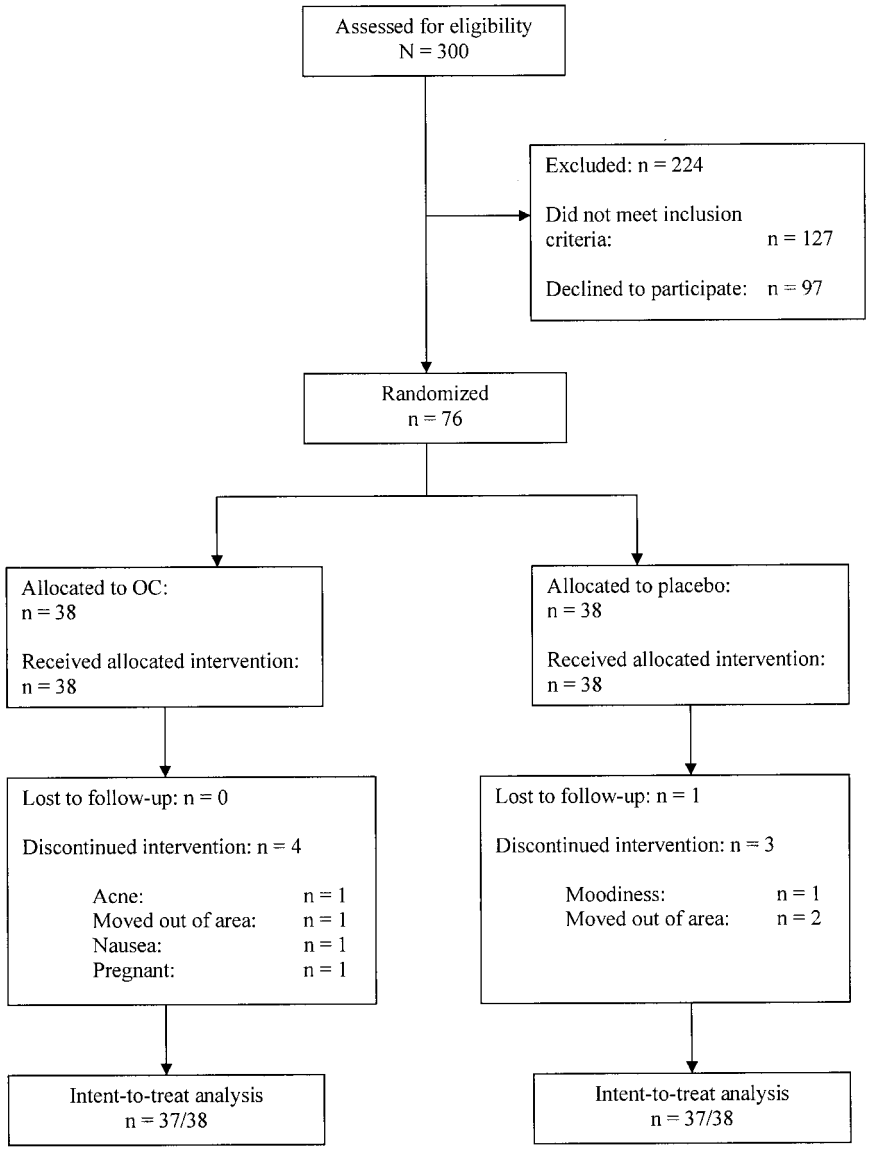

Fig. 1. Flow of participants through the trial. OC, oral contraceptive.

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For all analyses, data from all remaining participants is included (intent-to-treat).

The demographic characteristics of participants are shown in Table 1. Those enrolled included a diverse sample of adolescents by age, race, and ethnicity. Randomization seemed to be successful; the OC and placebo groups were similar at baseline on demographic characteristics, MMDQ scores, severity of dysmenorrhea, and medication use.

At baseline, 42% of participants described their dysmenorrhea as moderate, and 58% described it as severe. The participants also described experiencing substantial morbidity from dysmenorrhea. Fifty-five percent reported usually experiencing nausea, 24% vomiting, and 5% syncope in association with pain. Of those currently enrolled in school, 39% reported usually missing 1 school day monthly, and an additional 14% usually missed 2 or more days because of dysmenorrhea.

The primary comparison of MMDQ scores in cycle 3 demonstrated that the OC treatment was more effective than the placebo treatment for relieving the pain of dysmenorrhea (Fig. 2). Eight participants experienced amenorrhea during cycle 3 (4 in the OC group and 4 in the placebo group). Because the MMDQ was designed to measure pain during menses, we conducted the analysis of the main treatment effect in several ways to account for the occurrence of amenorrhea. First, we performed the comparison after imputing the MMDQ score for amenorrheic participants as 0 (OC group mean MMDQ 2.8, SD ± 3.4; placebo mean MMDQ score 5.5, SD ± 4.8; $P = .007$; 95% CI for difference

Table 1. Demographic and Baseline Characteristics of the Study Population (N = 76)

	Oral Contraceptive Group (n = 38)	Placebo Group (n = 38)	*P*
Age (y)	16.7 (± 2)	16.9 (± 2)	.75
Race	0.74		
White	8 (21.1)	12 (31.6)	
African American	13 (34.2)	10 (26.3)	
Hispanic	11 (28.9)	10 (26.3)	
Other	6 (15.8)	6 (15.8)	
Education (y)	0.71		
0–8	7 (18.4)	8 (21.1)	
9–12	26 (68.4)	22 (57.8)	
> 12	5 (13.2)	8 (21.1)	
Body mass index*	23.7 (± 4.4)	24.6 (± 4.6)	.46
Severity of dysmenorrhea			1.00
Moderate	16 (42.1)	16 (42.1)	
Severe	22 (57.9)	22 (57.9)	
Medication use†	16.2 (± 13)	16.1 (± 13)	.98
MMDQ score	11.1 (± 5)	11.8 (± 5)	.53

MMDQ, Moos Menstrual Distress Questionnaire.
Data are n (%) or mean (± standard deviation).
* Body mass index was calculated as the weight in kilograms divided by the square of height in meters.
† Total number of pills taken for pain during usual menses.

between means 0.77–4.63). Assigning an MMDQ score of 0, however, might overestimate the treatment or placebo effect. To account for this, we administered the MMDQ to 10 participants during a nonmenstrual week (no bleeding) and then imputed the mean MMDQ score of this sample (2.8) as the exit MMDQ score for the amenorrheic participants (OC group mean MMDQ 3.1, SD ± 3.2; placebo mean MMDQ score 5.8, SD ± 4.5; $P = .004$; 95% CI for difference between means 0.88–4.53). This more conservative estimate of the treatment effect is represented in Figure 2. Finally, we excluded those with amenorrhea from the analysis and obtained similar results (OC group mean MMDQ 3.1, SD ± 3.4; placebo mean MMDQ score 6.2, SD ± 4.7; $P = .004$; 95% CI for difference between means 1.01–5.05). We obtained similar results for the primary comparison using the Mann-Whitney *U* test for nonparametric data, $P = .002$. Treatment effects were similar among younger (< 18 years) and older (18–19 years) participants, among those who described themselves as white, African American, or Hispanic, and among those with moderate or severe dysmenorrhea (data not shown, all comparisons n = 37 for each group).

In addition to the MMDQ pain subscale, we assessed 4 secondary measures of pain: rating of worst pain, hours of pain on the worst day, days of any pain, and days of severe pain (Fig. 3). The rating of worst pain (Fig. 3A) decreased in both groups over time ($P = .001$, within-group effects, repeated-measures analysis of variance), and the decrease in the OC group was greater than the decrease in the placebo group ($P = .047$, between-group effects). Similar decreases in the OC and placebo groups were seen over time in the other measures of pain (Fig. 3B-D). Between-groups effects for these measures, however, did not reach statistical significance. For all measures, the placebo effect seemed to stabilize by cycle 3, whereas pain continued to improve among participants in the OC group. There was no evidence of an interaction of time and treatment.

At enrollment, participants reported usually using a variety of over-the-counter and prescription pain medications in variable amounts. Commonly used analgesics included acetaminophen, naproxen, ibuprofen, and aspirin; narcotic use was uncommon. Six percent of participants reported usually using no analgesic pills for dysmenorrhea, 33% reported using between 1 and 10 pain pills, 34% between 11 and 20, 16% between 21 and 40, and 11% more than 40 pain pills per menstrual cycle. During the enrollment menstrual cycle, participants used fewer pills for pain than their estimate of usual use (enrollment cycle mean pill use 5.8, SD ± 7.0 compared with reported mean usual pill use 15.8, SD ± 12.8; $P < .001$).

During the study, the number of analgesic pills used decreased in both groups, but there was a larger decline in the OC than the placebo group. By cycle 3, those in the OC group reported using a mean of 1.3

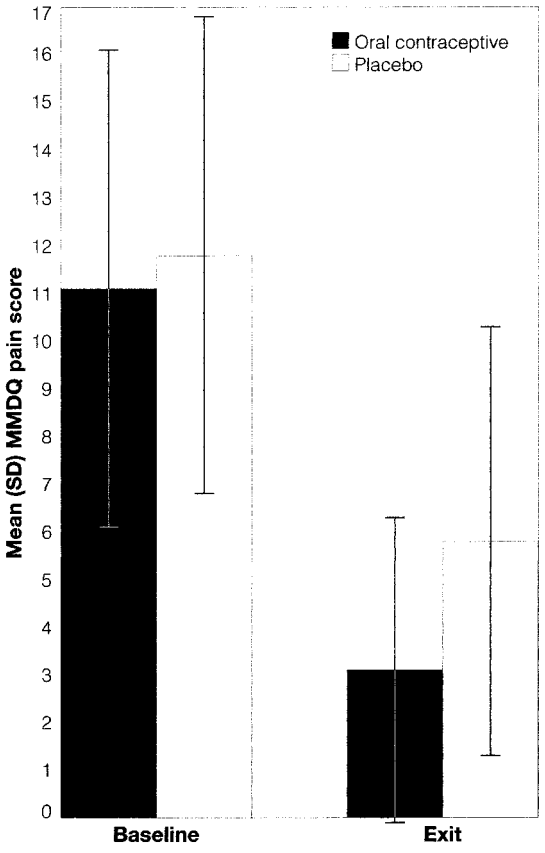

Fig. 2. Baseline and exit Moos Menstrual Distress Questionnaire (MMDQ) scores by treatment group. In each group (n = 37), 4 participants reported amenorrhea during the exit cycle. Comparison of mean MMDQ scores includes an imputed score for those with amenorrhea from a nonmenstrual week. SD, standard deviation.

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(SD ± 2.7) pain pills of any type compared with 3.7 (SD ± 6.8) pills in the placebo group ($P = .05$). Additionally, 61% of the OC users reported using no medications for pain compared with 36% of the placebo users during cycle 3 (OR .37, 95% CI 0.14–1.0).

At the exit visit, participants were asked if they thought they were taking OCs or placebos to assess the efficacy of blinding. Those participants in the OC group were more likely to be correct about their group assignment than those in the placebo group (81% correct for the OC group compared with 57% correct for the placebo group, OR 5.9, 95% CI 1.8–20.0). Most of those in the OC group who correctly guessed their group assignment cited improvements in pain or changes in menstrual bleeding as the reason rather than side effects from OCs (data not shown).

No serious adverse events related to OC use occurred and discontinuation due to adverse effects was uncommon. In the OC group 2 participants discontinued, 1 due to nausea and 1 due to acne, and in the placebo group 1 discontinued due to moodiness. Loss to follow-up was much lower than expected. However, we were unable to contact 1 participant after cycle 1 despite repeated attempts. One 18-year-old, sexually active participant discontinued condom use after enrollment due to ambivalence about pregnancy, became pregnant, and underwent termination of pregnancy with her mother's involvement. No sexually active participant reported discontinuing condoms secondary to believing she was in the OC group. One participant reported having unprotected sex, received emergency contraception from study staff, and did not become pregnant.

DISCUSSION

This trial demonstrated that a low-dose oral contraceptive was more effective than placebo for moderate or severe primary dysmenorrhea in adolescents. The improvement in dysmenorrhea during OC use was consistent across measures. Pain improved when measured by a validated pain scale (primary outcome) or by subjective reports of duration and intensity of pain (secondary outcomes). Most differences in secondary outcomes regarding pain intensity and duration, however, did not reach statistical significance in this small study. Regression toward the mean, as well as the treatment and placebo effects, may have contributed to the improvements in pain over time.

Our results agree with published observational studies in adults that show improvements of dysmenorrhea during OC use and support the common clinical practice of treating dysmenorrhea with OCs.[1] This trial demonstrates that OC-mediated improvements in dysmenorrhea extend to adolescents. A recent review by the Cochrane Collaboration[6] reported that the few published randomized control trials examining the efficacy of OCs for dysmenorrhea were conducted more than 20 years ago using OCs with much higher doses of estrogen and progesterone. This trial demonstrates that a modern, low-dose OC is effective for dysmenorrhea.

This study has several strengths. First, we included an ethnically diverse sample ranging in age from early to late adolescence, with both moderate and severe dysmenorrhea. Treatment effects were similar regardless of age or dysmenorrhea severity; however, a larger study would be needed to explore adequately differences in treatment effect related to demographic or other factors. Second, treatment discontinuation and loss to follow-up were uncommon. This was surprising, based on published data showing

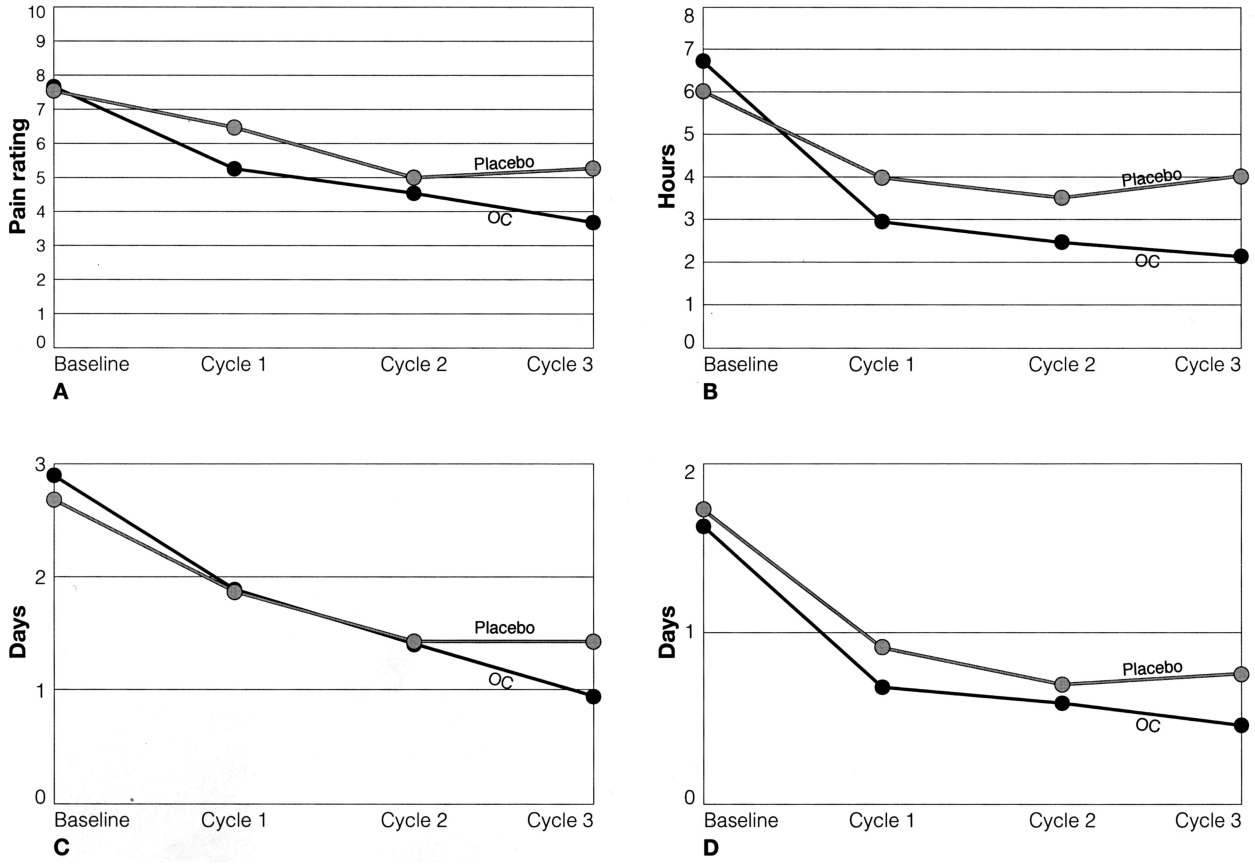

Fig. 3. Secondary pain outcomes. **A.** Rating of worst pain. **B.** Hours of pain on worst day. **C.** Days of any pain. **D.** Days of severe pain. Mean values for oral contraceptive (OC) or placebo group at baseline and by menstrual cycle.
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high rates of discontinuation among adolescents who use OCs for contraception. The strong motivation of those enrolling in a research study or the pain relief experienced during treatment may have contributed to the low discontinuation rate. Robinson et al[7] found that among adolescents using OCs for contraception, those who experienced an improvement in dysmenorrhea were 8 times more likely to continue OCs than those not experiencing this beneficial effect.

This study has limitations. Participants reported missing school as well as other important activities, which is typical of adolescents experiencing dysmenorrhea. We were unable to determine whether improvements in pain and decreased medication use during the study were associated with decreases in absenteeism and activity restriction. We intended to compare changes in behavior during the study to the baseline behavior pattern; however, behaviors and schedules were too erratic among this group of adolescents to use change as a measure of response. Future studies should explore other ways to measure behavioral changes associated with pain relief in adolescent populations. This small study lacked statistical power to demonstrate effects on secondary measures of pain improvement and to explore interactions between the treatment effect and demographic factors such as race or educational level.

Oral contraceptives and nonsteroidal anti-inflammatory medications are a mainstay of treatment for dysmenorrhea among adult women. Over-the-counter nonsteroidal anti-inflammatory medications are also widely used by adolescents, including those in this study. However, OCs may have unique advantages for treatment during adolescence. Oral contraceptive use is associated with improvements in acne and dysfunctional uterine bleeding, which are common during adolescence.[13,14] Oral contraceptive use also prevents pregnancy, which is often unintended and ends in abortion among adolescents.[15]

In conclusion, the results of this unique randomized trial support the use of low-dose OCs for the treatment of dysmenorrhea in adolescent girls. Oral contraceptives should become an important treatment option for the millions of adolescents who experience high morbidity from dysmenorrhea and are currently undertreated.

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