Ethinylestradiol 20 μg/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: a randomized controlled trial

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Objective: To investigate the efficacy and safety of ethinylestradiol 20 μg/drospirenone 3 mg in a flexible extended regimen ($Flexible_{MIB}$) compared with placebo to treat endometriosis-associated pelvic pain (EAPP).
Design: A phase 3, randomized, double-blind, placebo-controlled, parallel-group study, consisting of a 24-week double-blind treatment phase followed by a 28-week open-label extension phase with an unblinded reference arm.
Setting: Thirty-two centers.
Patient(s): A total of 312 patients with endometriosis.
Intervention(s): Patients were randomized to $Flexible_{MIB}$, placebo, or dienogest. The $Flexible_{MIB}$ and placebo arms received 1 tablet per day continuously for 120 days, with a 4-day tablet-free interval either after 120 days or after ≥3 consecutive days of spotting and/or bleeding on days 25–120. After 24 weeks, placebo recipients were changed to $Flexible_{MIB}$. Patients randomized to dienogest received 2 mg/d for 52 weeks in an unblinded reference arm.
Main Outcome Measure(s): Absolute change in the most severe EAPP based on visual analog scale scores from the baseline observation phase to the end of the double-blind treatment phase.
Result(s): Compared with placebo, $Flexible_{MIB}$ significantly reduced the most severe EAPP (mean difference in visual analog scale score: −26.3 mm). $Flexible_{MIB}$ also improved other endometriosis-associated pain and gynecologic findings and reduced the size of endometriomas.
Conclusion(s): $Flexible_{MIB}$ improved EAPP and was well tolerated, suggesting it may be a new alternative for managing endometriosis.
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Key Words: Endometriosis, flexible extended regimen, low-dose estrogen/progestin, pain relief

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Endometriosis is a gynecologic disorder characterized by the presence of endometrial glands and stroma outside the uterus (1). Being a sex hormone–dependent disorder, it affects women of reproductive age (2), with an estimated prevalence among the general population of 10% (3–5) and a higher prevalence of approximately 25%–50% among women with infertility (4–7). Endometriosis is a chronic condition with variable pain

symptoms, including menstrual pain, lower abdominal pain during the nonmenstrual period, lower back pain, defecation pain, and dyspareunia (1, 2), which can reduce quality of life (QOL) (8, 9).

Laparoscopic removal of endometriosis lesions can ameliorate pain but is associated with complications and a high recurrence rate (2, 10, 11). More radical surgery has lower recurrence rates (12), and even in cases of deep infiltrating endometrioses, resection of the nodule with part of the bowel may resolve symptoms without affecting fertility. An alternative to surgery is the use of long-term hormonal therapies; however, few therapies have been thoroughly investigated or approved for treating endometriosis (2, 13). Gonadotropin-releasing hormone agonists are widely used, but their duration of use is limited because of low estrogen (E) status and loss of bone mass (14). Progestins have recently been used more commonly, and low-dose estrogen/progestin (EP) products are also used as off-label first-line treatments (2, 15).

The most commonly used EP products are administered on a 28-day (21 + 7 placebo) cyclic regimen. Although the 28-day cyclic regimen mimics the length of a natural menstrual cycle, there is no scientific/medical rationale for this approach (16, 17). Treatment guidelines from the American Congress of Obstetricians and Gynecologists recommend extended-cycle combined oral contraceptives as initial treatment (18). Extended EP regimens may involve 12 weeks' administration rather than 3 weeks of active tablets followed by 1 week of placebo tablets, thereby reducing the number of withdrawal bleeds. Since publication of the first clinical trial of an extended-cycle EP regimen in 1977 (19), many additional studies have been conducted (20–22). Extended-cycle EP regimens suppress ovarian function more reliably than 28-day cyclic regimens, with greater improvement of symptoms associated with menstruation (21, 23).

Hormone withdrawal symptoms experienced with 28-day EP products are common during drug-free intervals (24). Often dysmenorrhea is a typical symptom of endometriosis-related pain; therefore, it has been suggested that extended-cycle EP products, which reduce the frequency of menstrual periods, may be particularly beneficial in patients with endometriosis (25). However, patients receiving fixed extended-cycle EP products frequently experience irregular bleeding/spotting while taking active tablets (26).

A more recent development is a flexible extended EP product comprising ethinylestradiol 20 μg/drospirenone (DRSP) 3 mg (Flexible Management of Intracyclic Bleeding [Flexible$_{MIB}$]; Yaz Flex; Bayer). The Flexible$_{MIB}$ regimen consists of a repeat cycle of 120 consecutive days of active tablet followed by a 4-day tablet-free interval, either after the 120 days or after ≥3 consecutive days of bleeding and/or spotting between days 25 and 120 (27). Studies of Flexible$_{MIB}$ have shown that extending the established 28-day cyclic regimen to a flexible extended regimen does not change the steady-state pharmacokinetics of ethinylestradiol or DRSP (28) and have confirmed the efficacy and tolerability of Flexible$_{MIB}$ for contraception (27, 29) and dysmenorrhea (30). Therefore, Flexible$_{MIB}$ could provide a valuable additional treatment choice for women with endometriosis. The aim of this study was to assess the efficacy and safety of Flexible$_{MIB}$ for endometriosis-associated pelvic pain (EAPP).

MATERIALS AND METHODS

Study Design

This phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (weeks 1–24) followed by an extension phase (weeks 25–52) was conducted in Japan with an unblinded reference arm. Upon completion of the double-blind treatment phase, both Flexible$_{MIB}$ and placebo groups were unmasked. Placebo treatment during the double-blind treatment phase was changed to Flexible$_{MIB}$ in an extension phase. The objective of the double-blind treatment phase was to confirm the superiority of the Flexible$_{MIB}$ regimen for the treatment of EAPP compared with placebo for 24 weeks. The objective of the open-label extension phase was to investigate the long-term safety of the Flexible$_{MIB}$ regimen. A marketed product containing dienogest served as an unblinded reference arm to compare the vaginal bleeding pattern of Flexible$_{MIB}$.

This study was conducted according to the Declaration of Helsinki and Good Clinical Practice protocols and met all local legal and regulatory requirements. The protocol was reviewed and approved by each study site's independent ethics committee/institutional review board, and all patients provided written informed consent.

Patients

We included patients aged ≥20 years with a clinical diagnosis of endometriosis who had pelvic tenderness, induration in the cul de sac, or uterine immobility, as well as patients diagnosed as having endometriosis by laparotomy/laparoscopy or by the identification of endometriomas. Patients who had undergone surgical treatment for endometriosis by laparotomy or laparoscopy within 2 months of the start of the study were excluded. Additional inclusion and exclusion criteria are provided in the Supplemental Materials, available online.

Treatment

Patients were randomized (2.5:2.5:1) to Flexible$_{MIB}$, placebo, or dienogest (unblinded reference arm). Patients randomized to Flexible$_{MIB}$ received one tablet per day, and treatment began between the first and fifth day of menstruation. Tablets were administered continuously for 120 days, followed by a 4-day tablet-free interval. In the event of ≥3 consecutive days of spotting and/or bleeding on days 25–120 of the cycle, patients began and completed the 4-day tablet-free interval, then started the next cycle of treatment. Patients randomized to placebo received one tablet daily following the same instructions as the Flexible$_{MIB}$ group for 24 weeks, after which these patients were changed to Flexible$_{MIB}$ for the open-label extension phase. Patients randomized to dienogest for the unblinded reference arm received one tablet twice daily at a total daily dose of 2 mg/d.

Randomization was via an Interactive Web Response system, with numbers generated by a Randomization

Management Group from Bayer and was stratified by baseline visual analog scale (VAS) score (<60 vs. ≥60 mm). Placebo tablets were identical in appearance to Flexible$_{MIB}$ tablets to maintain masking.

Endpoints

The primary endpoint was change in the most severe EAPP, which was defined as the difference in most severe EAPP between the baseline observation phase and the end of the double-blind treatment phase evaluated by VAS score. Secondary efficacy variables included pelvic pain, dyspareunia, and defecation pain. Induration in the cul de sac, limitation of uterine mobility, pelvic tenderness, size and number of endometriomas, endometrial thickness, and serum levels of E_2 and P were also investigated. Patients were asked about rescue medication intake and interference with daily activities and sleep related to EAPP. At weeks 24 and 52 (or at discontinuation), treatment was assessed for each individual patient by the investigator using the Clinical Global Improvement/Change subscale of the Clinical Global Impression rating scale, with possible ratings of very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse. Patients were also asked to provide an overall assessment of treatment satisfaction by choosing one of seven categories from very much satisfied to very much dissatisfied.

Safety endpoints included a comparison of adverse events (AEs), pregnancies, clinical laboratory variables, and other additional safety variables between Flexible$_{MIB}$ and placebo.

Assessments

Patients were followed-up every 4 weeks and underwent a pregnancy test at each visit. Endometriosis-associated pelvic pain was rated using a 0–100-mm VAS, which is a validated measure of endometriosis-related pain and widely used in clinical trials (31). Secondary pain variables were evaluated using a scale from 0 (no pain) to 10 (extreme pain) or VAS score. Patients provided daily ratings in an electronic patient diary for the worst pain during the previous 24 hours.

Induration in the cul de sac, limitation in uterine mobility, and pelvic tenderness were assessed by gynecologic examination and rated by the investigator on a 4-point scale as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The size and number of endometriomas and endometrial thickness were measured by transvaginal ultrasound.

Interference with daily activities and sleep was rated by the patient daily using a scale from 1 (not at all) to 5 (extremely).

Patients were monitored for AEs throughout the study, with AEs assessed for seriousness, intensity, and relationship to study medications. Bleeding events were recorded in patients' diaries.

Statistical Analyses

Enrollment of 300 patients was planned, allowing for 125 patients each in the Flexible$_{MIB}$ and placebo groups and 50 subjects in the unblinded reference arm. The method used to estimate sample size is provided in the Supplemental Materials. Statistical analyses were performed using SAS version 9.2 (SAS Institute). All analyses were conducted on the full analysis set (ie, all randomized patients who received one dose or more of study drug). The primary efficacy variable was compared between the Flexible$_{MIB}$ and the placebo groups using analysis of variance, with treatment group and baseline VAS score (<60 vs. ≥60 mm) included as fixed effects. Secondary efficacy variables were analyzed descriptively. All data were expressed as the mean ± SD.

RESULTS

Patients

The study was conducted between October 5, 2012, and December 15, 2014 and included 312 patients from 32 centers in Japan. Of these, one patient randomized to placebo received no treatment; therefore, the full analysis set comprised 311 patients (Fig. 1). In the Flexible$_{MIB}$ and placebo group, by week 24, 43 patients had discontinued treatment, and an additional 43 patients discontinued treatment during the open-label extension phase. Reasons for discontinuation during the 24-week double-blind treatment phase and the open-label extension phase, respectively, included patient withdrawal of consent (46.5% and 39.5% of not completed patients), AEs (32.6% and 39.5%), protocol-driven decision point (7.0% and 9.3%), protocol violation (7.0% and 7.0%), lost to follow-up (4.7% and 0%), desire for pregnancy (2.3% and 0%), and lack of efficacy and physician decision (both 0% and 2.3%). Patient demographics were similar between treatment groups (Supplemental Table 1). Most randomized patients had a clinical diagnosis of endometriosis, with very few cases visually confirmed by laparoscopy. All patients in the full analysis set were Asian; patients' mean age was 35.2 years, and mean body mass index was 21.2 kg/m^2.

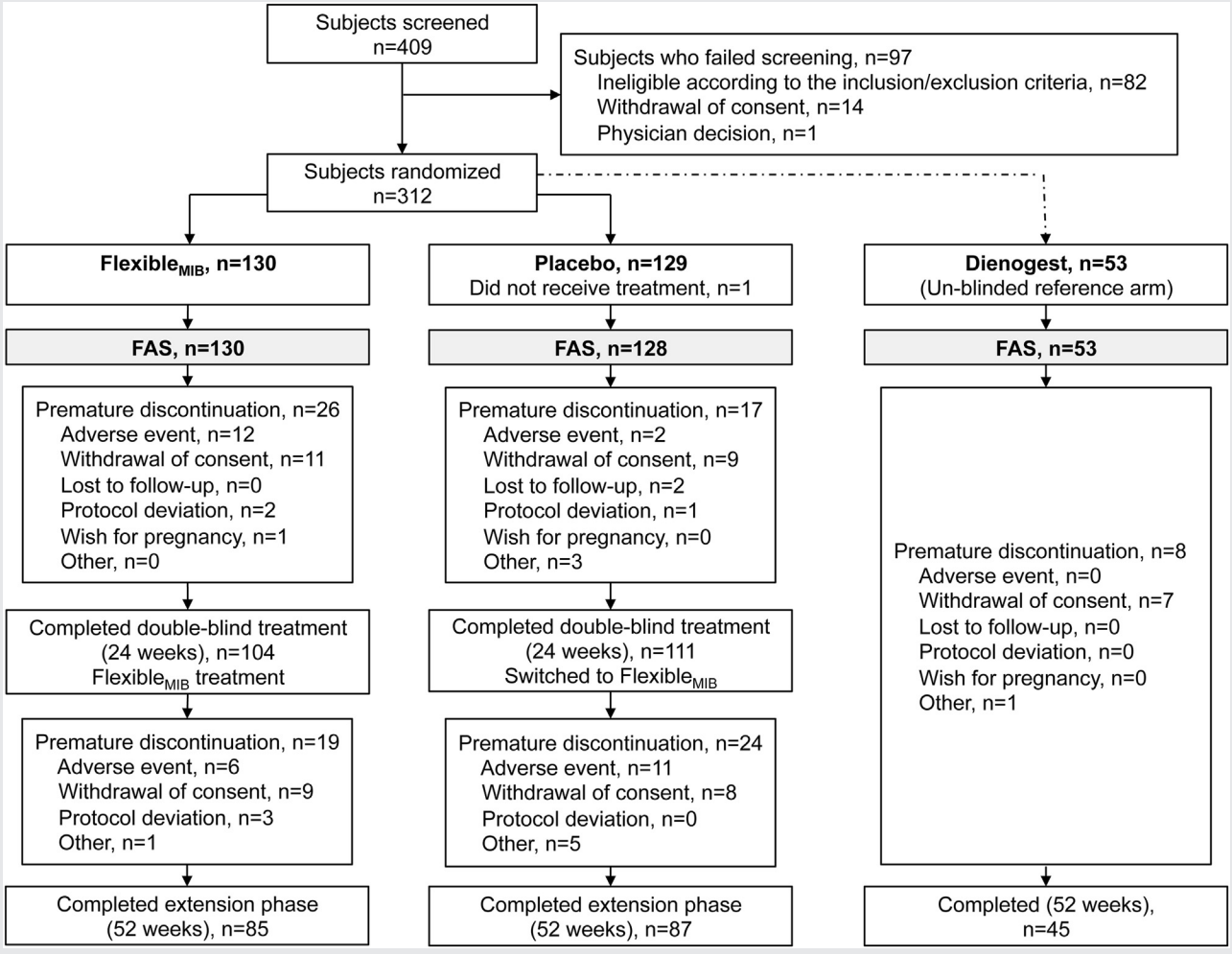
Efficacy

At 24 weeks, Flexible$_{MIB}$ was superior to placebo for alleviating daily-recorded most severe EAPP (least squares mean difference −26.3 mm; 95% confidence interval −31.6 to −20.9; $P<.0001$; Table 1). Furthermore, improvements from baseline to week 24 were greater with Flexible$_{MIB}$ than with placebo for all analyzed secondary pain measures (Fig. 2A). Flexible$_{MIB}$ also showed greater improvements from baseline to week 24 for average pain and the number of days with pain for any VAS score compared with placebo.

Gynecologic Findings

Improvements in induration in the cul de sac, limitation in uterine mobility, and pelvic tenderness were greater with Flexible$_{MIB}$ (Fig. 2B). The proportion of patients classified as having "none" or "mild" induration in the cul de sac improved from 63.1% at baseline to 85.6% at week 24 in the Flexible$_{MIB}$ group, and from 71.9% to 74.8% in the placebo group. Similarly, the proportion of Flexible$_{MIB}$ recipients with "none" or "mild" limitation of uterine mobility improved from 70.8%

FIGURE 1



Patient flow during the double-blind treatment phase (week 24) and the open-label extension phase (week 52) of the study (full analysis set [FAS]).

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to 81.7%, compared with a slight increase from 71.1% to 72.1% with placebo. Finally, the proportion of patients with "none" or "mild" pelvic tenderness improved from 57.7% to 85.6% among patients who received Flexible$_{MIB}$, and from 63.3% to 64.9% in the placebo group.

There was a slight reduction from baseline to week 24 in the number of endometriomas in the Flexible$_{MIB}$ group (2.0 ± 1.5 vs. 1.2 ± 1.0) but not in the placebo group (1.3 ± 0.9 vs. 1.4 ± 0.8); similarly, the geometric mean size of endometriomas decreased over the same period in the Flexible$_{MIB}$ group (29.87 ± 1.58 mm vs. 24.33 ± 1.79 mm) but not in the placebo group (28.86 ± 1.57 mm vs. 28.84 ± 1.59 mm). The proportion of patients with serum E_2 levels ≥27.2 pg/mL decreased in the Flexible$_{MIB}$ group from baseline to week 24 (95.4% vs. 11.5%); there were no remarkable changes in the placebo group (94.5% vs. 92.8%). The change of endometrial thickness from baseline to week 24 was from 10.7 ± 3.8 mm to 4.2 ± 2.4 mm in the Flexible$_{MIB}$ group and from 10.9 ± 3.9 mm to 8.6 ± 4.1 mm in the placebo group.

Rescue Medication use, Interference with Daily Activity and Sleep, and Patient Satisfaction

Flexible$_{MIB}$ showed improvements regarding interference by EAPP in daily activity and sleep, and high levels of patient satisfaction with treatment (Supplemental Materials). However, the frequency of rescue medication use remained unchanged.

Safety

Double-blind treatment phase. Overall, treatment-emergent adverse events (TEAEs) were reported in 102 of 130 patients (78.5%) in the Flexible$_{MIB}$ group vs. 86 of 128 patients (67.2%) in the placebo group. Rates of study drug–related TEAEs were higher with Flexible$_{MIB}$ than with placebo (56.9% vs. 21.9%, respectively), and the majority of TEAEs were mild in intensity (72.3% and 60.2% with Flexible$_{MIB}$ and placebo, respectively). Twelve patients (9.2%) in the

TABLE 1

Change in VAS score for most severe EAPP as recorded daily by patients.

	Flexible$_{MIB}$		Placebo		Dienogest	
Variable	**n**	**mean ± SD (mm)**	**n**	**mean ± SD (mm)**	**n**	**mean ± SD (mm)**
Severest EAPP						
Baseline	130	77.2 ± 16.5	128	77.7 ± 15.6	53	76.3 ± 16.5
Week 24	114	40.5 ± 25.1	117	66.4 ± 21.8	50	25.9 ± 23.5
Change from baseline (95% CI)	114	−36.6 ± 23.9 (−41.1, −32.2)	117	−10.7 ± 18.0 (−14.0, −7.4)	50	−50.0 ± 25.0 (−57.2, −42.9)
Least square mean change (SE)		−32.4 (2.20)		−6.2 (2.22)		
Least square mean difference (95% CI)		−26.3 (−31.6, −20.9); $P<.0001$				

Note: CI = confidence interval.

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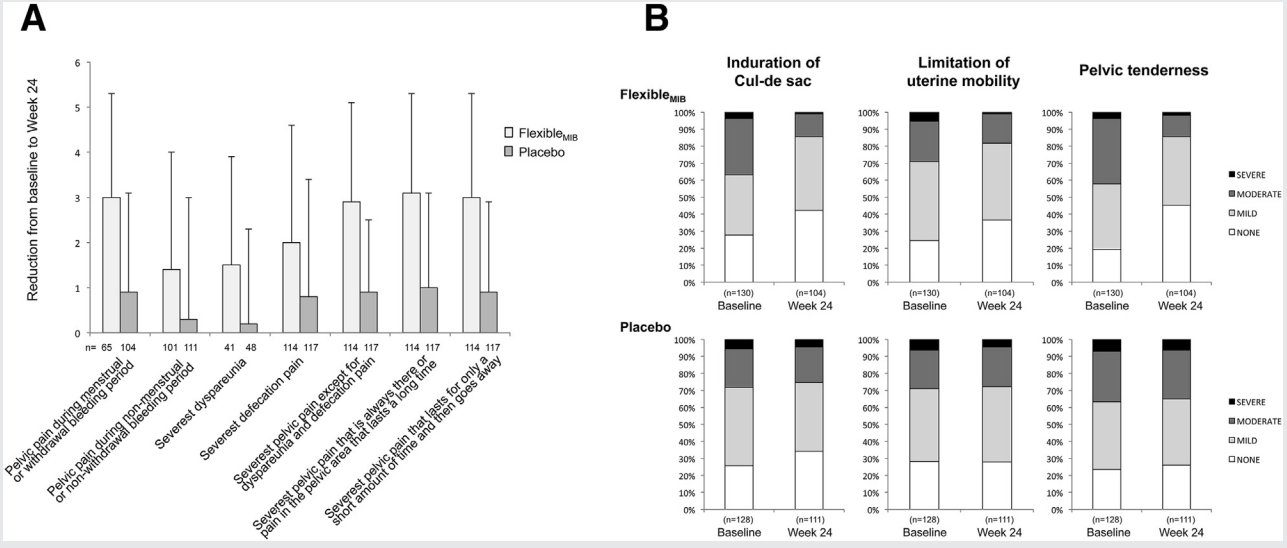
Flexible$_{MIB}$ group and two patients (1.6%) in the placebo group reported TEAEs that resulted in discontinuation of treatment. The most frequently reported TEAEs were nasopharyngitis, genital hemorrhage, and headache (Supplemental Table 2). One patient in the Flexible$_{MIB}$ group reported a treatment-emergent serious AE (deep vein thrombosis and pulmonary embolism), which was judged by the investigators to be study drug–related. No deaths were reported. There were no clinically relevant abnormalities observed in vital signs, physical findings, or other safety variables, including urinalysis and gynecologic examinations (Supplemental Table 3).

Open-label extension phase. Overall rates of TEAEs were almost identical in both groups after patients receiving placebo were changed to Flexible$_{MIB}$ (119 of 130 [91.5%] and 117 of 128 [91.4%] in patients originally randomized to Flexible$_{MIB}$ and placebo, respectively), as were the rates of study drug–related TEAEs (66.2% and 60.9%, respectively) and TEAEs resulting in discontinuation of the study drug (13.8% and 10.2%, respectively). The majority of TEAEs were mild (80.0% and 74.2% in Flexible$_{MIB}$ vs. placebo changed to Flexible$_{MIB}$ groups, respectively). Three patients who changed to Flexible$_{MIB}$ reported treatment-emergent serious AEs: pneumothorax (n = 1) and hemorrhagic ovarian cyst (chocolate cyst; n = 1), which were judged unrelated to the study drug, and deep vein thrombosis (n = 1), judged as drug-related. There were no deaths.

Bleeding pattern. During the first reference period (days 1–90), the numbers of bleeding or spotting days were 27.4 ± 14.7 days in the Flexible$_{MIB}$ group, 25.1 ± 8.2 days in the placebo group, and 43.4 ± 21.3 days in the dienogest group. During the second reference period (days 91–180), the numbers of

FIGURE 2



(**A**) Reduction from baseline to week 24 in pain measures associated with endometriosis; (**B**) gynecologic endpoints.

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bleeding or spotting days were 20.2 ± 13.0 days in the Flexible$_{MIB}$ group, 22.5 ± 10.6 days in the placebo group, and 26.1 ± 25.8 days in the dienogest group.

DISCUSSION

Endometriosis is a chronic condition with wide-ranging pain symptoms, including menstrual pain, lower abdominal pain during the nonmenstrual period, lower back pain, defecation pain, and dyspareunia, as well as other disorders, including infertility (1, 2). Of these symptoms, pelvic pain is the most common, occurring both during the nonmenstrual period and during the menstrual period associated with uterine contraction. The variable pain considerably affects QOL, including daily activity and sleep. Because the primary purpose of medical treatments for endometriosis is to alleviate pain to manage the variety of symptoms, therapy must be suitable for long-term use and associated with a low incidence of adverse drug reactions that further deteriorate QOL.

Although GnRH agonists are widely used, treatment duration is limited because of low E status and loss of bone mass (14). Recently, progestins have been used more commonly, following confirmation of their efficacy for endometriosis. However, as reported for monotherapies with progestins, a high frequency of irregular vaginal bleeding, especially soon after beginning treatment, may result in treatment withdrawal and deteriorating QOL (32, 33). Despite off-label use, guidelines have recommended EP combination products as a medical therapy for endometriosis (13, 34). However, all approved products involve a 28-day cyclic regimen, and more favorable regimens are needed when considering QOL.

A 2-year, self-controlled study in 50 women with surgically diagnosed endometriosis and moderate to severe dysmenorrhea demonstrated a significant reduction from baseline in VAS-measured pain with continuous use of a combination of ethinylestradiol 20 μg and desogestrel 150 μg (mean difference −45 mm; $P<.001$) (25). In addition, a recent meta-analysis of data from three randomized clinical trials and one prospective, controlled cohort study in patients (n = 557) with endometriosis who had undergone laparoscopic excision of ovarian endometriomas demonstrated a lower recurrence of dysmenorrhea with continuous vs. cyclic oral contraceptive regimens (risk ratio 0.24; $P=.04$) and a reduction in cyst recurrence rates (risk ratio 0.54; $P=.07$) (35).

To our knowledge our study is the first randomized controlled clinical trial evaluating a flexible extended regimen of ethinylestradiol 20 μg/DRSP 3 mg for managing endometriosis-associated pain. Our results demonstrate that, compared with placebo, Flexible$_{MIB}$ showed statistically significant improvements in pain scores from severe EAPP at 24 weeks. Flexible$_{MIB}$ effectively alleviated all EAPP variables, improved gynecologic findings, and reduced the size of endometriomas. However, because no statistical analysis was performed, the significance of these results is unclear. Flexible$_{MIB}$ was associated with improvements in interference with daily activity and sleep and with high levels of patient satisfaction. Reductions in serum E_2 levels suggest that Flexible$_{MIB}$ inhibited follicular maturation and ovulation in patients with endometriosis, whereas reductions in endometrial thickness suggest that Flexible$_{MIB}$ had a thinning effect on the endometrium.

At week 24 the overall incidence rate of TEAEs in the Flexible$_{MIB}$ group was slightly higher compared with the placebo group (78.5% vs. 67.2%). However, at week 52, after changing from placebo to Flexible$_{MIB}$, the TEAE incidence rates were identical between the groups (91.5% in the Flexible$_{MIB}$ group vs. 91.4% in the placebo switched to Flexible$_{MIB}$ group). Unlike headache, we considered genital hemorrhage to be a TEAE specific to Flexible$_{MIB}$ at weeks 24 and 52. The commonly observed TEAEs, considered specific to Flexible$_{MIB}$, were related to the reproductive system and coagulation factors and nausea. These TEAEs are well known adverse effects of EP combination products; therefore, the overall profile of common AEs related to Flexible$_{MIB}$ seen in our study is considered similar to that reported for EP combination products in general (33).

We encountered two subjects with deep vein thrombosis. Both cases occurred 3 months after starting treatment when the rare but serious risk of thrombosis is considered higher than during chronic treatment (36). One subject was 45 years old, and increasing age is a well-known risk factor for thrombosis (37–39). With fewer breaks in hormone therapy, women experience more steady hormonal levels and, therefore, less hormonal fluctuation. Several extended-cycle combined oral contraceptives have been authorized for use in the United States since 2003. Since 2007 a continuous 365-day combined active pill containing levonorgestrel 90 μg and ethinylestradiol 20 μg is available in the United States. After the introduction of extended combined oral contraceptives, experience with new regimens has been accumulating (40, 41). Currently there is no evidence to suggest that risks with extended-regimen combined oral contraceptives are greater (or lower) than with conventional 28-day regimens. Epidemiologic research has found that venous thromboembolism risk tends to increase after a pill-free interval of ≥4 weeks (42). This may suggest that hormonal fluctuations have a negative effect on the risk of venous thromboembolism, so that it seems to be unlikely that reduced frequency of pill-free intervals would increase the risk of thrombosis and thromboembolism.

Over the 180-day study period the number of bleeding/spotting days in the Flexible$_{MIB}$ group was similar to that in the placebo group but markedly smaller than that in the dienogest group. The number of bleeding/spotting days further decreased with continued treatment in the Flexible$_{MIB}$ group, although not as remarkably as in the dienogest group. A statistical analysis was not performed on these results; therefore, the significance of these findings is unclear. Dienogest showed good efficacy and was well tolerated. We used dienogest as an unblinded reference to assess the vaginal bleeding pattern of Flexible$_{MIB}$. The unblinded comparison with dienogest makes direct comparison of efficacy and safety difficult and may be viewed as a limitation of our study; however, an effective double-blind design with dienogest was considered inappropriate because of differences in dosing, the flexible intake regimen of the study drug, and the expected bleeding patterns.

Another study limitation is that the menstrual pattern may have indicated to the patient whether she had received active treatment or placebo, effectively "unblinding" the patient and thus influencing the assessment of pain. Nevertheless, the placebo control is widely believed to generate evidence superior to an open or uncontrolled study design.

In conclusion, Flexible$_{MIB}$ effectively improved pain in endometriosis and was well tolerated. Patients reported high levels of treatment satisfaction, suggesting that Flexible$_{MIB}$ may provide a new alternative for managing endometriosis.

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